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Editorial

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Warning: Ebola arrived in Columbus land

A few years ago, only some students of geography knew that Ebola was the name of a small river in the Democratic Republic of Congo. In 1976, in the village of Yambuku, a man died of a rare hemorrhagic fever which alerted the scientific world. Rumor has it that this man bought a fruit bat and later cooked and ate it, along with his family; some days later, all of them died. The cause of these deaths was a virus that was later called the Ebola virus (1). After this event, the epidemic spread throughout the town and then to other places. Today, about 4 000 people worldwide have been killed by the virus, including one case in the United States, two in Spain and one in Brazil. Only 1 in 10 infected patients survive and poor calculations estimate 20 000 people infected, especially in the West African republics.

A virus is a DNA (deoxyribonucleic acid) or RNA (ribonucleic acid) particle, no longer than 300 nanometers, so it is only visible with electron microscopes. The virus cannot be classified as living or dead substances because they have no brain, gastrointestinal tract, nor organs; they are simple agents that replicate at an incredibly rapid speed and destroy the living cells that they touch (2,3). Viruses may date back to 4 500 million years, when the Earth was formed, and over time, they became infectious pathogens of plants and animals, including humans. Some are common and relatively benign, as in the case of the flu, herpes, warts, etc., but others are aggressive and deadly; for example, in 1919, the Spanish flu virus caused about 20 million deaths, while HIV/AIDS has caused more than 30 million so far.

The Ebola virus is a natural host of bats that eat fruits, since they do not develop the disease. When a sensitive animal eats fruit contaminated by bat saliva, the disease spreads (4); for example, gorillas are susceptible to this virus and about 8 000 have died because of it.

Ebola epidemic was described by the World Health Organization (WHO) as extremely serious and has only been compared to AIDS, which erupted in the eighties. Ebola propagation has been overwhelming despite medical efforts (5). Infection occurs only by direct contact, not by air. The virus is found in body fluids such as saliva, feces, urine, blood, vomit, semen, sweat, tears, etc., and is also transmitted by consumption of contaminated meat.

Its symptoms are clear and appear from 2 to 21 days after contamination; the first symptoms are a simple headache and lack of appetite, followed by fever, vomiting, stomach pain, diarrhea, muscle and joint pain, decay, generalized bleeding in gums, nose, rectum, and finally, death. Only 15% of the population is immune to the disease because of natural defenses (6).

At the conference entitled "How and when will mankind disappear?", presented at the XVIII Meeting of the Latin American Association of National Academies of Medicine, in Spain and Portugal (ALANAM, by its acronym in Spanish) (7), one of the possible answers to this question was the possible arrival of a terrestrial or extraterrestrial virus that cannot be cured.

What have health authorities done against the Ebola virus? The most affected African countries claim that the West has not done enough; however, the International Red Cross, Medecins Sans Frontieres and WHO have sent 3 000 experts to the most affected countries —Guinea, Sierra Leone, Senegal, Liberia, Zaire, Congo and Nigeria— to face the emergency. All passengers leaving these countries are examined at destination, go through follow-ups and are declared Ebola free if, after 21 days of stay in possible infection places, they show no symptoms. Although an army of brave doctors and virologists work tirelessly to find a cure and a vaccine against this disease, nothing really effective has been found so far (8).

In the United States, two promising drugs have been developed from monoclonal antibodies extracted from laboratory mice that have been contaminated with Ebola RNA: ZMpp and TKM.ebola. Also, a vaccine made from modified vesicular stomatitis virus is being studied, while tests are being made to remove the VP30 gene, responsible for virus replication (9,10). There are several institutions that contribute to this research: the World Bank allocated 400 million dollars and the International Monetary Fund provided 130 million dollars for emergency financial assistance. All countries of the world are on high alert against this scourge, which extends exponentially.

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ORIGINAL RESEARCH

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Malignant bone tumors in Pediatrics. Five year experience in a pediatric referral center

Tumores óseos malignos en pediatría. Experiencia de cinco años en un centro de referencia pediátrico

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| Abstract |

Background: Osteosarcoma (OS) and Ewing's Sarcoma (ES) are the two most common malignant bone tumors in children. A retrospective review of the records of children diagnosed in a pediatric hospital over a five year period (2008-2013) was performed.

Objective: To present the experiences acquired during the treatment of these types of tumors and to compare the results obtained with those reported in the literature.

Methodology: The database of the Oncology and Pathology Service of Fundación Hospital de la Misericordia (HOMI) was reviewed to identify patients with primary bone tumors referred for histopathology analysis.

Results: 22 patients were diagnosed with OS, with a mean age of 11.9 years. 96% of cases were located in the lower extremities. All patients received neoadjuvant chemotherapy and 86% underwent surgical treatment; 13% survived. 15 patients were diagnosed with ES, with a mean age of 12.4 years. 67% of cases were located in flat bones, 53% of patients had metastasis when diagnosed, and all received neoadjuvant chemotherapy. 40% of patients received surgical intervention and 20% received radiotherapy. Survival at the completion of the reseearch was 33%.

Conclusions: Cure and survival rates are lower than those reported in the literature despite efforts to improve treatments.

Keywords: Osteosarcoma; Ewing's Sarcoma; Disease Progression; Recurrence; Neoplasm Metastasis (MeSH).

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| Resumen |

Introducción. El osteosarcoma (OS) y el sarcoma de Ewing (SE) son los tumores óseos malignos más frecuentes en edad pediátrica. En el presente estudio se realiza la revisión de los tumores malignos primarios de hueso diagnosticados en un hospital pediátrico de referencia en un período de cinco años (2008-2013).

Objetivos. Mostrar la experiencia en el tratamiento de osteosarcomas y sarcomas de Ewing y comparar los resultados con lo reportado en la literatura.

Materiales y métodos. Se revisó la base de datos del Servicio de Oncología y Patología de la Fundación Hospital de la Misericordia (HOMI) para identificar los pacientes con tumores primarios de hueso remitidos para estudio histopatológico.

Resultados. 22 pacientes con edad promedio de 11.9 años tuvieron diagnóstico de OS; 96% de los casos se localizaron en la extremidad inferior, 100% de los pacientes recibieron quimioterapia neoadyuvante, 86% recibieron manejo quirúrgico y 13% sobrevivieron. 15 pacientes con edad promedio de 12.4 años tuvieron diagnóstico de SE; 67% de los casos se localizaron en huesos planos, 53% de los pacientes presentaron metástasis al diagnóstico, 100% recibieron quimioterapia neoadyuvante, 40% fueron llevados a cirugía y 20% recibieron radioterapia. La sobrevida fue de 33% al finalizar esta investigación.

Conclusiones. Las tasas de curación y sobrevida son menores a las reportadas en la literatura a pesar de esfuerzos en mejorar los tratamientos.

Palabras clave: Osteosarcoma; Sarcoma de Ewing; Progresión de la enfermedad; Recurrencia; Metástasis de la neoplasia (DeCS).

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Introduction

Osteosarcoma (OS) and Ewing's sarcoma (ES) are the most common malignant bone tumors in children. OS is a mesenchymal tumor characterized by osteoid production; it occurs at all ages but is more common in children, with an estimate yearly incidence of 3.9 white children per million and 4.5 million African American children per million, and a similar distribution in men and women (1). Most osteosarcomas occur during the first two decades of life and the coincidence of OS with the pubertal peak implies a cause-effect relationship between accelerated bone growth and malignant transformation (2). Other factors that may support this relationship are, on the one hand, the predilection of OS for the metaphyseal of fast growing bones like the distal femur, the proximal tibia and the proximal humerus and, on the other, its earlier appearance in girls than in boys, coinciding with earlier pubertal development (3).

The second most common malignant bone tumor in children and young adults worldwide is ES. It belongs to the Ewing family of tumors/primitive neuroectodermal tumors (PNET), which, in turn, includes bone and extraosseous ES, Askin tumor of the chest wall and PNET. ES shows a slight male predilection, with a male:female ratio of 1.2:1 (4,5). Unlike OS, most ES occur in the flat bones of the axial skeleton, particularly the pelvis and costal arches; when they occur in long bones, they tend to compromise the diaphysis of bones and are more common in the femur, tibia and fibula.

Genetic mutations play a major role in the onset of both types of tumors. Patients with hereditary retinoblastoma have up to 1 000 times more risk of developing an OS due to germline mutations in the Rb gene. Moreover, the loss of heterozygosity, structural rearrangements or specific mutations of the gene are present in 60-70% of sporadic OS (6). Abnormalities in genes that regulate the cell cycle, such as p53, p16, Cyclin D1, MDM2, among others, have been implicated in the genesis of non-hereditary OS (7).

Evidence proves that OS presents greater chromosomal rearrangements with an average alteration of one for every 10Mpb. Recently, the phenomenon of chromothripsis or rearrangement of hundreds of genomic portions of the same chromosome produced by a single event, which is frequent in bone tumors (25%) and particularly in OS (3), was described. Contrarily, ES is characterized by the presence of a relatively simple karyotype, with few numerical and structural aberrations; in 85% of cases, a reciprocal translocation between chromosome 11 and 22t (11:22) is seen, which is why it is considered a pathognomonic disease (4).

The clinical picture is similar for both tumors: the main symptom is pain and usually inflammation or swelling at the site of the lesion; often, patients experience lameness and occasional pathological fractures. That the patient mentions a predominantly minor trauma related to the appearance of clinical manifestations is not unusual. Systemic symptoms such as fever and weight loss are rare in OS, but in ES, they can be associated with increased erythrocyte sedimentation rate (ESR), mild anemia or leukocytosis. The presence of increased serum lactate dehydrogenase (LDH) levels has been correlated with tumor severity and worse prognosis (4,8).

In the diagnostic approach to bone tumors, anteroposterior and lateral radiographies in the site of the lesion show changes in bone density, like the diaphyseal osteolysis in ES and lytic, sclerotic or mixed metaphyseal lesions in OS, usually accompanied, in both cases, with cortical ruptures and periosteal reaction with extension to soft tissues —in over 90% of cases of OS and ES— (5). Nuclear magnetic resonance (NMR) is optimal to assess bone involvement caused by the tumor and the presence of joint and vascular involvement, as well as "skip" metastasis and infiltration to adjacent soft tissues (3,5,8). CAT scan is the best method to determine lung metastases in the extension study.

Pulmonary metastases are evident in the images of 20% of the patients with OS at the moment of diagnosis and microscopic metastases may be found in 80% of the cases (9). Similarly, up to 25% of patients with ES develop metastatic disease, especially in the lungs, and other common locations such as bone and bone marrow. Spreading to lymph nodes, liver or central nervous system is rare in both entities (4,5,8). All patients who have a confirmed diagnosis of bone OS or ES are advised to take a high resolution computed tomography (CT) in the chest to look for pulmonary lesions; in the case of ES, a bilateral aspirate and biopsy of the bone marrow, and a bone scintigraphy with Tc^{99} or PET-FDG are also performed to search for bone marrow or bone metastases (4).

OS treatment begins with induction or neoadjuvant chemotherapy, followed by surgery, ideally with the purpose of rescuing or preserving the limbs, and finalizes with post-surgical chemotherapy. There are several therapeutic schemes that involve combinations of drugs such as doxorubicin, high doses of methotrexate, cisplatin and ifosfamide, carboplatin and etoposide, and their average duration ranges from 35 to 40 weeks. Event free survival rate is 70% (10) and overall survival rate is 80% at five years (11) with the use of neoadjuvant chemotherapy or induction chemotherapy.

Previously, ES was treated with surgery or isolated radiotherapy and had a very high mortality rate, so the use of adjuvant chemotherapy was proposed; in consequence, current protocols combine chemotherapy, local control of the disease and, in some cases, radiotherapy (6).

The drugs currently used for treating the localized disease are ifosfamide, etoposide, cyclophosphamide, doxorubicin, vincristine and actinomycin, which are administered in cycles every two weeks; remarkable improvement of event-free survival at five years, for up to 73% of patients, has been achieved (12,13).

For both tumors, using neoadjuvant chemotherapy facilitates surgery and augments the possibilities of saving the limbs, because the number of candidate patients for salvage surgery increases as a result of the reduction of the initial tumor size. The surgical approach has a significant influence on the probability of cure and survival of long-term patients and chemotherapy helps controlling micrometastases by diminishing the risk of recurrence. The goals of surgery are to remove the tumor and to maintain the greatest possible functionality of the limb, but the local control can only be achieved with wide resection margins, which, sometimes in unresectable tumors, imply amputation or disarticulation of the limbs (14).

Preserving the limbs with resected bone reconstruction, using various techniques such as autologous, vascularized or not grafts and allografts usually found in bone banks, and stents that may be expandable, should be attempted as much as possible (4,14).

Unlike OS, ES tumor is sensitive to radiation, so radiotherapy plays an important role in the treatment of inoperable tumors since the objective is to reduce their size and make them resectable; similarly, it is useful for patients with para-spinal masses, which constitutes an urgency due to neurological involvement. Postoperative radiotherapy is recommended for resected tumors with positive margins or low necrosis, and is also used for palliation in cases of recurrent disease and for patients with lung metastases at initial diagnosis (8).

The presence of metastasis is the most important adverse prognostic factor for OS; when detected during the diagnosis, the

survival rate decreases up to 30% (11). Similarly, for patients with metastatic ES, prognosis is adverse; different studies have shown that increasing standard chemotherapy does not improve the outcome (12) and even raises the risk of toxicity and secondary malignancies (15), achieving free-event survivals at five years of only 22% (12).

The degree of response of the primary tumor to preoperative chemotherapy as a prognostic factor has also been exposed in several studies (16). For both OS and ES, tumor necrosis percentage of the surgical specimen is measured. Patients with better prognosis are those whose necrosis is higher than 90% of the tumor, and are denominated responders (3). The latest reports indicate that the best response will be shown by patients diagnosed with OS and necrosis of 100% (17).

Some recurrence is found in 30 to 40% of patients with OS and ES (18); 80% of patients with OS relapse in their lungs, either in a combined or isolated way, and the remaining 20% relapse in other sites, including the bones. Local recurrence is 5% (11) and the survival rate at five years after a recurrence is only 10-13% in patients with ES (18,19).

This study aims at describing the characteristics and the experience gained while managing such tumors at Fundación HOMI in Bogota, since there are no similar reports in Colombia.

Materials and methods

The database of the Oncology and Pathology Service of Fundación HOMI in Bogota was reviewed to identify patients with primary bone tumors referred for histopathology between May 2008 and May 2013. Authorization from the ethics committee of the institution was obtained prior to the review of the database and the principle of privacy and confidentiality was preserved.

This study included children between 1 and 18 years old at diagnosis. Patients with OS received a protocol with ifosfamide, doxorubicin and cisplatin until 2012, and then, the possibility of measuring levels of methotrexate in the institution arose, so it was added in high doses ($12g/m^2$) to the treatment. Patients with ES received a protocol with ifosfamide, etoposide, doxorubicin, cyclophosphamide, vincristine and actinomycin. Patients who did not continue with the treatment in the institution were excluded since follow up could not be performed. Once pathology reports were confirmed, a review of medical records was conducted.

Results

40 patients were found in the database, but three were excluded because they did not continue with treatment in the institution. Of 37 patients included in the study, 22 (59%) were diagnosed with OS and 15 (41%) with ES; no other primary malignant bone tumor was found. The characteristics of patients, both with OS and ES, are described in Table 1.

Osteosarcoma

The average age at diagnosis was 11.9. All tumors were located in long bones, 96% of them in the lower limbs. At diagnosis, lactate dehydrogenase (LDH) was requested to 18 patients with OS and the value ranged between 288 and 4492 mg/dl. 50% of these patients had high levels (greater than 500). Simple radiography was abnormal in 95% of cases. CT was taken to some patients and confirmation was obtained through a NMR in all cases.

20 of the 22 patients with OS were taken to surgery between three and eight months after diagnosis, nine patients were amputated (55%) and 11 underwent salvage surgery (45%). Two patients did not receive surgical treatment because their disease progressed during treatment and died. The pathology study reported 100% necrosis of the tumor in three patients while they were alive (Table 2) and, among them, one patient presented metastatic disease at diagnosis with survival rate of 36 months. Mortality was 78% among patients with post-chemotherapy necrosis below 90% (non-responders).

Table 1. Characteristics of patients diagnosed with osteosarcoma and Ewing's sarcoma.

Characteristics		Osteosarcoma n (%)	Ewing's sarcoma n (%)
Gender	Total Patients	22 (59)	15 (41)
	Male	12 (54)	9 (60)
	Female	10 (46)	6 (40)
Primary tumor localization	Femur	14 (64)	1 (7)
	Tibia	7 (32)	5 (33)
	Humerus	1 (4)	-
	Vertebra	-	3 (20)
	Pelvis	-	2 (13)
	Costal arch	-	2 (13)
	Astragalus	-	1 (7)
	Boulder	-	1 (7)
Reason for consultation	Pain	21 (95)	13 (87)
	Edema	9 (40)	3 (20)
	Mass	4 (18)	4 (27)
	Trauma	9 (40)	2 (13)
	Limitation	5 (22)	1 (7)
	Pathological fracture	1 (4)	1 (7)

Source: Own elaboration based on the data obtained in the study.

Table 2. Responsiveness to chemotherapy of the primary tumor in living patients with osteosarcoma.

	n 16 (%)	Alive
Stage I	2 (13%)	0
Stage IIA	3 (19%)	0
Stage IIB	5 (30%)	1
Stage III	3 (19%)	2
Stage IV	3 (19%)	3

Source: Own elaboration based on the data obtained in the study.

Of the 22 patients, seven (32%) had metastasis at diagnosis, all in lungs. The overall survival of patients with metastasis at diagnosis was 28% and ranged from 10 to 36 months, while for those without metastasis was 40% and ranged from 12 to 40 months.

10 of these patients (45%) had disease progression, and four presented lung metastases at diagnosis. The most common site of progression was the lung (58%), followed by local progression (32%) and other sites such as brain and liver (11%). Seven of the patients whose disease progressed during treatment (70%) died between 1 and 13 months later; two of them were not monitored.

The recurrence of the disease of seven patients (32%) was documented: six of them died between 6 to 12 months after the diagnosis. One was not monitored.

At the time of the study, a total of five treated patients diagnosed with OS (22%) were alive.

Ewing's sarcoma

The average age at diagnosis was 12.4 years. Although the most common location of the primary tumor was the flat bones, the primary location for 33% of them was the tibia. Eight patients with metastasis at diagnosis (53%) — four located in the lung (50%), two in bone marrow and bone (25%), one in lung and bone (12.5%) and bone (12.5%)— were included in this study (Table 1).

At diagnosis, the leukocyte count was between 6 240 and 22 160; the leukocyte count for 35% was higher than 11 000 and 13% of patients had anemia at diagnosis. LDH was requested to 10 patients and the value ranged between 160 and 2 169; 60% of them had high levels.

Simple radiography was abnormal for 63% of patients; CT was taken for some of them and, in all cases, the diagnosis was obtained using NMR.

6 of the 15 patients diagnosed with ES (40%) underwent surgery, which took place three to eight months after diagnosis. 5 out of 6 patients (84%) underwent salvage surgery and 1 out of 6 (16%) underwent amputation. The remaining nine patients (60%) were not suitable for surgery due to tumor localization. The pathology study of patients undergoing surgery showed necrosis of 100% of the tumor in three of them, between 90% and 99% in one and less than 90% in two. Among the operated patients, three had metastasis at diagnosis; two of them were good respondents (necrosis 100%) but despite this, they died between 17 to 32 months after diagnosis; a non-respondent patient died eight months after diagnosis. The remaining three operated patients and two of the nine unoperated patients were alive by the end of this investigation.

Out of the 15 patients diagnosed with ES, eight presented metastases at diagnosis and survival ranged between 8 to 32 months, while those without metastases survived between 3 and 55 months.

Disease progressed in four patients (27%); three showed progression in the form of lung metastases, one presented metastases since the moment of diagnosis and all of them died within 2 to 3 months after progression.

Five patients (33%) had disease recurrence: two died within two months, one of them with multiple metastases, one died two years later, one is receiving second-line treatment and the other receives palliative treatment.

Discussion

The characteristics of the patients evaluated, in terms of tumor location, are very similar to those reported in the literature, which states that the most common primary site for OS is the femur, and for ES is the flat bones. However, it is noteworthy that 33% of cases of ES were located in the tibia and vertebral involvement ranked second in number, exceeding the frequency of location in pelvis and ribs. All patients presented pain as an initial common symptom, nevertheless, this is not a specific sign of this type of tumors.

Initial laboratory studies show that 35% of children with ES had leukocytosis at diagnosis. 50% of patients with OS and 60% of patients with ES had elevated levels of LDH. 75% of OS and 80% of ES patients, that passed away, had elevated levels of LDH at diagnosis, confirming the worst prognosis influenced by this factor (4,8).

Regarding imaging studies, the sensitivity of plain radiography was good for patients with OS —95% of the studies reported the lesion— while the performance for ES was much lower —only 63% of the studies were reported as abnormal— thus, turning plain radiography into a great diagnosing tool at primary levels of care, where patients initially consult and where the suspected diagnosis appears. For all patients, diagnosed suspicion was confirmed through MRI, which is ideal for assessing local tumor involvement (3,5,8). In the extension study, tomography is the best method to confirm the presence of lung metastases (4).

In this series, the incidence of metastasis was higher than that reported in the literature, with rates of 32% for patients with OS and 53% with ES, which might suggest that diagnosis is made at a later stage. Location at lungs and metastases at diagnosis were found for all patients with OS, while only 50% of patients with ES experienced it, noting involvement of other bones and bone marrow instead.

All treatment modalities, such as chemotherapy or radiation therapy and surgery aim at controlling micrometastases, achieving adequate necrosis, decreasing tumor size and locally controlling the disease, thus reducing the possibilities of recurrence. All patients received neoadjuvant chemotherapy and 20% of patients received radiotherapy.

Of the 22 patients with OS, 20 were taken to surgery, 11 of them with limb preservation; however, with ES, the experience was less encouraging as only 6 out of 15 patients could be surgically treated and only five limbs were salvaged. Of patients with OS, 3 of the 20 taken to surgery had necrosis of 100% and all were alive at the time of the study; one of them even had metastases at diagnosis. Although the degree of necrosis constitutes a prognostic factor, 2 of the 3 patients with 100% necrosis died.

The progression of the disease was established during treatment and became another adverse prognostic factor. 45% of patients with OS and 27% with ES had disease progression, which was directly related to poor survival. OS patients died between 1 and 13 months after the diagnosis of disease progression, whereas those who were diagnosed with progressive ES died between 2 and 3 months later.

Relapse rates reported in the literature range between 30% and 40% with a mortality of 80-90% (18,19). These figures are similar to the findings in this investigation, in which, on the one hand, 32% of cases of OS relapsed and all of them died within three years and, on the other, 33% of patients with ES relapsed; three of them died before two years and two were alive and being controlled upon completion of the study.

Although patients have clinical manifestations and usual location that could lead to a rapid diagnosis of the disease, usually, proper diagnosis takes longer, therefore, there is a delay in the therapeutic approach; this situation contributes to lower cure and survival rates than those reported in the literature despite efforts to improve treatments.

Conflict of interests

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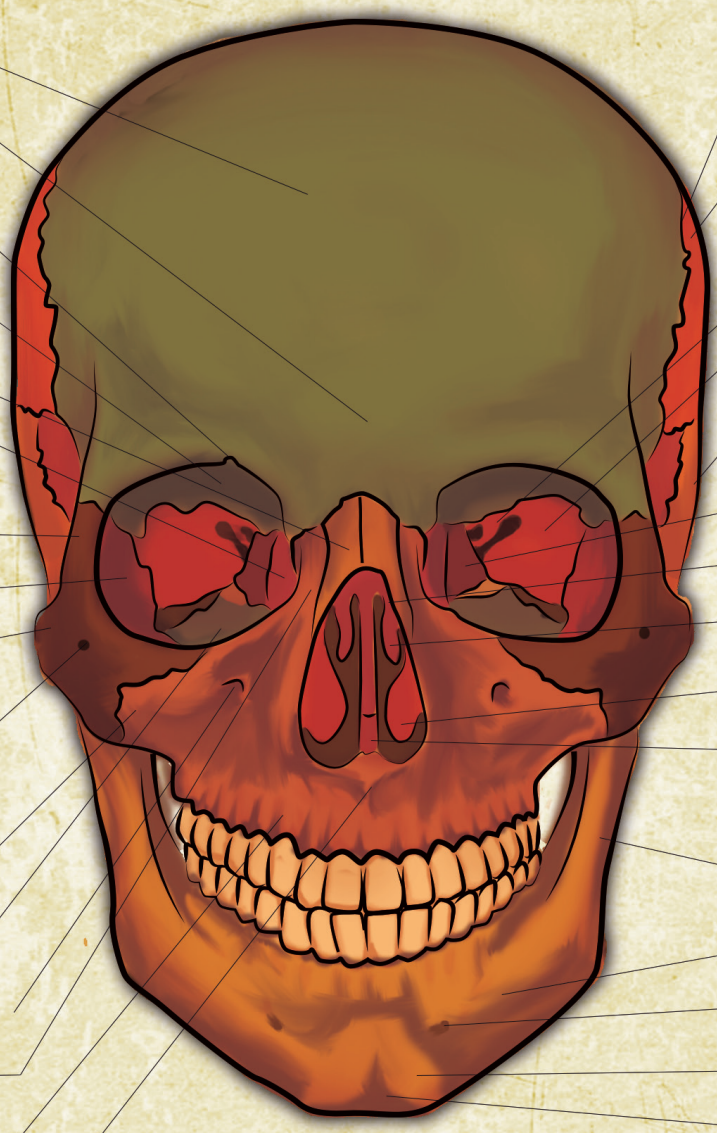
Cráneo Vista Frontal



Hueso Frontal
- Glabela
- Escotadura Supraorbitraria
- Cara Orbitaria

Hueso Nasal

Hueso Lagrimal

Hueso Cigomático
- Apófisis frontal
- Cara orbitaria
- Apófisis temporal
- Agujero cigomaticofacial

Hueso Maxilar
- Apófisis cigomática
- Cara orbitaria
- Agujero Infraorbitario
- Apófisis frontal
- Apófisis alveolar
- Espina nasal anterior

Sutura coronal

Hueso Parietal

Hueso Esfenoides
- Ala menor
- Ala mayor

Hueso Temporal

Hueso Etmoides
- Lámina orbitaria
- Lámina perpendicular
- Concha nasal media

Concha Nasal Inferior

Vómer

Mandíbula
- Rama
- Cuerpo
- Agujero mentoniano
- Tubérculo mentoniano
- Protuberancia mentoniana

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"Mapas anatómicos"
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ORIGINAL RESEARCH

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Inference of the phenotypic resistance profile of *Pseudomonas aeruginosa* through an interpretative reading of the antibiogram in a pediatric hospital. 2006-2014

Inferencia del perfil fenotípico de resistencia de Pseudomonas aeruginosa con la lectura interpretada del antibiograma en un hospital pediátrico entre los años 2006 y 2014

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| Abstract |

Introduction: *Pseudomonas aeruginosa* behaves as an opportunistic pathogen involved in hospital infections, with high capacity to generate resistance to antibiotic treatment. The interpretative reading of the antibiogram makes possible inferring these resistance mechanisms and establishing appropriate antibiotic treatment.

Objective: The interpretative reading of the antibiogram seeks to infer the resistance phenotype of *P. aeruginosa* at Fundación Hospital de la Misericordia (HOMI, by its acronym in Spanish) between 2006 and 2014.

Materials and methods: Descriptive cross-sectional study where a search of positive antibiogram reports for *P. aeruginosa* was performed. The resistance phenotype was deduced based on the interpretative reading of the antibiogram.

Results: A sample of 463 positive antibiograms for *P. aeruginosa* was obtained; these samples were taken from children aged 0 to 17, showing a higher prevalence among infants and toddlers. The antibiograms mainly came from male subjects (62.2%). The most frequent hospitalization services were: PICU —pediatric intensive care unit— (30.2%) and general hospitalization (27.3%). The most common sources of isolation were: blood (24.4%) and urine (23.8%). 11 phenotypes were characterized, being the most common: natural phenotype (63.2%), loss of porin OprD (5.7%) and partial and full AmpC derepression (8.4% and 8.2%, respectively).

Conclusion: Isolation of *P. aeruginosa* at HOMI predominantly shows a natural phenotype. The interpretative reading of the antibiogram allowed inferring 11 phenotypes.

Keywords: *Pseudomonas Aeruginosa*; Nosocomial Infections; Antibiotics; Antibiogram (MeSH).

Arango JJ, Leal AL, Montilla MP, Camacho-Moreno G. Inference of the phenotypic resistance profile of *Pseudomonas aeruginosa* through an interpretative reading of the antibiogram in a pediatric hospital. 2006-2014. Rev. Fac. Med. 2016;64(3):409-15. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.51770.

| Resumen |

Introducción. *Pseudomonas aeruginosa* se comporta como un patógeno oportunista implicado en infecciones intrahospitalarias y tiene alta capacidad de generar resistencia al manejo antibiótico. La lectura interpretada del antibiograma permite inferir estos mecanismos de resistencia y establecer el antibiótico más apropiado.

Objetivo. La lectura interpretada del antibiograma busca inferir el fenotipo de resistencia de *P. aeruginosa* en la Fundación Hospital de la Misericordia (HOMI) entre 2006 y 2014.

Materiales y métodos. Estudio descriptivo de corte transversal donde se realizó la búsqueda de informes de antibiogramas positivos para *P. aeruginosa* y se dedujo el fenotipo de resistencia según la lectura interpretada del antibiograma.

Resultados. Se obtuvo una muestra de 463 antibiogramas positivos para *P. aeruginosa* aisladas de niños entre 0 y 17 años, con predominio en lactantes y preescolares de género masculino (62.2%). Los servicios de hospitalización más frecuentes fueron unidad de cuidado intensivo pediátrico (30.2%) y hospitalización general (27.3%). Los sitios de aislamiento más frecuentes fueron sangre (24.4%) y orina (23.8%). Se caracterizaron en total 11 fenotipos, los más frecuentes fueron natural (63.2%), pérdida de porina OprD (5.7%) y desrepresión parcial (8.4%) y total (8.2%) de AmpC.

Conclusión. Los aislamientos de *P. aeruginosa* en el HOMI tienen de manera predominante un fenotipo natural. La lectura interpretada del antibiograma permitió inferir 11 fenotipos.

Palabras clave: *Pseudomonas aeruginosa;* Pruebas de sensibilidad microbiana; Antibióticos (DeCS).

Arango JJ, Leal AL, Montilla MP, Camacho-Moreno G. [Inferencia del perfil fenotípico de resistencia de *Pseudomonas aeruginosa* con la lectura interpretada del antibiograma en un hospital pediátrico entre los años 2006 y 2014]. Rev. Fac. Med. 2016;64(3):409-15. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.51770.

Introduction

Pseudomonas aeruginosa is a Gram negative, non-fermenting bacillus that has the ability to survive on inert surfaces and produce biofilms (1,2); this feature allows survival in hospital environments and growth in standard culture media, since their nutritional requirements are few (3). It has a genome with 6.3 million base pairs, which encodes 5 570 genes, and is rich in virulence factors (4).

In addition, *P. aeruginosa* is a pathogen involved in nosocomial infections associated with high morbidity and mortality rates, prolonged hospital stay and higher treatment costs. It also behaves as an opportunistic nosocomial agent, especially in patients with risk factors such as cystic fibrosis, prolonged hospitalization in critical care units and immunodeficiency (4).

Within the studied *P. aeruginosa* phenotypes, the wild or natural is characterized by being sensitive to carboxypenicillins, ureidopenicillins, ceftazidime, cefepime, cefoperazone, aztreonam and carbapenems (1), but it is also recognized by the intrinsic expression of resistance to a wide range of antibiotics and the development of mechanisms of antimicrobial resistance during operation via plasmids and integrons or mutations in the gene coding (5); this provides resistance to usually active compounds (6).

The intrinsic resistance of this bacteria is given by the low permeability of the outer membrane cell, the presence of inducible chromosomal β-lactamases (AmpC) and MexAB-OprM efflux system expression (7). Some strains can produce other β-lactamases such as oxacilinases (OXA), extended spectrum β-lactamases (ESBL) or carbapenemases (3). Based on the amino acid sequence, the used energy source and the substrate, efflux systems have been characterized in five superfamilies (5,8).

Another important mechanism is the aminoglycoside resistance, which occurs due to the enzymatic modification of antibiotics and affects the affinity of *P. aeruginosa* 30s ribosomal subunit. The involved enzymes are phosphoryltransferase (APH), adenyltransferases or nucleotidyltransferase (AADoANT) and acetyltransferase (AAC); methylation cases are also described in the 16s subunit of ribosomal RNA (9,10). Fluoroquinolone resistance is caused by changes in the DNA gyrase (affectation of genes gyrA and parC) and topoisomerase IV and active efflux systems (11).

This bacterium is inherently resistant to penicillin, aminopenicillins —β-lactamases inhibitors—, first and second generation cephalosporins, ceftriaxone, cefotaxime, oral third generation cephalosporins, chloramphenicol, nitrofurantoin, sulfonamides, trimethoprim, tetracyclines, novobiocin and nalidixic acid (1). Although there are cases of resistance to colistin, these mechanisms are still unknown and have been linked to alterations in the regulatory protein PmrA or outer membrane protein OprH; however, most strains remain sensitive (12).

In recent decades, there has been a global spread of bacterial resistance, considered as a growing and complex emergency, which was declared a public health problem in 1998 by the World Health Organization (WHO) (13).

The use of broad-spectrum antimicrobials has caused the onset of multidrug-resistant strains and, despite the importance of the mechanisms of resistance and their continuous identification, few antibacterial agents have been developed, leaving a limited number of therapeutic options for the management of patients with *P. aeruginosa* (14).

The techniques used for identification of resistance mechanisms include phenotypic and genotypic or *geneticoes*. The first is based on the sensitivity to antibiotics of different bacteria and its main objective is to guide the physician when deciding the ideal antibiotic treatment according to patient clinic and history. This technique is performed using the antibiogram, where the sensitivity of bacteria to different antibiotics is obtained *in vitro*, thus predicting efficacy *in vivo* through a qualitative or quantitative result, which will suggest whether the bacteria is sensitive or resistant to an antibiotic and will also determine minimum inhibitory concentration (MIC).

Based on MIC values established by various committees that take into account the microbiological, pharmaceutical and clinical efficacy properties, some breakpoints are set on susceptibility tests and interpretation is defined as suceptible, intermediate or resistant. These committees include the Clinical & Laboratory Standards Institute in the U.S., which is the basis for this study.

Based on the results of the sensitivity tests, the interpretative reading of the antibiogram was performed; this tool was described by Patrice Courvaline in 1992, and takes into account three foundations: a) phenotypic characterization of resistance according to the study of sensitivity regarding antibiotic groups of the same family, b) deduction based on the corresponding resistance phenotype of the involved biochemical mechanism, and c) inference of the phenotype previously established from the resistance mechanism deduced (1,15)

The Fundación HOMI is an exclusively pediatric institution with 305 beds: 15 beds for the pediatric intensive care unit (PICU), 24 for pediatric intermediate care, 12 for the neonatal intensive care unit (NICU), 49 for the oncohematology service, 6 for hematopoietic stem cell transplantation, 12 for the burn unit and the rest for general pediatrics. This capability makes the institution a center of national reference that treats patients at high risk of infection with *P. aeruginosa*.

The institutional report of 2013, provided by the Group for the Control of Antimicrobial Resistance in Bogotá (GREBO, by its acronym in Spanish), reported a frequency of infection by *P. aeruginosa* in PICU of 7% in a total of 250 isolates and ranking sixth among other germs; in the non-ICU area, the infection rate was also 7% for a total of 804 isolates, ranking fifth. The same report showed antibiotic resistance to piperacillin tazobactam of 8.2%, cefepime of 6.8%, imipenem of 14.1% and meropenem 11.4%.

This paper seeks to understand the resistance profiles of isolates of *P. aeruginosa* and to infer the resistance mechanisms prevalent in the institution in order to design control measures to expand and optimize the antimicrobial management through knowledge of institutional susceptibility to this germ.

Materials and methods

This was a descriptive cross-sectional study.

Definition of study subjects

Population: all patients hospitalized in HOMI during 2006 and 2014 with antibiotic susceptibility reports testing positive for *P. aeruginosa.*

Sample: all antibiograms obtained.
Unit of analysis: antibiograms report.
Inclusion criteria: antibiograms reports testing positive for *P. aeruginosa* in patients hospitalized in HOMI during 2006 and 2014, identified through the Vitek (Biomereux, France) automated system.
Exclusion criteria: incomplete antibiograms reports testing positive for *P. aeruginosa* in hospitalized patients and reports of patients evaluated by outpatient consultation in HOMI.

Description of the interventions

Susceptibility testing reports were identified, and the variables sex, age, date and place of hospitalization of patients at the time of sampling were considered.

When susceptibility testing reports were identified, an interpretive reading was made and possible mechanisms of bacterial resistance were suggested.

Procedures

1. Identification of antibiograms: positive reports were sought in the WHONET 5.6® database.

2. Deduction of the resistance mechanism: through the antibiogram, the analysis of bacterial phenotype and the identification of possible mechanisms of resistance were conducted; for analyzing the resistance profiles, the WHONET 5.6® software was used, and for interpretation of the criteria, the CLSI 2012 standards were taken into account (16).

Sensitivity tests were analyzed for five antibiotics: piperacillin tazobactam (PTZ), cefepime (FEP), ceftazidime (CAZ), imipenem (IPM) and meropenem (MEM).The interpreted reading was based on the paper by Vila *et al.* (1), which was modified taking into account the antibiogram report obtained at HOMI (Table 1 and 2).

Table 1. Enzymatic resistance mechanisms.

Resistance phenotypes					
PTZ	CAZ	CEF	IMP	MER	Inferred resistance mechanism
S	S	S	S	S	Natural
I	I	S/I	S	S	Partial AmpC derepression
R	R	I/R	S	S	Total AmpC derepression
S	S	S/I	S	S	Class A β-lactamase- Non-ESBL
S/I	R	R	S	S	Class A β-lactamase- ESBL
S	R	R	I/R	I/R	GES-2
I/R	S	R	S	S	OXA-1, OXA-31
R	R	I/R	S	S	OXAs- ESBL
R	R	R	I/R	I/R	Metallo-β- lactamase

PTZ: piperacillin tazobactam; CAZ: ceftazidime; CEF: cefepime; IMP: imipenem; MER: meropenem; R: resistant; S: suceptible; I: intermediate. Source: (1).

Table 2. Deficiency of porins and active efflux systems.

Resistance phenotypes					
PTZ	CAZ	CEF	IMP	MER	Resistance mechanism
S	S	S	R	I	Porin OprD Loss
I/R	I/R	I/R	S	I	MexAB-OprM system
I/R	I/R	R	S	S	MexCD-OprJ system
I/R	I/R	I/R	R	I	MexEF-OprN system
I/R	I/R	I/R	S	S	MexXY-OprM system

PTZ: piperacillin tazobactam; CAZ: ceftazidime; CEF: cefepime; IMP: imipenem; MER: meropenem R: resistant; S: suceptible; I: intermediate. Source: (1).

Statistical analysis

A descriptive analysis of absolute and relative frequencies for qualitative and quantitative variables was performed. For the latter, central tendency and dispersion measures were calculated.

Ethical considerations

Since the study is observational, it was classified as an investigation without risk as stipulated in Resolution 8430 of 1993 by the Ministry of Health (17). The protocol was taken to the Scientific Research and Teaching Unit of the Department of Pediatrics at Universidad Nacional de Colombia and to the Ethics Committee of Fundación HOMI, where it was evaluated and approved.

Results

During the six years of the study, 463 reports were obtained for positive antibiograms of *P. aeruginosa* strains, mostly in male patients (61.6%). 62.9% of the samples were obtained from lactating patients, 15.1% from preschool children, 14.5% from schoolchildren and 7.6% from adolescents. The most frequent isolation sites were blood (25.5%), urine (20.7%) and tracheobronchial secretion (13.8%) (Table 3). The most frequent isolation area in the hospital was the intensive care unit (29.4%), followed by general hospitalization (28.1%) and emergency room (16.6%). The most common phenotype was natural (66.5%), followed by partial and full AmpC derepression (8.4% and 8.2%) and OprD porin loss (6%).

The resistance rates found for each antibiotic by hospital area were: meropenem in PICU, 7%; in NICU, 3.5%, and in ICU, 8.4%. Cefepime in PICU was 11.9%; in NICU, 3.5%, and non-ICU, 1.4%. Piperacillin tazobactam in PICU was 12.1%; no resistance was found in NICU, and in ICU, 14.3%.

Table 4 shows that the most common phenotype in critical care areas was natural (57%), followed by porin OprD loss (12%) and partial and total AmpC derepression (9.5% and 8.9%, respectively). In non-critical hospital areas, natural phenotype was the most frequent (71.5%), followed by partial and total AmpC derepression (7.9% each) and metallo-β-lactamase (6.6%).

Table 5 shows that the most common phenotype was natural in all critical units, being predominant in pediatric intensive care (56.6%). In general, the most common phenotypes were porin OprD loss and AmpC derepression in the PICU; partial derepression of AmpC and Class A β-lactamase non-ESBLs in NICU; total and partial AmpC

derepression in the oncology unit; metallo-β-lactamase, followed by total or partial AmpC derepression and porin OprD loss in general hospitalization; metallo-β-lactamase and partial AmpC derepression in hospitalization for surgery; total AmpC derepression and OXA-1, OXA-31 in the burn unit, and total and partial AmpC derepression and porin OprD loss in emergency room.

Table 3. Distribution of isolates of *Pseudomonas aeruginosa*, according to sample type, service and resistance phenotype, 2006-2014.

Variables	Categories	n	%
Type of sample	Blood	118	25.5
	Urine	96	20.7
	Tracheobronchial	80	17.3
	Skin	64	13.8
	Stool	30	6.5
	Peritoneum	26	5.6
	Catheter	25	5.4
	Cerebrospinal fluid	9	1.9
	Bone	9	1.9
	Others	4	0.9
	Pleural fluid	2	0.4
Hospital isolation area	Pediatric critical care units	136	29.4
	General hospitalization	130	28.1
	Emergency room	77	16.6
	Surgery	57	12.3
	Oncology	25	5.4
	Neonatal critical care units	22	4.8
	Burn unit	15	3.2
	Hematopoietic transplant unit	1	0.2
Phenotype	Natural	308	66.5
	Partial AmpC derepression	39	8.4
	Total AmpC derepression	38	8.2
	Porin OprD loss	28	6.0
	Metallo-β-lactamase	26	5.6
	Class A β-lactamase- No ESBL	15	3.2
	Class A β-lactamase- ESBL	3	0.6
	OXA-1, OXA-31	2	0.4
	MexEF-OprN system	2	0.4
	GES-2	1	0.2
	MexXY-OprM system	1	0.2
Total		463	100

Source: Own elaboration based on the data obtained in the study.

Table 4. Phenotype frequency distribution according to hospital isolation of *Pseudomonas aeruginosa*, 2006-2014.

Variable	Categories	Hospital area				Total	
		Critical care		Non-critical care			
		n	%	n	%	n	%
Phenotype	Natural	90	57.0	218	71.5	308	66.5
	Porin OprD loss	19	12.0	9	3.0	28	6.0
	Partial AmpC derepression	15	9.5	24	7.9	39	8.4
	Total AmpC derepression	14	8.9	24	7.9	38	8.2
	Metallo-β-lactamase	10	6.3	16	5.2	26	5.6
	Class A β-lactamase-No ESBL	7	4.4	8	2.6	15	3.2
	Class A β-lactamase-ESBL	1	0.6	2	0.7	3	0.6
	GES-2	1	0.6	0	0.0	1	0.2
	MexEF-OprN system	1	0.6	1	0.3	2	0.4
	OXA-1, OXA-31	0	0.0	2	0.7	2	0.4
	MexXY-OprM system	0	0.0	1	.3	1	0.2
Total		158	100	305	100	463	100

Source: Own elaboration based on the data obtained in the study.

Table 6 shows that the natural phenotype predominated in all samples except in pleural fluid, where derepression of AmpC and metallo-β-lactamase phenotypes were predominant. Skin, urine and blood presented natural phenotype, followed by AmpC derepression and metallo-β-lactamases in the two last tissues. In tracheobronchial secretion and blood, after the natural phenotype, the most frequent was porin OprD loss, and in catheter, natural phenotype was followed by class A β-lactamase non-ESBL phenotype.

Discussion

P. aeruginosa is found repeatedly in patients within a specific context —hospitalized, immunocompromised, treated with broad-spectrum antibiotics, carriers of instrumented or prosthetic materials, patients with severe infection, prolonged hospitalization and presence of cross infections— so it constitutes the cause of hospital-acquired infections (HAI) (6). The prognosis of infection, compared with other agents, is reserved because the antibiotic treatment may not be effective in many cases, even in patients treated properly and early (3).

This bacterium is a lethal pathogen that is credited with 35% mortality in bacteremia and 69% in ventilator-associated pneumonia (18). This high mortality rate represents the potential to improve therapies and interventions.

In this study, the collected sample is important since it found that male infants are the patients with greater isolation of the pathogen; such isolation was seen in blood, urine and tracheobronchial secretion, and the most common hospital areas were PICU, general hospitalization and emergency department.

Table 5. Frequency distribution of the resistance phenotype of *Pseudomonas aeruginosa* according to the isolation area, 2006-2014.

Variable	Categories	Hospital isolation area																Total	
		Pediatric critical care units		Neonatal critical care units		Oncology		Hematopoietic transplant unit		General hospitalization		Surgery		Burn unit		Emergency Room			
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Phenotype	Natural	77	56.6	13	59.1	19	76	1	100	93	71.5	36	63.2	11	73.3	58	75.30	308	66.50
	Porin OprD loss	19	14	0	0	1	4	0	0	2	1.5	3	5.3	0	0	3	3.90	28	6.00
	Total AmpC derepression	13	9.6	1	4.5	3	12	0	0	8	6.2	3	5.3	3	20	7	9.10	38	8.20
	Partial AmpC derepression	11	8.1	4	18.2	2	8	0	0	12	9.2	6	10.5	0	0	4	5.20	39	8.40
	Metallo-β-lactamase	9	6.6	1	4.5	0	0	0	0	6	4.6	8	14	0	0	2	2.60	26	5.60
	Class A β-lactamase-Non- ESBL	4	2.9	3	13.6	0	0	0	0	5	3.8	1	1.8	0	0	2	2.60	15	3.20
	Class A β-lactamase- ESBL	1	0.7	0	0	0	0	0	0	2	1.5	0	0	0	0	0	0.00	3	0.60
	GES-2	1	0.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0.00	1	0.20
	MexEF-OprN system	1	0.7	0	0	0	0	0	0	1	0.8	0	0	0	0	0	0.00	2	0.40
	OXA-1, OXA-31	0	0	0	0	0	0	0	0	0	0	0	0	1	6.7	1	1.30	2	0.40
	MexXY-OprM system	0	0	0	0	0	0	0	0	1	0.8	0	0	0	0	0	0.00	1	0.20
Total		136	100	22	100	25	100	1	100	130	100	57	100	15	100	77	100	463	100

Source: Own elaboration based on the data obtained in the study.

Table 6. Frequency distribution of *Pseudomonas aeruginosa* strains according to tissue insulation, 2006-2014.

Variable	Category	Isolation tissue																				Total	
		Skin		Tracheo bronchial		Cerebrospinal fluid		Catheter		Peritoneum		Pleural fluid		Bone		Blood		Urine		Stool		Others			
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Phenotype	Natural	40	62.5	45	56.3	7	77.8	18	72	23	88.5			4	44.4	74	62.7	76	79.2	19	63.3	2	50	308	66.50
	Partial AmpC derepression	8	12.5	8	10	1	11.1	1	4			1	50	2	22.2	8	6.8	7	7.3	3	10			39	8.40
	Total AmpC derepression	3	4.7	7	8.8	1	11.1	4	16	2	7.6					9	7.6	5	5.2	5	16.7	2	50	38	8.20
	Class A β-lactamase-Non- ESBL	2	3.1	4	5			1	4	1	3.8					7	5.9							15	3.20
	Class A β-lactamase-ESBL			1	1.3											2	1.7							3	0.60
	GES-2															1	0.8							1	0.20
	OXA-1, OXA-31	1	1.6	1	1.3																			2	0.40
	Metallo-β-lactamase	5	7.8	4	5							1	50	3	33.3	7	5.9	5	5.2	1	3.3			26	5.60
	Porin OprD loss	5	7.8	9	11.3			1	4							10	8.5	2	2.1	1	3.3			28	6.00
	MexEF-OprN system			1	1.3															1	3.3			2	0.40
	MexXY-OprM system																	1	1					1	0.20
Total		64	100	80	100	9	100	25	100	26	100	2	100	9	100	118	100	96	100	30	100	4	100	463	100

Source: Own elaboration based on the data obtained in the study.

Discussion

P. aeruginosa is found repeatedly in patients within a specific context —hospitalized, immunocompromised, treated with broad-spectrum antibiotics, carriers of instrumented or prosthetic materials, patients with severe infection, prolonged hospitalization and presence of cross infections— so it constitutes the cause of hospital-acquired infections (HAI) (6). The prognosis of infection, compared with other agents, is reserved because the antibiotic treatment may not be effective in many cases, even in patients treated properly and early (3).

This bacterium is a lethal pathogen that is credited with 35% mortality in bacteremia and 69% in ventilator-associated pneumonia (18). This high mortality rate represents the potential to improve therapies and interventions.

In this study, the collected sample is important since it found that male infants are the patients with greater isolation of the pathogen; such isolation was seen in blood, urine and tracheobronchial secretion, and the most common hospital areas were PICU, general hospitalization and emergency department.

The most common phenotype in all areas and isolates was natural, being more frequent in non-critical areas. However, other 10 phenotypes, including partial or complete AmpC derepression (resistance to narrow spectrum aminopenicillins and cephalosporins inducible by cefoxitin and imipenem, sensitive only to carbapenems, resistance to piperacillin tazobactam) porin OprD loss (resistance to carbapenems), metallo-β-lactamase (carbapenemases), class a β-lactamase non-ESBL and ESBL (resistance to carboxypenicillins, ureidopenicillins, ceftazidime, cefepime, cefpirome and aztreonam), OXA-1, OXA-31 (no inhibition by clavulanic acid, sulbactam or tazobactam, with hydrolytic activity in ceftazidime, cefepime, cefpirome and aztreonam), GES-2, and MexEF-OprN and MexXY-OprM systems (possible involvement in the activity of beta-lactams, carbapenems, fluoroquinolones, macrolides, tetracyclines, chloramphenicol, novobiocin and lincomycin) (8).

It is noteworthy that PICU, a place where the use of carbapenems is high, the loss of porin OprD and AmpC derepression were the most frequent resistance mechanisms. In the oncology unit, the service in which the use of carbapenems is restricted to unstable patients, total and partial derepression of AmpC were more frequent.

In general hospitalization services, the most common phenotype was metallo-β-lactamase, followed by partial AmpC derepression and OprD porin loss, which can be related to the pressure for selection to which patients treated there are subjected, including oncohematology and rheumatology undergoing immunosuppression. In surgery hospitalization, metallo-β-lactamase and partial AmpC derepression were more frequent, which can be correlated with the arrival of critically ill patients who require a surgical procedure for improvement, prior to the empirical use of broad-spectrum antibiotics, leading to selection pressure.

In the burn unit, the phenotype AmpC derepression and OXA-1, OXA-31 were more frequent due to the high probability of colonization and infection in these patients. In the emergency room, the AmpC derepression phenotype was more frequent, which can be correlated with the acquisition of the infection in non-associated health care areas, that is, this is a community phenotype.

This study shows that multiple resistance phenotypes in a non-negligible percentage can occur simultaneously and confirms that infection with *P. aeruginosa* is polyclonal; one of the main causes is the indiscriminate use of antibiotics at hospital level since there is a selection pressure. Therefore, knowing the rates of resistance and the institutional phenotype profile allows optimizing the selection of antimicrobials in the institution and establishing which antibiotic of choice is in each of the services, especially in an empirical manner.

HOMI is a pediatric referral institution in Colombia that handles a wide range of highly complex pathologies; there, the characterization of *P. aeruginosa* is essential in the context of rational use of antibiotics and to reduce the resistant strains of the institution.

This work has biases derived from secondary sources originated by bacterial isolates and, as only single records of the antibiograms were analyzed, it is not possible to differentiate between colonization and infection. Since the inference is interpreted according to the reading of the antibiogram, molecular techniques should be applied to confirm the findings.

This study is derived from a thesis that is in the repository of Universidad Nacional de Colombia (19).

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Conflict of interests

None stated by the authors.

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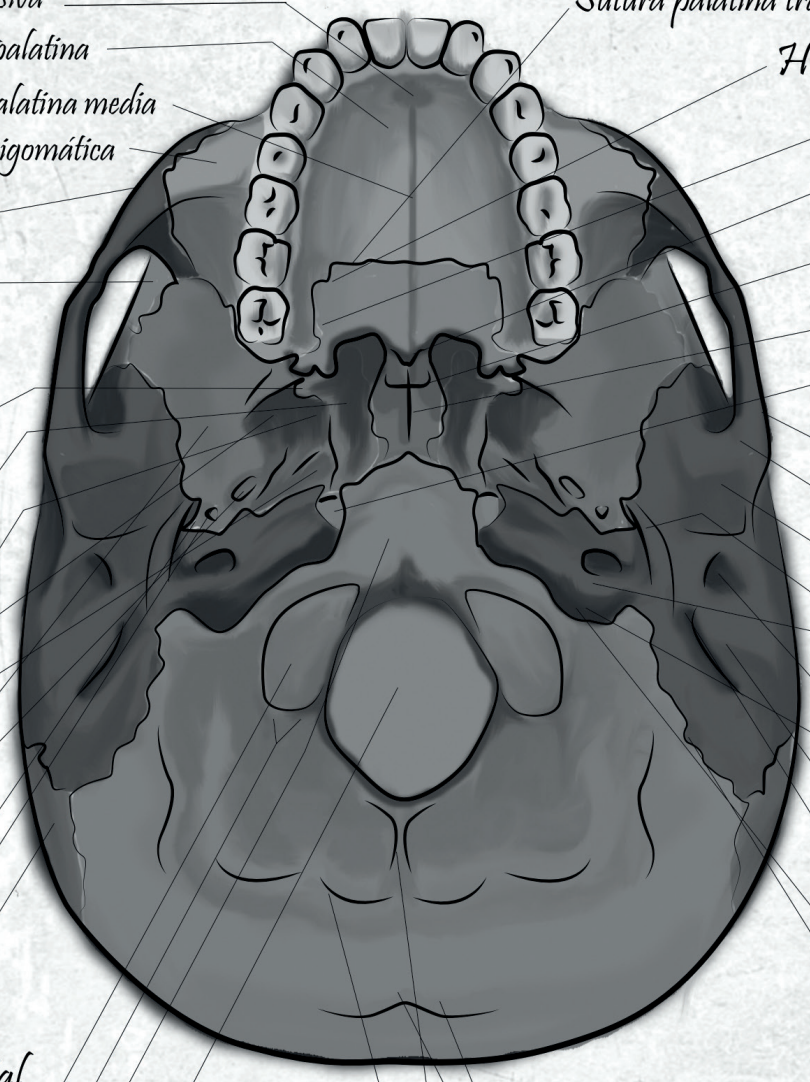
Cráneo Vista Inferior



Maxilar
- Fosa incisiva
- Apófisis palatina
- Sutura palatina media
- Apófisis cigomática

Hueso Cigomático

Hueso Frontal

Hueso Esfenoides
- Apófisis pterigoides
  - Gancho
  - Lamina medial
  - Fosa pterigoidea
  - Lámina lateral
- Fosa escaloidea
- Ala mayor
- Agujero oval
- Agujero espinoso
- Espina

Hueso Parietal

Hueso Occipital
- Condulo occipital
- Condulo y fosa condileos
- Porción basilar
- Agujero magno
- Línea nucal inferior
- Cresta occipital externa
- Línea nucal sup.
- Protuberancia occipital ext.

Sutura palatina transversa

Hueso Palatino
- Lámina horizontal
- Espina nasal posterior

Vómer

Ala

Agujero rasgado

Hueso Temporal
- Apófisis cigomática
- Tuberculo articular
- Fosa mandibular
- Apófisis estiloides
- Conducto timpánico
- Conducto auditivo externo
- Conducto mastoideo
- Apofisis mastoides
- Agujero estilomastoideo
- Fosa yugular
- Agujero mastoideo

César Alexander Eslava Franco
"Mapas anatómicos"
Universidad Nacional de Colombia

ORIGINAL RESEARCH

DOI: http://dx.doi.org/10.15446/revfacmed.v64n3.53961

Intensive chemotherapy in children with acute lymphoblastic leukemia. Interim analysis in a referral center in Colombia

Quimioterapia intensiva en niños con leucemia linfoblástica aguda. Análisis ínterin en un centro de referencia en Colombia

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| Abstract |

Background: Acute lymphoblastic leukemia is the most common cancer in children. In developed countries, overall survival rates are around 80%, while in developing countries, survival rate is much lower due to high rates of relapse, and abandonment and complications arising from the disease treatment.

Objectives: To assess induction mortality, relapse and treatment abandonment. To describe the most frequent side effects of chemotherapy. To evaluate survival rates of patients and compare the findings found in this study with the existing literature.

Material and methods: A retrospective cohort study was conducted on patients aged 1 to 18 with acute lymphoblastic leukemia, who received treatment under the BFM ALL IC 2009 protocol at Fundación Hospital La Misericordia (HOMI), from November 2012 to December 2014.

Results: 119 patients were included. Death occurred in two cases during induction (1.67%) and in nine (7.7%) due to treatment, all of them caused by infection/sepsis and in complete remission. Six patients abandoned treatment (5%), while seven relapses occurred (5.9%). All patients experienced some type of side effect related to chemotherapy, the most frequent being febrile neutropenia (41.2%) and grade 3-4 infections (15.8%). Overall survival and event-free survival rates were 79.9% and 73.3%, respectively.

Conclusions: Evaluating complications of treatment and death allows adopting measures and strategies to reduce such complications.

Keywords: Lymphoblastic Leukemia; Pediatrics; Side Effects; Survival (MeSH).

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| Resumen |

Introducción. La leucemia linfoblástica aguda es el cáncer más frecuente en los niños. La sobrevida en países desarrollados está alrededor de 80%, mientras que en países de bajos ingresos la tasa de supervivencia es menor debido a altas cifras de recaída, abandono de tratamiento y complicaciones relacionadas con el tratamiento.

Objetivos. Hacer una evaluación de muerte en inducción relacionada con el tratamiento, las recaídas y los abandonos de tratamiento; describir las reacciones adversas más observadas relacionadas con medicamentos de quimioterapia; evaluar la sobrevida, y comparar los hallazgos con publicaciones previas.

Materiales y métodos. Estudio de cohorte retrospectivo. Se incluyeron pacientes con edades entre 1 y 18 años, con diagnóstico de leucemia linfoblástica aguda tratada entre noviembre de 2012 y diciembre de 2014 en la Fundación Hospital La Misericordia de Bogotá (HOMI) y a quienes se les había aplicado tratamiento con el protocolo BFM ALL IC 2009.

Resultados. Se incluyeron 119 pacientes. Se presentaron dos (1.67%) muertes en inducción y nueve (7.7%) relacionadas con tratamiento —todas por infección/sepsis y en remisión completa—, seis abandonos (5%) y siete recaídas (5.9%). Todos los pacientes presentaron algún tipo de reacción adversa relacionada con medicamentos de quimioterapia, las más frecuentes fueron neutropenia febril (41.2%) e infecciones grado 3-4 (15.8%). Las sobrevidas global y libre de evento fueron de 79.9% y 73.3%, respectivamente.

Conclusiones. La evaluación de los efectos deletéreos del tratamiento y muerte durante tratamiento permiten tomar medidas para disminuir estas complicaciones.

Palabras clave: Leucemia linfoblástica; Pediatría; Toxicidad de medicamentos; Sobrevida (DeCS).

Trujillo AM, Linares A, Sarmiento IC. [Quimioterapia intensiva en niños con leucemia linfoblástica aguda. Análisis ínterin en un centro de referencia en Colombia]. Rev. Fac. Med. 2016;64(3):417-25. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.53961.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common neoplasm in pediatric patients (1). Overall cure rates for childhood ALL have improved over the years and current survival rates vary from 75% to 85% in patients treated in high-income countries (2); with the continuous improvement of survival rates, the goal of current clinical protocols is to reduce adverse reactions related to treatment (3). In contrast, in low-income countries, the possibilities of cure are lower, probably due to disease status at diagnosis, treatment abandonment, high rates of relapse and death caused by toxicity or side effects related to treatment (2).

In Colombia, the Cancer Registry of Cali (RPCC by its acronym in Spanish) reported a rate of 41% of survival in children with leukemia between 1994 and 2003 (4); the Protocol of Public Health Surveillance on Childhood Cancer reported that high mortality in children with leukemia is given by deaths during the first year of treatment, possibly because of poor access to treatment, low intensity treatment and toxicity caused by it. It also mentions that the causes of such low survival rates have not been identified, so intervention on them has not been possible (5).

Better cure rates are affected by additional barriers; the evaluation in children with ALL by Suarez *et al.* in Bogotá (6) reports that delays due to non-medical reasons in treatment are common and predict treatment failure. The same study also reported mortality during induction of 7%, death in complete remission of 3% and abandonment rates of 9% (6). According to information provided by the National Institute of Health of Colombia, 455 new cases of ALL were confirmed in 2013, with an overall mortality related to treatment of 15.6% (7).

In a study conducted in Central America, specifically in low-income countries, overall mortality related to treatment of 9.3% and mortality during induction of 5.5% were described (2).

Within the International BFM Study Group (Berlin-Frankfurt-Münster) (I-BFM-SG), the ALL strategy committee has developed several protocols with optimal clinical results over the last 20 years, most of them derived from the original BFM. Chemotherapy treatments proposed by the BFM for resource-limited countries have some changes aimed at local needs and conditions. In 2007, an amendment to the Intercontinental BFM 2002 Protocol was defined as more suitable for the diagnosis and treatment of children with ALL in Colombia (8). This protocol was adapted and applied for about five years at Fundación Hospital La Misericordia in Bogotá (Fundación HOMI), referral center for care of children with ALL in Colombia.

In 2012, the implementation of a modified version of the "Protocol for study and treatment of childhood lymphoblastic leukemia, ALL PINDA 2009, ALL IC BFM 2009" was decided. This approach to treatment is the same currently used in Argentina, Uruguay, Chile and Colombia, where the protocol is conducted by the National Cancer Institute.

In 2014, the BFM group published their experience with the BFM ALL IC 2002 treatment protocol, showing results from 15 countries of three continents, most of them with average incomes, as in the case of Colombia. The results of the implementation of this protocol show an improvement in the outcome of treatment for ALL, with event-free survival of 74% and overall survival of 82% (9).

There are no publications in Colombia that evaluate the results obtained with this type of treatment strategies, including survival and deleterious effects. This work aims at conducting an interim assessment of death during induction, treatment-related death (in remission), relapse and treatment abandonment, as well as at describing the most frequent adverse reactions observed with chemotherapy drugs, assessing overall and general event-free survival rates, and comparing —by risk group— previous outcomes with previous reports to assess the results of the implementation of this protocol at the institution.

Materials and methods

The description of a cohort of patients was performed. The inclusion criteria for the study were: age under 18, confirmed acute lymphoblastic leukemia diagnosis at Fundación HOMI between November 1, 2012 and December 31, 2014, treatment using the protocol BFM ALL IC 2009 (Table 1) in the same institution and continuity in treatment during the time of evaluation; those who started treatment and abandoned are also included until the time of abandonment. Exclusion criteria included being diagnosed in other institutions and being transferred to Fundación HOMI to continue treatment. Information was collected from clinical records.

This study was approved by the ethics committee of the institution prior to the review of the database, and the principle of privacy and confidentiality was preserved. Follow-up time was considered in months and was measured from the moment of diagnosis of the disease until the outcomes, which were defined as death during induction, death related to treatment, relapse, abandonment and transfer. The follow-up was done until September 30, 2015 and lasted between 9 and 34 months. The protocol was valid until the date of termination of the study.

Qualitative variables were presented as absolute and relative frequencies for the descriptive analysis. Similarly, a survival analysis was performed using Kaplan-Meier and Log Rank test for comparison of curves. High risk patients received prophylactic or therapeutic radiation accordingly to their condition.

Diagnosis

Diagnosis of ALL was confirmed with the presence 25% or more lymphoblasts in bone marrow. Flow cytometry based on EuroFlow panel criteria (10) was used for immunological classification of tumor cells, karyotype cytogenetic assessment was performed, and translocations t (12:21), t (4:11) and t (9:22) were identified with fluorescence in situ hybridization (FISH).The involvement of the central nervous system (CNS) was determined through identification of the cells using the cytospin method, for posterior classification according to the status:

Status 1: No clinical evidence disease, including facial paralysis that may be attributable to leukemia; no images —computerized axial tomography scan (CT scan) or magnetic resonance imaging (MRI) taken by suspicion— with evidence of CNS abnormalities attributable to leukemia, normal fundus or cerebrospinal fluid with no blasts and no other evidence of CNS leukemia.
Status 2: Blasts clearly identifiable in a CSF cytocentrifuge with cell count of <5/uL and CSF ratio of red blood cells (RBCs): leukocytes (LEU) ≤100:1; with this ratio between RBCs and LEU, a lumbar puncture is considered non-traumatic and CSF non-contaminated with blood. Lymphoblasts in a CSF cytocentrifuge and ratio GR: LEU> 100:1; with this ratio between erythrocytes and leukocytes, lumbar puncture is considered traumatic and CSF contaminated with blood or as a traumatic lumbar puncture —CSF contaminated with blood— associated with an initial leukocyte count of >50000/uL.

Table 1. Chemotherapy treatment protocol BFM ALL IC 2009.

Induction	**Induction**			
	Prednisolone		60 mg/m2/d. Days 1-28	
	Vincristine		1.5 mg/m2/d. Days 8, 15, 22, 29	
	Daunorubicin		30 mg/m2/d. Days 8, 15 (22, 29 intermediate and high risk)	
	L asparaginase		5000 UI/m2/d. Days 12, 15, 18, 21, 24, 27, 30, 33	
	Intrathecal therapy		Methotrexate. Days 1, 12, 33	
	Phase Ib			
	Mercaptopurine		60 mg/m2/d. Days 36-63 (28 days)	
	Cyclophosphamide		1000 mg/m2/d. Days 36, 64	
	Mesna		1:1 cyclophosphamide	
	Cytarabine		75 mg/m2/d. Days 38-41, 45-48, 52-55, 59-62	
	Intrathecal therapy		Methotrexate. Days 45, 59	
Consolidation	**Protocol mM (ALL B and T SR-IR)**		**Block HR1 (x2) (ALL B and T HR)**	
	Mercaptopurine	25 mg/m2/d. Days 1-56	Dexamethasone	20 mg/m2/d. Days 1-5
	Methotrexate *	2 gr/m2/d every 14 days (x4). Days 8, 22, 36, 50	Vincristine	1.5 mg/m2/d. Days 1, 6
	Calcium Folinate	15 mg/m2 (x3) 42, 48, 54 h after MTX	Methotrexate	5 gr/m2/d. Day 1
	Intrathecal therapy	Methotrexate. Day 2	Calcium Folinate	15 mg/m2 (x3) 42, 48, 54 h after MTX
	*5 gr/m2/day in ALL T SR-IR		Cyclophosphamide	200 mg/m2/d. Days 2 -4 every 12 hours. Five doses
			Mesna	1:1 cyclophosphamide
			Cytarabine	2000 mg/m2/d. Day 5 (2 doses total)
			L asparaginase	25.000 UI/m2/d. Day 6
			Intrathecal therapy	MTX / Ara-C / Prednisone. Day 2
	Block HR2 (x2) (ALL B and T HR)		**Block HR3 (x2) (ALL B and T HR)**	
	Dexamethasone	20 mg/m2/d. Days 1-5	Dexamethasone	20 mg/m2/d. Days 1-5
	Vincristine	1.5 mg/m2/d. Days 1 and 6	Cytarabine	2000 mg/m2/d. Days 1-2 every 12 hours. Four doses
	Methotrexate	5 gr/m2/d. Day 1	Etoposide	100 mg/m2/d. Days 3-5 every 12 hours. Five doses
	Calcium Folinate	15 mg/m2 (x3) 42, 48, 54 h after MTX	L asparaginase	25.000 UI/m2/d. Day 6
	Ifosfamide	800 mg/m2/d. Days 2-4 every 12 hours. Five doses	Intrathecal therapy	MTX / Ara-C / Prednisone. Day 2
	Mesna	1:1 ifosfamide		
	Daunorubicin	30 mg/m2/d. Day 5		
	L asparaginase	25.000 UI/m2/d. Day 6		
	Intrathecal therapy	MTX / Ara-C / Prednisone. Day 2		
Reinduction	**Protocol II Phase A**			
	Dexamethasone		10 mg/m2/d. Days 1-21	
	Vincristine		1.5 mg/m2/d. Days 8, 15, 22, 29	
	Doxorubicin		30 mg/m2/d. Days 8, 15, 22, 29	
	L asparaginase		10.000 UI/m2/d. Days 8, 11, 15, 18	
	Protocol II Phase B			
	Thioguanine		60 mg/m2/d. Days 36-49 (14 days)	
	Cyclophosphamide		1000 mg/m2/d. Day 36	
	Mesna		1:1 cyclophosphamide	
	Cytarabine		75 mg/m2/d. Days 38-41, 45-48	
	QT intrathecal		Methotrexate. Days 38 and 45 (MTX / Ara-C / Prednisone RA)	
	Maintenance			
	Methotrexate		50 mg/m2/d	
	Mercaptopurine		20 mg/m2/week	
	Intrathecal therapy		Methotrexate (SR-IR x4) MTX / Ara-C / Prednisone (HR x6)	

SR: standard risk; IR: intermediate risk; HR: high risk. Source: Own elaboration based on the data obtained in the study.

Status 3: Abnormal mass in the brain and/or meninges detected through CT/MRI, cranial nerve palsies, regardless of origin; although CSF does not show blasts nor abnormal masses in the images, isolated compromise of the retina is evident but with CFS with no blasts nor masses in CT/MRI or a non-traumatic lumbar puncture with a cell count CSF>5/uL and most of the blasts in the cytocentrifuge.

Risk classification

Risk classification was established by the BFM group considering clinical and laboratory criteria evaluated in previous protocols; according to the characteristics described in Table 2, patients were classified as standard risk, intermediate risk and high risk.

Table 2. Risk classification of BFM ALL IC 2009 Protocol.

Characteristics	Standard risk (all criteria must be met)	Intermediate risk	High risk (at least one criterion must be met)
Age at diagnosis	>1 year and/or <6 years	< year and/or ≥6 years	
Leukocytes at diagnosis	<20000/uL	>20000/uL	
Response to steroids at day 8	<1000 blast cells/uL	<1000 blast cells/uL	>1000 blasts/uL
MRD in bone marrow on day 15	<0.1%	<10%	>10%
Bone marrow on day 15	M1 (<5% blasts by morphology) or M2 (>5 y <25% blasts by morphology)	M1 or M2	M3
Bone marrow on day 33	M1 (<5% blasts by morphology)	M1	M2 or M3
Molecular biology	Negative for t (9:22) (BCR/ABL) or t (4:11) (MLL/AF4)	Negative for t (9:22) (BCR/ABL) or t (4:11) (MLL/AF4)	Positive for t (9:22) (BCR/ABL) or t (4:11) (MLL/AF4) or hypodiploidy ≤45 chromosomes

Source: Own elaboration based on the data obtained in the study protocol.

Outcomes

Treatment-related death, defined as death during induction or death in complete remission occurred; the first death was specified as death in the first 33 days of treatment and the second, as death after this period without clinical or paraclinical evidence of disease activity.

Secondary outcomes were abandonment, defined as the interruption of treatment for four or more weeks without medical reason, transfer to another institution due to the change of treatment center by the insurer, and relapse in bone marrow caused by the reappearance of lymphoblasts ≥25% in bone marrow.

In the SNC, relapses were established by the appearance of cells >5/uL CSF and indisputable lymphoblasts identified in cytocentrifuge or intracerebral mass in CT/MRI without blasts in cerebrospinal fluid (CSF), peripheral blood (PB) or bone marrow (BM) —a biopsy may be necessary for diagnosis—. In the testicles, relapses were verified by a steady insensitive unilateral or bilateral increase of one or both testicles, with volume >2 and deviations measured with the Prader orchidometer —the diagnosis must be confirmed through biopsy— and combined by simultaneous compromise of two or more compartments or locations; BM relapse is considered compromised when >5% lymphoblasts.

Another outcome was the description of adverse reactions to chemotherapy drugs, which were evaluated based on the criteria of the National Cancer Institute (NCI CTC v2.0): incidence of infections, defined as those with identified pathogen and antibiotic treatment and sepsis; incidence of cardiac, liver toxicity and mucositis grade 3 and 4; requirement for admission to the intensive care unit and transfusion requirement, which includes transfusions of red blood cells, platelets, fresh frozen plasma and cryoprecipitate.

Statistical analysis

The event-free and overall survival were estimated according to the Kaplan Meier method. Event-free survival was defined as the period between the start of treatment and presentation of an event (whichever comes first: death, relapse, second malignancy, transfer or abandonment), for those who have not presented any, the event was the last control alive. Overall survival was defined as the time between the start of treatment and the last control alive, regardless of the condition of the disease.

Results

The sample includes 119 patients who meet the inclusion criteria in the specified period. Demographic characteristics are shown in Table 3.

Mortality

Of 119 patients, two (1.67%) died during induction, nine (7.7%) died in remission related to treatment due to infection/sepsis, seven of them were classified as high risk, two as intermediate risk, and there were no deaths in those with standard risk. Deaths that occurred during the treatment stages were: two (18%) in phase Ib, two (18%) in block HR1#1, two (18%) in block HR 3#1, one (10%) in HR3 block HR3#2 and two (18%) in protocol II phase A.

Abandonment and relapse

Six abandonments (5%) and seven relapses occurred (5.9%), the latter in two high-risk patients and five in intermediate-risk patients. Five relapses (71.4%) were isolated bone marrow, one (14.3%) was isolated CNS and one (14.3%) was isolated testicular. In two patients, relapses occurred after completing treatment —at 30 and 26 months after diagnosis—; one patient was considered high risk and the other intermediate risk. The remaining five patients —a high-risk patient and four-intermediate risk patients— relapsed within the first year of treatment.

Drug-related adverse reactions

A description of the adverse reactions related to chemotherapy drugs used in the treatment for each phase and risk group was made (Table 4 and 5).

All the patients had some adverse reactions related to chemotherapy drugs; the most frequent was febrile neutropenia during induction phase for all risks and in the consolidation phase for high risk patients. In the mM protocol, lower incidence of complications in general was found, as well as less febrile neutropenia, grade 3-4 infections and admission to the pediatric intensive care unit (PICU). The transfusion requirement was high in all groups of patients, especially in the induction phase.

Table 3. Patient characteristics and results of initial treatment according to the risk group in the total population.

	Total		Standard risk		Intermediate risk		High risk	
	n	%	n	%	n	%	n	0,0712
Gender	**119**	**100**	**11**	**100**	**73**	**100**	**35**	**100**
Female	38	31.9	5	45.4	34	46.6	13	37.1
Male	81	68.1	6	54.6	39	53.4	22	62.9
Age	**119**	**100**	**11**	**100**	**73**	**100**	**35**	**100**
1-6 years	49	41.2	11	100.0	31	42.5	7	20.0
6-10 years	29	24.4	0	0.0	21	28.7	8	22.9
10-15 years	29	24.4	0	0.0	15	20.5	14	40.0
>15 years	12	10.0	0	0.0	6	8.3	6	17.1
Leukocyte count at diagnosis	**119**	**100**	**11**	**100**	**73**	**100**	**35**	**100**
<10,000	68	57.1	9	81.8	42	57.5	18	51.4
10.000-20.000	15	12.6	2	18.2	11	15.1	2	5.7
20.000-50.000	13	10.9	0	0.0	9	12.3	3	8.6
50.000-100.000	11	9.2	0	0.0	6	8.2	5	14.3
>100.000	12	10.0	0	0.0	5	6.8	7	20.0
CNS status	**119**	**100**	**11**	**100**	**73**	**100**	**35**	**100**
1	118	99.1	11	100.0	73	100.0	3. 4	97.0
2	0	0.0	0	0.0	0	0.0	0	0.0
3	1	0.9	0	0.0	0	0.0	1	3.0
Immunophenotype	**119**	**100**	**11**	**100**	**73**	**100**	**35**	**100**
B	108	90.7	11	100.0	68	93.1	29	82.9
T	11	9.3	0	0	5	6.9	6	17.1
Translocation 9:22	**119**	**100**	**11**	**100**	**73**	**100**	**35**	**100**
Negative	87	73.1	8	72.7	51	69.8	28	80
Positive	2	1.7	0	0.0	0	0.0	2	5.7
Not available	30	25.2	3	27.3	22	30.2	5	14.3
Translocation 4:11	**119**	**100**	**11**	**100**	**73**	**100**	**35**	**100**
Negative	80	67.2	7	63.6	46	63.0	27	77.1
Positive	0	0.0	0	0.0	0	0.0	0	0.0
Not available	39	32.8	4	36.4	27	37.0	8	22.9
Translocation 12:21	**119**	**100**	**11**	**100**	**73**	**100**	**35**	**100**
Negative	63	52.9	6	54.5	35	47.9	22	62.8
Positive	13	10.9	2	18.2	8	10.9	3	8.6
Not available	43	36.2	3	27.3	30	41.2	10	28.6
Kariotype	**119**	**100**	**11**	**100**	**73**	**100**	**35**	**100**
Normal	74	62.2	8	72.7	47	63.4	19	54.3
Hyperdiploid	8	6.7	0	0.0	5	6.8	3	8.6
Complex	9	7.6	0	0.0	5	6.8	4	11.4
Not available	28	23.5	3	27.3	16	23.0	9	25.7
Good	107	89.9	11	100.0	73	100.0	23	65.7
Poor	8	6.7	0	0.0	0	0.0	8	22.9
Not evaluable (debulking)	4	3.4	0	0.0	0	0.0	4	11.4
<1%	47	39.5	11	100.0	36	49.3	0	0.0
1-10%	38	31.9	0	0.0	36	49.3	2	5.7
>10%	32	26.8	0	0.0	0	0.0	32	91.4
Not available	2	1.8	0	0.0	1	1.4	1	2.9
Complete remission on day 33*	**118**	**100**	**11**	**100**	**73**	**100**	**34**	**100**
No	9	7.6	0	0.0	1	1.4	8	23.5
Yes	109	92.4	11	100.0	72	98.6	26	76.5

*<5% blasts by morphology. Source: Own elaboration based on the data obtained in the study.

Table 4. Adverse reactions related to medication per treatment phase in protocol ALL IC BFM 2009.

Treatment phases	IA		IB		mM		Blocks		IIA		IIB	
	n	%	n	%	n	%	n	%	n	%	n	%
Number of patients	**119**	**100**	**116**	**100**	**74**	**100**	**26**	**100**	**94**	**100**	**89**	**100**
Transfusional requirement	111	93.3	113	97.4	4	5.4	25	96.1	29	31	60	67.4
Thrombosis	11	9.2	1	0.9	0	0.0	4	15.4	1	1.1	0	0.0
Allergy *	0	0.0	3	2.6	0	0.0	14	53.8	2	2.1	0	0.0
Febrile neutropenia	72	60.5	98	84.5	7	9.4	26	100.0	61	65.1	32	35.9
Grade 3-4 infections	26	21.8	38	32.7	3	4.0	20	76.9	20	21.3	8	9.0
PICU	11	9.2	18	15.5	0	0.0	13	50.0	12	12.8	2	2.2
Other infections †	43	36.1	52	44.8	6	8.1	18	69.2	33	35.1	15	16.8
Grade 3-4 Transaminitis	33	27.7	29	25.0	4	5.4	26	100.0	20	21.3	15	16.8
Grade 3-4 hyperbilirubinemia	3	2.5	4	3.4	1	1.3	5	19.2	1	1.1	0	0.0
Grade 3-4 Cardiotoxicity	0	0.0	2	1.7	0	0.0	7	26.9	5	5.3	0	0.0
Grade 3-4 mucositis	1	0.8	4	3.4	2	2.7	5	19.2	7	7.4	0	0.0
Fungal infection	16	13.4	43	37.1	0	0.0	3	11.5	14	15.1	4	4.5
Positive galactomannan	2	1.7	6	5.2	0	0.0	1	3.8	1	1.1	0	0.0
Death	2	1.7	2	1.7	0	0.0	5	19.2	2	2.1	0	0.0

PICU: pediatric intensive care unit.

* In IB protocol to cytarabine and in blocks to E. coli asparaginase.

† Infections with clinical diagnosis, without identified pathogen and antibiotic treatment.

Source: Own elaboration based on the data obtained in the study.

Table 5. Adverse reactions related to medications per treatment phase and risk group in protocol BFM ALL IC 2009.

	Induction			IB			Protocol mM		Blocks	II Phase A			II Phase B		
	SR	IR	HR	SR	IR	HR	SR	IR	HR	SR	IR	HR	SR	IR	HR
	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
Transfusional requirement	81.8	93.1	97.1	100.0	98.6	96.9	9.0	4.8	96.1	45.5	23.8	40.0	63.6	63.3	83.3
Thrombosis	0.0	12.3	5.7	0.0	1.4	0.0	0.0	0.0	15.4	0.0	1.6	0.0	0.0	0.0	0.0
Allergy *	0.0	0.0	0.0	0.0	1.4	6.2	0.0	0.0	53.8	18.2	0.0	0.0	0.0	0.0	0.0
Febrile neutropenia	63.6	57.5	65.7	100.0	82.2	84.4	18.2	7.9	100.0	72.7	58.7	75.0	54.5	26.6	50.0
Grade 3-4 infections	9.0	20.5	28.6	18.2	35.6	31.2	0.0	1.6	76.9	27.3	20.6	20.0	18.2	3.3	16.7
PICU	0.0	5.5	20.0	0.0	15.1	21.9	0.0	0.0	50.0	9.1	7.9	25.0	0.0	0.0	11.1
Other infections †	18.2	31.5	51.4	54.5	41.1	93.7	18.2	3.2	73.1	63.6	22.2	50.0	18.2	8.3	38.9
Grade 3-4 Transaminitis	9.1	32.9	22.8	54.5	21.9	31.2	9.1	4.8	100.0	45.5	41.3	30.0	45.5	25.0	22.2
Grade 3-4 hyperbilirubinemia	0.0	0.0	8.6	0.0	4.1	3.1	9.1	0.0	19.2	0.0	1.6	0.0	0.0	0.0	0.0
Grade 3-4 Cardiotoxicity	0.0	0.0	0.0	0.0	1.4	3.1	0.0	0.0	26.9	0.0	0.0	5.0	0.0	0.0	0.0
Grade 3-4 mucositis	0.0	0.0	2.8	9.1	2.7	3.1	9.1	1.6	19.2	9.1	6.2	10.0	0.0	0.0	0.0
Fungal infection	9.1	16.4	8.6	63.6	30.1	43.7	0.0	0.0	11.5	18.2	7.9	30.0	0.0	3.3	11.1
Positive galactomannan	0.0	1.4	2.8	27.3	2.7	3.1	0.0	0.0	3.8	9.1	0.0	0.0	0.0	0.0	0.0
Death	0.0	0.0	5.7	0.0	1.4	3.1	0.0	0.0	19.2	0.0	3.1	0.0	0.0	0.0	0.0

SR: standard risk; IR: intermediate risk; HR: high risk; PICU: pediatric intensive care unit.

* In IB protocol to cytarabine and in blocks E. coli asparaginase

† Infections with clinical diagnosis, without identified pathogen and antibiotic treatment.

Source: Own elaboration based on the data obtained in the study.

Comparison with previous studies

After comparing the adverse reactions to chemotherapy drugs observed in this study (ALL IC-BFM 2009 protocol) with those reported in the Intercontinental Trial BFM ALL IC 2002 (9) (Table 6), the main findings were lower incidence of infections for all risks —demarcated as an identified infection pathogen requiring antibiotics IV or septic shock— and increased incidence of liver toxicity and mucositis in the Intercontinental Trial BFM ALL IC 2002.

Table 6. Comparison of incidence of grade 3 and 4 non-hematologic complications.

	Standard risk		Intermediate risk		High risk	
	ALL IC-BFM 2009 Protocol (%)	BFM ALL IC-2002 Protocol (%)	ALL IC-BFM 2009 Protocol (%)	BFM ALL IC-2002 Protocol (%)	ALL IC-BFM 2009 Protocol (%)	BFM ALL IC-2002 Protocol (%)
Infections	9.0	22.8	11.4	19.2	26.9	40.3
Transaminitis	11.3	13.8	11.8	11.6	21.9	25.0
Hyperbilirubinemia	0.0	0.0	0.8	1.9	3.4	6.5
Cardiotoxicity	0.0	0.5	0.0	0.9	3.4	0.0
Mucositis	3.4	3.6	1.5	7.3	3.4	27.9

Source: Own elaboration based on the data obtained in the study.

Interim survival analysis in the sample

Overall survival at the moment of this evaluation was 79.9%, similar for patients with phenotype B and T. According to the risk, survival was 100% for standard risk, 85.4% for intermediate risk and 62.5% for high risk (Figure 1).

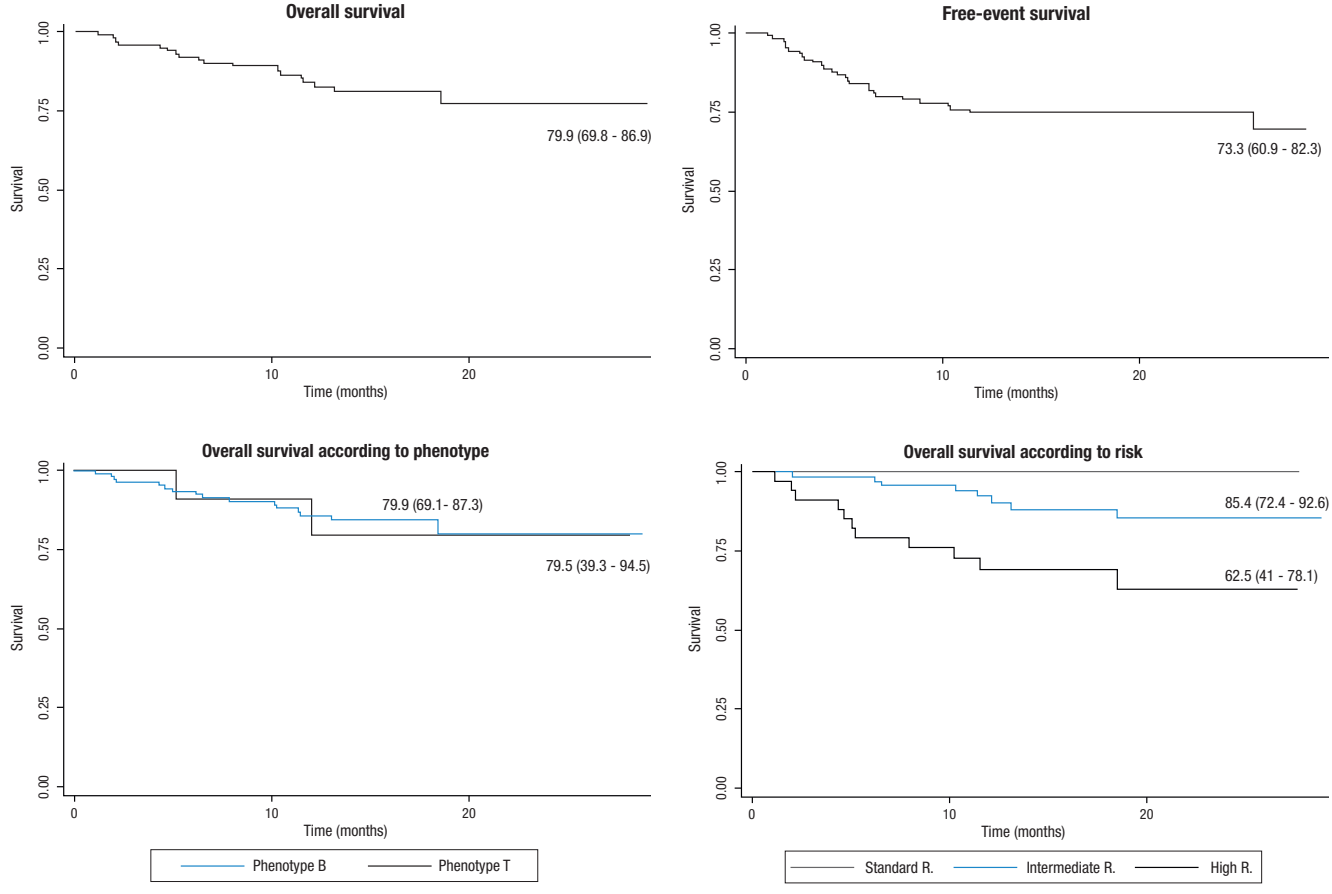

Figure 1. Probability of 2-years survival curves. Source: Own elaboration based on the data obtained in the study.

Discussion

Acute lymphoblastic leukemia is the most common malignancy in children (1); although overall cure rates have improved in high-income countries, most patients live in low-income countries, where the possibility of cure is much lower (2).

Comparing the mortality results found in this study with those reported in Latin America (2) and with specific numbers of Colombia (6,11), lower incidence of death during induction is observed; a possible explanation is that the patients of this protocol are hospitalized during the first month of treatment for the induction phase, so the detection and treatment of complications is timely.

The pediatric oncology unit of service of Fundación HOMI has evaluated death induction along different ALL protocols based on the BFM strategy: 9.6% during 1996-2000, 6.5% after this, and 3.5% for the previous protocol to BFM ALL IC 2012. Support measures and experience with the protocol during induction may explain the decline in death.

When the incidence of death in induction and death in complete remission is compared against the Intercontinental Trial BFM ALL IC 2002 (9), no significant differences are observed in the mortality rate (2.77% vs. 1.67%).

Seven relapses (5.9%) occurred: two after completing treatment at 26 and 30 months after diagnosis, and five during treatment. The factors assessed, and that may have contributed to relapse, included two patients with positive minimal residual disease (MRD) at the end of induction, which increases risk of relapse as demonstrated in multiple studies (12,13).

Another factor that may be related is the intensity of treatment: three of the seven patients who relapsed experienced delays (one for medical reasons and two by administrative constraints). The remaining four underwent appropriate treatment intensity and did not experience unjustified delays. The study by Suarez *et al.* (6) showed that a four-week or longer delay for initiation of treatment phase Protocol II, was associated with lower survival at two years (67% vs. 88%, p=0.016); it was also evident that, regardless the cause of the delay, this is associated with lower survival.

The incidence of abandonment was lower than that reported by previous studies in Bogotá (5% vs. 9%) (6): previous data in the institution showed 25% of abandonment. This decrease could be related to regulatory strategies —guidelines for attention of leukemias in children— that have been implemented within the institution by a multidisciplinary team, which accompanies the patient and provides psychosocial support in order to ensure that patients understand the importance of compliance and to achieve full management of the disease in a single institution, according to the directions of the current regulation for the attention of children with leukemia.

This study identifies in detail, and for the first time, adverse reactions related to chemotherapy drugs, since information that describes complications related to the treatment of ALL in children is not found in previous publications in Colombia. Deaths, both during induction and complete remission, were all caused by sepsis and occurred more frequently in high risk patients during the consolidation blocks.

A study conducted in Central America (2) reported that the incidence of death related to treatment in patients during complete remission was lower than what was found in this investigation (7.7% vs. 3.8%), which can be explained by late consultation or failure to deliver timely treatment to patients during episodes of febrile neutropenia. Death related to treatment, without detailed description of the causes, has been reported in previous assessments published about ALL in Colombia, where protocols of lower treatment intensity were used and rates of 6.17% and 3% were reported in the study by Buendía *et al.* (11) and by Suarez *et al.*, respectively (6).

The comparison of toxicity reported in this research with the Intercontinental Trial BFM ALL IC 2009 (Table 6) shows that the incidence of grade 3-4 infections or septic shock was lower for all risks. This may be related to a very low percentage of microbial agent identification. The incidence of liver toxicity and mucositis was higher in the Intercontinental Trial BFM ALL IC 2002, which has no clear explanation.

The most frequent complications included febrile neutropenia, found in most patients during phase IB regardless of risk stratification, in all high risk patients during consolidation and in phase A of Protocol II. This complication allowed anticipating all the recommendations on fever and consultation to emergency care, as well as the administration of antibiotics within two hours.

One of the limitations of this study, when evaluating the overall and event-free survival, was that this research is an interim evaluation of the implementation of a protocol, so the follow up is of maximum of 34 months; however, it is very important for childhood cancer treatment centers to make these assessments, particularly aiming at more intensive treatment strategies. This study shows 73.3% event-free survival rate —considering abandonment as an event— at two years, which is higher than the 67% reported by an evaluation conducted at the National Cancer Institute in Colombia (6).

The results of this evaluation have allowed taking actions to reduce deaths during complete remission: on the one hand, education to caregivers about fever and signs for early consultation to emergency room and, on the other, implementation of a protocol of febrile neutropenia with priority attention and administration of antibiotics within two hours of consultation in the emergency room, and at the onset of fever in hospitalized patients. In addition, abandonments are strictly followed by the institution and informed to the insurance company of the patient for active search.

The results show a decrease in mortality during induction; treatment-related mortality is within expectations of an intensive chemotherapy protocol and strategies are being implemented to reduce these numbers. Abandonment is below 10%, and follow-up time is still short; however, overall and event-free survival is higher than that in previous treatment protocols.

Conflict of interests

None stated by the authors.

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Cráneo Vista Lateral

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"Mapas anatómicos"
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ORIGINAL RESEARCH

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Neuropsychology and electroencephalography to study attention deficit hyperactivity disorder

Neuropsicología y electroencefalografía para estudio de trastorno de déficit de atención con hiperactividad

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| Abstract |

Introduction: In a previous study carried out with children from first to third grade in an elementary school, the authors of this research evidenced that different profiles of neuropsychological difficulties and functional status of brain structures exist at subcortical and cortical levels. Such results differ from those obtained in preschool children.

Objective: To correlate data obtained through neuropsychological assessment and EEG in Mexican children from fourth grade through sixth grade in an elementary school diagnosed with ADHD.

Materials and methods: A qualitative syndromic analysis was used to establish predominant neuropsychological mechanisms. A qualitative analysis of EEG was conducted to determine functional and maturational aspects of children's development.

Results: Findings of correlations between neuropsychological and electrophysiological data showed diversity of neuropsychological difficulties and specific EEG patterns. The possibility of high correlation between data of qualitative neuropsychological analysis and functional analysis of electroencephalographic phenomenon is discussed.

Conclusions: Final results suggest an important predictive level regarding clinical profiles obtained through the joined work of the clinical qualitative instruments used in this study.

Keywords: Neuropsychology; EEG; ADHD (MeSH).

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| Resumen |

Introducción. En un estudio anterior con niños de primero a tercero de primaria se demostró que, a diferencia de la edad preescolar, no existe un único perfil de dificultades neuropsicológicas y estado funcional de las estructuras cerebrales a nivel cortical y subcortical.

Objetivo. Correlacionar la evaluación neuropsicológica con el registro electroencefalográfico (EEG) en alumnos mexicanos de escuela primaria —cuarto-sexto grado— con diagnóstico de trastorno de déficit de atención con hiperactividad (TDAH).

Materiales y métodos. Se utilizó el análisis sindrómico cualitativo del estado funcional de los mecanismos cerebrales del nivel cortical y subcortical para los datos neuropsicológicos. El EEG se analizó por medio del método clínico cualitativo visual para valorar el nivel de madurez y funcionalidad de las estructuras corticales y subcorticales.

Resultados. Se encontró la ausencia de un único cuadro clínico de dificultades neuropsicológicas con un único patrón afectado en el EEG. Se discutió el alto nivel de coincidencia clínica de los datos de análisis neuropsicológico y el EEG clínico cualitativo, cuya combinación interdisciplinaria presentó un alto nivel de correspondencia entre el nivel de madurez de diferentes estructuras cerebrales con las manifestaciones clínicas observadas.

Conclusiones. Los resultados sugieren un importante nivel predictivo acerca del cuadro clínico por medio del análisis y trabajo conjunto de las herramientas de valoración clínica cualitativa utilizadas.

Palabras clave: Neuropsicología; EEG, TDAH (DeCS).

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Introduction

Various psychological and neuropsychological studies have contributed to the detailed description of the clinical picture

presented by children with attention deficit hyperactivity disorder (ADHD), not only regarding the effect of the alteration (1-5), but also, other psychological processes that may be involved (6-8). These findings do not necessarily establish a relationship between what is observed at clinical behavioral level, and the functional or developmental stage of the central nervous system.

Some authors have tried to correlate the clinical picture of ADHD with possible alterations in the central nervous system structures (9-10); most imaging studies such as positron emission tomography (PET) and functional magnetic resonance coincide in pointing out that subjects suffering from this syndrome reflect an underlying deficit in the frontal lobes and the right hemisphere (11,12). However, these studies have focused on studying the central nervous system without considering the cognitive and behavioral aspects of children with attention deficit disorder.

It should be noted that the ADHD syndrome is diganosed with the help of the questions listed in the DSM-IV TR (13) and DSM-V manuals (14), and after applying the questionnaire, the behavioral level and the structural or functional aspects of the central nervous system are individually assessed. Although neuropsychological, neurological and psychological evaluation data have been analyzed (15,16), the findings have not been correlated with each other, with particular neuropsychological difficulties nor with specific electroencephalographic data to establish typical patterns of brain electrical activity in children with ADHD at various stages in preschool and elementary school children.

Previous studies have analyzed the execution of neuropsychological evaluation tasks through EEG data in Mexican preschool children diagnosed with ADHD by neuropediatrics (17,18). These studies showed the typical difficulties from the neuropsychological viewpoint, whose origin cannot be interpreted only as frontal or cortical. Among the encountered difficulties, not only severe problems with regulation, control and motor sequential organization were found, but also with spatial analysis and synthesis, therefore, rejecting the hypothesis of a single alteration of predominantly cortical frontal systems (19-21).

In subsequent studies with preschool children diagnosed with ADHD, an insufficient level of non-specific general cerebral activation was established, which was corroborated with data obtained from EEG (17). In this work, the visual qualitative analysis of the examination revealed a dysfunctional state in the deep structures of the brain stem based on the appearance of particular patterns of electrical brain activity; these patterns are related to the outbreaks of synchronized waves in the central and posterior regions of both hemispheres (17,22).

After analyzing a broader preschool population of Mexican and Russian children, it was observed that in those diagnosed with ADHD using the DSM-IV TR (13) questionnaire, no pattern correlated with the immature functional status of the cerebral cortex was identified in the EEG (18,23-25); however, the presence of unfavorable EEG patterns was observed at the subcortical level, specifically at the upper brain stem (fronto-thalamic) and lower brain stem (diencephalic) in all cases evaluated. 16 to 50 preschool children diagnosed with ADHD were evaluated in this study.

In the case of the fronto-thalamic level, patterns synchronized as slow waves are recorded in the anterior sectors of both hemispheres, whereas in the diencephalic case, slow sharp waves are recorded in the caudal sectors simultaneously in both hemispheres. In both cases the record was taken using monopolar assembly, which is not usual for the commonly used visual analysis (22,26,27). On the contrary, these two patterns have been presented separately in the children's control group —those without developmental and learning problems— of the same age. The results of this study allowed rethinking the functional role of cortical-frontal structures in the ADHD syndrome in preschool children, confirming the involvement of subcortical regulatory systems at fronto-thalamic and diencephalic levels with higher probabilities than those presented at the frontal cortex level.

Studies involving the population of children in the first three grades of elementary school showed that, unlike preschool age, there is no single profile of neuropsychological difficulties and functional status of cortical and subcortical brain structures (28).

This work aims to continue the line of research that links EEG patterns with neuropsychological performance to correlate the data obtained through neuropsychological assessment with EEG records in Mexican children attending the last three years of elementary school and who were diagnosed with ADHD.

Materials and methods

Subjects

14 right-handed children (nine boys and five girls), diagnosed with ADHD and 10 children with no learning disability (five boys and five girls) were included. All children were regular students in urban public elementary schools in Puebla, Mexico, aged between 9 and 12, and were enrolled in fourth, fifth and sixth grades. The ADHD diagnosis was established and confirmed in writing by a specialist —paidopsychiatrist or neurologist— from outside the research team. Children in the control group showed no signs of hyperactivity, neurological or psychiatric diseases or psycho-pedagogical problems.

All children participated in accordance with the Declaration of Helsinki, with understanding and informed consent of each parent and school teachers; this study was also approved by the local ethics committee.

Procedure

All children were administered the qualitative neuropsychological assessment in a single 60-minute session outside school hours within its facilities. Then each child underwent EEG recording while awake at the clinical headquarters of Universidad Autónoma de Puebla. The results of both assessments were analyzed and contrasted with the aim of establishing the agreement from the neuropsychological and electroencephalographic point of view, in order to indicate the state of maturity and functionality of cortical and subcortical brain structures.

Neuropsychological assessment

Children Brief Neuropsychological Assessment (29) was used for neuropsychological assessment; this instrument qualitatively assessed the functional brain systems based on psychological and neuropsychological theories by Vygotsky (30) and Luria (31,32), and also assessed neuropsychological factors such as functional brain mechanisms (33). Particularly, the functional status of regulation and control, sequential motor organization, phonemic integration, kinesthetic integration, spatial integration and overall activation tone of the brain (arousal) were analyzed for the visual, motor and verbal tasks.

The analysis of the results is based on a qualitative assessment by experts of the presence of specific types of errors or the lack of them, which point the weak functional state of cortical and subcortical brain mechanisms (34-37).

Electroencephalogram

Participants were recorded with NicView System (Nicolet Biomedical Inc.) EEG equipment, with sampling rates of 250 Hz, according to the international 10-20 system in the following cortical regions: F_3, F_4, F_7, F_8, T_3, T_5, T_4, T_6, P_3, P_4, O_1 and O_2. The registration was carried out under wakefulness conditions performing the following operations: a) opening and closing the eyes, b) photostimulation (8-12 Hz) and c) hyperventilation (90 sec).

Monopolar and bipolar montages were used for each record. The monopolar montage allowed assessing the functionality status of different levels of the brain stem through the identification of synchronous deflected patterns that can be seen in the visual analysis; these patterns, depending on their location, expressiveness and representation, indicate the involvement of various subcortical levels. Bipolar montage allowed assessing the functionality state of various caudal areas of the central nervous system (22,27).

EEG visual qualitative analysis

The assessment of the functional status and degree of brain maturation was performed through EEG visual qualitative analysis, and was based on the correlation of the lines identified in the EEG record with the functional status of the brain and, in particular, with its structures (38). The qualitative analysis of EEG was performed by assessing four blocks of parameters identified based on the systemic organization of the brain (22,29); these parameters are used to assess the overall functional state of the cerebral cortex and its correspondence with age norms, general brain effects, functional status of cortical areas particularly related to each hemisphere, and subcortical regulatory systems status (18,22,27). The same qualitative analysis allows to differentiate artifacts from the particular patterns of EEG.

The visual clinical analysis was established by two experts on the subject and those patterns corresponding to the above parameters were selected. In each subject, an average of 20 minutes of electroencephalogram records were analyzed to obtain a homogeneous analysis of each study. In addition, the Kendall correlation coefficient test was used to assess the level of agreement among experts in the visual analysis of the electroencephalogram.

It is important to remember that these types of analysis are necessary to obtain a quantitative average of the opinions or prejudices about a phenomenon or fact.

Results

Neuropsychological assessment data analysis allowed establishing the particular characteristics of the performance of control children and children with ADHD. Similarly, observing the differences in the performance of the assessment tasks by children was possible based on the presence and absence of particular errors.

Children had no difficulties in phonemic and tactile kinesthetic value integration tests, so no differences were found. By contrast, differences were observed in 1) tasks that assess the regulation and control of the activity; 2) the motor sequential organization and dynamic praxis and 3) the spatial analysis and synthesis. In all these cases, errors were committed by children diagnosed with ADHD (Figure 1).

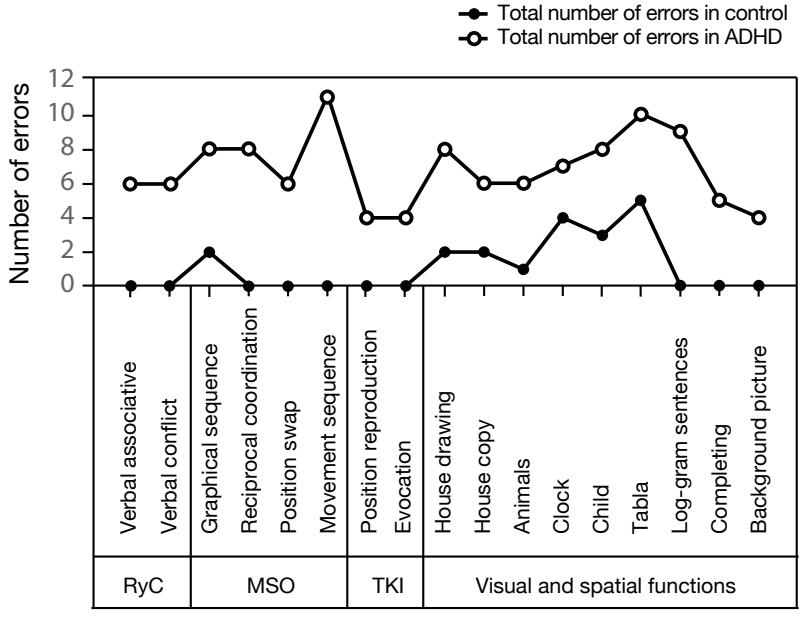


Figure 1. Number of errors for each task in the protocol. R&C: regulation and control; MSO: Motor sequential organization; ICT: tactile kinesthetic integration. Source: Own elaboration based on the data obtained in the study.

To specify the type of commitment and to systematize the sample, a qualitative analysis of the types of errors under the concept of the three brain function blocks proposed by Luria (33) was performed. Syndromic analysis set specific profiles for each subject reflecting the functional status of the different brain mechanisms (Table 1).

The qualitative analysis based on the systematization of error types (Table 1) allowed finding three predominant clinical profiles: 1) regulation and control difficulties (11 cases), 2) lack of activation in the cortical tone work (2 cases), and 3) severe difficulties in spatial functions (1 case). The patterns identified along with the characterization of EEG data according to the three established profiles are presented below.

Table 1. Types of errors observed in children with attention deficit hyperactive disorder related to brain function blocks.

Function block I General activation system	Function block II Spatial analysis and synthesis	Function block III Programming and control system
• Slowing down • Latencies • Micrography • Simplifications • Graphic disturbance • Motor disorganization	• Absence of essential features • Absence of global image • Disintegration of elements • Stereotyped drawings • Incomprehension of gram- logical complex sentences • Rotation of figures during copying • Search and latencies in hand position	• Impulsivity and anticipation to activities • Loss of focus • Intrusions • Difficulties in keeping quiet • Disorganized evocation • Difficulty in automation and motor patterns simplification • Absence of self-verification and self-correction

Source: Own elaboration based on the data obtained in the study.

Profile 1. Functional regulation and control deficit

Children with this profile presented impulsivity errors, rotation of elements, perseverance and lack of planning, which are not observed in children of the control group. Table 2 shows the graphic performance while drawing a clock and a copy of a house made by profile children and by children of the control group.

Table 2. Examples of graphic performance: one children when drawing a clock and copying a house.

Drawing	Control group	ADHD I profile
• a) Clock		
• b) House		

Source: Own elaboration based on the data obtained in the study.

Simplifications, impulsivity and loss of focus were observed in associative conflict and sequential organization motor tests in dynamic praxis in hands and fingers.

Regarding EEG qualitative visual analysis, in this group of subjects two variants were found: one pointing unfavorable functional status of the superior brain stem, mainly at the fronto-thalamic level (eight children), which is reflected as slow synchronized waves in the frontal records that appear in both hemispheres, and another which presents features of the diencephalic level, which is characterized by bilateral synchronized patterns in the form of slow waves in subsequent records (three children).

An example of the diencephalic and fronto-thalamic levels is shown in Figure 2. EEG patterns were bilateral and synchronous, allowing the verification of their subcortical origin, according to the visual clinical model of interpretation.

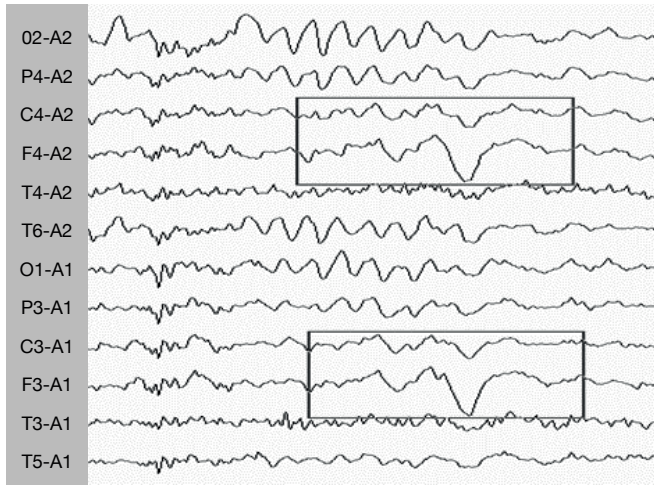


Figure 2. Functional changes in brain electrical activity in the form of synchronous and bilateral waves on the theta band in front and central sectors (monopolar records) groups. Source: Own elaboration based on the data obtained in the study.

Through the Kendall correlation coefficient, coincidence among experts in the analysis of EEG was determined. The test showed a level of agreement between subjects of 0.974 ($p<0.05$).

Profile 2. Difficulties in visual and spatial functions

Children with this profile presented errors such as lack of proportion and integration in the task of copying a clock and a house (Table 3).

The visual qualitative analysis of EEG of this child shows deviant patterns of electrical activity in caudal sectors —occipital and parietal— (Figure 3). The data is consistent with results of neuropsychological assessment, which allows confirming expressive difficulties in spatial functions.

The EEG visual qualitative analysis of this child shows deviant patterns of deep origin in the brain stem, including paroxysmal discharges in parietal cortical areas.

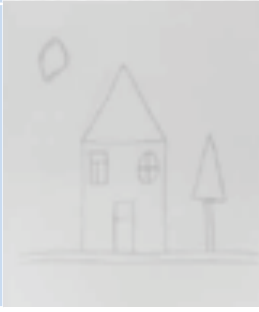
Through Kendall correlation coefficient, coincidence among experts in the analysis of EEG was determined. The test showed a level of agreement between subjects of 0.861 ($p<0.06$).

Profile 3. Lack of activation in the cortical tone work

For this group of children, all graphic tasks show traits of instability demonstrated in specific errors such as micro and macro letters, omissions, slowing, problems with tilt, spaces between the perceptual elements and loss of baseline (Table 4).

Regarding non-graphical tasks, slight kinesthetic integration difficulties, traits of impulsivity, slowing and praxical motor inaccuracies, low capacity to perform all tasks of evaluation, requests of breaks and support by adults were observed (Figure 4).

Table 3. Examples of graphic performance when drawing a clock and copying a house corresponding to profile 2.

Drawing	Control group	ADHD II profile
• a) Clock		
• b) House		

Source: Own elaboration based on the data obtained in the study.

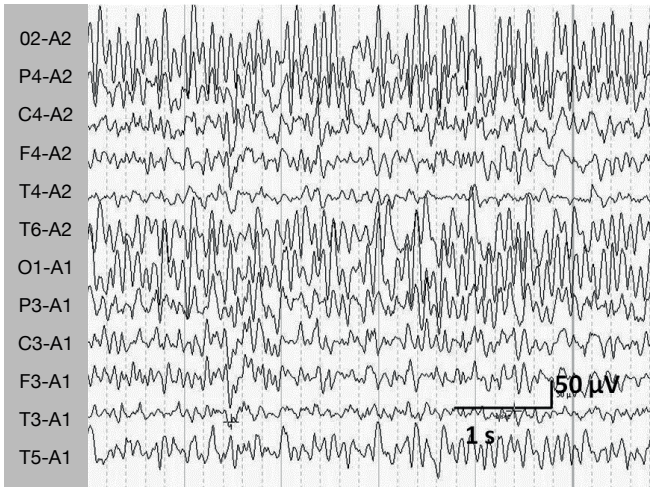


Figure 3. Synchronic and bilateral functional changes in the form of hypersynchronic alpha rhythm or groups of sharp waves in the caudal sectors (monopolar record). Source: Own elaboration based on the data obtained in the study.

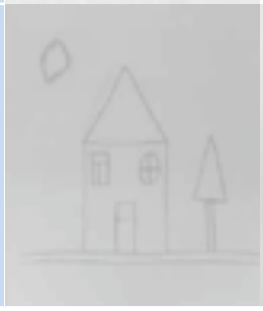
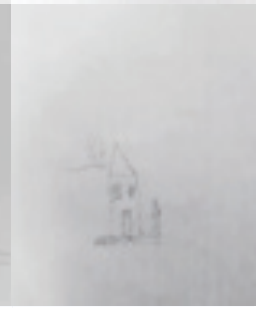
The visual qualitative analysis of EEG identified a non-optimal functional status in the lower brain stem. The same functional status of EEG was observed in three profile 1 children with prevalence of difficulties in regulation and control.

Through Kendall correlation coefficient, coincidence among experts in the analysis of EEG was determined. The test showed a level of agreement between subjects of 0.885 ($p<0.05$).

Discussion

Several disciplines have been involved in the study of attention deficit disorder in preschool and school-age children since children with this condition are the main source of clinical diagnosis of these disorders. Questionnaires such as DSM-IV TR and the DSM V, where the individual is categorized within a large list of possibilities through a series of questions aimed at identifying behavioral traits, are widely used evaluation tools. In many cases, children can only be classified into diseases such as ADHD or combined diseases when the focus is solely on observable symptoms or those that are noticed by a primary caregiver. Thus, the child is no longer perceived as an individual with a unique set of difficulties and problems (37). At the same time, the presence or absence of these behavioral symptoms does not establish a clear relationship with the level or type of cortical or subcortical brain structures.

Table 4. Examples of graphic performance when drawing a clock and copying a house corresponding to profile 3.

Drawing	Control group	ADHD III profile
• a) Clock		
• b) House		

Source: Own elaboration based on the data obtained in the study.

In some previous studies, identifying different characteristics of inadequate functional status of various neuropsychological mechanisms, including regulation and control, motor sequential organization (20), spatial analysis and synthesis (19,20) and cortical tone regulation, was possible (18,21). These studies have found that preschool children are often diagnosed with attention deficit in the presence of all these problems simultaneously, which implies that in children who are diagnosed with attention deficit in preschool, specifically between ages 5 and 6, it is common to see difficulties with regulation and control, lack of integration and spatial orientation, and constant fluctuations in the general state of activation.

In contrast, this work has found that the difficulties associated with different brain mechanisms may be presented separately in children of school age, in particular in the three final grades of the elementary school. As noted by the results, the data allow appreciating at least three different neuropsychological profiles, which were not observed in the case of preschool children with the same diagnosis.

In cases of EEG visual data qualitative analysis, patterns different from those observed in preschoolers were found. It is worth mentioning that neuropsychological difficulties profiles may be clinically related to electroencephalographic profiles.

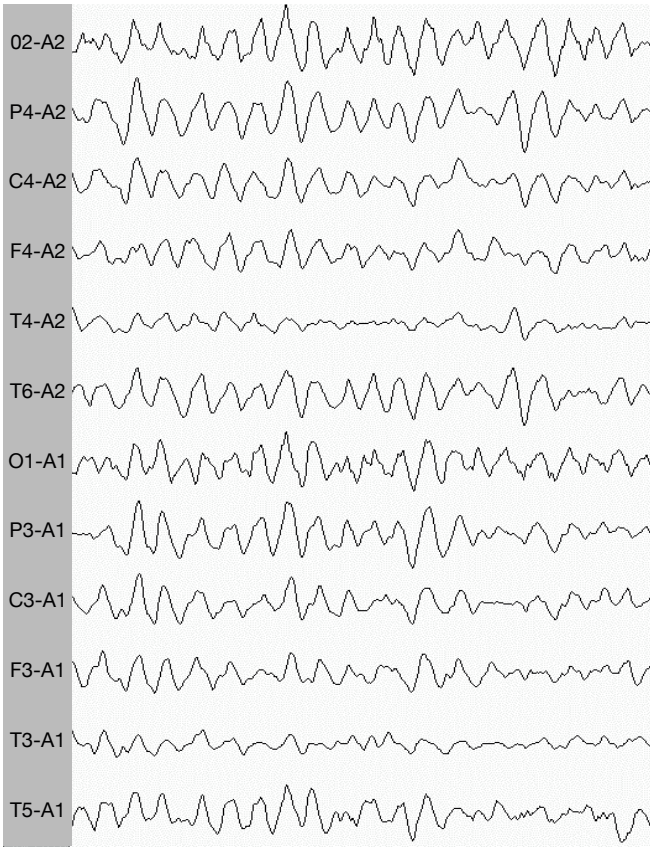


Figure 4. Functional changes in synchronous and general activity in the form of slow alpha of hypothalamic origin. Source: Own elaboration based on the data obtained in the study.

Previous studies with preschool children have shown that those diagnosed with attention deficit and difficulties characterized by functional deficit in regulation and control, spatial integration and insufficient activation of arousal brain activation —based on a visually qualitative analysis— present patterns of immaturity in the fronto-thalamic regulatory system —superior stem— and dysfunctionality in non-specific regulation related to ascending effects from the reticular formation at diencephalic level (17,18,30). These results were obtained in various populations of Mexican and Russian children (17,18,22,27). In this paper, the visual qualitative analysis of the electroencephalogram allowed to establish three types of electroencephalographic patterns.

In the cases with difficulties in the regulation and control mechanism, EEG analysis revealed diverted bioelectric patterns from fronto-thalamic source that signal the state of immaturity of the frontal cortex and the different thalamic nuclei (25,27,29,39). Such patterns are expressed as theta-synchronized slow waves in the anterior sectors. There is no data in the literature in favor of the non-optimal participation state of this regulatory system in groups of children between 6 and 8 years old diagnosed with ADHD (29,30,40). Neuropsychological assessment in these children reveals typical errors of simplification, impulsiveness, loss of focus and inability to perform tests with dynamic praxis; a correlation between standard errors is also evident in neuropsychological tests in the presence of immature states at anterior brain stem structures level and, at the same time, it was established that the level of the cerebral cortex corresponds to the age norm in all these cases.

As to the cases of alterations in general activation of brain work, the analysis showed changes in the electrical activity originated in the brain stem and the midbrain. In other studies, the authors noted that the presence of bilateral slow waves in the caudal sectors is related to the low level of cortical excitability (41) and correlates with the low level of activation from the lower stem and the reticular formation (22,27,42). These patterns of brain electrical activity were found in children with neuropsychological profile 2; based on the neuropsychological evaluation, these children require constant support, are exhausted before performing tasks and demonstrate instability traits in all graphic and motor tasks.

In cases of regulation and control difficulty and non-optimal status of tone activation of brain work, a positive overall maturity level of the brain was observed. Deviant electroencephalographic patterns are related to the weak state of subcortical operation, which was demonstrated in the synchronized nature of deviant patterns.

Finally, for the only case of this sample with severe difficulties with space obtained in the neuropsychological evaluation, EEG analysis revealed an unfavorable functional state in the parieto-occipital cortical structures along with a state of immaturity of the lower brain stem. Classical neuropsychological literature exposes that spatial difficulties are related to functional deficits in posterior cerebral areas (16,28), so it is interesting to note that patterns of synchronized high amplitude sharp waves are recorded in the parieto-occipital sectors.

Thus, the combination of syndromic neuropsychological qualitative analysis with qualitative visual analysis of EEG allowed establishing a relationship between the functional status of neuropsychological mechanisms with the non-optimal functional status of the various subcortical levels. Such interdisciplinary combination of neuropsychological assessment, accompanied by EEG visual qualitative analysis showed a high level of correspondence between the level of maturity or functional state of different cortico-subcortical structures with clinical manifestations observed.

The data from this research does not indicate that these variants may be the only ones that can be identified. Thus, some studies have found cases suggesting the involvement of the right hemisphere and other combinations of difficulties (30,43,44).

One limitation of this study is undoubtedly the small sample size, which is related to the need for having a homogeneous population of children in the last three grades of regular elementary school who have the same diagnosis issued by a third specialist, and the possibility to participate in the study of neuropsychological evaluation and EEG recording.

Despite this limitation, this study found that school-age children who are diagnosed with ADHD are not a homogenous group and are qualitatively different. Both neuropsychological and electroencephalographic analyzes can set several variants. These data cast doubt on the clinical efficacy of a single diagnosis with a generalizing name such as attention deficit, as it becomes clear that children cannot be differentiated from traditional questionnaires answered by caregivers in relation to purely behavioral traits. These diagnostics have the potential to clarify the relationship between different levels of analysis which lack adequate predictive level.

Conclusions

The qualitative neuropsychological assessment allows addressing various clinical pictures that reject the idea of a single diagnosis of attention deficit disorder.

Qualitative visual analysis of EEG confirms the absence of a single clinical picture, so it is possible to identify various patterns diverted through visual qualitative analysis of the electroencephalogram.

The search for correspondence between the electrophysiological correlation of EEG and neuropsychological assessment can become

an important means for the accuracy of functional mechanisms underlying the difficulties of learning and development.

Conflict of interests

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ORIGINAL RESEARCH

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Association between anger management and cigarette consumption in adolescents

Asociación entre control de la ira y consumo de cigarrillos en adolescentes

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| Abstract |

Introduction: Cigarette smoking in adolescents is associated with a set of variables such as sex, age, anxiety disorders, depression and secondhand smoke (parents, siblings and friends). However, the association between anger management and smoking among adolescent students has been poorly studied in Colombia.

Objective: To quantify the association between anger management in high school students in Cartagena, Colombia.

Materials and methods: A cross-sectional survey designed for adolescent students of sixth and seventh grade in high school. Anger management was quantified through a seven-item version of the Spielberger's Inventory for State-Trait Anger Expression (Cronbach's alpha: 0.73) and through the input of the participants who have smoked at least once.

Results: A total of 1 090 students between ages 10 to 18 (μ=12.3, σ=1.1), attending sixth and seventh grades, took part in the study; 565 (52.1%) were female. A group of 269 students (24.7%) reported low anger control, and 127 (11.7%) stated they had smoked at least once. After age and sex adjustment, the association between anger and smoking was not statistically significant (OR=1.35; 95%CI: 0.89-2.04).

Conclusions: Anger management is a variable independent from cigarette smoking among teenager students.

Keywords: Anger; Smoking; Adolescent; Students; Cross-Sectional Studies (MeSH).

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| Resumen |

Introducción. En adolescentes, el consumo de cigarrillos se asocia a un conjunto de variables como género, edad, trastornos de ansiedad, depresión y padres, hermanos y amigos fumadores. No obstante, en Colombia se ha explorado poco la asociación entre el control de la ira y el tabaquismo en adolescentes escolarizados.

Objetivo. Cuantificar la asociación entre el control de la ira y el consumo de cigarrillos en estudiantes de bachillerato de Cartagena, Colombia.

Materiales y métodos. Investigación transversal en la que participaron estudiantes de sexto y séptimo grado. Se cuantificó el control de la ira con siete ítems del Inventario Ira Estado-Rasgo de Spielberger (alfa de Cronbach 0.73) y con el informe de consumo de cigarrillos alguna vez en la vida.

Resultados. Participaron 1 090 estudiantes de sexto y séptimo grado entre 10 y 18 años (μ=12.3, σ=1.1), de los cuales 565 (52.1%) fueron mujeres. 269 (24.7%) adolescentes reportaron bajo control de la ira y 127 (11.7%) consumo de cigarrillos alguna vez en la vida. Después de ajustar por edad y sexo, la asociación entre control de la ira y consumo de cigarrillos no fue estadísticamente significativa (OR=1.35; IC95%: 0.89-2.04).

Conclusiones: El control de la ira es independiente al consumo de cigarrillos en estudiantes adolescentes.

Palabras clave: Ira; Hábito de fumar; Adolescente; Estudiantes; Estudios transversales (DeCS).

Cogollo-Milanés Z, Gómez-Bustamante EM. [Asociación entre control de la ira y consumo de cigarrillos en adolescentes]. Rev. Fac. Med. 2016;64(3):435-8. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.55100.

Introduction

Regular consumption of cigarettes is the most important cause of preventable diseases; however, preventive interventions of long-term illnesses caused by smoking, which may appear in adulthood, in childhood and adolescence, have not been implemented satisfactorily (1). Similarly, some public health measures implemented are inefficient, as children and adolescents continue with regular consumption of cigarettes even after being intervened (2,3).

In adolescents, cigarette smoking is associated with a set of variables or proximal, intermediate and distal determinants (4-7). In Colombia, for example, the first group of determinants shows that consumption is more frequent in men than in women, increases progressively with age and is associated with depressive symptoms (8-10).

In other contexts, among the proximal determinants, some research on adolescent populations have studied the relation between anger management and cigarette smoking; however, the available findings are not consistent. On the one hand, Nichols *et al.* (11) showed a statistically significant relationship between anger management and cigarette consumption, while Griffins *et al.* (12) found no relation at all. These associations have not been explored in Colombian adolescent students, but knowing them may support the implementation of strategies for the prevention of smoking from a comprehensive perspective of all the determinants related to the initiation, transition to regular consumption and consolidation of the dependence on nicotine, while positively influencing the general welfare of adolescents (13).

The objective of this research was to estimate the relation between anger management and at least one-time consumption of cigarettes in a sample of adolescent students of public schools in Cartagena, Colombia.

Method

Design and ethical considerations

An observational, analytical and cross-sectional study was designed; the study was reviewed and approved by the Research Ethics Institutional Committee of Universidad de Cartagena. Parents or legal guardians signed a written informed consent for authorizing the participation of the adolescents. Students also consented their participation in this study.

Participation in this study represented minimal risk to students, since, according to Resolution 8430 of 1993 (14), no physical nor psychosocial intervention was conducted.

Population and sample

The participation of sixth and seventh grade students from public educational institutions of Cartagena was requested. A cluster sampling was used and each cluster was represented by students of the same classroom, who were selected through a simple random sampling. A sample of 800 students was planned for an expected frequency of low anger control of 25%, with a margin of error of 3% in the estimated prevalence, and confidence level of 95% (15).

To the initial estimate of students, 20% more were included, which meant the addition of 160 students in order to remedy the eventual loss of participants due to the school absence during the days in which information was gathered, and possible incomplete forms that are usually found in this type of research (16).

The calculation of the sample considered the possible association between low anger management and history of cigarette consumption. The Odd Rathios (OR) for the association was estimated at 2.0, which is considered a moderate ratio between two variables; for this estimate, an alpha error value of 5% and beta error of 20% were taken, which gave the study a power of 80% to reject the null hypothesis (15). Also, the sample size allowed the estimation of a sufficiently accurate confidence interval (17).

Measurements

Students from 20 schools completed an anonymous questionnaire in the classroom under the supervision of a research assistant. The questionnaire included questions about age, sex, education level and at least one time consumption of cigarettes. Anger management was also quantified using the Spielberger's State-Trait Anger Expression Inventory, in a version of seven scales. Each scale offered three response options that were rated from 0 to 2: much, little or nothing. Total scores ranged from zero to fourteen (18). Since data showed a non-symmetrical distribution, a cutoff of seven, representing the third quartile, was taken to indicate anger under control.

The instrument used has shown high internal consistency in Spanish students (19) and this sample shows acceptable evidence of internal consistency (Cronbach's alpha 0.73), an estimator of reliability and validity (20).

Statistical Analysis

Frequencies and percentages for the variables studied were estimated. In addition quartiles, minimum value, maximum value, mean (μ) and standard deviation (σ) were identified for scores on anger control. To estimate the correlation between anger and cigarette consumption at least once, OR was calculated with confidence intervals of 95% (CI95%). Computations were performed using SPSS package version 16.0 (21).

Results

A total of 1 090 students between ages 10 to 18 (μ=12.3, σ=1.1) participated in this study, of which 676 (62.0%) were 10 to 12 years old, 565 (51.8%) were women and 525 (48.2%) men. The distribution by completed grade showed that 629 (57.7%) were in sixth grade and 461 (42.3%) in seventh grade. Regarding the main variables of interest, 127 (11.7%) of the respondents reported cigarette consumption at least once in their life and 963 (88.3%) denied such consumption.

Scores for anger control were found between 0 and 14, with a mean of 4.6 (σ=2.9), median 4.0, mode 3.0, 25th percentile of 2.0 and 75th quartile of 6.0. The distribution of values was skewed and the test was performed according to Shapiro-Francia. A total of 269 (24.7%) students had scores of seven or more and were categorized as students with low anger control.

A raw association between low anger control and at least one-time consumption of cigarettes did not reach a statistically significant value. The association continued to be not significant even after adjusting age and sex (OR=1.35, 95%CI: 0.89-2.04). Table 1 shows details of the participants based on those who reported at least one-time consumption of cigarettes.

Table 1. Comparison of participants based on those who reported at least one-time consumption of cigarettes.

Variable	Smokers (%)	Non-Smokers (%)	OR (CI 95%)
Age 13 to 18	60.6	35.0	2.86 (1.96-4.18)
Male	66.9	45.7	2.40 (1.63-3.56)
Seventh grade	49.6	41.3	1.40 (0.96-2.02)
Low family income *	74.0	77.4	1.20 (0.78-1.83)
Low anger control	30.7	23.9	1.41 (0.94-2.12)

* Equal or less than three minimum wages.
Source: Own elaboration based on the data obtained in the study.

Discussion

Since no significant association was found, this study is evidence that anger is a variable unrelated to cigarette consumption in adolescent students from Cartagena. Some previous studies reporting on this relation are mentioned below.

Griffins *et al.* (12), with a sample of 5 442 sixth graders in New York City, found no statistically significant relation between the variables. Similarly, Aseltine *et al.* (22) observed in a group of 939 high school students from Boston that anger and hostility in response to negative life events is not associated with marijuana use. However, Nichols *et al.* (11), also with a group of sixth graders in New York, found that low anger control and lifetime consumption of cigarettes kept a significant statistical correlation.

It is possible that the observed differences are related to the complexity of the concept "anger" (23); also the question asked only referred to lifetime consumption of cigarettes and frequency may often become a determining factor; Rubinstein *et al.* (24) showed that anger in adolescents only increased cigarette consumption in those who had a daily pattern of consumption and who reported occasional use.

Some research show that negative emotional states —stress, general dissatisfaction, sadness, angst, hostility and irritability— are related to cigarette smoking (8,25-31). Similarly, suppression, control or expression of anger are complex variables that influence a broad and diverse set of individual, family, cultural and social factors that may influence smoking practices (32-34).

Preventive interventions should strengthen those individual characteristics or conditions that reduce the onset of smoking and discourage experimentation. Furthermore, preventive measures for the initiation of cigarette smoking should consider as many determinants as possible —proximal, intermediate and distal— and, given the high complexity of the phenomenon, actions must be taken at both inter-sectoral and cross-sectoral levels (4-13,25-31,35,36).

Since few studies have explored this association, this research is a contribution to the knowledge of the relationship between anger control and smoking in adolescents. However, limitations included the participation of students from public educational institutions, including only sixth and seventh grade students, and a cohort composed only by young adolescents.

In conclusion, anger control is independent from cigarette smoking in sixth and seventh grade adolescents from public educational institutions in Cartagena. Studies on other individual variables related to cigarette smoking should be conducted in order to obtain more input for possible preventive actions. Also, the student sample should include participant with a higher average age, from both public and private schools.

Conflict of interests

None stated by the authors.

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ORIGINAL RESEARCH

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Nutritional condition and IGF-1 and IGFBP-2 serum concentrations in students aged 7 to 9 attending two educational institutions

Estado nutricional y niveles séricos de IGF-1 e IGFBP-2 en escolares de 7 a 9 años en dos instituciones educativas

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| Abstract |

Introduction: Nutritional vulnerability is more evident during childhood, since malnutrition has an impact on academic performance and is linked to different diseases during this period. Likewise, an increase in the incidence and prevalence of obesity in children has been observed, therefore, researches that assess nutritional conditions of children attending schools may have high-impact results in terms of public health.

Objective: To relate children's nutritional condition by using anthropometry, with serum concentrations of insulin-like growth factor 1 (IGF-1) and its binding protein 2 (IGFBP-2).

Materials and methods: A cross-sectional observational and comparative study was performed in children aged 7 to 9 attending two schools, one from the public sector and the other from the private sector. An anthropometric assessment was performed in 157 children, while IGF-1 and IGFBP (enzyme immunoassay) serum concentrations were measured in 81 children. Pearson's coefficient, analysis of variance (ANOVA), Dunnet's test and Games Howell's test, with a 95% confidence interval and a $p<0.05$ statistical significance, were considered for performing the statistical analysis.

Results: Overweight and obesity were found in 46 subjects; the prevalence of obesity was higher in boys, while overweight prevalence was higher in girls. A direct relation between IGF-1 and height ($p<0,05$) was observed, while an inverse relation between IGFBP-2 and BMI ($p<0,001$) was found.

Conclusions: IGF-1 serum concentrations were higher in students attending the public school.

Keywords: Insulin-Like Growth Factor I; School; Children; Nutritional Status; Insulin-Like Growth Factor Binding Protein 2; Adiposity (MeSH).

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| Resumen |

Introducción. Una de las etapas con mayor vulnerabilidad del estado nutricional es la infancia, pues en este periodo la desnutrición interfiere con el desempeño escolar y se asocia a enfermedades; asimismo, se ha observado aumento de la incidencia y prevalencia de obesidad en niños, por lo que investigaciones de evaluación nutricional en población escolar pueden tener alto impacto en salud pública.

Objetivo. Relacionar el estado nutricional —antropometría— con niveles séricos del factor de crecimiento similares a la insulina 1 (IGF-1) y su proteína enlazante 2 (IGFBP-2).

Materiales y métodos. Estudio observacional de corte transversal comparativo entre estudiantes de 7 a 9 años de dos colegios, uno público y otro privado, mediante el cual se realizó valoración antropométrica de 157 niños y medición de niveles séricos de IGF-1 e IGFBP-2 (enzimoinmunoanálisis) en 81 niños. Para el análisis estadístico se tuvo en cuenta coeficiente de Pearson, análisis de varianza (ANOVA), test de Dunnet y Games Howell, intervalo de confianza del 95% y significancia estadística de $p<0.05$.

Resultados. Se registró sobrepeso y obesidad en 46 sujetos; la obesidad fue más prevalente en niños mientras que el sobrepeso en niñas. Se encontró relación directa entre IGF-1 y talla ($p<0.05$) y relación inversa entre IGFBP-2 e IMC ($p<0.001$).

Conclusiones. Las concentraciones séricas de IGF-1 fueron mayores en la institución pública.

Palabras clave: Factor I del crecimiento similar a la insulina; Niños; Estado nutricional; Proteína 2 de unión a factor de crecimiento similar a la Insulina; Adiposidad (DeCS).

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Introduction

Nutrition is key for growth and human development and may be affected by economic, cultural, social, and physiological factors, among others (1,2). Nutritional vulnerability is more evident during childhood, since the onset of malnutrition during this period is associated with capacity and learning constraints and interferes with an adequate school performance. The effects of malnutrition on health and education have effects on economic and human capital costs that must be assumed by the society (2). Similarly, malnutrition by excess has become a public health problem in recent years.

In Colombia, a high prevalence of malnutrition caused by both deficiency (acute and chronic) and excess (obesity and overweight) is evident. According to the results of the National Survey on Nutrition and Food 2010 (ENSIN, by its acronym in Spanish) (3), a prevalence of low height for age of 12.6% and low weight for height of 1.1% was obtained, as well as a prevalence of overweight of 13.7% and obesity of 5.2% in the group of children aged 5 to 9. These findings can affect growth and development in this stage of life, determining the incidence of new diseases and affecting economic development.

Type 1 insulin-like growth factor (IGF-1) is a polypeptide anabolic hormone secreted in multiple tissues, whose serum concentrations come mainly from the liver (4,5); its synthesis is regulated by the growth hormone (GH) (5) and by other factors, including nutrition, which plays an important role (6,7). IGF-1 has multiple functions related to metabolic and growth processes and is responsible for certain actions of GH (5). It has also been observed that IGF-1 exerts insulin-like activities and that concentrations of this hormone are regulated by the interaction with its binding proteins (IGFBPs), for which six types have been described (4,7): IGFBP-1, IGFBP-2 and IGFBP-3 are predominant in blood (5).

Recent studies suggest that IGFBP2 is involved in alterations associated with obesity (8-10). As this is the main IGFBP expressed during childhood and is also the most produced by adipocytes, its determination is of great interest to study the relation between nutrition, growth and metabolism.

In this sense, this paper projects the evaluation of the relations between anthropometric variables, and energy and nutrient intake with IGF-1 and IGFBP-2 serum concentrations in children from two educational institutions, one public and another private.

Materials and methods

A cross-sectional comparative observational study was conducted in students aged 7 to 9 from one private and one public school, where anthropometric and food consumption variables were compared with IGF-1 and IGFBP-2 serum levels.

This study was conducted in two schools that receive mainly children from families of socioeconomic strata 1 and 2:

1. Llano Oriental School, a public school located in the locality of Bosa in Bogotá, D.C., which receives 1184 students distributed in morning and afternoon school hours; during the morning, preschool and elementary school children are attended and during the afternoon middle and high school students. Students receive daily school snacks provided by the Department of Education of the District, which are consumed in the classroom at the beginning of their break.

2. Liceo Integral Los Alisos, a private school located in the municipality of Soacha, Cundinamarca, which provides elementary, middle and high school education to 418 students in one school day. Children have a break during which they can consume food in the playground.

The selection criteria were: age between 7 and 9, no pubertal development initiation, enrollment in the selected educational institutions, informed consent reviewed and signed by parents or legal guardians and the children, no drug consumption in the last month and absence of diseases such as diabetes, hypoglycemia and growth hormone deficiency that could affect the results.

For anthropometric data, the World Health Organization (WHO), which describes the standardized technique for measuring height, weight and waist circumference was considered. A Tanita electronic scale was used to measure weight —the subjects were measured in light clothes and barefoot— and for measuring height, a stadiometer (SECA) was used. Based on these data, the body mass index (BMI) kg/m^2 was calculated. The waist circumference (WC) was measured in the horizontal plane, at the midpoint between the last right rib and the iliac crest using an inelastic tape fiber glass. These data were taken by two nutritionists and a nursing assistant.

During the initial phase, the universe consisted of all students from 7 to 9 years old enrolled in the two educational institutions during the second half of 2014, which accounted for 372 children —142 subjects from Liceo Integral Los Alisos and 230 from Llano Oriental School—; only 185 of these children met the selection criteria. Seven children did not provide a blood sample nor attended anthropometric assessments. This way, a total of 178 children were studied, but due to the time elapsed since the signing of consent and data collection, 21 children turned 10 years and were not included in the statistical analysis. Thus, the target population was composed of 157 subjects (70 boys and 87 girls).

The information obtained in the nutritional assessment of children was interpreted using the growth curves established by the WHO for children and adolescents (11). According to the indicators weight/height, height/age and WC/age, five subgroups were formed: 1) low size and risk of low size; 2) eutrophic; 3) appropriate weight with high WC; 4) overweight and 5) obesity. WC in children was classified according to percentiles of the Center for Disease Control and Prevention and the National Center for Health Statistics (12).

The anthropometric study was conducted on a sample of 157 subjects, whereas hormonal measurements were performed on a subsample of 81 children. In order to keep statistical balance, a subsample size was established taking into account the 18 children with obesity for the analysis of IGF-1 and IGFBP-2. All children were Tanner stage 1 without clinical manifestation of sexual development.

Blood samples were collected from the antecubital vein after 12 hours of fasting, centrifuged at 3500rpm for five minutes and the obtained serum was stored at -80°C. IGF-1 and IGBP-2 serum levels were determined by double junction enzyme-linked immunosorbent assay (ELISA) using KAP1581 kits for IGF-1 and KAPME05 for IGFBP-2 and according to the manufacturer's protocols. This process was performed with DS2/DSX automated equipment.

In addition, a written survey about the nutritional background, with a frequency table of food consumption —for which parents provided information on dietary intake of students for specific food groups, especially proteins— and family history was conducted.

Data were stored in Microsoft Excel program and SPSS version 18.0 was used for statistical analysis. The first part consisted of a descriptive analysis of weight, height, BMI, WC, IGF-1 and IGFBP-2, and several statistics tools were used as measures of central tendency (mean, average), form (histograms), position (percentiles, and box diagrams), and dispersion (varianza, central deviation), which allowed an overview of the relation between variables.

At a later stage, the relation between variables was determined in order to assess the possible association between nutritional status,

IGF-1 and IGFBP-2. Inferences and hypotheses evaluations were conducted through the Pearson coefficient, Chi square, analysis of variance (ANOVA), Kruskal Wallis, and Dunnet and Games-Howell. For comparison of groups and association between nutritional status, IGF-1 and IGFBP-2, a technical analysis of variance (ANOVA) was used when data was (parametrically) normal and homogeneous; after observing significant results, an analysis of multiple comparisons with different means using Dunnet method was performed to recognize the relevant differences.

The Games-Howell test was used for pairwise comparison and for evaluating IGF-1 serum levels based on food consumption. Scatter plots of the IGF-1 values were performed for each of the food groups. The relationship between variables was identified to test the hypothesis of equality of means between each class; associations were calculated with $p<0.05$ as statistically significant with confidence interval of 95%. The numerical variables were expressed as mean, standard deviation and percentages.

This research was approved by the Ethics Committee of the Faculty of Medicine from Universidad Nacional de Colombia, it considered all ethical aspects under Resolution 8430 of 1993 by the Ministry of Health of Colombia and was classified as minimum risk for health participants; the information provided to children met the requirements of article 15 of the aforementioned resolution. In addition, each participant provided informed consent signed by parents or legal guardians.

Results

Table 1 shows the statistical information of the anthropometric variables weight, height, WC and BMI of the study population (n=157).

Table 1. Anthropometric variables of the study subjects.

Statistical	Weight (Kg)	Height (cm)	WC (cm)	BMI Weight (kg)/ height (m)^2
Average	29.8	128.6	62.4	17.9
Standard deviation	6.8	6.9	8.4	2.8
Minimum	19.5	111.8	48.8	13.2
25th percentile	24.6	123.3	56.2	15.9
75th percentile	33.3	134.7	67.0	19.6
Maximum	50.6	144.0	85.7	27.1

WC: waist circumference; BMI: body mass index. Source: Own elaboration based on the data obtained in the study.

The analysis of the nutritional status of the participants was based on body mass index (BMI/age) and was classified into eutrophic, overweight, obesity, thinness and thinness risk (Figure 1). Children were classified according to height/age into appropriate, risk of low height and low height (Figure 2), finding the coexistence of malnutrition by excess and deficit. Thinness was evidenced only in girls of the private institution and there was a delay in height in girls from both institutions, as well as a significant percentage of overweight boys and girls in both institutions, predominantly obese boys and overweight girls (Figure 1).

Those with the highest WC average (65.1±3.6cm and 73.4±8.1cm, respectively) were ranked in the overweight and obesity nutritional groups. Children with high WC and proper weight presented WC 63.3±3.5, whereas the eutrophic and low height risk group showed WC 56.0±1.4cm and 54.7±3.8cm, respectively. An analysis of the results of IGF-1 and IGFBP-2 serum levels measured in the subgroup of 81 children are presented below.

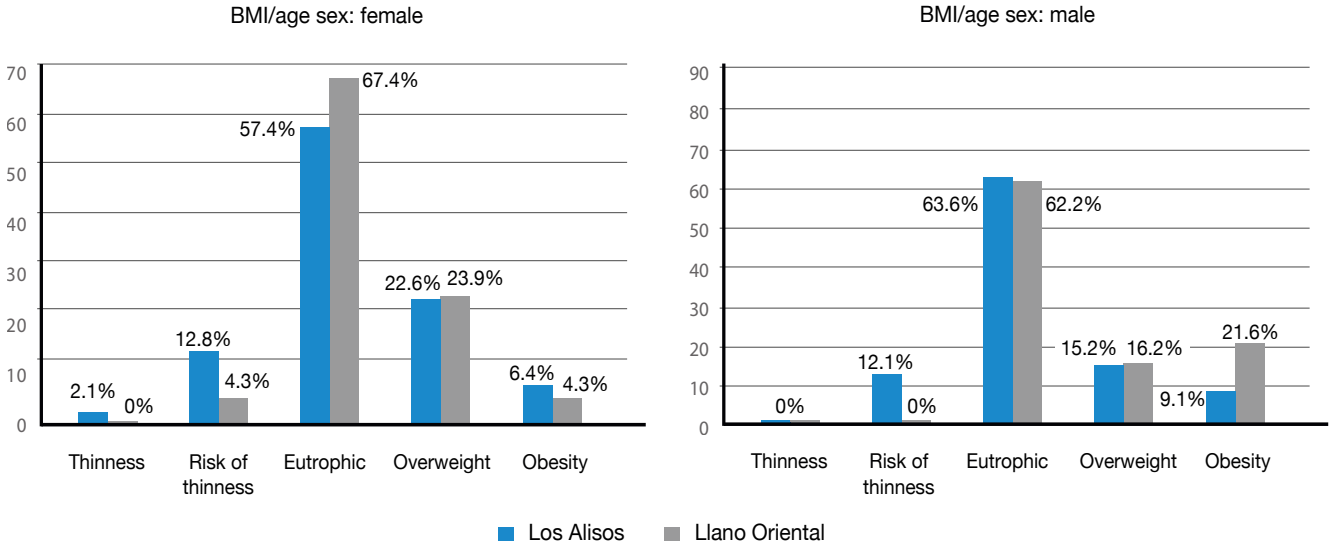

Figure 1. Nutritional status according to BMI/age. Source: Own elaboration based on the data obtained in the study.

The relationship between IGF-1 and nutritional status can be seen in Figure 3, where a strong association between IGF-1, BMI and CC is evident; however, a relation between IGF-1 and height is suggested. Also the inverse relation between IGFBP-2 serum levels and BMI is identified.

Figure 4 displays the box plots that show the position of the data, where the lowest levels of IGF-1 are found in children with height delay. Dunnet test confirms the significant difference between the groups delay in height and proper height.

Higher levels of IGF-1 were mainly seen in overweight children from Llano Oriental School (Figure 5). To clarify the possible relation between obesity and IGF-1, serum levels of IGF-1 in obese subjects were compared with eutrophic children (controls) and a significant difference ($p=0.035$) was observed, indicating that the adiposity level is related to IGF-1 serum levels.

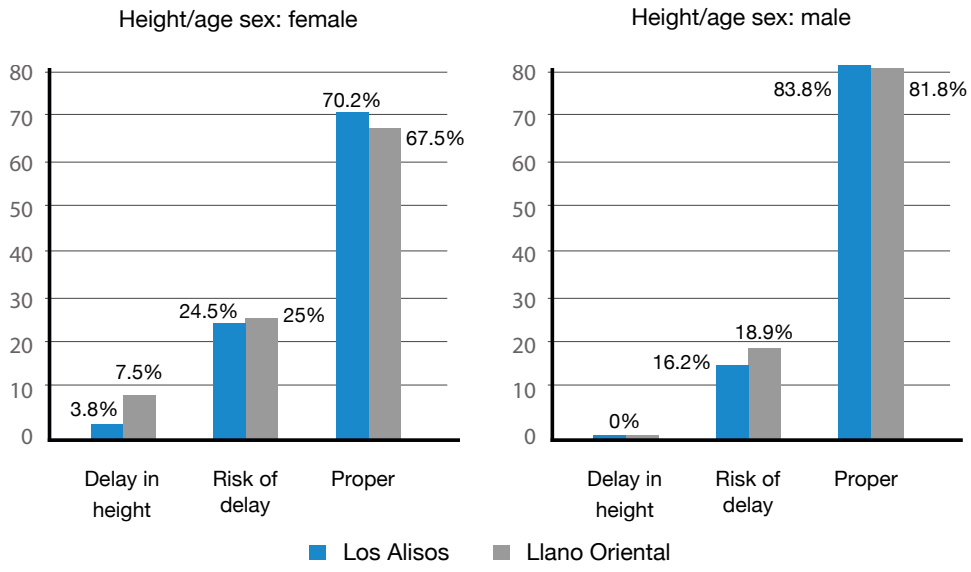

Figure 2. Nutritional status according to height/age. Source: Own elaboration based on the data obtained in the study.

Table 2. Statistical summary of IGF-1 and IGFBP-2 concentrations.

	(ng/ml)	(ng/ml)
Average	300.93	230.19
Standard deviation	150.23	83.70
Count	81	81
Minimum	65.42	21.92
Maximum	734.62	442.09
25th percentile	195.74	170.75
Median	245.26	221.74
75th percentile	385.61	288.04

Source: Own elaboration based on the data obtained in the study.

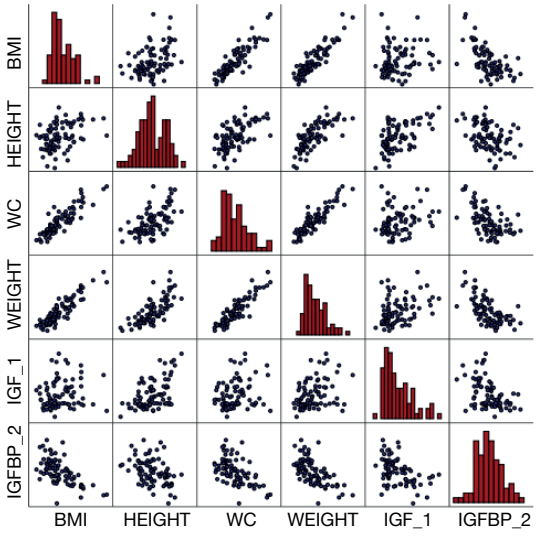

Figure 3. Scattering matrix between anthropometric and hormonal variables. IGF-1: type 1 insulin-like growth factor; IGFBP-2 binding protein of type 2 IGF-1; BMI: body mass index; WC: waist circumference. Source: Own elaboration based on the data obtained in the study.

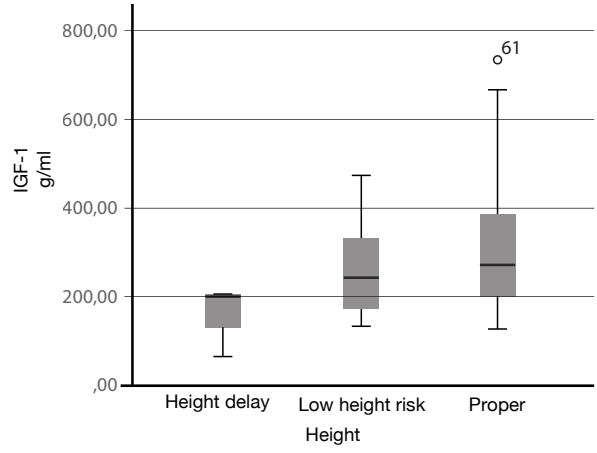

Figure 4. Box plots of IGF-1 serum levels according to height/age. Source: Own elaboration based on the data obtained in the study.

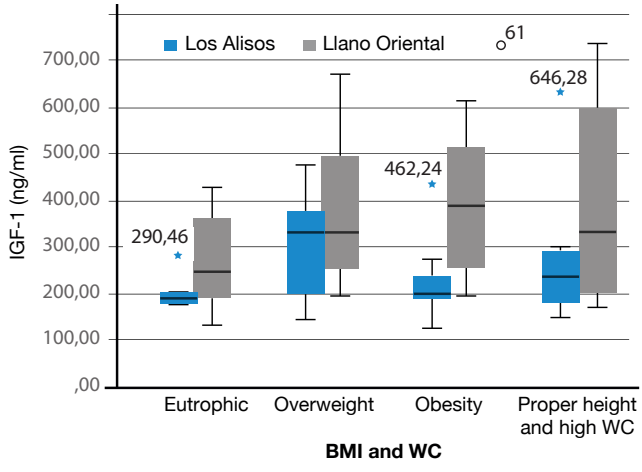

Figure 5. Box plot for circulating levels of IGF-1 according to weight/height and CC/age per institution. IGF-1: type 1 insulin-like growth factor; WC: waist circumference. Source: Own elaboration based on the data obtained in the study.

Figure 6 compares the relative frequency histograms of IGF-1 for both educational institutions; there is a positive asymmetry observed in both cases. While lower concentrations of IGF-1 are present in the students of Liceo Integral Los Alisos, the highest values of this variable were found in Llano Oriental School.

Different p values are shown in Table 3 to compare the mean, median and distribution groups —classified according to BMI/age and height/age—.

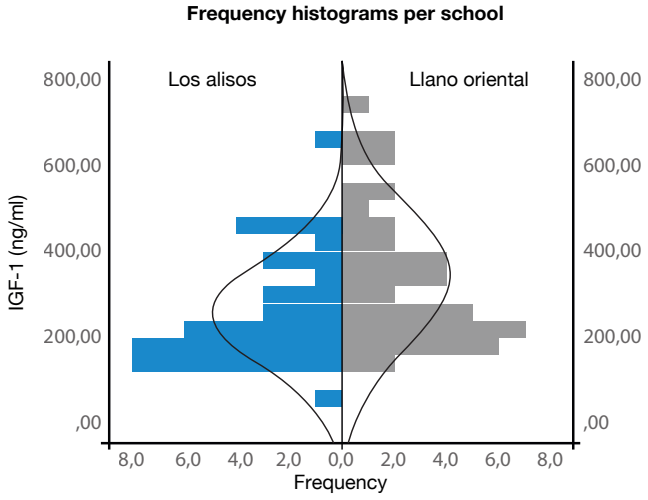

Figure 6. Frequency histograms of IGF-1 per educational institutions.IGF-1: type 1 insulin-like growth factor.Source: Own elaboration based on the data obtained in the study.

Table 3. Comparison of height and IGF-1, IGFBP-2 and BMI p value.

Category	ANOVA p value	Median p value	P value (Kruskal-distribution)
IGF-1/height	0.097	0*	0.024*
IGFBP-2/BMI	0*	0.234	0.129

ANOVA: variance analysis; IGF-1: type 1 insulin-like growth factor; IGFBP-2 type 2 binding protein of IGF-1. * Significance level p<0.05.

Source: Own elaboration based on the data obtained in the study.

Figure 7 shows a diagram of boxes indicating the position of IGFBP-2 serum levels in relation with BMI classification; also, it is observed that children with lower IGBP-2 values are those with obese and overweight. The greatest statistical significance is observed in the obese group after using Dunnet test.

To study the relation between intake of macronutrients —proteins, lipids and carbohydrates— and IGF-1 serum levels, a descriptive analysis was performed between the means of this hormone and the count of the most frequent categories of consumption of food groups.

In this research, only one possible link to the source of protein food was found in children who consumed milk and dairy products daily and those who ate eggs 2 to 3 times a week, who showed the highest IGF-1 values. Within other food groups, it became clear that occasional use of additions of fat was associated with lower levels of IGF-1.

It is important to note that the high weekly consumption of fast foods, soda, fat additions and processed food, accompanied by a low consumption of vegetables and fruits, indicates inadequate eating habits in this group of children and could explain the high levels of overweight and obesity found.

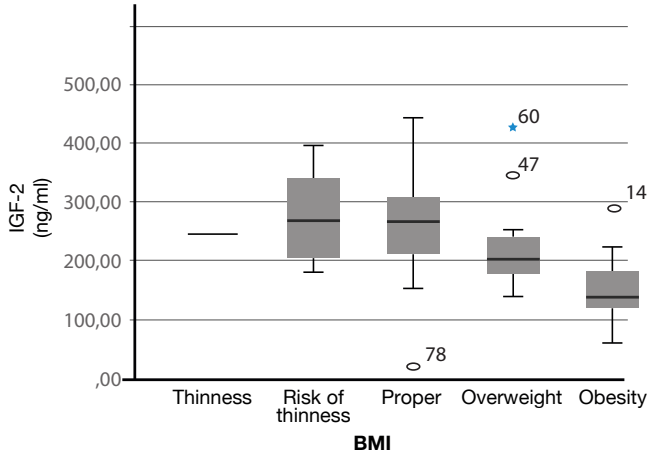

Figure 7. Box plot IGFBP-2 and BMI. IGFBP-2: type 2 binding protein of IGF-1. Source: Own elaboration based on the data obtained in the study.

Discussion

Malnutrition due to both excess and deficit was found: in 0.6% of children thinness was observed and in 3.2% delay in height, which is inferior to the data reported by the ENSIN 2010 (3) —thinness 2.1% and delay in height 10%—. Low height risk and low height were observed only in girls, and the only case of thinness was found in a girl from Liceo Integral Los Alisos.

This study shows a higher prevalence of overweight (19.1%) and obesity (10.2%) compared to national data reported by ENSIN 2010 (13.4% and 4.1%, respectively) (3).When analyzing the results by sex, obesity is more prevalent in boys, while overweight is more common in girls. These findings can be compared with those reported in previous Colombian studies conducted in Bogotá (13) and Medellín (14), where similar data were presented and the coexistence of malnutrition, overweight and obesity was evident. In Latin America, other studies have also reported similar results in school children from Ecuador (15) and Perú (16).

Malnutrition during childhood caused by deficit can affect intellectual and cognitive ability by reducing school performance and learning life skills. Therefore, this condition impairs human and professional development and affects the progress of the community and the country (2,17). Also, excess weight has important consequences since it is associated with metabolic disorders (dyslipidemias, insulin resistance, diabetes, hypertension, among others) (18) that may occur at an early age; in addition, an obese child may suffer social discrimination, low self-esteem and depression (19). Similarly, overweight during childhood and adolescence has been associated with higher probabilities of eating disorders such as anorexia and bulimia (18).

When analyzing the nutritional status and IGF-1, a proportional relation between circulating levels of this hormone with height was observed. Low IGF-1 levels were also found in children with delay in height, which agrees with previous studies (20-22). These results are explained by the interaction of the GH-IGF-1 hormonal axis.

It has been shown that malnutrition is associated with a state of GH resistance (23), which would explain the low functionality of this hormone to regulate the synthesis and availability of IGF-1 in subjects with chronic malnutrition or stunting. In turn, a positive relation between IGF-1 levels and BMI was found, relation that has not been observed in all studies when recording normal (24), low (25,26) and high values (26,27). These differences may occur since this growth factor is affected by sex, age, degree of obesity and

genetic factors, which generates conflicting results. It is important to note that most studies have been conducted in adults and there is little research with school population linking obesity with circulating levels of IGF-1.

It is necessary to clarify the relation between IGF-1 and diet. This study did not find a clear influence of the intake of protein sources, but a relation (although small) between a consumption of dairy and eggs with IGF-1 concentrations was found. Previous studies in rats show that the decrease in energy intake and marked protein deprivation decrease levels of IGF-I (28,29). Most human studies have been conducted in adults (30-32), so data are still scarce in school children. A multiethnic study of populations living in the US found no association between IGF-1 and protein consumption (33), like other studies in adults (34).

When comparing the levels of IGF-1 per educational institution, it was found that they were higher in the public institution, which may be attributed to increased access and availability of food and nutrients, since these subjects received school snacks from the district daily, as opposed to the private school children, who eat what their parents send from home or buy packaged foods with high sugar content in the school store. It is noteworthy that the highest prevalence of obesity was observed in Llano Oriental School.

In this research an inversely proportional relation between IGFBP-2 and nutritional status was also found: the lowest values of this binding protein were found in children diagnosed with obesity, which is consistent with several previous studies (8,10,35). IGFBP-2 is the major IGFBP secreted by white preadipocytes during adipogenesis (8,9). The correlation found between decreased circulating IGFBP-2 and BMI could be related to a profile of unfavorable secretion of adipocytes of the binding protein and, simultaneously, with increased leptin and decreased adiponectin (34). Leptin has significant effects on maintaining normal weight and glucose metabolism and has been proven to increase hepatic transcription of IGFBP-2 when administered by peripheral or central route in mice with lipodystrophy (36-38). Regarding obesity, a possible leptin resistance has been reported, which could explain the low serum levels of IGBP-2 observed in this study (37,38); however, the mechanisms by which leptin regulates the production of IGFBP-2 have not been fully elucidated.

On the other hand, the analysis of food consumption showed inadequate eating habits in both, boys and girls, consisting of low consumption of fruits and vegetables, which violates the recommendations of five daily servings by the WHO. In addition, a high intake of high caloric density foods such as soft drinks, fast foods, fat additions and packaged food was found, highlighting the importance of working in food and nutrition education with families, students, school stores and staff.

In this study a high prevalence of overweight and obesity in the two educational institutions, whose socioeconomic strata is low, was observed, which is why greater attention should be paid to the promotion of healthy lifestyles, including changing eating habits, self-care practices and promotion of physical activity in the school population to reduce the risk of developing chronic conditions such as cardiovascular disease, diabetes and cancer that could permanently influence their quality of life.

Conclusions

In the educational institutions studied in this work, a coexistence of malnutrition caused by deficit and excess weight was observed, as well as low prevalence of thinness and risk of thinness and high prevalence of overweight and obesity. Obesity was more prevalent in boys and overweight in girls, while poor eating habits given by low consumption of fruits and vegetables and high intake of caloric foods were evident.

A direct relation between IGF-1 and height and between IGF-1 levels and BMI was found. Since an inverse relation between IGFBP-2 and BMI was observed, this may suggest that IGFBP-2 is a predictor of adiposity in children; however, it was no possible to establish a direct relation of IGF-1 with protein consumption, except for dairy and egg.

This work can be a baseline that evidence more fully the current situation of the school population by relating not only anthropometric variables but also including hormone variables.

This paper is the result of the thesis for the Master's degree in Physiology of one of the authors, entitled "The relation between nutritional status, serum levels of insulin-like factor growth (IGF-1) growth and its type 2 binding protein (IGFBP -2) in school children from two educational institutions in Bogotá and Soacha (2014)" (39).

Conflict of interests

None stated by the authors.

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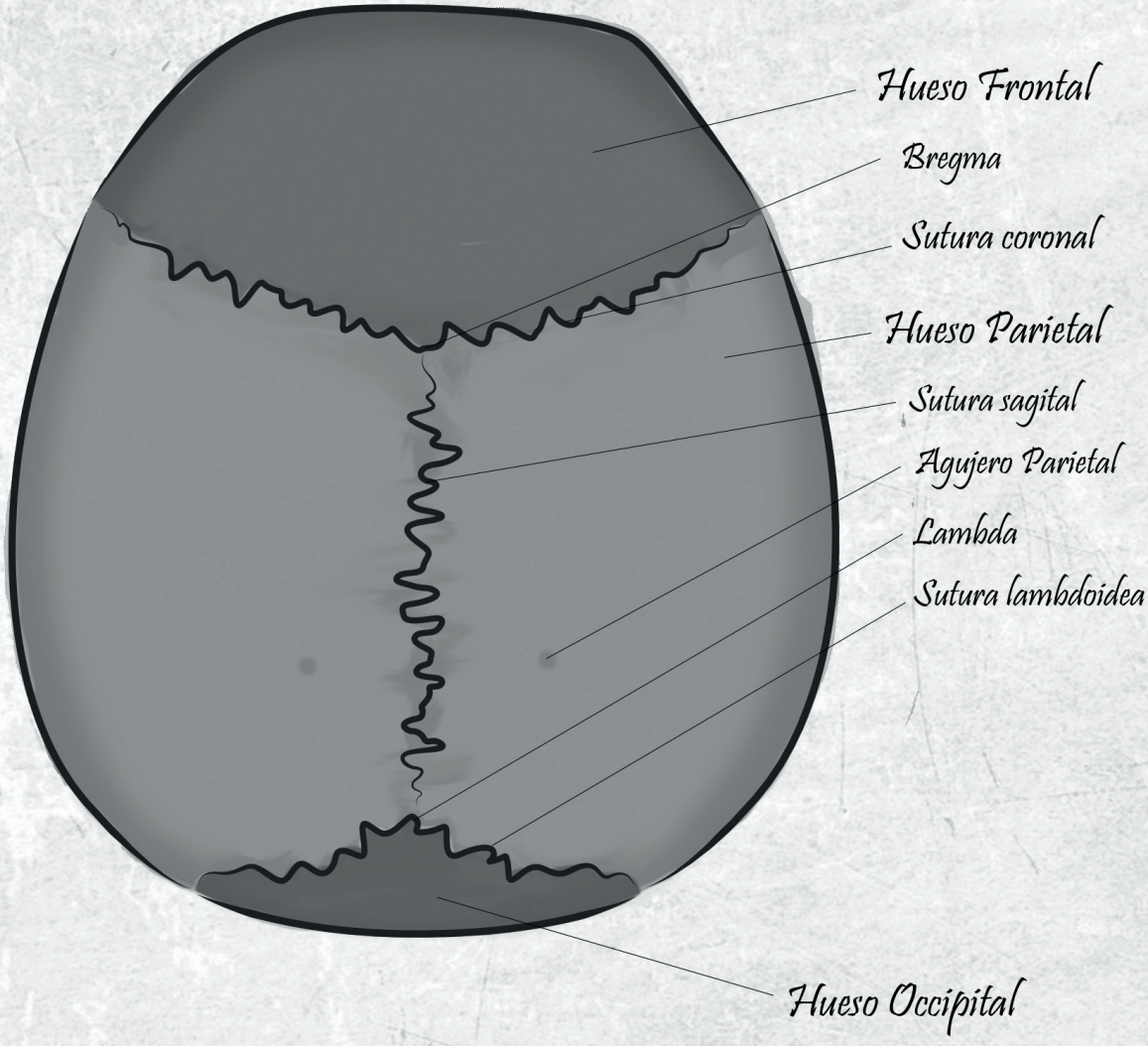

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"Mapas anatómicos"
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ORIGINAL RESEARCH

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Frequency of bullying perceived in clinical practices of last year interns of a medicine school: cross sectional study

Frecuencia de matoneo percibido en prácticas clínicas de estudiantes de internado en último año de una facultad de medicina. Estudio de corte transversal

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| Abstract |

Introduction: During the medical internship year, students attend several hospitals and are observed and influenced by postgraduate students, general practitioners and other interns, who provide them with fundamental support regarding professional training. Bullying is defined as an aggressive behavior that occurs between a perpetrator and a victim in different scenarios and authority relationships, such as clinical practices at Medicine programs.

Objective: To describe the perceived frequency of bullying among a group of interns of the Faculty of Medicine from Universidad Nacional de Colombia during internship.

Materials and methods: A transversal analytical study was performed through a questionnaire applied to 82 medical interns of the School of Medicine from Universidad Nacional de Colombia.

Results: The perceived frequency of bullying was 90%. Statistically significant differences were not found in the stratified analysis by sex or place of practice. In most cases, bullying was perpetrated by other interns, while residents and specialists showed a lower frequency.

Conclusion: Perceived frequency of bullying was higher than expected according to the existing literature. These results can be used as a basis for new studies.

Keywords: Students; Health Occupations; Bullying; Education, Medical; Questionnaires (MeSH).

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| Resumen |

Introducción. Durante el año de internado, los estudiantes acuden a diversos hospitales y se encuentran bajo la mirada e influencia de estudiantes de posgrado, médicos generales, otros médicos internos y especialistas que brindan un apoyo importante en su formación. El matoneo o bullying es un comportamiento agresivo que se da entre un atacante y una víctima y que puede ocurrir en múltiples escenarios con diferentes relaciones de poder como las prácticas clínicas en la carrera de Medicina.

Objetivo. Describir la frecuencia de matoneo percibida en un grupo de médicos internos de la Universidad Nacional de Colombia.

Materiales y métodos. Estudio de corte transversal analítico realizado a través de una encuesta aplicada a 82 médicos internos de la Universidad Nacional de Colombia.

Resultados. Se encontró una percepción de matoneo del 90% sin diferencias estadísticamente significativas al realizar el análisis estratificado por género y lugar de rotación. Las conductas de matoneo son llevadas a cabo en su mayoría por pares académicos y en menor medida por residentes y especialistas.

Conclusiones. La percepción de matoneo resultó ser mayor a la reportada en la literatura. Estos resultados pueden emplearse como información de base para nuevos estudios.

Palabras clave: Estudiantes; Empleos en salud; Acoso escolar; Educación médica; Cuestionarios (DeCS).

Sánchez NF, Bonilla LP, Rodríguez ML, Sandoval G, Alzate JP, Murcia NV, *et al.* [Frecuencia de matoneo percibido en prácticas clínicas de estudiantes de internado en último año de una facultad de medicina. Estudio de corte transversal]. Rev. Fac. Med. 2016;64(3):447-52. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.54003.

Introduction

The attention given to bullying management is important at all levels of education; however, greater concern is seen on elementary schools and high schools than on higher education (1-3).

Medical Subject Headings (MeSH) define the word 'bullying' as "aggressive behavior that is intended to cause physical or psychological damage, verbally or physically, due to the imbalance of power, strength or status between the aggressor and the victim" (5). The British Medical Association points out this practice as "a persistent behavior towards an individual, which consists in intimidating, demeaning, offensive or malicious treatment and undermines confidence and self-esteem of the receptor" (4).

Bullying can include humiliation or ridicule in public, limited opportunities or privileges, exclusion from decision making, change in roles and daily activities abruptly and/or without prior notice, and also lack of information at certain times (6). In Colombia, Law 1620 of 2013 addresses bullying, but the scope of this document is limited to schools and does not include universities (1). Since prevalence decreases with age, the study of bullying has been of interest in basic education; however different research findings conclude that there is an increase of this issue during the university period (2,3).

According to Silva-Villarreal *et al.* (7), medical students are an emotionally vulnerable population that is exposed to stressful situations; Bastías *et al.* (4) noted that "medical training has been traditionally considered difficult and demanding" and for this reason, students are at risk of both generating or suffering bullying.

In Colombia, Paredes *et al.* (2) reported a prevalence of 19.68% of bullying in undergraduate medical students. In the opinion of students, bullying has effects on their mental health, social life and image of the medical profession (4).

In England, Timm (8) conducted a study with nursing and medical students, and found that 18% of them have experienced or witnessed humiliating or offensive comments by a physician/professor (44%). In the same country, Quine (9) found that residents of medical specialties are also victims, and reported that, at some point, they felt affected by this dynamic (9).

Similarly, in Saudi Arabia, Alzahrani (10) reported that 28% of students have been victims of bullying, finding the highest prevalence during the internship. In Pakistan, Mukhtar *et al.* (11) found that 66% of students had experienced bullying in the past six months, while Ahmer *et al.* (12) reported that 52% of students had experienced bullying and established that the main offenders were professors, with 46%.

Timm (8) suggests that the training of health professionals is associated with negative role models affecting student empathy on the long term, which can trigger behaviors such as bullying; on the other hand, Kassebaum & Cutler (13) state that the culture of abuse is considered as part of medical training, as a normal behavior and even as a useful learning experience.

The psychological consequences of this behavior are relevant in educational processes and have an impact on work life and interaction with peers. Bastías *et al.* discuss on how Silver (4) concluded that changes in the attitude of professionals towards their patients could be the result of hostile and punitive damages received during medical school and, also, how Perales *et al.* (4) suggest that the stress suffered by medical students during their training is high, which could endanger their mental health.

Other actions related to bullying behaviors include non-verbal and hierarchy dynamic behavior, which underestimate emotional expressions and generate actions aimed at confirming that "bullying is not always expressed through yelling" (14); these actions include ignoring, denying and deceiving.

Considering how prevalent this dynamic is in medical schools and recognizing the importance of this practice in the training process, the objectives of this research are to determine and to describe the frequency of bullying perceived by resident physicians of the Faculty of Medicine from Universidad Nacional de Colombia during their last year of studies (2).

Materials and methods

Descriptive cross-sectional study in which students of the last year of the medical major, who agreed to participate, were included; a sample of 72 participants was studied for a prevalence of 20%.

This scale is an adaptation of the "Workplace bullying in junior doctors questionnaire" by Dr. Lyn Quinne, who works for the "Centre for Research in Health Behaviour" at the University of Kent in England (9). This Spanish version is used by Paredes *et al.* (2) but with no evidence of validation. The questionnaire consists of 49 questions, of which 45 are part of the original Likert scale and four were suggested by non-formal expert consensus.

A total group of 89 students of the last year of Medicine responded a self-administered survey one day before their graduation ceremony. Informed consent was obtained verbally to maintain anonymity in the questionnaires and data analysis was performed using STATA 12.1 program

Based on the type of variables and their distribution, data were presented in proportions and median summary and interquartile range (IQR) were presented as measures. To identify the differences between groups, the x^2 test and Fisher's exact test were used. To evaluate possible associations of OR prevalence, the 0.05 statistical significance was utilized. This study was approved by the Ethics Committee of the Faculty of Medicine from Universidad Nacional de Colombia and privacy was preserved throughout the process.

Results

Participation was 92% (n=82), with an average age of 24 (IQR:2), median socioeconomic status 3 (IQR:1) and the highest record related to place of origin was the Andean region.

When assessing a possible association with the perception of bullying during internship, 74 of 82 participants (90.24%) perceived themselves as victims of some type of behavior related to bullying. In addition, 38 students (46.34%) said they had perceived this dynamic during the first five semesters of the major with an OR=0.6 (95%CI:0.08-3.36) and 42 students (51.22%) between the sixth and tenth semester with OR=1.49 (95%CI:0.26-10.28).

Table 1 summarizes the main findings reported on behaviors referred *to overload* of *extra responsibilities in comparison with other peers* (52.44%) and *requests to perform activities outside the professional or academic activities* (47.56%).

There are common offenders for certain actions: first, residents and specialists, followed by academic peers (other interns) and finally, professors.

The item *'possible triggers of bullying behaviors'* had a low response rate (39%). Those who answered this question identified the way of thinking or expression as the main cause (Table 2). Within the group *'Others'*, academic performance and being a student from Universidad Nacional were found as causes of bullying behavior. Only 76 participants answered the *Sex* variable in the survey.

Table 1. Perceived frequency of bullying by medical interns during their last year of training.

Bullying behavior	Total % (n)	Frequency								Aggressor agent %	
		Never		Occasionally		Once a week		More than once a week			
		n	%	n	%	n	%	n	%		
Overload of extra responsibilities	52.44% (43/82)	39	47.5	33	40.2	2	2.4	8	9.76	Resident	27.8
										Specialist	20.2
										Academic peer	5
Request to perform activities outside professional or academic fields	47.56% (39/81)	42	51.2	32	39	1	1.2	6	7.32	Specialist	30
										Resident	28.7
										Academic peer	6.2
Victim of gossip	45.12% (37/82)	45	54.8	33	40.2	1	1.2	3	3.66	Academic peer	38.7
										Specialist	6.2
										Resident	5
Assignment of activities without notice	42.69% (35/82)	47	57.3	29	35.3	3	3.6	3	3.66	Resident	26.8
										Specialist	19.5
										Professor	3.6
Academic pressure	41.46% (34/82)	48	58.5	31	37.8	1	1.2	2	2.44	Only agent to which the question is directed: professor	
Nicknames	35.37% (29/82)	53	54.6	23	28	1	1.2	5	6.10	Academic peer	24.3
										Resident	13.4
										Specialist	13.4
Extra or unjustifiable shifts or activities	26.83% (22/82)	60	73.1	21	25.6	0	0	1	1.22	No aggressor was suggested	
Attitudes directed towards ignoring students	24.39% (20/81)	61	74.3	14	17	2	2.4	4	4.88	Specialist	10.1
										Professor	6.3
										Resident	6.3
No information regarding rule changes	24.39% (20/80)	60	73.1	16	19.5	1	1.2	3	3.66	No aggressor was suggested	
Belittled efforts	21.95% (18/82)	64	78	16	19.5	0	0	2	2.44	Specialist	11.5
										Resident	8
										Professor	0
Derision in front of others	21.93% (18/82)	64	78	15	18.2	2	2.4	1	1.22	Specialist	13.4
										Resident	9.7
										Academic peer	2.4
Teasing by professors	20.73% (17/82)	65	79.2	15	18.2	2	2.4	0	0	Only agent to which the question is directed: professor	
Teasing or destructive comments	19.51% (16/81)	65	79.2	14	17	2	2.4	0	0	Academic peer	10.1
										Specialist	5
										Professor	1.2
Deliberate rejection during activities	13.42% (11/82)	71	86.5	10	12.2	0	0	1	1.22	Resident	6
										Academic peer	3.6
										Professor	2.4
Violence against property	12.20% (10/82)	72	87.8	10	12.2	0	0	0	0	Unknown	2.4
										Academic peer	2.4
										Resident	2.4
Taunts from classmates regarding relationship with professors	9.76% (8/81)	73	89	8	9.7	0	0	0	0	Only agent to which the question is directed: academic peers	
Hidden belongings	8.54% (7/82)	75	91.4	7	8.5	0	0	0	0	Academic peer	6
										Nursing staff	2.4

Bullying behavior	Total % (n)	Frequency								Aggressor agent %	
		Never		Occasionally		Once a week		More than once a week			
		n	%	n	%	n	%	n	%		
Verbal and non-verbal threats	6.1% (5/82)	77	93.9	4	4.8	0	0	1	1.22	Academic peer	4.8
										Professor	1.2
										Specialist	1.2
Aggressive emails or messages on mobile phone	6.1% (5/82)	77	93.9	4	4.8	0	0	1	1.22	Resident	3.6
										Academic peer	1.2
										Chief of interns	1.2
Physical violence	4.88% (4/82)	78	95.1	4	4.8	0	0	0	0	Academic peer	2.4
										Professor	1.2
										Specialist	1.2
Aggression through social networks	3.66% (3/82)	79	96.3	3	3.6	0	0	0	0	Academic peer	3.6

Source: Own elaboration based on the data obtained in the study.

Table 2. Internal factors identified by interns as the cause of perceived bullying.

Unresponsive	61%
Way of thinking or expressing	17%
Being a woman	11%
Other	8.5%
Being a man	6%
Physical appearance	2.4%
Election or sexual orientation	0

Source: Own elaboration based on the data obtained in the study.

After evaluating the results classified by gender, the perception of bullying was found mostly documented in males. 41 interns (54.67%) reported being victims of bullying behaviors, the most frequent being *overload of extra responsibilities* and *requests for activities not related to academic or job skills*. Among women, 28 interns (37.33%) reported perceiving bullying behaviors during their internship year, the most frequent being *victims of gossip*. The survey did not inquire about sexual harassment, but one of the respondents reported having been victim of "inappropriate attitudes" by fellow male peers. No significant differences were found in the frequency of perceived bullying by sex (OR=1.42 95%CI:0.24-8.32), however, there was a significant difference of 13.64% (X^2=4.73, p=0.03) in the frequency of perceived bullying related to the statement "my belongings were hidden or stolen during my internship". Similarly, more than 28% of women reported "being a victim of gossip" by academic peers (Fisher=9.09, p=0.04) (Table 3).

Table 4 summarizes the response actions of interns to perceived bullying behaviors.

Among those surveyed, 76 reported several practice sites, and since interns from Universidad Nacional de Colombia often attend several practice places during their internship year, this variable was considered (Table 5).

Most of the interns did at least one of their rotations in Bogota (67.11%); 21 doctors (27.63%) reported having completed their internship only in Bogota and 25 (32.89%) in other cities. There was no association between the number of rotation sites and the perception of bullying (x^2=2.67, p=0.75).

Discussion

Bullying is a phenomenon studied in several fields, especially by those related to academic training given the impact this may have on the quality of life and prevalence in different levels of training (7). There is no standardized or recognized methodology that can be used to assess bullying behaviors in medical students; in this study, a non-validated questionnaire was applied, therefore, the conclusions that can be obtained from the results are doubtful.

A perception of bullying of 90.24% was found, which exceeds the frequency of 20% reported in the study by Paredes *et al.* (2), conducted in Colombia, and even the report by Silva-Villareal *et al.* (7) of 39.8% in basic and preclinical cycles of the Medicine major at Universidad de Panamá.

The high level of perceived bullying is worth noting because almost all students reported being victims of at least one aggressive behavior during their internship; most of them perceived these behaviors less than once a week. Practices related to bullying often vary in severity and frequency, but the data obtained and the instrument used do not provide tools to estimate their actual impact on academic, social and emotional performance of victims.

The perceived frequency of bullying increases as the major develops, which is consistent with the findings of Alzahrani (10). This may be influenced by variables such as time elapsed between the event and its registration, induction of responses or possible degrees of involvement of the specific event.

Within the group of interns interviewed, perceived bullying practices were related to overload, expressed in the increased responsibilities, and the request to perform activities unrelated to professional or academic fields, which was the most frequent bullying behaviour; besides the main aggressor agents were residents and specialists. A striking association of hierarchy dynamics and power relations was evident between the different levels of training in the field of medicine (8).

Although most medical interns who reported being victims were men, no increased risk of being a victim of bullying associated with this sex was found, and no other significant differences except for variables *'my belongings were hidden or stolen during the internship'* were found more frequently in men; *being a victim of gossip* was more common in women, and as a trigger for bullying, *the way of thinking or expressing* had a higher prevalence, which coincided with the findings reported by Paredes *et al.* (2). There was no association of bullying with the number of rotations during the internship, an aspect that was not previously analyzed by any of the authors consulted.

Regarding the actions to respond to bullying behaviors, the results were similar to other studies (2): ignoring the behavior is the usual response. It is evident that looking for support from competent authorities to mitigate or denounce these actions was not common; this aspect can be related to people's fear of reporting the assault, which may be motivated by fear of loss of "force" in a hierarchical culture (8).

Table 3. Perceived frequency of bullying by interns in their last year.

Bullying behavior	Female n=32 (%)	Male n = 44 (%)	Total n=76 (%)
Overload of extra responsibilities	16 (41.03%)	23 (58.97%)	39 (51.32%)
Request to perform activities outside professional or academic fields	14 (37.84%)	23 (62.16%)	37 (49.33%)
Victim of gossip	17 (48.57)	18 (51.43)	35 (46.06%)
Assignment of activities without notice	14 (42.42%)	19 (57.58%)	33 (43.43%)
Academic pressure	14 (45.16%)	17 (54.84%)	31 (40.79%)
Nicknames	10 (37.03%)	17 (62.96%)	27 (35.53%)
Extra or unjustifiable shifts or activities	9 (47.37%)	10 (52.63%)	19 (25%)
Attitudes directed towards ignoring students	7 (35%)	13 (65%)	20 (26.67%)
Change of rules without notice	5 (29.41%)	12 (70.59%)	17 (22.66%)
Belittled efforts	5 (27.78%)	13 (72.22%)	18 (23.68%)
Derision in front of others	6 (40%)	9 (60%)	15 (19.74%)
Teasing by professors	4 (26.67%)	11 (73.33%)	15 (19.74%)
Teasing or destructive comments	5 (31.25%)	11 (68.75%)	16 (21.34%)
Deliberate rejection during activities	4 (36.36%)	7 (63.64%)	11 (14.48%)
Violence against property	3 (30%)	7 (70%)	10 (13.16%)
Taunts from classmates regarding relationship with professors	2 (33.33%)	4 (66.67%)	6 (7.89%)
Hidden belongings	0 (0%)	6 (100%)	6 (7.89%)
Verbal and non-verbal threats	1 (20%)	4 (80%)	5 (6.58%)
Aggressive emails or messages on mobile phone	2 (40%)	3 (60%)	5 (6.58%)
Physical violence	0 (0%)	3 (100%)	3 (3.95%)
Aggression through social networks	1 (33.33%)	2 (66.67%)	3 (3.95%)

Source: Own elaboration based on the data obtained in the study.

Table 4. Actions taken by interns in response to perceived bullying in the last year of studies.

Action	n=63
Ignoring what was happening	38 (43.3%)
Confronting the person who generated the dynamic	18 (22%)
Reporting the issue to someone else	10 (12.1%)
Making formal complaints	7 (8.5%)
Threatening to report the situation to an authority	2 (2.4%)
Requesting the change of the group or place of rotation	2 (2.4%)
Requesting support from university welfare services	1 (1.2%)
Other	1 (1.2%)

Source: Own elaboration based on the data obtained in the study.

Table 5. Frequency of bullying perceived by interns by number of practice sites during internship.

No. practice sites	No bullying reports		Bullying reported		Total	
	n	%	n	%	n	%
1	4	57.1	38	55	42	55.2
2	2	28.5	24	34.7	26	34.2
3	1	14.2	2	2.9	3	3.9
4	0	0	1	1.4	1	1.3
5	0	0	3	4.3	3	3.9
6	0	0	1	1.4	1	1.3
Total	7	100	69	100	76	100

Source: Own elaboration based on the data obtained in the study.

Conclusions

The perception of bullying in this study was higher than expected according to the sources consulted (2,7); this information could account for an underlying problem that requires further study.
One of the elements that may have influence on the high perception of bullying is the inheritance of hierarchical patterns, as well as the low rate of complaint and request for help.

When addressing training or the strengthening of health skills, there is a reference to education that must thrive despite the difficulties of the current system, which limits the autonomy and initiative of a doctor (15); under these circumstances, new problems arise, such as the difficulty for teamwork (16), and even the depersonalization of health care (17). The academy allows the training of doctors with advanced scientific, technical-ethical, and social preparation (18); however, the required skills do not often take into account humanization of health as a key aspect of training and performance of health professionals.

The limitation of this study is that the information used as the basis for this research was provided by a non-validated survey-like instrument, so its results are highly subjective and could only be comparable with findings of other surveys using a similar instrument.

There is a need to generate validated instruments for documenting bullying situations during the training of medical students and for allowing optimal characterization of the situation and possible interventions for surveillance.

Conflict of interests

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ORIGINAL RESEARCH

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Neuropediatrics postgraduate students' learning process through hidden curriculum at Universidad Nacional de Colombia

Aprendizaje a través del currículo oculto en estudiantes del posgrado en Neuropediatría de la Universidad Nacional de Colombia

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| Abstract |

Based on the importance of a comprehensive professional training, this research aims at observing and describing the learning process achieved through the hidden curriculum of students enrolled in the Neuropediatrics Specialization Program at Universidad Nacional de Colombia in 2012 y 2013.

A qualitative study to explore students' training, transmission of attitudes, values and ethical aspects was performed through the implementation of a semi-structured interview and a focal group. For this group of students, learning through the hidden curriculum is real and educational, allows having a better approach to patients and acquiring appropriate tools for a successful job performance. Nevertheless, it is still insufficient to address ethical dilemmas such as delivery of bad news and patients' deaths. Thus, complementing this type of learning with explicit training on bioethics is required.

Keywords: Medical Education; Graduate Program; Curriculum; Ethics, Medical (MeSH).

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| Resumen |

Basándose en la importancia de la formación integral del profesional, se pretendió observar y describir el aprendizaje logrado a través del currículo oculto en los estudiantes matriculados en la especialidad en Neuropediatría de la Universidad Nacional de Colombia en 2012 y 2013.

A través de la aplicación de una entrevista semiestructurada y de un grupo focal, se realizó un estudio cualitativo que exploró aspectos de la formación, la transmisión de actitudes y valores y los aspectos éticos de los estudiantes.

Para este grupo de alumnas el aprendizaje a través del currículo oculto es real y formativo, les permite una mejor aproximación a sus pacientes y les da las herramientas para un desempeño profesional exitoso; sin embargo, es aún insuficiente para resolver dilemas éticos como enfrentar la explicación de malas noticias y el momento del final de la vida. Se requiere entonces complementar este aprendizaje con enseñanzas explícitas en el área de la bioética.

Palabras clave: Educación médica; Currículo; Ética médica (DeCS).

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Introduction

Medical science has greatly progressed in the past century, and has generated a flood of information and technologies that may be overwhelming for doctors and medical students, causing both to lose sight of other important aspects of training such as social and human factors and ethics, thus, creating a gap between contents and everyday situations (1) that are essential for the training of any individual (2).

Acquisition of learning related to values, attitudes and behaviors that characterize a professional in medicine is thought to be easier when teachers set an example; this approach is known as the hidden curriculum.

The hidden curriculum, defined as a set of rules, customs, beliefs, symbols and values, unrecognized or explicitly specified in the official syllabus (3), may vary depending on the population and the context in which it is presented; for this reason, no pre-established content or a specific form of teaching is pointed out. This type of education is a significant source of learning, which can train or distort students based on how it is presented to them (4).

There is a strong debate between those who believe that such teaching method cannot rely only on learning through that which is hidden, and even argue that in reality this is not a method for meaningful learning, and those who think that such an important issue should be a specific subject and that it should be included in the regular syllabus (1,4-6).

In postgraduate medicine training, the pedagogical model is mainly based on andragogy, which relies on the interest and the experiences of students and their ability to find different routes to access information that will enable more knowledge acquisition (7). Here, the professor becomes a guide and a counselor and students are the true sculptors of their knowledge.

Then, what should be transmitted by the medicine professor to students? Other than knowledge, as expected, values such as ethics, honesty, loyalty and the ability to interact with the patient should also be transmitted (8,9). Despite the importance of this topic, studies on the learning process of values in postgraduate programs, more specifically of medicine students, are scarce, leaving a gap in this area of knowledge.

This study attempts to find an approach to the vision of students of the Specialization in Neuropediatrics on why and how these hidden contents correlated to the management of moral and ethical issues are taught, as well as their impact on the students training.

Methods

A qualitative and descriptive research performed with the participation of graduate students of Neuropediatrics of Universidad Nacional de Colombia enrolled during the academic periods of the years 2012 and 2013 was performed. This was a two-stage study and was conducted as follows:

First, an individual semi-structured interview with students of second, third and fourth year was done with the purpose of exploring specific aspects of the hidden curriculum. This interview included topics such as the relationship with the professors and among graduate students, the perception of their situation regarding their peers, the attitudes of professors and other professionals, and how those attitudes have an impact on training.

Second, and based on the categories established through the interviews, a discussion was held within a focus group in which all active students of the graduate program in Neuropediatrics engaged.

The identity of the participants was not disclosed at any of the stages of the study; all students were instructed on maintaining the confidentiality of the information and identities, and an informed consent for participation was required.

Results

Semi-structured interviews

The interviews were answered by five out of six students (all female) enrolled in the second, third and fourth year of studies during 2013. The respondents were between 26 and 36 years old.

Three main categories resulted from the analysis of the results obtained in the interviews: 1) the characteristics of the graduate program in Neuropediatrics and the teaching staff, 2) the everyday life of a resident in Neuropediatrics taking into account the relationships created within the professional context and some aspects of their training, and 3) the aspects of the program related to teaching ethics and values.

The following items correspond to the findings of the categories mentioned above:

1) Characteristics of the Neuropediatrics graduate program and teaching staff

According to students, the ideal professor should be honest, ethical and kind; a professor must be someone who likes and knows how to teach, capable of empathically approaching a patient and his family and of teaching how to communicate effectively with them. However, the fact that teachers have a high knowledge level related to the profession, in order to accurately teach a subject, should not be left aside. These ideal qualities, as reported by students, are characteristic in their teachers, because they are perceived as fair, equitable and tolerant with their students and willing to teach them all.

In general, professors are able to convey knowledge not only about academics, but about a special style of medical behavior: students are taught how to create a medical record and perform a physical examination, about the way to introduce themselves, and how to communicate and behave in front of patients and their relatives, which is knowledge that is relevant for professional performance and perceived by students as positive aspects. Nevertheless, the gap occasionally found between professors and students limits this type of learning.

Three of the participants stated that they grasped techniques for addressing patients from their professors, which is considered a positive aspect; witnessing how professors approach their patients is deemed as a kind gesture and is, perhaps, one of the most valuable educational experiences for their future professional performance.

All students consider that the specialization program provides them with both academic, and care and practice opportunities; the diversity of patients and the willingness of professors and other professionals to teach them turns this environment into an optimal setting for learning.

2) The everyday life of a Neuropediatrics resident

Regarding the relationships between the student group, some aspects of comprehensive training and what is considered "correct" become a complex issue and cause discrepancies. The students consider that they are well treated and have not been discriminated by professors, but there are different views on the relationships between them: on the one hand, three students believe that they have a close relationship with their professors, which has allowed them to establish a friendship and do well in the academic and healthcare environment, and that such relationship is easier to establish with a partner of the same year of study, since understanding each other is simple; on the other hand, two of them express that relationships are difficult to establish, mainly because of a competitive environment.

While respondents consider that a neuropediatrician should be an overall skilled person, in social, ethical and academic terms, for them and at that particular moment of their lives, time should be restricted to merely academic activities (research, academy and assistance) because that is what is required for their training, although spaces for other activities related to a comprehensive training are necessary.

3) Aspects of the program related to teaching ethics and values

Three of the respondents believe that the program teaches them to face ethical dilemmas such as communicating with patients and their relatives, and informing bad news resulting from the diagnosis and prognosis of patients, which is essential in their training. When asked if they believed when they started their studies that giving bad news was an important part of their training in Neuropediatrics, the answer was:

> "Yes, I saw once a person giving bad news in a poor way, the father was destroyed; and how he was informed [...] it could have been completely different [...] It was already a topic of interest to

> me, I think, learning how to give a piece of news as humanely as possible, answering every question without giving way to false expectations. Doing it right is a challenge" (Interview No. 4.)

On the other hand, three students expressed that a better approach to facing a catastrophic illness and how to present it to the family is still required. Their answer was:

> "No, that's a very difficult part, nobody explains it; one hears it from professors, sometimes in relation with intellectual disabilities in children, but the most serious things that we have to face in the hospital, no one tells you [...] we do not have the space, ethics seminars or meetings to talk about a patient in ethical terms" (Interview No. 2).

Other aspects that help reinforcing the learning of ethical issues, according to students, are related to sharing and interacting with the patients and their relatives, and deal with the human aspects of these diseases, as well as participating in interdisciplinary workshops to learn different viewpoints and interacting in other environments with other specialties allow them to recognize themselves as neuropediatricians with strengths and weaknesses.

All students recognize the importance of explicitly opening such spaces in a way that allows a better development of skills.

Focal group results

7 out of 9 graduate students in Neuropediatrics gathered for discussion; they were distributed as follows: two first-year students, two third-year students, two fourth-year students and one second-year student.

Based on the results of interviews previously conducted, the following points were discussed by this focal group:

1. *Gains and difficulties during the course of the postgraduate program.* They believe that they have had more gains than loses; they have gained good friends, good personal and professional experiences and learned about leadership besides from what is strictly academic. Nonetheless, the little time available for personal and family matters may lead to frustration. Time and money are scarce to adequately meet academic and administrative activities, to share with relatives and to have a couple and friends.
2. *Is the academy more important than the complete development of values in Neuropediatrics?* They believe that the academy is immersed in comprehensiveness; becoming a good human being is very important to meet the needs of the patient.
3. *Are the ethical dilemmas of a neuropaediatrician restricted to giving bad news or are there other aspects that influence the performance in this specialty?* There are unresolved dilemmas, for example, the relationship with other colleagues or the proper way to handle the relationship with the pharmaceutical industry; what you learn is learned by imitating other specialists, but what is good or bad remains unclear.

It is also necessary to check how far the diagnostic study and the treatment of patients with a neurological injury may go, if interest on the patients and the search for a solution to their problem becomes the starting point, as well as the moment when a doctor becomes fierce, regardless of the opinion and the situation of the family.

There is a major concern about desensitization to the pain of patients and their family, contradictory to the reason why a person engages in Neuropediatrics; this probably occurs as a defense response to a prolonged exposure to stressful and frustrating situations that are not easy to handle or that do not allow knowing if they are being handled properly or whether related feelings are good or not.

Discussion

It is clear that the hidden curriculum exists and constitutes a means for transferring knowledge to healthcare professionals as a part of integrality in health. Both academic and personal development, as well as ethical aspects can be communicated. This learning is achieved by observation and imitation, as well as through discussions and presentations of different dilemmas generated by daily practice.

In Medicine, interaction with patients is assessed as very positive during training; as mentioned by the participants of this study, "sharing and interacting with the patients and their families teaches us about the human aspects of these diseases". This finding is similar to that obtained by Henriksen & Ringted (10), who created sessions during the course of a subject that included patients presenting their diseases to medical students; this experience showed how the students had a stronger learning from the academia, which was rich in experiential aspects and facilitated the relationship with patients in the future.

Also, and as part of the hidden curriculum, there is space for academic excellence in the daily work environment, which generates rivalries between students and that can hinder relations between them; as some residents refer in this work, academic excellence creates an environment of competitiveness. Haidet & Stein (11) suggest how sometimes hierarchies are set according to "scores" and that those who fail the correct answers end up being intimidated, leading to unpleasant feelings and the creation of stressful environments, far from what is known as medical professionalism.

This leads to consider that there are several sources for the hidden curriculum: one, from professors, which is valued by students consulted for this research as a positive aspect, since they are able to convey comprehensive knowledge, not only on academic matters but with a special style of physician behavior relevant for their professional development; another from the social environment of the group, which pushes towards eminently academic aspects that foster competitiveness and individuality (12) and which make students change their interest from ethical, social or familiar aspects to "academic excellence"; and finally, from patients, which makes the students want to improve both academically and personally. Studies conducted in Japan and the United Kingdom (13) show how the persistence of hierarchies and distant relationships between the medical contexts affects work performance and how the doctor-patient relationship is established.

The students acknowledged communicating bad news as one of the greatest ethical challenges. Graduate students of Pediatrics at Universidad de Chile were interviewed about these issues (14) and responded that they are rarely taught these communication skills and find it difficult to follow the example of a professor.

Regarding other ethical aspects of their professional practice, the students feel that there is a limited approach to resolving these dilemmas. In a study conducted with residents of 13 specialties (15), it was found that, for them, ethical issues are left aside and approaching them represents great difficulty. It is striking that in the study by Goold & Stern (16), the relationship with patients was the aspect that caused most concern, while giving bad news was considered less important; findings contrary to those obtained in this study, where students face a particular difficulty with giving bad news, but feel that, through the experience, they can learn about the interaction with patients and their families. This difference may

be generated because, in Neuropediatrics, chronic or involutive diseases are more common, implying greater exposure to these types of situations. This is also acknowledged by palliative care experts, who noted that in the undergraduate medical studies little is taught about these conditions and how to deal with them (16,17).

Although empathy is essential in any doctor-patient relationship, regardless of the conditions and diseases, the importance and need to integrate the academic aspects with this feeling is recognized, since treating neuropediatric patients is highly complex and emotionally charged. As Cutler *et al.* demonstrate in patients with psychiatric disorders, the need for empathy, generated by the medical and non-medical environment, is acknowledged in similar fields (18). These authors also consider that doctors find spiritual enrichment through cultural and complementary activities is essential, but different from those directly related to the medical field.

In this sense, Goldie *et al.*, in their study on undergraduate students of Medicine during their early years, found that molding obtained by observing the behavior of their instructors is key for their training as future professionals (19); the group of neuropediatrics students interviewed in this research had similar considerations: they think that observing the work performed by their professors teaches them about the content and the layout of their specialty.

These students, just like the residents of different specialties evaluated by Ratanawongsa *et al.* (20), admit that the hidden curriculum allows them to learn about ethical issues, but that it is necessary to make the learning of many related concepts that have to do with professional practice explicit.

What would be, then, the ideal model of teaching ethics and values in graduate programs of Medicine? Probably a balance between theoretical guidance on professionalism and ethics, alternated with the molding achieved directly in the practice environment that could lead to more effective learning on the acquisition of values for medical practice (21).

Conclusions

Learning through the hidden curriculum for graduate students in neuropediatrics is achieved through observation of professor attitudes, the relationship between peers and with patients and families. Once again, the need for professorial training for doctors who serve a double role is confirmed, so that the way of teaching medicine is carried out taking into account the integrity of the patient and the student. As mentioned by Pinilla:

> "A teacher is a guide and a support for each student as a citizen, whose life plans includes being an integral and competent professional [...]; therefore the social function of the university professor, along with his team of students, is to generate solutions to problems of a person in the position of the patient, a community or a society" (22, p275)

Through the hidden curriculum, neuropediatrics students learn skills to interact properly with their patients, both in scientific and social and ethical aspects.

The professor-student relationship is based on academic and welfare aspects; other features such as encouraging humanistic, artistic or cultural activities are little known.

The development of spaces for discussion of the different ethical issues inherent to the specialty, which should be led by experts who should act as guides toward an ethical and professional behavior in neuropediatrics, is required.

While this is evidence of the need for training in ethics and values for a group of medical students in a specific context, it is worth considering generalizing these actions at different levels and areas of training, because this topic is rarely treated and needs to be more visible for the sake of professional practice and patient care.

This paper is based on the graduation paper for the Master's degree in Education pursued by the author Angélica Uscátegui Daccarett (23).

Conflict of interests

Angelica Uscátegui is a professor of the Academic Unit of Neuropediatrícs at Universidad Nacional de Colombia.

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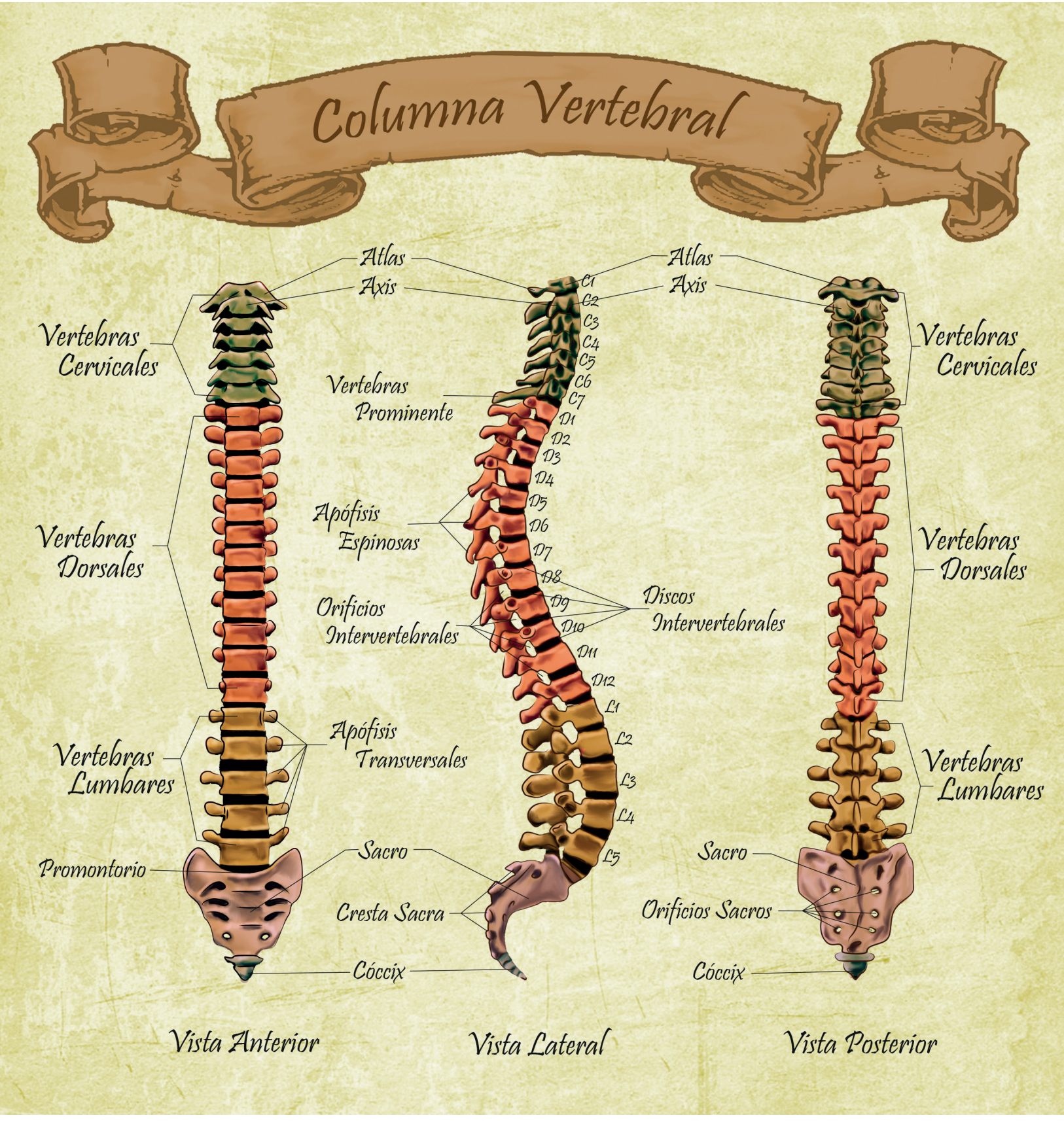

César Alexander Eslava Franco
"Mapas anatómicos"
Universidad Nacional de Colombia

ORIGINAL RESEARCH

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Clinical validation study of the SignCare Vital Signs Monitor of Fundación Cardiovascular de Colombia

Estudio de validación clínica del monitor de signos vitales SignCare de la Fundación Cardiovascular de Colombia

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| Abstract |

Introduction: In Colombia, due to the difficult access to health services and to geographic conditions, the implementation and innovation of telemedicine technological tools is a priority. Having a validated vital signs monitor (VSM) improves proper medical treatment and diagnosis.

Objective: To design and perform clinical trials for the SignCare VSM.

Materials and methods: A device for continuous monitoring of electrocardiography, respiration, oxygen saturation, temperature and noninvasive blood pressure (NIBP) was designed. This device was validated in a laboratory in order to ensure a robust prototype, close to the level of commercial medical devices. Clinical trials were performed through a cross-section study with 98 patients, whose vital signs were measured using the SignCare monitor and a commercial monitor. These two measurements were compared using Pearson's correlation coefficients.

Results: There were no statistically significant differences between the results obtained with the SignCare VSM and the commercial monitor. The highest correlations were found for the following items: heart rate by electrocardiogram (r=0.844), heart rate by oxymetry (r=0.821), body temperature (r=0.895), systolic blood pressure (r=0.780), and diastolic blood pressure (r=0.811).

Conclusions: The SignCare device is as reliable as the commercial monitor in the qualitative detection of morphologic alterations of electrocardiogram records, as well as in breathing, temperature, oxygen saturation and blood pressure parameters, which makes it recommendable for clinical use in adult population.

Keywords: Physiologic Monitoring; Vital Sign; Validation Studies (MeSH).

Rodríguez-Salazar LA, Gamboa-Delgado EM, Plata-Rangel S, Mantilla-Prada OA, Sarmiento-Caraballo E, Rincón-Riveros JD. Clinical validation study of the SignCare Vital Signs Monitor of Fundación Cardiovascular de Colombia. Rev. Fac. Med. 2016;64(3):459-63. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.49339.

| Resumen |

Introducción. Debido a las dificultades geográficas y de acceso a los servicios de salud en Colombia, la implementación e innovación con herramientas de telemedicina se convierte en un tema prioritario; contar con un monitor de signos vitales validado favorece el tratamiento médico oportuno.

Objetivos. Diseñar y realizar la validación clínica del monitor de signos vitales SignCare.

Materiales y métodos. Se diseñó un equipo para el monitoreo constante de las señales de electrocardiografía, respiración, saturación de oxígeno, temperatura y presión arterial no invasiva. El dispositivo fue validado en el laboratorio para asegurar un prototipo robusto a nivel de dispositivos médicos comerciales. La validación clínica se hizo mediante un estudio de corte transversal en 98 pacientes a los que se les realizaron mediciones con el monitor SignCare y con un monitor comercial. Se compararon estas dos mediciones mediante coeficientes de correlación de Pearson.

Resultados. No hubo diferencias estadísticamente significativas en cuanto a los resultados obtenidos con el monitor SignCare y con el monitor comercial. Las mayores correlaciones se presentaron en la frecuencia cardíaca por electrocardiograma (r=0.844), frecuencia cardíaca por oximetría (r=0.821), temperatura corporal (r=0.895), tensión arterial sistólica (r=0.780) y tensión arterial diastólica (0.811).

Conclusiones. El monitor SignCare es tan confiable como el monitor comercial para la detección cualitativa de alteraciones morfológicas del registro electrocardiográfico, lo que hace posible su recomendación para uso clínico en población adulta.

Palabras clave: Monitoreo fisiológico; Signos vitales; Estudios de validación (DeCS).

Rodríguez-Salazar LA, Gamboa-Delgado EM, Plata-Rangel S, Mantilla-Prada OA, Sarmiento-Caraballo E, Rincón-Riveros JD. [Estudio de validación clínica del monitor de signos vitales SignCare de la Fundación Cardiovascular de Colombia]. Rev. Fac. Med. 2016;64(3):459-63. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.49339.

Introduction

In Colombia, plenty of factors that affect patients, such as long distances, extended times for authorization of remissions and the lack of higher complexity referral centers, increase the need of technological tools for the first level of medical care to facilitate and support remote medical treatment through real-time communication with specialized staff, and monitoring of physiological and electrocardiographic changes that allow for an immediate remote compatibility with medical specialties. In order to create technological tools to address this issue, domestic companies must produce the necessary hardware and software for adjusting medical devices to the needs of the country and implementing real-time communication technologies to create a real continuous care network to treat a referred patient.

Vital signs monitors (VSM), also known as physiological parameter monitors, are electronic devices that measure and display biological information about patients under constant monitoring. They are often used with patients suffering from critical illnesses, where heart rate, electrocardiographic signal, arterial pressure and oxygen parameters, as well as temperature measurements provide essential diagnostic information that enables the medical staff to make decisions on the treatment to be used in each pathology (1,2).

Because of the importance of VSM in current health care services, it is necessary to perform a process of clinical validation of these devices to guarantee enough reliability and accuracy before establishing their daily use in a clinical context. Taking this into account, this study describes the clinical trials of the SignCare VSM, manufactured by Fundación Cardiovascular de Colombia (FCV), by means of comparing its measurements with a commercial device (Mindray PM-8000) and with the manual method of vital signs measurement, as suggested by Association for the Advancement of Medical Instrumentation (AAMI) (3,4).

Materials and procedures

SignCare VSM description

The SignCare monitor is an integrated system that allows recording physiological parameters such as heart rate, breathing, temperature, oxygen saturation and NIBP, and then displays the information on the integrated monitor screen. Additional equipment has data transmission systems that send physiological parameters data via Internet, allowing the use of information in real time through a web platform controlled by a central monitoring station.

The monitor includes rechargeable batteries that provide energy independence for at least three hours; additional equipment includes an adapter that allows charging the battery, thus ensuring continuous use. Portability features involve a user-centered design, and an easy and intuitive touch screen for handling. The hardware is FPGA-based (field programmable gate array) and uses an FDA-Approved Real-Time Operative System (uC-OSII). This device was validated in a laboratory in order to ensure a robust prototype, with the same level of quality as commercial monitors (3-5).

This device represents a tool for health care and communication improvement in the processes involving the referral of patients to higher complexity health centers, giving place to opportunities for future developments and applications according to the different needs of the country. The continuous monitoring and communication with the receiving health centers while they await for the patients will represent better life expectancies, particularly in cardiovascular, gynecological, obstetrical, respiratory, pediatric and trauma services, by speeding up the whole process and increasing control of the risk factors of patients.

Design of the study

A cross-sectional study was performed, following a validated protocol based on the recommendations by AAMI for monitoring equipment validation (3-5). The study protocol consisted of the following items:

Clinical assessment of the SignCare VSM

Various tests were performed to compare heart rate, breathing, oxygen saturation, temperature, NIBP measurements and the waveforms obtained through the SignCare VSM, against those obtained with Mindray PM-8000 VSM. The patients in this study were selected through a non-random sample of the population that attended the emergency service of the FCV. The sample size was calculated using Epidat 3.1, with a 95%CI, a base population from the metropolitan area of 1 000 000 approx., and a design effect of 1 (6,7). Based on the previous calculation, 98 subjects were included in the study, a sample size with sufficient statistical capacity to test differences in each of the clinical variables measured by both monitors (Table 1). Individuals with background of cardiovascular, mental or sensorial perception diseases, that could compromise the understanding of the study procedures, as well as pregnant, neonate and pediatric patients, were excluded.

The subjects were chosen during their stay in the emergency service of FCV, where tests were performed in a temperature-controlled room (20°C), in decubitus supine position.

Personal data variables of all participants such as age, sex, origin and comorbidities were taken into account. Each patient was monitored for approximately 30 minutes, obtaining three simultaneous measurements of physiological parameters through SignCare VSM and Mindray PM-8000 VSM. Two trained nursing staff members did the qualitative assessment of the morphology of the registered electrocardiography waves, providing visual evidence for each patient. For all physiological parameters, statistical evidence was used in order to establish the correlation degrees between both monitors.

Statistical analysis

The vital signs measurements collected from 98 patients using the SignCare VSM and a commercial monitor were analyzed. A general description of the variables of interest was done; for this purpose, continuous variables were described as averages with standard deviation (SD) and the variables category as absolute (n) and relative (%) frequencies. Also, the comparison of measurements obtained with the SignCare VSM and the commercial Mindray PM-8000 VSM was performed.

This study suggests a statistical hypothesis of equality between the results of both monitors to prove the effectiveness of the SignCare VSM, while having the commercial monitor as a reference. Comparisons with a p value lower than 0.05 were considered as statistically significant differences. Furthermore, Pearson correlation coefficients between measurements of both monitors were established according to variable distribution.

The data were transferred to digital files using Microsoft Office Excel. The database was cleaned and analyzed using Stata 12.1 (Stata Corporation) for results.

Table 1. Sample calculation for the clinical trial.

Variable	Standard deviation	Precision	Sample size
Heart rate	15.7	3	98
Respiratory rate	4.3	2	18
Temperature	1	0.5	16
Diastolic	25	5	98
Systolic	15	5	35

Source: Own elaboration based on the data obtained in the study.

Ethical considerations

This study was approved by the research ethics committee of FCV, under the principles established on the Helsinki Declaration and on the Resolution 8430 of 1993 by the Ministry of Health of Colombia. Since this study is classified as non-invasive, it constitutes a low risk research as stipulated by article 10 of the aforementioned resolution; therefore, there was no risk to the health of the subjects that took part in it. All participants entered the study after signing an informed consent where risks, benefits and confidentiality of information were expressed.

Results

Clinical assessment of the SignCare VSM

The average age of the 98 subjects was 51.08±19.75 and 50% of the patients were female. 89.8% did not declare any comorbidity, and the remaining 10.2% were divided into 10 types of comorbidities.

Some of the comorbidities registered were atrioventricular block (1.02%) and aortic valve dissection (1.02%). In the clinical study, three samples per patient were taken for each physiological parameter with both the SignCare VSM and the commercial VSM. When comparing the vital signs measurements obtained by both monitors, there were not statistically significant differences for most of them.

Statistically significant differences were only found for the following variables: respiratory rate (resp/min) in sample 1 (p=0.002); respiratory rate (resp/minute) in sample 3 (p=0.000); body temperature (°C) in samples 1 (p=0.000) and 3 (p=0.038), and systolic arterial pressure (mmHg) in sample 1 (p=0.046). However, these differences were not clinically relevant and do not represent a difference that may affect the patients' health since the difference margin is minimum. The main results are shown in Tables 2 and 3.

Table 2. Description of the general characteristics of the patients studied.

Characteristic	n	%
Sex		
Female	49	50.0
Male	49	50.0
Comorbidities		
None	88	89.80
Ventricular dilated cardiomyopathy, severe mitral regurgitation	1	1.02
Aortic valve dissection	1	1.02
Atrioventricular block, closed thoracotomy	1	1.02
Arterial hypertension	1	1.02
CX cardiac blockage	1	1.02
Dyspnea heart failure in apnea treatment	1	1.02
Myocardial infarction	1	1.02
Cardiac blockage	1	1.02
Valve surgery	1	1.02
Cardioverter	1	1.02
Education Level		
No registered	13	13.27
None	1	1.02
Elementary incomplete	2	2.04
Elementary complete	21	21.43
High-school incomplete	20	20.41
High-school complete	21	21.43
Technical studies	17	17.35
Undergraduate studies	3	3.06
Age (years) *	51.08	19.75

* Average and standard deviation of age in years. Source: Own elaboration based on the data obtained in the study.

After analyzing all measurements, high correlation levels among vital signs measured by both monitors can be observed. Higher correlations were found for heart rate obtained from ECG (r=0.844), heart rate obtained from SPO2 (r=0.821), body temperature (r=0.895), systolic blood pressure (r=0.780) and diastolic blood pressure (0.811). Moderate correlations were found for respiratory rate (r=0.498) and SPO2 (r=0.603). Figures 1-4 show correlation between both devices.

Table 3. Comparison of measurements obtained with the SignCare Vital Signs Monitor and the commercial monitor.

Variables	SignCare VSM		Commercial monitor		p
	Avg ±	SD	Avg ±	SD	
Heart Rate from ECG(beats/minute)					
Sample 1	73.11	15.37	73.69	15.49	0.537
Sample 2	72.60	12.63	73.57	17.29	0.313
Sample 3	72.53	12.03	73.21	14.47	0.447
Heart rate from SPO2(beats/minute)					
Sample 1	71.32	16.77	69.93	16.25	0.422
Sample 2	69.42	14.54	70.17	14.12	0.431
Sample 3	70.07	14.02	70.70	14.32	0.461
Respiratory rate (resp/minute)					
Sample 1	15.44	11.25	18.64	5.38	0.002
Sample 2	16.68	13.64	18.70	6.72	0.171
Sample 3	14.97	10.66	18.80	5.60	0.000
SPO2(%)					
Sample 1	94.17	10.94	94.65	13.88	0.677
Sample 2	95.47	2.52	95.52	10.01	0.966
Sample 3	95.58	2.47	95.40	10.05	0.854
Body temperature (°C)					
Sample 1	33.61	1.66	33.95	1.57	0.000
Sample 2	34.58	1.71	34.69	1.51	0.173
Sample 3	34.87	1.19	35.00	1.15	0.038
Systolic blood pressure (mmHg)					
Sample 1	129.18	17.75	124.70	24.83	0.046
Sample 2	126.92	19.48	125.10	18.77	0.157
Sample 3	124.91	17.64	122.26	24.37	0.121
Diastolic blood pressure (mmHg)					
Sample 1	75.71	10.94	76.25	13.81	0.619
Sample 2	74.73	10.80	74.82	11.67	0.896
Sample 3	74.20	11.54	72.74	12.40	0.089

SD: Standard deviation; p: p value determined by Student's t-test. Source: Own elaboration based on the data obtained in the study.

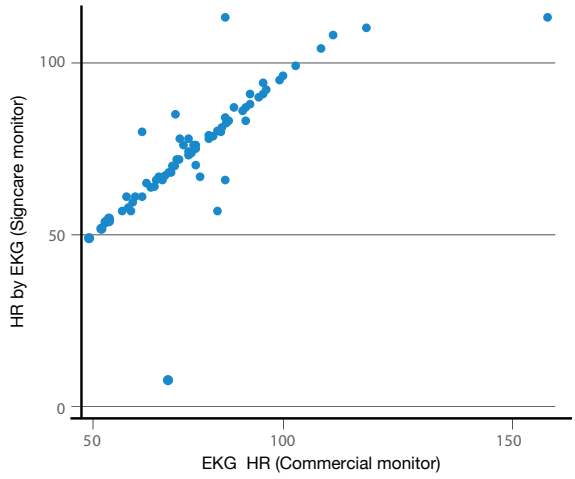

Figure 1. Correlation of heart rate measurements obtained from ECG between the two vital signs monitors. Source: Own elaboration based on the data obtained in the study.

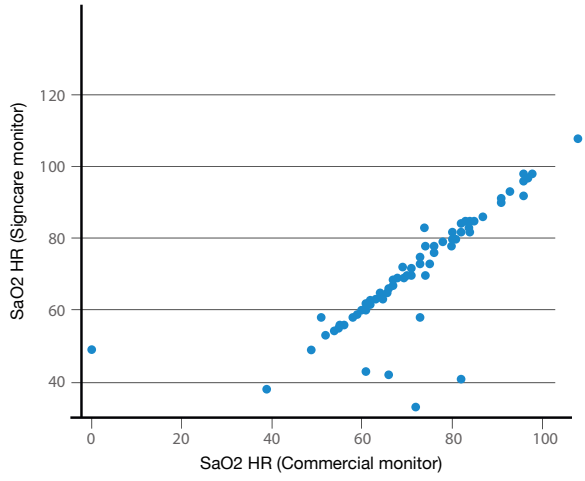

Figure 2. Correlation of heart rate measurements obtained from SPO2 between the two vital signs monitors. Source: Own elaboration based on the data obtained in the study.

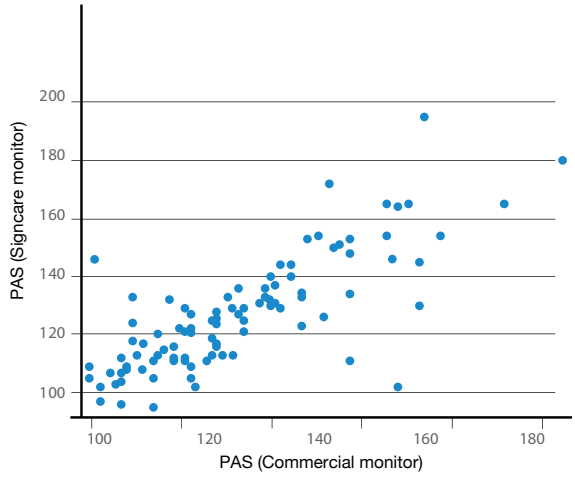

Figure 3. Comparison of systolic blood pressure between the two vital signs monitors. Source: Own elaboration based on the data obtained in the study.

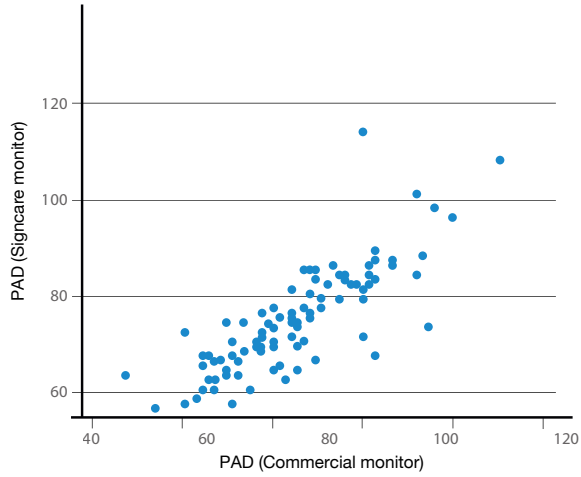

Figure 4. Comparison of diastolic blood pressure between the two vital signs monitors. Source: Own elaboration based on the data obtained in the study.

Discussion

This paper shows that the SignCare VSM reached high degrees of correlation with vital signs values for heart rate, SPO2, temperature, NIBP, and respiratory frequency obtained through the Mindray PM-8000 device. The analysis conducted using the Student's t-test allowed confirming that the SignCare VSM is as reliable as the Mindray PM-8000 VSM for the qualitative detection of morphologic alterations in electrocardiographic records and the physiological parameters of breathing, temperature, oxygen saturation and NIBP.

Although some samples of respiratory rate, body temperature and systolic blood pressure had a low statistical level of correlation, it does not represent a clinically significant margin, since differences are minimal. Doing a quantitative assessment of the electrocardiographic parameters was not possible since these devices cannot print nor store biological signals. Because of this, two trained evaluators, using photos and videos, registered in a form the presence or absence of alterations in the morphology of the p wave, QRS complex, ST segment and T wave in electrocardiography measurements of both monitors. In conclusion, it is considered that the SignCare VSM fulfilled the validation criteria issued by AAMI, which makes possible its recommendation for clinical use in adult population.

Conflict of interests

None stated by the authors.

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Acknowledgements

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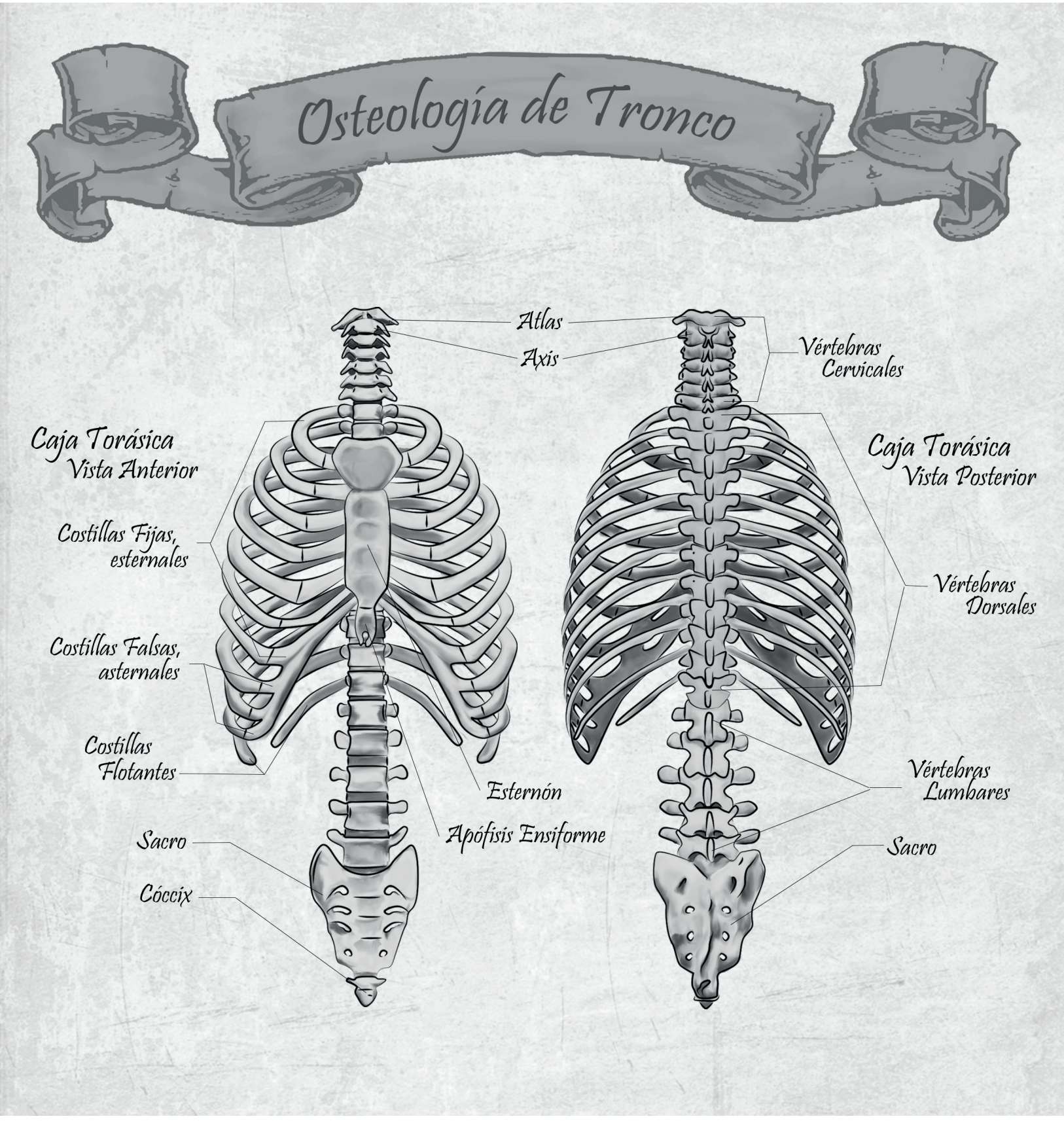

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"Mapas anatómicos"
Universidad Nacional de Colombia

ORIGINAL RESEARCH

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Effects of high-intensity interval training on the anthropometric profile of overweight and obese adult women

Efectos del entrenamiento físico intervalado de alta intensidad sobre el perfil antropométrico de mujeres adultas con sobrepeso u obesidad

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| Abstract |

Introduction: Sedentary lifestyle, overweight and obesity in adult women have high prevalence.

Objective: To determine the effects of a high intensity interval training program on the anthropometric profile of overweight or obese women.

Materials and methods: 24 adult women, including 16 with overweight and 8 with obesity, between 26 and 49 years of age, were selected to participate in a two month high intensity training program (three sessions per week). Weight, height, BMI, muscle mass percentage, and fat mass and visceral fat percentages were assessed.

Results: The adherent group (≥75% assistance) was composed by 16 participants, while the non-adherent group (assistance <75%), by 8 participants. No significant differences were found among both groups previous to and after the intervention (p≥0.05).The non-adherent group did not show any significant change, while the adherent group improved (p<0.05) their variables of weight (p<0.001), BMI (p<0.001), fat mass percentage (p<0.001), muscle mass percentage (p<0.001) and visceral fat percentage (p=0.020) after the intervention.

Conclusions: The training program improved the anthropometric profile of the participants without requiring specialized equipment or involving high costs, thus, this procedure is recommended for the treatment of malnutrition by excess in this type of population.

Keywords: Physical Exercise; Overweight; Obesity (MeSH).

| Resumen |

Introducción. Existe una alta prevalencia de sedentarismo, sobrepeso y obesidad en mujeres adultas.

Objetivo. Determinar los efectos de un programa de entrenamiento intervalado de alta intensidad sobre el perfil antropométrico de mujeres con sobrepeso u obesidad.

Materiales y métodos. 24 mujeres adultas (16 con sobrepeso y 8 con obesidad) entre 26 y 49 años fueron reclutadas para participar en un programa de entrenamiento de alta intensidad durante dos meses (tres sesiones/semana). Se evaluó peso, talla, IMC, porcentaje de masa muscular, porcentaje de masa grasa y porcentaje de grasa visceral.

Resultados. El grupo adherente (asistencia ≥75%) quedó compuesto por 16 participantes y el grupo no adherente (asistencia <75%) por ocho participantes. No existieron diferencias significativas pre y post intervención entre ambos grupos (p≥0.05). El grupo no adherente no presentó cambios importantes mientras que el grupo adherente mejoró (p<0.05) las variables peso (p<0.001), IMC (p<0.001), porcentaje de masa grasa (p<0.001), porcentaje de masa muscular (p<0.001) y porcentaje de grasa visceral (p=0.020).

Conclusiones. El programa de entrenamiento mejoró el perfil antropométrico de las participantes sin requerir implementos ni costos elevados para su desarrollo, por lo que es un procedimiento recomendable para el tratamiento de la malnutrición por exceso.

Palabras clave: Ejercicio físico; Sobrepeso; Obesidad (DeCS).

Rivera-Torres I, Delgado-Floody P. Effects of high-intensity interval training on the anthropometric profile of overweight and obese adult women. Rev. Fac. Med. 2016;64(3):465-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.55104.

Rivera-Torres I, Delgado-Floody P. [Efectos del entrenamiento físico intervalado de alta intensidad sobre el perfil antropométrico de mujeres adultas con sobrepeso u obesidad]. Rev. Fac. Med. 2016;64(3):465-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.55104.

Introduction

Chile has evolved and its economy, technology and culture have progressed in such a way that, in recent decades, it has positioned itself as a developing country. However, there is an alarming increase of chronic non-communicable diseases: 93% of women are sedentary and 64% are overweight or obese (1); both pathologies are associated with the development of insulin resistance, type 2 diabetes and cardiovascular disease (2-5). The traditional pharmacology has not provided an effective response to battle obesity, instead, physical activity has proven to be one of the most effective solutions to counteract the effects associated with this condition (6). This benefit grows if the activity is performed regularly and intensity increases (7).

Obesity is defined as an excess of body fat or adipose tissue, and is produced by the increase in energy consumption and the reduction in caloric expenditure (8). This condition generates a series of processes that develop resistance to leptin, resulting in a vicious cycle of weight gain induced by genetic and environmental factors (9).

Physical exercise has been proved to be one of the most effective ways to prevent and treat modern chronic diseases (10). When training is aerobic, although beneficial health effects are generated, high volumes of exercise are required to produce significant changes in the body; taking into account that the lack of physical activity of the population is mainly caused by lack of time (11), considering methods that produce more sudden and profound effects is necessary. Low-volume, high-intensity interval training (HIIT) should be considered as a method for battling the negative effects of chronic diseases associated with lifestyle (12,13), as there is evidence that the accumulation of a variety of HIIT is effective for improving cardiopulmonary fitness, VO2max (14), metabolic capacity and insulin sensitivity (15,16).

The purpose of this study was to determine the effects of a high-intensity interval training program on the anthropometric profile of overweight or obese women.

Materials and methods

Participants

24 adult women, aged 26 to 49, voluntarily participated in this study and went through a HIIT program for two months, in the facilities of Universidad Mayor, Temuco Campus; 16 participants were overweight and 8, obese. The invitation was made through voluntary and free registration in three exercise sessions per week (24 sessions in total).

The study design was quasi-experimental and two study groups were created according to the percentage of assistance to the program by the participants: the adherent group (AG), with attendance to exercise sessions ≥75% (minimum 18 sessions, n=16, age: 38.4±13), and the non-adherent group (NAG), with assistance <75% (less than 18 sessions, n=8, age: 32.2±6). Each participant acted as self-supervisor after comparing the pre and post intervention.

The protocols coincided with the Declaration of Helsinki of 2013; the study was approved by the School of Nutrition of Universidad Mayor and each participant signed an informed consent to participate in the research.

Inclusion criteria included female subjects, aged 18 to 60 and at least three of the following factors: 1) high percentage of total fat >21%; 2) BMI >25, 3) sedentary lifestyle with the aim of performing <50 minutes per week of physical activity, and 4) percentage of muscle mass decreased by <40%.

Exclusion criteria considered the presence of any history of osteoarticular or ischemic disease, arrhythmias, tachycardias or chronic obstructive pulmonary disease that prevented doing HIIT exercises.

Procedures

Weight, muscle mass percentage (% MM), body fat percentage (% BFP) and visceral fat were determined through a double bioelectrical impedance assessment —using an bioelectrical impedance meter OMROM HBF-510LA—, barefoot, in light clothes and without metal objects. Height was determined with the aid of a precision height rod —Health o Meter®, USA—, graduated at 0.1mm; to calculate body mass index (BMI), the Quételet formula was used. Overweight was classified as 25.0-29.9 kg/m^2, and obesity as ≥30 kg/m^2.

Design of the intervention program

An interval exercise program with the 1x2x3 method (17) was designed; three sets per exercise were run for 60 seconds, each with an intensity that induced muscle failure at the end of this period and two minute breaks between sets. This methodology is similar to other studies (18,19).

The exercises were focused on abdominal muscles and knee and hip extensors, and they were performed with multi - joint movement chains (Table 1). The progression of the exercises was done to break the adaptability of the study subjects to the accumulation of stimuli.

Table 1. Exercise protocol used in the intervention.

	Characteristic							
Intensity	Muscle failure after a minute of exercise.							
Progression	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
	Half squat	Deep squat	Deep squat with side kick	Deep squat with jump side kick jump	Deep squat with side kick jump Crunch exercise	Deep squat with side kick jump Crunch exercise Cross-legged crunch	Deep squat with side kick jump Crunch exercise Cross-legged crunch Thrust	Deep squat with side kick jump Crunch exercise Cross-legged crunch Thrust
Progression	9 minutes	9 minutes	9 minutes	18 minutes	18 minutes	30 minutes	40 minutes	40 minutes
Method	One-minute exercise – two-minute passive rest to reach recovery pulse - three repetitions three times a week, on alternate days.							
Materials	No equipment implementation is required							

Source: Own elaboration based on the data obtained in the study.

Statistical analysis

Data are presented as mean ± standard deviation. All variables showed normal behavior (p≥0.05) and were measured through Shapiro Wilk test. A Student's t-test was used to evaluate pre- and post-intervention differences and for comparison between groups and independent groups. All analyzes were performed using SPSS version 22.0 and the confidence level was 95% (p<0.05).

Results

The NAG (participation <18 sessions) did not show significant changes after the intervention, whereas the AG (participation ≥18 session) presented significant changes with HIIT intervention in the following variables: weight (p<0.001), BMI (p<0.001), BFP% (p<0.001),% MM (p<0.001) and visceral fat% (p=0.020) (Table 2).

Table 2. Features of pre and post high-intensity interval training intervention.

Variables	Test	Non-adherent group (≥18 sessions) (n=8)	Adherent group (<18 sessions) (n=16)	Comparison between groups p
Weight	Pre	68.40±11.72	74.70±13.28	0.268
	Post	68.08±11.14	72.29±12.61	0.432
	V %	-0.48	-3.61	
	p value	0.376	**<0.001**	
BMI	Pre	28.11±4.69	29.63±4.60	0.457
	Post	27.97±4.46	28.66±4.36	0.719
	V %	-0.51	-3.27	
	p value	0.337	**<0.001**	
% Body fat	Pre	42.36±5.72	43.86±5.79	0.556
	Post	42.06±5.70	41.66±5.86	0.873
	V%	-0.71	-5.02	
	p value	0.140	**<0.001**	
% MM	Pre	24.11±1.73	24.26±2.40	0.877
	Post	24.20±1.89	25.26±2.49	0.304
	V%	0.36	4.12	
	p value	0.630	**<0.001**	
% Visceral Fat	Pre	8.25±2.38	7.75±2.35	0.629
	Post	8.25±2.40	7.44±2.22	0.417
	V%	0.00	-4.00	
	p value	0.999	0.020	

% MM: muscle mass percentage; BMI: body mass index; V%: percentage change between pre and post intervention. Source: Own elaboration based on the data obtained in the study.

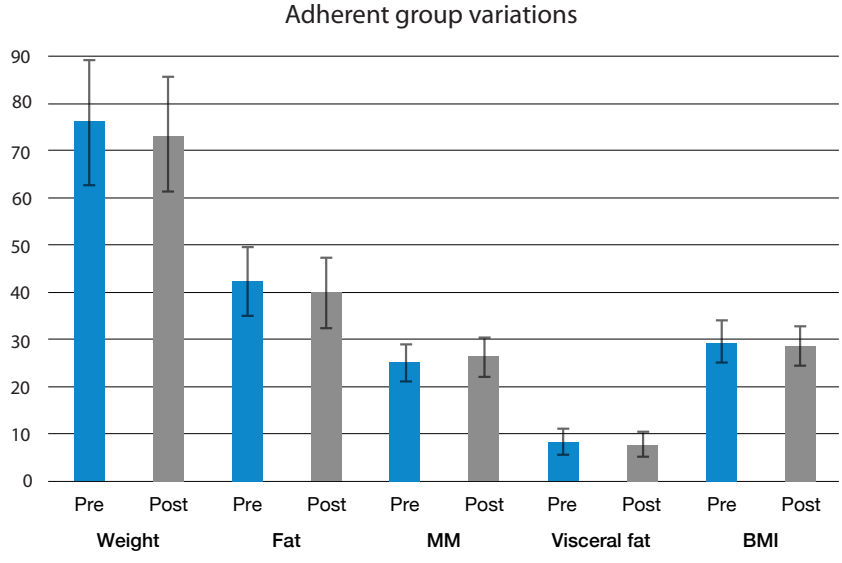

Figure 1. Significant variations - adherent group. Source: Own elaboration based on the data obtained in the study.

Discussion

The purpose of this study was to determine the effects of a of high-intensity interval training program on the anthropometric profile of 8 overweight women and 16 obese women. The results indicated that the implementation of this program or training method, without the use of specialized equipment, allowed achieving changes in body composition, especially in reducing the fat mass of the adherent group.

Overnutrition was associated with the development of insulin resistance and risk factors for cardiovascular disease (20). In this research, weight and BMI reported changes after eight weeks of HIIT ($p<0.001$), results that differed from other studies where similar methodologies were applied but failed to achieve significant changes in nutritional status (21,22); higher weight losses in subjects with obesity and morbid obesity were reported only in cases in which patients also received counseling and nutrition education (23). In addition, fat mass percentage significantly decreased by 5.02% in the adherent group ($p<0.001$).

The research conducted by Zhang *et al.* (24) implemented a 12-week training program with Asian women that included high-intensity sprint and showed a decrease in the percentage of body fat, thus making HIIT the most effective method to control visceral and subcutaneous fat. The study by Kordi *et al.* (25), with sedentary women, proved that high-intensity interval training is an appropriate method for reducing body fat and improving anthropometric indices; likewise, Mancilla *et al.* (26) implemented this method on subjects with impaired glucose and excess weight, achieving a body fat reduction of 4.2kg. Postmenopausal women showed similar results through aerobic and overload exercise (27) and brisk walking (28).

In this study, muscle mass increased by 1.25%, similar to other groups of study with pre-diabetic predisposed subjects (29), where resistance exercises were applied until muscle failure for three months. A group of elder Japanese women proved that when obesity is combined with muscle weakness, there is a greater risk of developing mobility limitation than with only obesity (30), which is why it must be a priority in the treatment of women with this condition if quality of life is intended to improve.

In the research by Zapata-Lamana *et al.* (31), performed with adult women for three months, a physical exercise program, similar to the reported in this study, was implemented; improvements in cardiovascular health were observed when blood lipids and cholesterol were significantly altered.

This research allowed producing significant changes in the variables studied without requiring a high duration per session, which confirmed that this type of HIIT methodologies are time-efficient, improve muscle function and produce skeletal muscle adaptations that result in an increased fat and glucose oxidation (32-35); this is evident in the increase of % MM and the decrease of BFP% of the studied overweight or obese women.

It is important to incorporate, for future research, psychosocial variables to assess, from a holistic perspective the effect of physical exercise as the main limitation of this study is that only anthropometric variables were considered.

Conclusions

The intervention conducted in this study improved the anthropometric profile of women with overnutrition subjected to intervention and that accomplished adherence to the program (>18 sessions); similarly, the patients significantly reduced their weight and body fat ($p<0.001$). It is noteworthy that this program managed to meet the target without requiring additional equipment.

The evaluation of plasma levels, aerobic capacity and blood pressure are planned for future research in order to further complement the benefits of this program.

Conflicts of interest

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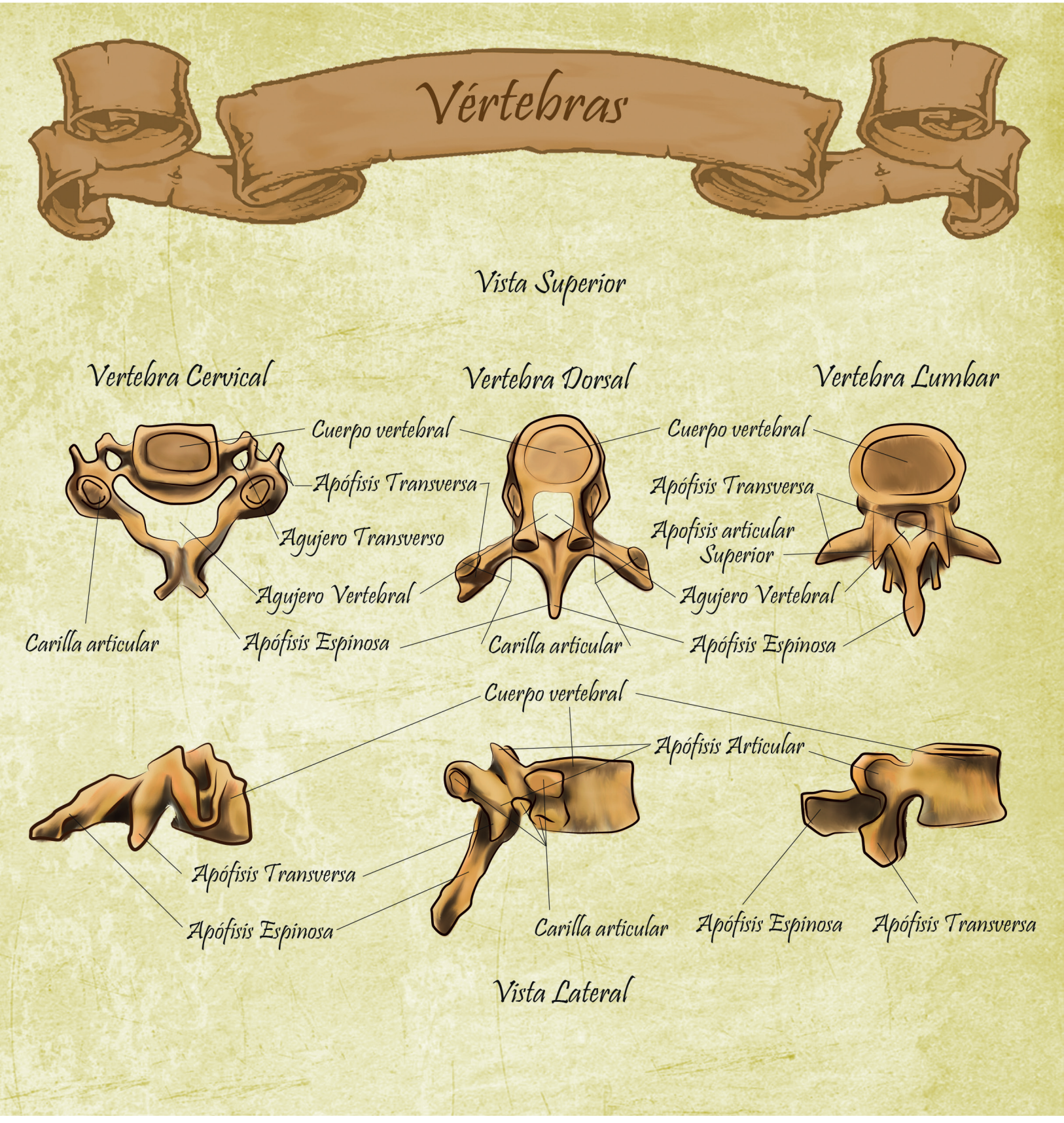
Vértebras



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"Mapas anatómicos"
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ORIGINAL RESEARCH

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Use of the ROSE risk score for predicting mortality and cardiovascular events in adult patients at 7 and 30 days of syncope

Aplicación del puntaje de riesgo de la escala ROSE para predicción de mortalidad y desenlaces cardiovasculares mayores en pacientes adultos con síncope a 7 y 30 días

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| Abstract |

Introduction: The use of the ROSE risk score after syncope provides the possibility of identifying patients at risk of death or other important adverse events after 30 days of admission to the emergency department.

Objective: To evaluate the performance of ROSE score in terms of mortality prediction and major adverse events at 7 and 30 days in adult patients with syncope admitted to the emergency department.

Materials and methods: A prospective cohort study in patients with syncope who were admitted to the emergency room was performed. An operational analysis of the predictive ability for detection of possible complications was done by calculating sensitivity, specificity, positive and negative predictive values and ROC curves.

Results: 60 patients were evaluated. An area under the curve for prediction of mortality or major outcome at 7 and 30 days of 0.62 (95%CI: 0.45-0.78) was obtained, with sensitivity of 60%, specificity of 18.18%, PPV of 6.25% and NPV of 83%.

Conclusion: ROSE score showed low sensitivity for predicting mortality or serious outcomes at 7 and 30 days. Its high negative predictive value makes it a useful prognostic tool in low risk patients.

Keywords: Syncope; Cardiovascular; Prognosis (MeSH).

Paz-Meneses MA, Mora-Pabón G. Use of the ROSE risk score for predicting mortality and cardiovascular events in adult patients at 7 and 30 days of syncope. Rev. Fac. Med. 2016;64(3):471-5. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.53015.

| Resumen |

Introducción. El puntaje de riesgo ROSE para síncope tiene la capacidad de identificar pacientes en riesgo de presentar mortalidad o cualquier otro desenlace adverso mayor a los 30 días de su ingreso a urgencias.

Objetivo. Evaluar el rendimiento pronóstico del puntaje para predicción de mortalidad o desenlaces adversos mayores a 7 y 30 días en pacientes adultos con síncope en el servicio de urgencias.

Materiales y métodos. Estudio de cohorte prospectivo en pacientes con síncope admitidos en urgencias. Se realizó un análisis operativo de la capacidad predictiva de detección de riesgo de complicaciones calculando sensibilidad, especificidad, valor predictivo positivo (VPP) y negativo (VPN) y curvas ROC.

Resultados. Se evaluaron 60 pacientes en los que se obtuvo un área bajo la curva para predicción de mortalidad o desenlaces mayores, tanto a los 7 como a los 30 días, de 0.62 (IC95%: 0.45-0.78), con sensibilidad de 60%, especificidad de 18.18%, VPP de 6.25% y VPN de 83%.

Conclusión. El puntaje ROSE mostró una sensibilidad baja para predicción de mortalidad o desenlaces serios mayores a 7 y 30 días. Su alto valor predictivo negativo la hace una herramienta de pronóstico con utilidad en los pacientes de bajo riesgo.

Palabras clave: Síncope; Cardiovascular; Pronóstico (DeCS).

Paz-Meneses MA, Mora-Pabón G. [Aplicación del puntaje de riesgo de la escala ROSE para predicción de mortalidad y desenlaces cardiovasculares mayores en pacientes adultos con síncope a 7 y 30 días]. Rev. Fac. Med. 2016;64(3):471-5. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.53015.

Introduction

Syncope is a major syndromic complex which supposes great challenge for diagnosis and therapy to health personnel in charge of patient care. The importance of the initial study, and short and

medium term risk assessment, lies in the difference between the relatively benign causes represented by vasovagal episodes and potentially fatal causes in a short period of time, such as conditions secondary to cardiovascular disease (1).

The economic burden, both direct and indirect, is highly relevant; this cost is primarily represented by intra-hospital expenses generated by the decision to hospitalize a patient with syncope, decision often unnecessarily taken by fear or lack of knowledge from health personnel about the life-threatening event. A new study finds that in a university hospital, 100% of patients admitted to the emergency room due to syncope were hospitalized (2); however, if early and medium term risk identification tools are used, lower costs can be achieved through outpatient management (3).

Literature shows that multiple works have been developed on risk stratification scores, most of them obtained from the emergency department for short-term prognosis. Some of them, like the San Francisco Syncope Rule (SFSR), the Boston Syncope Rule, Oesil, Steps and Egsys, have shown deficiencies mainly when attempting external validation, exposing different results (4,5). This study evaluated the ROSE risk score diagnostic performance in a cohort of patients admitted for syncope to the emergency room.

Materials and methods

All patients older than 18, who attended the emergency rooms of Fundación Hospital San Carlos and Fundación Santafé de Bogotá due to syncope, between August 2013 and February 2014, were included. Syncope is defined as a transient altered state of consciousness and postural tone with spontaneous recovery without neurological deficit (except for amnesia after the event).

We excluded patients with loss or alteration of consciousness that was not secondary to transient cerebral hypoperfusion (consumption of alcohol or hypoglycemia), with head trauma presented before the syncopal episode, with a known history of epilepsy —typical seizure episode or prolonged postictal seen or described by witnesses— and persistent neurological deficit suggestive of acute vascular brain attack or transient cerebral ischemia.

The study was approved by the ethics and research committees of the two institutions involved and patients signed an informed consent to participate. Follow-up was conducted through the review of medical records, if the patient was hospitalized during the follow-up period or by telephone, if the patient had been discharged. A descriptive analysis of demographic characteristics, data specific to the syncopal event, history, physical examination and paraclinical exams requested at admission was made.

The following were considered as adverse outcomes: death, acute myocardial infarction, need for percutaneous or surgical coronary revascularization, severe aortic stenosis, aortic dissection, cardiac tamponade, pulmonary embolism, dilated cardiomyopathy with a left ventricular rejection fraction of <35%, diagnosis of major bradyarrhythmias and electrotherapy —pacemaker implant, pauses longer than three seconds, 2:1 AV Block, Type II Mobitz AV block, complete AV block, bradycardia under 30 bpm, alternating bundle branch block, pacemaker malfunction related to capture fault—, diagnosis of tachyarrhythmia —ventricular or sustained supraventricular tachyarrhythmia—, defibrillator implant, cardiac resynchronization therapy device implant, malfunction of cardioverter-defibrillator or cardiac resynchronization therapy device due to inadequate treatment of sustained ventricular arrhythmias, significant bleeding —need for transfusions, endoscopy requiring endoscopic treatment due to bleeding or need for surgical intervention due to bleeding—, lesions after the syncopal event that could affect life —head trauma, spinal fracture or long bones— and emergency readmission.

The description of all the variables that make up the ROSE score was made for each patient: abnormality of electrocardiogram (presence of pathological Q waves, except for Lead III), presence or absence of anemia (HB ≤9 g/dl), bradycardia (heart frequency ≤50 lpm), abnormal rectal examination when gastrointestinal bleeding was suspected, chest pain with syncope, abnormal brain natriuretic peptide (BNP) (≥300 pg/ml) and oxygen saturation abnormal to the environment (<94%).

All causes and major cardiovascular adverse events were considered as primary outcomes, while events such as mortality and independent major adverse events were considered as secondary outcomes.

A univariate analysis was conducted according to the nature of the variables: qualitative variables are presented with absolute numbers and proportions, while quantitative variables are presented with measures of central tendency (average) and statistical dispersion (standard deviation). A Kolmogorov–Smirnov test was performed to define the statistical tests that would be used for bivariate analysis and whether quantitative variables followed a normal distribution. For the prediction of the primary outcome at 7 and 30 days, the operating characteristics of the test were evaluated, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Data were analyzed through the SPSS V19 program.

Results

During the August 2013 - February 2014 period, 60 patients were selected. The average age was 66.47±20.3 and 56.7% (n=34) of the population were females. Demographic characteristics are shown in Table 1.

Table 1. Demographic characteristics of the study population.

Characteristic		n (%)
Age ($\bar{x}$, σ)		66.4 (20.3)
Female		34 (56.7)
Race	Mestizo	51 (85.0)
	Caucasian	7 (11.7)
	Indigenous	2 (3.3)
Weight ($\bar{x}$, σ)		60.4 (10.2)
Size ($\bar{x}$, σ)		1.6 (0.08)
BMI		24.7 (3.7)

$\bar{x}$: average; σ: standard deviation; BMI: body mass index.

Source: Own elaboration based on the data obtained in the study.

In this population, 31.7% (n=19) had previous syncopal events; of these, 42% (n=8) registered a single syncopal event in the last six months, 15.8% (n=3) two episodes and 36.9% (n=7) three or more episodes. Other frequent antecedents were previous heart disease (25%) and heart failure diagnosis (21.7%) (Table 2).

The characteristics of the syncope episode commonly showed prodromal symptoms (51.7%) and dyspnea (36.7%). The average time elapsed between the time of syncope and consultation to the emergency department was three hours (RIQ=1.87-16.25). The average hospital stay for the study of syncope and management of complications was 8.9 days (0.5 to 60) (Table 3).

Table 2. Medical history of the study population.

Medical history	n (%)
Previous diagnosis of heart disease	15 (25.0)
Ischemic cardiopathology	9 (15.0)
Valvular heart disease	3 (5.0)
Dilated cardiomyopathy	5 (8.3)
Congenital heart disease	1 (1.7)
Diagnosis or clinical evidence of heart failure	13 (21.7)
Diagnosis or clinical evidence of peripheral arterial disease	5 (8.3)
Diagnosis or clinical evidence of chronic kidney disease	9 (15.0)
Previous diagnosis of stroke	3 (5.0)
Arrhythmias	4 (6.7)
Pacemaker	1 (1.7)
Implantable cardioverter defibrillator	1 (1.7)

Source: Own elaboration based on the data obtained in the study.

Table 3. Characteristics of the syncope episode of the study population.

Syncope characteristics	n (%)
Dyspnea	22 (36.7)
Dehydration	1 (1.7)
Gastrointestinal bleeding	1 (1.7)
Chest pain	25 (41.7)
Syncope during exertion	1 (1.7)
Syncope in supine position	7 (11.7)
Syncope with high temperature	3 (5.0)
Post-trauma unconsciousness	17 (28.3)
Prodromal symptoms	31 (51.7)
Palpitations	8 (13.3)
Blurry vision	16 (26.7)
Diaphoresis	19 (31.7)
Nausea	17 (28.3)
Piloerection	7 (11.7)

Source: Own elaboration based on the data obtained in the study.

The physical exam at admission found mainly: systolic blood pressure of 125.1±23.3 mmHg, diastolic blood pressure of 72.5±13.7 mmHg, heart rate of 68.5±17.7 bpm, respiratory rate of 19.6±9.5 rpm and oxygen saturation of 90.05±12.4%. Electrocardiogram at admission found alterations in 76.7% (n=46).

The main abnormal electrocardiographic findings were: non-specific changes in ST-T (54.3%), axis deviation (34.8%), sinus bradycardia (32.6%), left ventricular hypertrophy (30%), intraventricular conduction block (26%) and atrioventricular block (15%). 10.9% of patients had a pre-excitation pattern; the corrected mean of the QT interval was 412ms (normal). Within laboratory data taken on admission to the emergency unit, the obtained values of the variables that are part of the ROSE risk score were taken into account. 40% of the study population (n=24) showed values greater than or equal to BNP 300 pg/ml (abnormal) with a median of 524.5 pg/ml (225.75-1727). Regarding hemoglobin, the average was 13.7 g/dl.

The incidence of the outcome at 7 and 30 days of follow up was 40% (n=24) and 8.3% (n=8), respectively (Table 4). 80% (n=40) of patients had a high risk score at admission, and 31.2% of them had an adverse outcome. All patients with a composite outcome between at 7 and 30 days already had such outcome before 7 days had passed. The association evaluated with a Pearson's chi-squared test was 1.522 with p=0.217.

Table 4. Outcomes at 7 and 30 days of follow-up.

Outcomes	7 days n (%)	30 days n (%)
Death	-	2 (3.3)
AMI	8 (13.3)	3 (5.0)
Arrhythmias	10 (16.7)	2 (3.3)
FV	3 (5.0)	4 (6.7)
TV	2 (3.3)	2 (3.3)
Ventricular pause	1 (1.7)	-
Ventricular pause	3 (5.0)	-
Asystole	3 (5.0)	-
Pulmonary embolism	-	1 (1.7)
Stroke	1 (1.7)	-
Intracranial hemorrhage	1 (1.7)	-
Significant bleeding	3 (5.0)	-
Transfusion	3 (5.0)	
Re-admission	-	1 (1.7)
Sepsis	1 (1.7)	-
CPR	-	2 (3.3)
Percutaneous coronary intervention	4 (6.7)	-
Pacemaker	5 (8.3)	2 (3.3)
CDI	2 (3.3)	2 (3.3)
Surgery of abdominal aortic aneurysm	-	1 (1.7)
Coronary artery bypass graft	-	1 (1.7)
Another cardiac surgery	-	1 (1.7)
Vasopressor	4 (6.7)	1 (1.7)
Antiarrhythmic	6 (10.0)	3 (5.0)
ICU	19 (31.7)	1 (1.7)
Ischemia	10 (16.7)	2 (3.3)
Bradycardia	6 (10.0)	-
Sinus pauses	1 (1.7)	-
Mobitz II	1 (1.7)	-
Third degree AV block	2 (3.3)	-
Paroxysmal (SVT)	4 (6.7)	-
TV	2 (3.3)	1 (1.7)

Source: Own elaboration based on the data obtained in the study.

Within components of ROSE risk score, 2 (3.3%) had fecal occult blood, 2 (3.3%) anemia (Hb≤9 g/dl), 24 chest pain (40%), 7 (11.7%) Q waves in EGG, 24 (40.7%) BNP>300 pg/mL, 15 (25%) bradycardia (<50lpm), and 39 (65%) SaO2<94%.

There was no loss of follow-up at 7 or 30 days. For prediction of primary outcome —major, serious and death—, the ROSE risk score showed sensitivity, specificity, PPV and NPV of 60%,

18.18%, 6.25% and 83.33% respectively. The area under the ROC curve was 0.62 (95%CI: 0.45 to 0.78) (Figure 1 and 2).

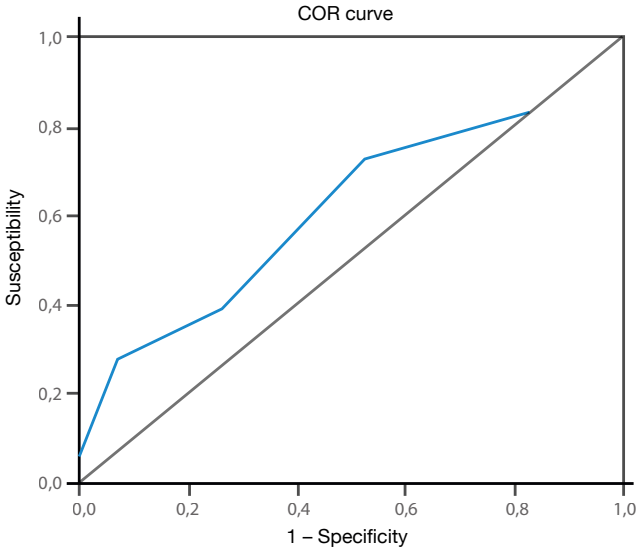

Figure 1. Curve of operating characteristic of the receiver of the ROSE scale for composite outcome at 7 days. Source: Own elaboration based on the data obtained in the study.

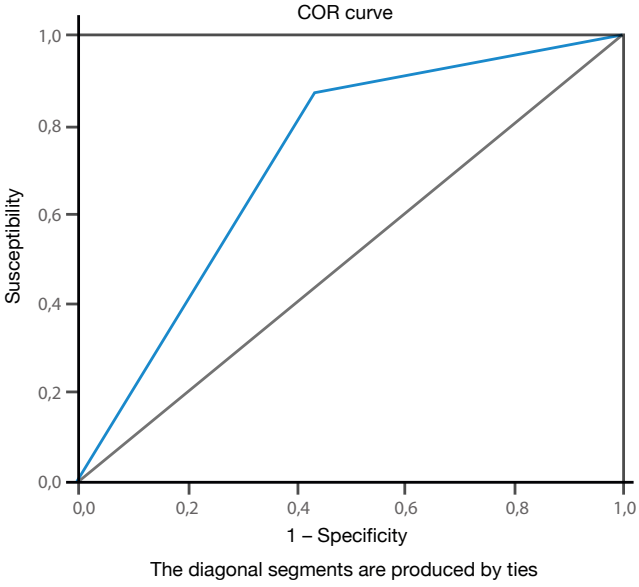

Figure 2. Curve of operating characteristic of the receiver of the ROSE scale for composite outcome at 30 days. Source: Own elaboration based on the data obtained in the study.

Discussion

The main finding of this study is that the ROSE risk score did not have adequate performance for prognosis in this Colombian cohort to find sensitivity, specificity, and low VPP for mortality and major events.

When comparing populations with syncope in this study with those of the original study by Reed *et al.* (6), it is possible to see that, in both, the average age was 65 and that patients had a higher prevalence of cardiovascular comorbidities and similar risks of greater complications. A striking difference found in this research is a lower prevalence of previous history of syncopal episodes compared to the original study (32% vs. 43%).

Previous history of syncope could represent more unidentified or previously unstudied cardiovascular comorbidity; however, as there are people with recurrent or frequent syncope, the neurally mediated mechanism or reflection is the most associated with these episodes and generates better prognosis and lower incidence of ominous events. In addition, patients present with higher prevalence of heart failure (21.7% vs. 5.1%) and high risk of sudden death; this important difference may explain the high prevalence (68%) of high BNP (>300 pg/ml) and why this population is sicker from a cardiovascular standpoint; however this is against adequate ROSE sensitivity rule.

The history of coronary artery disease —previous myocardial infarction— was also higher (15% vs. 10%), although it was not significant. In the original study, the cause of syncope was identified in the emergency department in 44% of cases, compared to what was found here, where most patients were hospitalized mainly due to uncertain diagnosis and short term prognosis.

76% of patients in this study had an abnormal electrocardiogram (ECG) on admission, ranging from subtle abnormalities to signs of significant structural heart disease; in contrast, the study of Reed *et al.* (6) found that 96% of patients had an ECG in sinus rhythm with no major abnormalities on admission.

The follow-up after one year of the cohort of patients who underwent the ROSE score allowed finding that 52% of the events were manifested after the first 30 days of evaluation. Sensitivity decreased while specificity increased (71.6% and 71.1%, respectively), which is a typical behavior of a diagnostic test with greater statistical power (7) and which leads to infer that the scale loses performance as the index event progresses.

It is important to assess the need for external validations since other scores found lower prognosis yield. Thus, e.g., Saccilotto *et al.* (8) conducted a systematic review that assessed 12 studies that used the San Francisco scale; in this study, the sensitivity and specificity of the scale varied considerably in relation to the original derivation —sensitivity of 87% and specificity of 52% in the systematic review, and sensitivity of 96% and specificity of 62% in the derivation—. Similarly, the external validation of this scale showed distant values (sensitivity 89% and specificity 69%). As a consequence, it can be said there are specific factors of the population that make risk scales have a different behavior (9,10).

The high negative predictive value of the ROSE scale (83%) must be emphasized, which would make this score a useful tool in low-risk patients. All patients experiencing an outcome until day 7 had no new events at 30 days, which reflects the need to broaden the sample of patients with syncope.

Prior to using BNP as a variable of cardiovascular adverse outcome with a risk score as ROSE, its usefulness as an independent risk factor in patients with syncope had already been evaluated. In the study of Reed *et al.* (11) the value of BNP for predicting adverse outcomes at three months in adult patients with syncope events was evaluated, finding that a value of 100 lpg/ml was more sensitive than that found in institutional risk prediction guides at three months of follow-up with similar specificity. It is likely that BNP is not useful for predicting outcomes in low risk groups, although no assessment of the issue is found. In this same study, more than 40% of patients had a BNP value greater than or equal to 300 pg/mL, representing a large sample of high risk patients for post-syncopal cardiovascular complications.

D'Ascenzo *et al.* (12) evaluated 43 315 patients with syncope and determined that 10.4% had underlying cardiac abnormalities, being bradyarrhythmia the most common (4.8%); this is far exceeded in this study, where bradyarrhythmia was the third most frequent electrocardiographic finding (32.6%), preceded by axis deviation and changes in ST segment and T wave.

An important limitation when considering the use of a serum marker for damage or myocardial overload, as in the case of BNP in the assessment of the prognosis of patients with syncope, is based on the fact that BNP itself could be identified only in older patients, with higher prevalence of structural heart disease and heart failure, diseases that imply a worse prognosis and increased incidence of cardiovascular complications. However, this measurement represents a more objective marker of heart disease or cardiac involvement from another source compared to a medical history and, a much more subjective, physical examination.

Regarding the general limitations of the study, the most important is sample size, followed by the high variability reported in the reading of the electrocardiogram, which may vary depending on the observer's experience. This makes a reliable standardized reading of these studies necessary, since the detection of electrocardiographic abnormalities allows the identification of patients with cardiogenic syncope, the main etiology associated with increased morbidity and mortality. Similarly, the follow-up time (30 days) can be considered minimal, because it limits the detection of long-term events.

Conclusions

Given the low calculated sensitivity and the small sample of patients, the ROSE risk score does not have a good diagnostic performance as a predictor of major cardiovascular outcomes and death at 30 days in the study population. Nevertheless, all patients with a low risk score (0) could be assessed on an outpatient basis given the high NPV.

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Conflict of interests

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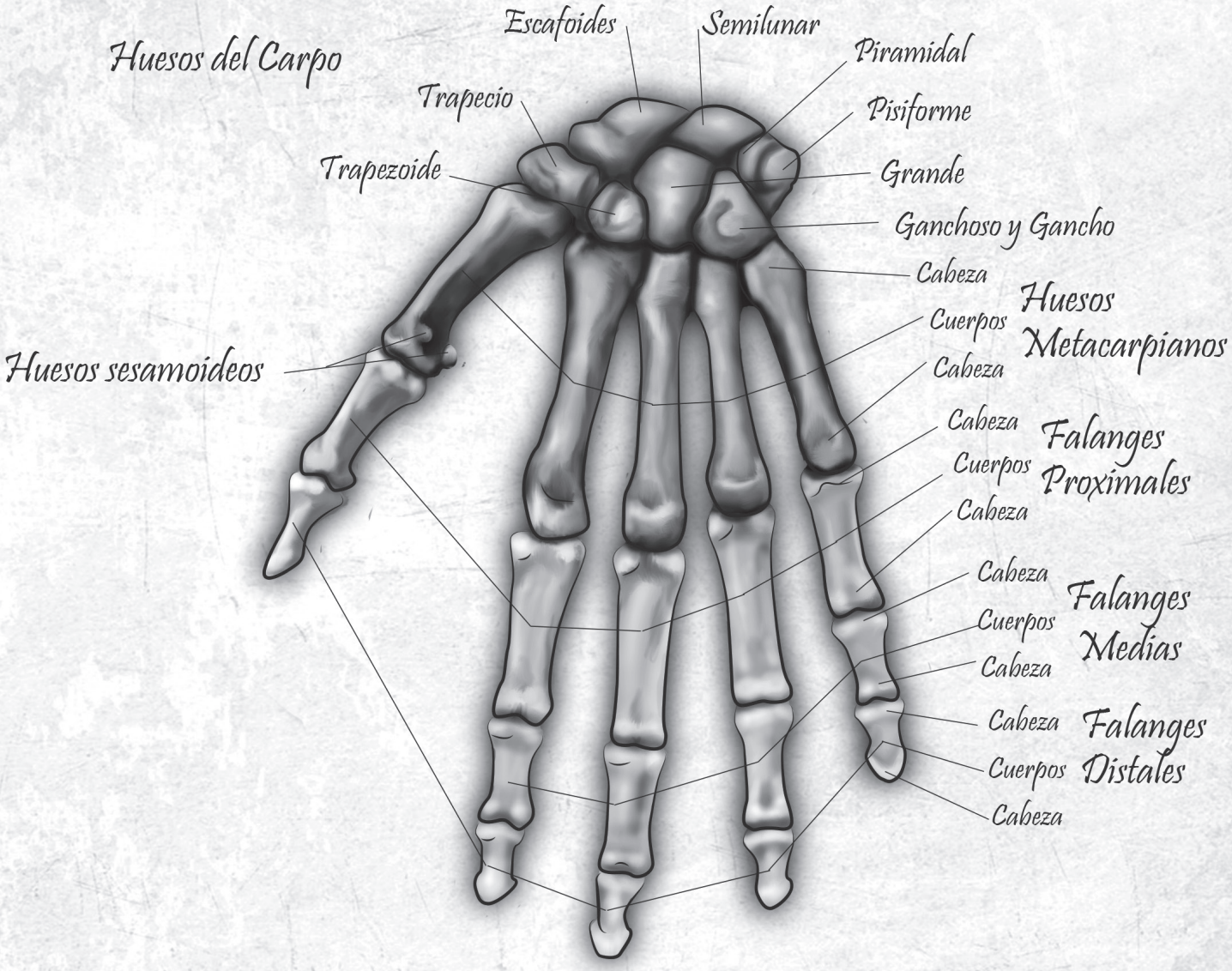

César Alexander Eslava Franco
"Mapas anatómicos"
Universidad Nacional de Colombia

ORIGINAL RESEARCH

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Use of EMG biofeedback for basic activities of daily living training in stroke patients. Pilot randomized clinical trial

Uso de biofeedback electromiográfico durante el entrenamiento de las actividades básicas de la vida diaria en pacientes con accidente cerebrovascular. Ensayo clínico aleatorizado piloto

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| Abstract |

Introduction: Sequels in stroke patients include hemiparesis and dependency for performing basic activities of daily living (BADL). EMG biofeedback has yielded some benefits but has been limited to repetitive movement, therefore, it is insufficient for current task-oriented neurorehabilitation paradigms.

Objective: To assess whether the application of EMG biofeedback in upper limbs during BADL training improves motor, occupational and satisfaction performances compared to BADL training without this feedback.

Materials and methods: A pilot randomized clinical trial was conducted with stroke patients of more than six months of evolution, who showed hemiparesis and no cognitive deterioration. These patients were randomly classified into two groups: control group, who underwent conventional occupational therapy (COT), and experimental group, who underwent COT+EMG-BF. Patients were given 10 therapy sessions. Entry, evaluation and data analysis were masked.

Results: Seven patients were included in each group, showing the same initial clinical and demographic characteristics ($p>0.05$). The group that underwent COT+EMG-BF showed a significantly better performance in all assessments. For example, the Barthel scale obtained a median of 100 points [85-100] for the COT+EMG-BF group versus 85 [80-90] for the control group ($p<0.05$), whereas ARAT score was 42 [40-47] points versus 20 [15-38] ($p=0.03$), respectively.

Conclusion: The combination of COT+EMG-BF for BADL may be considered as an alternative for treatment of stroke patients.

Keywords: Neurofeedback; Rehabilitation; Activities of Daily Living; Stroke; Occupational Therapy (MeSH).

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| Resumen |

Introducción. Las principales secuelas del accidente cerebrovascular (ACV) son la hemiparesia y la dependencia en actividades básicas de la vida diaria (ABVD). El biofeedback electromiográfico (BF-EMG) ha mostrado beneficios, pero su uso se ha centrado en el entrenamiento de movimientos aislados, lo que difiere del paradigma actual en rehabilitación.

Objetivo. Evaluar si la aplicación de BF-EMG durante el entrenamiento de ABVD mejora el nivel de independencia, el funcionamiento motor y la satisfacción en el desempeño comparado con entrenamiento de ABVD sin esta técnica.

Materiales y métodos. Ensayo clínico piloto en pacientes de 18 a 70 años con hemiparesia secundaria a ACV isquémico crónico. Los pacientes fueron aleatorizados en dos grupos: un grupo control con terapia ocupacional convencional (TOC) o un grupo experimental con TOC + BF-EMG. Se enmascaró el enrolamiento, la evaluación y el análisis de datos.

Resultados. Se reclutaron siete pacientes en cada grupo, control y experimental, con las mismas características demográficas y clínicas iniciales ($p>0.05$). El grupo TOC+BF-EMG mostró mejor rendimiento en todas las evaluaciones. En el índice de Barthel se obtuvo una mediana de 100 puntos (85-100) para el grupo TOC + BF-EMG en comparación a 85 (80-90) del grupo control ($p<0.05$), mientras que en el test de Arat fueron 42 (40-47) puntos frente a 20 (15-38) ($p=0.03$), respectivamente.

Conclusión. La combinación de TOC + BF-EMG en ABVD podría considerarse una alternativa en el tratamiento de personas con ACV.

Palabras clave: Neurorretroalimentación; Rehabilitación; Actividades cotidianas; Accidente cerebrovascular; Terapia Ocupacional (DeCS).

Garrido-Montenegro M, Álvarez-Espinoza E, Vergara-Ruiz S. [Uso de biofeedback electromiográfico durante el entrenamiento de las actividades básicas de la vida diaria en pacientes con accidente cerebrovascular. Ensayo clínico aleatorizado piloto]. Rev. Fac. Med. 2016;64(3):477-83. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.56213.

Introduction

According to the World Health Organization (WHO), cardiovascular diseases are the leading cause of death worldwide; among them, stroke is the third cause of disability-adjusted life year (DALY) (1). Most of the patients who survive have an incomplete motor recovery after six months; the main sequel is hemiparesis (50%), followed by cognitive, gait, affective, sensory and language deficits (2). A year after the stroke, 60% of patients present some kind of dependence. This figure increases to 66% at three years (3), which affects both families and the State socially and economically.

The effects of strokes alter the occupational performance of patients by making them unable to meet the expectations of their role and the demands of the activities performed on a daily basis. For example, changes in basic activities of daily living (BADL), which consist of body self-care tasks, show a dependence rate of 58.6% at six months and 50% at one year. Bathing, going upstairs and dressing are the most affected and the most difficult activities to achieve independently (4). For occupational therapists, training in BADL is paramount, but there is little evidence of techniques or tools that can facilitate this process.

Electromyographic biofeedback (EMG-BF) is recommended for the treatment of various conditions after a stroke (5), making patients more aware of muscle activity and helping to control the level of muscle contraction applied. However, the technique is used in the training of specific and repetitive movements, outside the context of functional activities of daily living, therefore, it is still insufficient for current paradigms of neurorehabilitation and the concept of rehabilitation for occupational therapy (OT). Therefore, this research uses the EMG-BF during the execution of BADL, explicitly including feedback in a functional and motivating therapeutic process. It also proposes a hypothesis consisting of the use of EMG-BF during BADL training for significantly improving the level of independence, motor functioning and performance satisfaction compared with BADL training without EMG-BF.

As discussed above, the objective of this research was to evaluate whether the application of EMG-BF in the upper limbs during BADL training improves the level of independence, motor functioning and satisfaction in performance, compared to training BADL without EMG-BF.

Materials and methods

Design, selection and description of participants

A randomized pilot clinical study was conducted with stroke patients. Two intervention procedures were proposed: a control group that underwent conventional occupational therapy (COT) and an experimental group that was treated with conventional occupational therapy plus EMG-BF (COT+EMG-BF).

Independence in BADL is a relevant parameter to be assessed during rehabilitation studies after a stroke (3,4); therefore, the sample size was calculated based on this variable and on another study of EMG-BF for which the Barthel index was used (6).

This research aimed to achieve an improvement of 40% of independence during BADL, with a statistical power of 80%, in a sample size of 14 patients per group —control and experimental—. However, as this is a pilot study, 50% of the sample was included, that is, seven patients per group. The sample was made up of patients suffering from the effects of a stroke, who lived in the Commune of Santiago, Chile, for eight consecutive months.

For selection, a non-probabilistic intentional sampling was conducted, considering the following inclusion criteria: age between 18 and 70 years old, hemiparesis as consequence of unilateral ischemic stroke of at least six months and a maximum of three years of evolution at the time inclusion, only one stroke or previous events without effects, active range of motion ≥20° for wrist extension and >10° for finger extension (7). Meanwhile, the exclusion criteria were sensory and perceptual disturbances, cognitive impairment in the Folstein Mini-Mental State Examination, affective disorders without treatment and painful shoulder or shoulder subluxation.

After signing the informed consent, patients were randomly assigned to one group. This process was conducted by a third party unrelated to the study and to the patients, who did not know the clinical record and maintained allocation concealment to researchers. For distribution, random number sequences generated by computer were used. All patients were enrolled by an internist and the assignment was made by an occupational therapist.

Data collection methods

Participants in both groups were evaluated before and after completing the intervention. To assess the primary outcome (level of independence) the Barthel index, which has a score range from 0 to 100 points, was used (8-12). The following tests were used for secondary outcomes: 1) Instrumental Activities of Daily Living (IADL), with score 0-8 (13); 2) Action Research Arm Test (ARAT) to assess manipulative ability with a score of 0-56 (14); 3) Motor Activity Log (MAL) to know self-perception of quality and use of the affected upper limbs in daily activities with score 0-5 (15,16); 4) Mini-Mental State Folstein to detect cognitive impairment during enrollment with score of 0-30 (17), and 5) Canadian Occupational Performance Measure (COPM) to quantify the self-perceived change in occupational performance and satisfaction with a score of 0-10 (18). Selected guidelines are consistent with correct psychometric measures (12,14,16,18).

The evaluators were two occupational therapists who had no contact with the patients and who were masked to the group of subjects. These therapists were familiar with the aforementioned tests and unified the application criteria through training with patients.

Procedures

The procedures followed the ethical standards of the Declaration of Helsinki and were reviewed and approved by the ethics committee of Universidad Central de Chile.

It is important to clarify that EMG-BF was used during the execution of BADL by patients and not during repetitive training of analytical movements. Both control and experimental groups attended 10 60-minutes intervention sessions, three times a week, and two evaluation sessions, one at the beginning and the other at the end of the study. Depending on the level of importance attributed to COPM assessment, two BADL were selected to be worked with each participant; these activities had to meet two criteria: being a bimanual activity and promoting the use of gravitational muscles of the upper limbs.

The session for the control group was structured as follows: 1) patient preparation (5 minutes) which involved explaining the activities during the session and removing all elements that may hinder the work; 2) low-impact therapeutic activities that promoted flexion, abduction and external rotation of shoulder, elbow extension, forearm supination, wrist extension, and extension and abduction of long fingers and thumbs (10 minutes); 3) BADL training with activation and facilitation of movement in shoulder, elbow, wrist and fingers accordingly (40 minutes) and 4) relaxation of the exercised segment (5 minutes).

For the experimental group, each session was structured as follows: 1) preparation of the patient, and apart from the activities performed by the control group, activities like skin cleansing and application of electrodes were added (5 minutes); 2) low-impact therapeutic activities that promoted flexion, abduction and external rotation of shoulder, elbow extension, forearm supination, wrist extension and extension and abduction of long fingers and thumbs (10 minutes); 3) BADL training with activation and facilitation of movement in shoulder, elbow, wrist and fingers, accordingly, using EMG-BF in the selected antigravity muscles (30 minutes); 4) ADL training without using EMG-BF (10 minutes), and 5) relaxation of the exercised segment (5 minutes). The feedback received by the patient through a visual and auditory stimulus was positive.

Four occupational therapists participated in the interventions; their criteria were unified through a written set of practice guidelines and classroom training for using EMG-BF. To verify the implementation of the intervention stages, each patient had a treatment log sheet where the auditor could check compliance.

The persons responsible for enrollment, assessment, recording and analysis of data were masked. Given the characteristics of the intervention, the occupational therapist could not be masked.

Data analysis

The descriptive statistical analysis of the variables was obtained with the median p25-p75. The significance level used in the analysis was $p<0.05$ with two tails. To compare variables between the two groups, the Wilcoxon test was used. Data also were analyzed and tested again by an outside statistician using the SPSS 19 software.

Results

For eight months, 90 patients were evaluated; 14 of them were recruited and randomized —7 in the control group and 7 in the trial group— without losing any of them during follow-up (Figure 1).

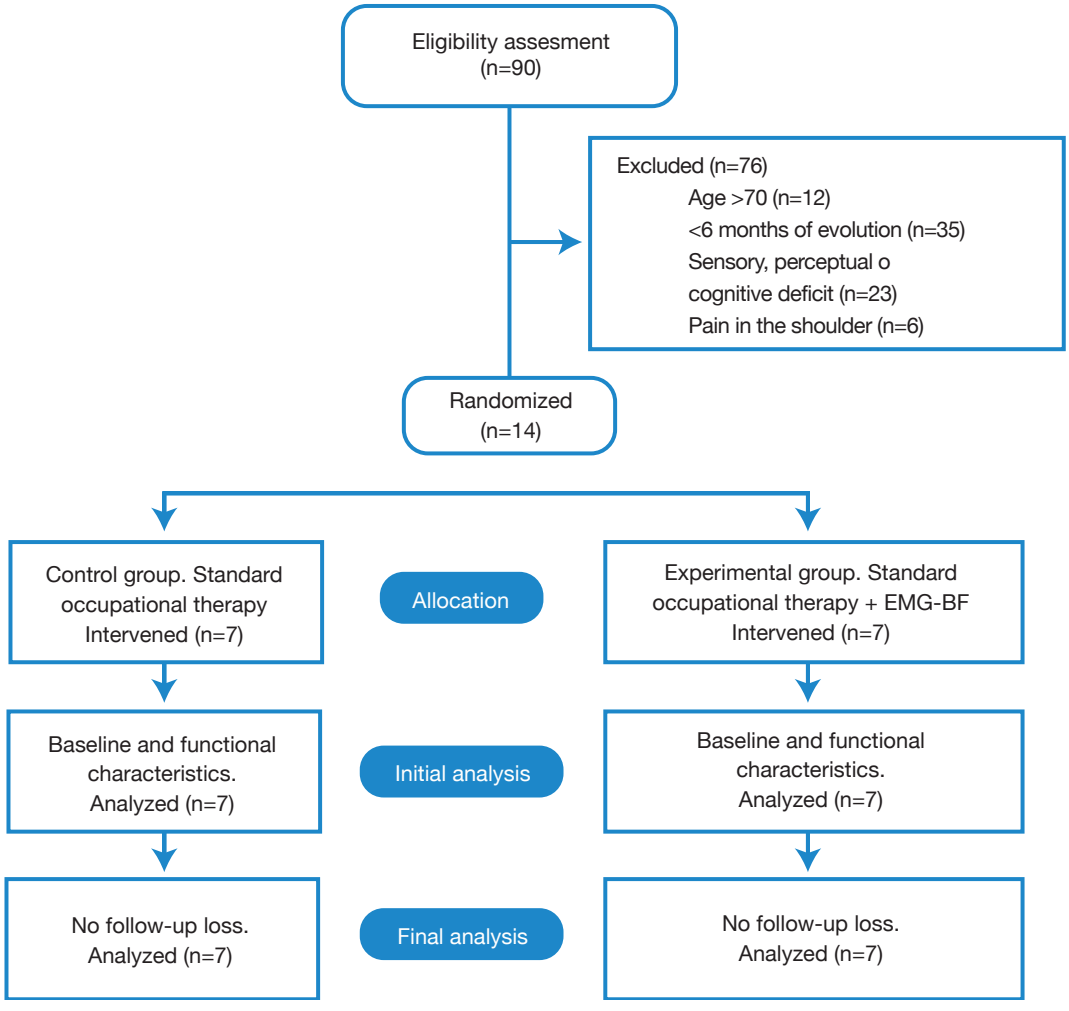

Figure 1. Flow chart of the study. Source: Own elaboration based on the data obtained in the study.

No dangerous actions occurred in any of the patients in both groups. The 14 patients were included in the intention-to-treat population and their demographic, clinical and functional baseline characteristics did not differ (Table 1).

Table 1. Demographic, clinical and functional characteristics of study participants.

Demographic characteristics		Control (n=7)	Experimental (n=7)	p value
Age		55 (37-63)	48 (35-60)	0.770
Female (%)		4 (57%)	3 (43%)	0.792
Years of schooling		11 (10-12)	12 (12-12)	0.693
Current work (%)		No (100%)	No (100%)	1
Laterality	Left	2 (29%)	1 (14.30%)	0.785
	Right	5 (71%)	6 (85.7%)	0.783
Clinical characteristics		**Control (n=7)**	**Experimental (n=7)**	**p value**
Stroke location	Left hemisphere (%)	3 (43%)	3 (43%)	1
	Right hemisphere (%)	4 (57%)	4 (57%)	1
Months of evolution		18 (14-21)	14 (9-20)	0.537
Associated therapies	Physiotherapy and kinesiology (%)	4 (57%)	5 (100%)	1
	Speech therapy (%)	3 (43%)	2 (20%)	0.847
Functional characteristics		**Control (n=7)**	**Experimental (n=7)**	**p value**
Barthel index		80 (75-80)	80 (75-85)	1
IADL		3 (2-3)	3 (2-3)	1
ARAT		15 (10-30)	15 (10-30)	1
MAL amount		1 (0-2.16)	1.16 (0.4-1.33)	0.920
MAL quality		0.9 (0-1)	0.3 (0.26-0.66)	0.537
COPM performance		2 (1-2.5)	1.5 (1.5-2)	0.777
COPM satisfaction		2 (1.5-2.25)	1.5 (1.25-2)	0.429

IADL: Instrumental Activity Daily Living; ARAT: Action Research Arm Test; MAL: Motor Activity Log; COPM: Canadian Occupational Performance Measure; median = p25-p75. Source: Own elaboration based on the data obtained in the study.

The protocol of the experimental group was modified because 10 and not 5 minutes were used for the conditioning of the patient, since the skin cleaning and electrode placement procedures took longer than expected. All other the steps of the protocol remained unchanged in both the control and the experimental group, which was verified through the treatment log sheet filled by the occupational therapist after each session.

The results related to independence show that the experimental group achieved significantly higher levels than the control group. BADL were evaluated using the Barthel index; the experimental group received 15 points more than the median of the control group, reaching 100 points ($p<0.05$). Also, 57% of patients in the experimental group reached the highest level of independence unlike the control group, where no patients achieved this level (Table 2 and Figure 2). This result shows a statistical power of 81%.

Table 2. Final results of evaluations.

Occupational performance	Control (n=7)	Experimental (n=7)	p value
Barthel index	85 (80-90)	100 (85-100)	0.038
Independent patients (%)	0 (0%)	4 (57%)	
IADL	4 (3-4)	6 (5-6)	0.001
Motor performance	**Control (n=7)**	**Experimental (n=7)**	**p value**
ARAT	20 (15-38)	40 (35-45)	0.026
Performance satisfaction	**Control (n=7)**	**Experimental (n=7)**	**p value**
MAL amount	1.33 (0.13-2.33)	3.16 (2.5-3.66)	0.017
MAL quality	0.5 (0.16-1)	1.33 (1-2)	0.011
COPM performance	2 (1-3)	3.5 (3-3.5)	0.004
COPM satisfaction	2 (2-2.5)	3.5 (3-4)	0.011

IADL: Instrumental Activity Daily Living; ARAT: Action Research Arm Test; MAL: Motor Activity Log; COPM: Canadian Occupational Performance Measure; median = p25-p75. Source: Own elaboration based on the data obtained in the study.

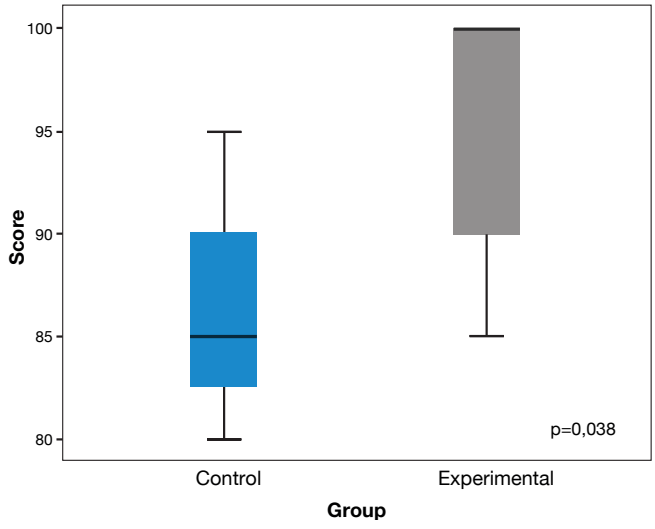

Figure 2. Final Barthel index. Source: Own elaboration based on the data obtained in the study.

The experimental group showed an increase of three points in its median for the IADL evaluated using the IADL proposal by Lawton & Brody (13), in contrast with the single point obtained by the control group (p=0009) (Table 2).

The experimental group also obtained significant improvements in motor functioning, unlike the control group, with final results of 40 points (Med=35-45) in the ARAT tests versus 20 (Med=15-38), respectively (p=0.026) (Figure 3).

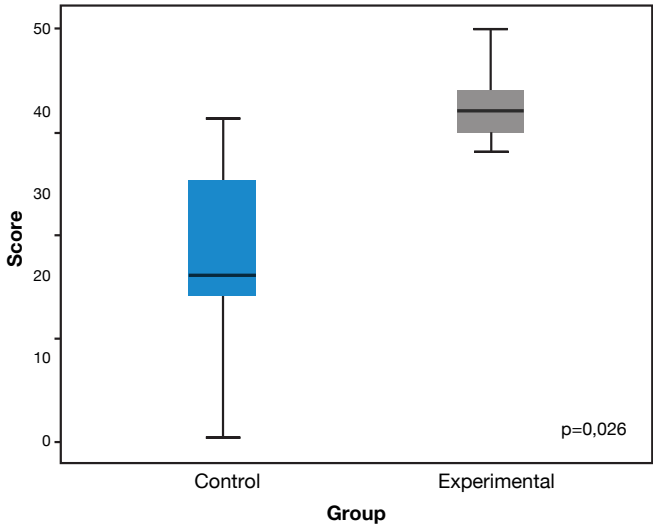

Figure 3. ARAT test results. Source: Own elaboration based on the data obtained in the study.

The results obtained in the self-perception assessments show significant differences in the experimental group in all aspects measured by MAL and COPM tests, in quantity, quality, performance and satisfaction. The results of the MAL test regarding quantity showed scores of 3.16 (Med=2.5-3.66) and 1.33 (Med=0.13-2.33) for the experimental and the control groups, respectively ($p<0.05$) (Table 2). In addition, according to the MAL test on quality, significant differences were found in the experimental group ($p<0.05$) (Table 2). Regarding COPM, the greatest statistical difference was obtained in the performance assessment, where the experimental group received a score of 3.5 (Med=3-3.5) versus 2 (Med=1-3) of the control group ($p=0.004$) (Table 2).

Finally, although patients of the experimental group achieved higher levels of satisfaction in the performance than the control group in COPM, the scores were similar ($p<0.05$) (Table 2).

Discussion

The novelty of this research relates to the evaluation of the EMG-BF application during training of basic BADL. This approach attempts to maximize the probabilities offered by a treatment that combines the use of EMG-BF with task-oriented therapy, a key contemporary paradigm in terms of vision, and a historical paradigm regarding motor learning in the work of the occupational therapist (19).

The use of the EMG-BF technique during the execution of a significant BADL was a major contribution to increasing independence, which achieved better results than those obtained in another study of EMG-BF in upper limbs (6). Not only progress was achieved in the selected activities, but also in other basic and even instrumental activities.

This is consistent with other studies on strokes that incorporate motivational activities such as games or virtual reality and that support the importance of considering the patient's motivation in the rehabilitation process because motor learning not only requires practice, but also motivation with functional objective activities for brain reorganization (20).

BADL were selected as the basis of treatment because these are the activities with the highest degree of alteration and dependence six months after the stroke (4); likewise, patients were allowed to make their own choice of BADL to work on, prioritizing them according to the self-perceived degree of importance. This motivated patients to take a more active role in treatment decisions and increase their independence, which is considered a positive factor in the clinical and functional evolution (21).

Moreover, the consequences associated with stroke often produce, to a greater or lesser extent, changes in the necessary sensory feedback for the control and motor learning, limiting the ability of patients to acquire, change or adjust skills because the actual functioning of their bodies is not perceived correctly. In this sense, other studies report the benefits of using EMG-BF in the rehabilitation of hemiparesis in upper and lower limbs after a stroke in contrast with conventional management (22-25), as well as the importance of simultaneous visual or auditory feedback for promoting better performance (26). Generally, and except for a couple of experiences of case studies in cases of gait training (27,28), the technique has been integrated into therapies whose work and measuring results are based on analytic movement or its components, without ensuring the transfer of individual movements to the complexity of an everyday activity.

In this study, the use of EMG-BF during the execution of a BADL provided an amplification of muscle signals through the visual-auditory feedback that compensated the feedback deficit of patients, allowing them a greater awareness and precision in muscle activation control during an activity. Awareness about muscle function during a motivating activity plays an important role in the acquisition of movement patterns because, if a process is hidden or is not perceived by the nervous system, it is less capable of correcting any problems in the quality of performance (29). Therefore, feedback, the use of therapeutic activities oriented to tasks, as well as motivation, play a fundamental role in motor learning and have shown to be a contribution to treatment (20,30,31).

In addition to the benefits achieved in BADL, finding better performance of ADLs was not expected since this aspect is not evaluated by other studies; this suggests that patients, having greater awareness of their motor skills, can transfer learning more effectively to other activities. This is seen in the independence achieved in activities such as meal preparation, housekeeping and purchases.

In relation to advances in motor performance, the results show that patients in the experimental group improved the functional mobility of the affected upper limb, a key factor for incorporation into everyday unimanual and bimanual activities, e.g. using a knife and fork, holding a glass, grabbing cleaning products, etc. The scores obtained at the end of the intervention are similar to other techniques of upper limbs rehabilitation after stroke, such as mirror therapy or restriction of movement therapy (32,33). In this regard, the results suggest that there is a relationship between the benefits obtained in objective motor evaluation (ARAT) and better subjective perception by patients, both on the incorporation of the affected upper limb in daily activities, and quality perception of their movements, one of the objectives of the study. In the same vein, the COPM test showed significant progress in the perception and satisfaction of performance in the chosen BADL, essential factors for achieving successful outcomes in rehabilitation (34).

The structure adopted in the intervention protocol favored the learning of patients. However, the time initially estimated for each session (one hour) was insufficient, since, on average, the sessions were one hour and five minutes long due to a longer time for conditioning of the patient (10 and not 5 minutes), an aspect to improve in future studies. It should also be noted that the EMG-BF surface did not allow obtaining reliable data on small upper limb muscles, which was possibly related to the fine motor tong activities being referred as more difficult by patients, for example, using keys to open doors, buttoning/unbuttoning, putting on/taking off bras, zipping/unzipping.

Finally, the potential limitations when generalizing the study results must be recognized taking into account the limited sample of individuals with chronic stroke that was tested. The results are only applicable to people with similar characteristics to the participant group. A greater number of patients is necessary to extrapolate the results, but this is still a significant and interesting alternative to the conventional use of EMG-BF.

Conclusion

The use of EMG-BF during BADL yielded significant progress in all defined parameters: motor, occupational and satisfaction levels, constituting a complement to the rehabilitation treatment of people with sequelae of stroke.

Contributions

Álvarez-Espinoza and Garrido-Montenegro participated in the conception, design, analysis and interpretation of results; Vergara-Ruiz participated in patient recruitment and data collection; all authors drafted, wrote and contributed to the revision of the text, as well as in the review and approval of the final version.

Ethical principles for medical research

Both the main author and the other authors declare that they have full access to all data in the study and take responsibility for the integrity of the data and the accuracy of its analysis.

Conflict of interests

None stated by the authors.

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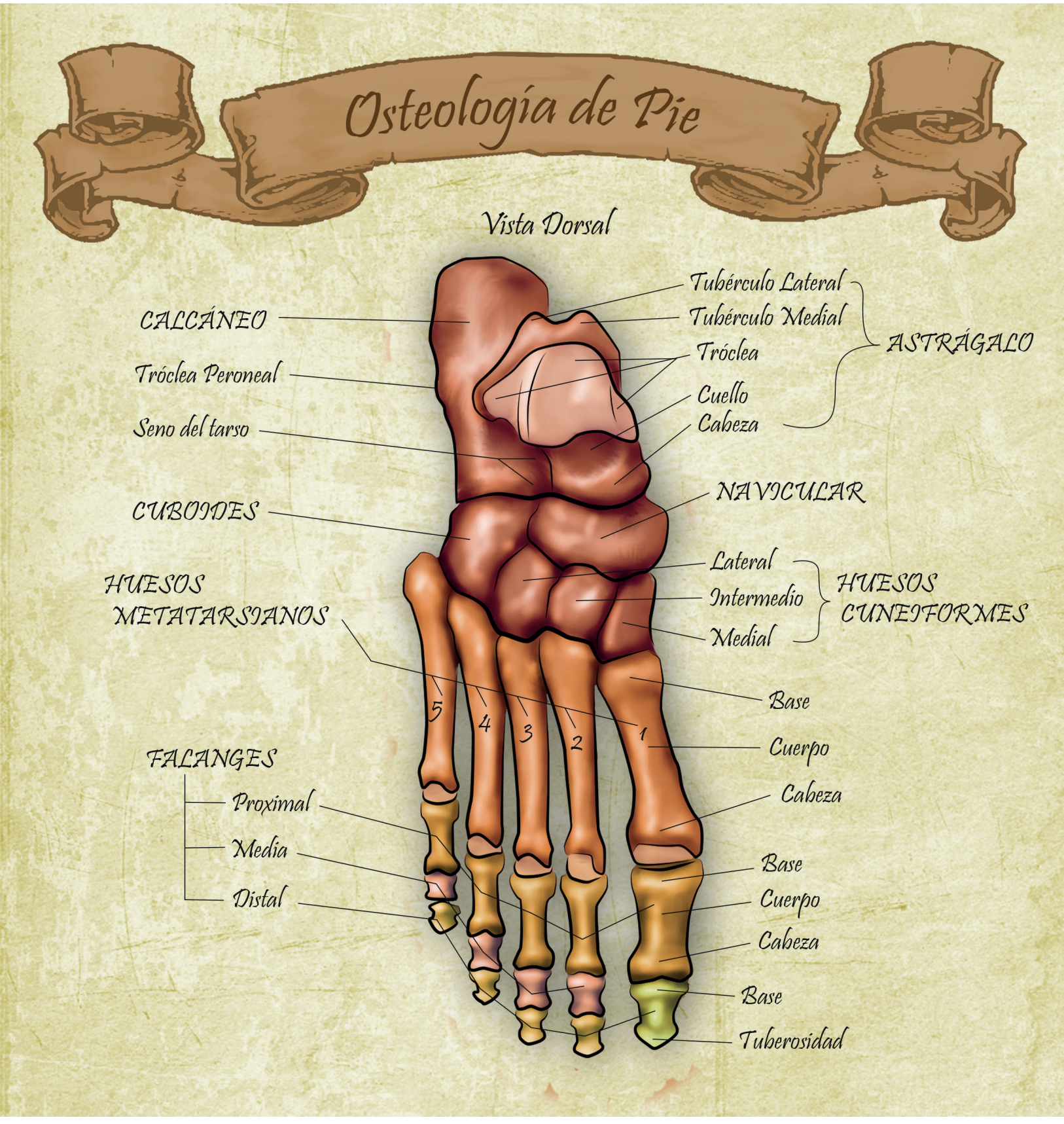

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ORIGINAL RESEARCH

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Secondary erythrocytosis due to hypoxemia as prognosis in exacerbated chronic pulmonary diseases

Eritrocitosis secundaria a hipoxemia como pronóstico en neumopatías crónicas exacerbadas

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| Abstract |

Introduction: Even though exacerbations are the main cause of emergency consultation in patients suffering from lung diseases, erythrocyte parameters are not assessed in their prognosis. Thus, determining the implications of erythrocyte parameters might contribute to define the usefulness of phlebotomy or red blood cells transfusion in these patients.

Objective: To establish a possible relationship between the different hematocrit levels with a 30-day prognosis in patients admitted with exacerbated chronic lung disease and hypoxemia.

Materials and methods: A study based on a 30-day follow-up was conducted. Variables were described using an additional categorization by hematocrit levels and an adjustment in a multivariate model through logistic regression.

Results: Follow-up was completed for 110 Patients. The frequency of anemia was 7.3% and of erythrocytosis, 14.5%. A significant association to the outcome using Anthonisen score (OR=10.45, 95%CI: 1.11-98.48, p=0.04), hypertension (OR=11.02, 95%CI: 1.32-91.75, p=0.026) and heart failure (OR=0.09, 95%CI: 0.01-0.82, p=0.032) was found.

Conclusion: This research could not determine any relationship between erythrocyte parameters and prognosis of patients suffering from pulmonary diseases; nevertheless, extreme values of hematocrits tended to have adverse outcomes.

Keywords: Polycythemia; Lung Diseases; Phlebotomy (MeSH).

Galindo JL, Granados CE, Galeano AC, Callejas AM, Sánchez VL. Secondary erythrocytosis due to hypoxemia as prognosis in exacerbated chronic pulmonary diseases. Rev. Fac. Med. 2016;64(3):485-91. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.52488.

| Resumen |

Introducción. Aunque las exacerbaciones de las neumopatías crónicas son las principales causas de consulta a urgencias de los pacientes que las padecen, los parámetros eritrocitarios no son evaluados en su pronóstico. Por tanto, determinar las implicaciones de los parámetros eritrocitarios podría ayudar a definir la utilidad de la flebotomía o la transfusión de eritrocitos en estos pacientes.

Objetivo. Establecer si hay relación entre los distintos niveles de hematocrito con pronóstico a 30 días en pacientes con neumopatía crónica exacerbada e hipoxemia.

Materiales y métodos. Estudio de seguimiento a 30 días. Se realizó la descripción de las variables con una categorización adicional por niveles de hematocrito y un ajuste en un modelo multivariado por regresión logística.

Resultados. Se completó el seguimiento en 110 pacientes. La frecuencia de anemia fue de 7.3% y de eritrocitosis de 14.5%. Se encontró asociación significativa al desenlace con la clasificación Anthonisen (OR=10.45, IC95%: 1.11-98.48; p=0.04), hipertensión arterial (OR=11.02, IC95%: 1.32-91.75; p=0.026) y falla cardiaca (OR=0.09, IC95%: 0.01-0.82; p=0.032).

Conclusión. Este estudio no pudo determinar relación alguna entre los parámetros eritrocitarios y el pronóstico de pacientes con enfermedades pulmonares crónicas; sin embargo, hubo una tendencia a que los valores extremos del hematocrito presentaran desenlaces adversos.

Palabras clave: Policitemia; Enfermedades pulmonares; Flebotomía (DeCS).

Galindo JL, Granados CE, Galeano AC, Callejas AM, Sánchez VL. [Eritrocitosis secundaria a hipoxemia como pronóstico en neumopatías crónicas exacerbadas]. Rev. Fac. Med. 2016;64(3):485-91. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.52488.

Introduction

Chronic lung diseases are common and their exacerbations are the main cause of consultation in the emergency department since they impair the quality of life of patients (1-3). In chronic obstructive

pulmonary diseases, exacerbations account for 25% of the causes of dyspnea in the emergency room and represent 500 000 to 726 000 hospitalizations annually in the United States, generating 25-30% of the costs related to this pathology (1,2,4).

Different variables have been decisive for the prognosis of exacerbations; however, despite the pathophysiological correlation between chronic lung diseases with hypoxemia and erythrocytosis development, red blood cell parameters have not been evaluated as predictors of these events (2,5).

Erythrocytosis could affect the prognosis of an exacerbation by altering the microvascular rheology of patients and decreasing tissue perfusion and cardiac output (6,7). In long-term observations, anemia has been identified as a factor involved in the development of adverse events in patients with stable chronic lung disease, whereas erythrocytosis has shown its inference on a better prognosis (8-11).

Determining the virtual implications of red cell parameters in patients with pulmonary exacerbations could help defining the particular use of measures such as phlebotomy or red blood cell transfusion.

Currently, phlebotomy remains a measure of regular use in clinical practice, as it is economical and easy to perform; nonetheless, specifications around its technique are variable in studies and in usual clinical practice (7,12). There are limited data on its usefulness, as there are no works on proper methodology to evaluate its effectiveness (13-17). Therefore, there is a big gap in the state of the art, which indicates the need to expand clinical research to achieve a better characterization of the risk and the need for treatment of secondary erythrocytosis in stable and exacerbated chronic lung disease.

This study aimed to determine whether there is a relationship between the red cell prognostic parameters and adverse outcomes at 30 days in patients admitted under the diagnostic impression of an exacerbated chronic lung disease and secondary hypoxemia.

Materials and methods

Study design

An observational study of a single prospective cohort was performed considering the patients admitted to Fundación Hospital San Carlos between March 2011 and October 2011 with a diagnostic impression of exacerbated chronic lung disease and secondary hypoxemia, as unit of analysis.

The selection of the cohort was done in order to determine prognostic factors (at 30 days of admission) related to hospital stay, need for mechanical ventilation, need for transfer to intensive care unit (ICU), rehospitalization and death. Demographic, clinical and paraclinical variables supported in the literature were included.

Patients

Patients over 18 years of age, with a history of chronic lung disease, hypoxemia at admission and diagnostic impression of exacerbation of, infectious or non-infectious, chronic lung disease were selected. Patients were required to have lived in Bogotá at least in the last six months to avoid variations in erythrocyte indices.

The following operating variables were established as admission and results analysis criteria:

1. The term chronic lung disease referred to chronic obstructive pulmonary disease, diffuse interstitial lung disease, asthma or obstructive sleep apnea/hypopnea syndrome of more than three months of evolution, established by any of the following events: specific reference of the diagnosis by the patient or relative, diagnostic documentation prior to evaluation by a pulmonologist or internist, abnormal lung function tests compatible with the diagnosis of the disease, or daily use of inhalers or theophylline for more than three months.
2. Anemia was defined as hemoglobin values below 13 g/dL in men and 12 g/dL in women, according to normality data recorded for Bogotá and Quito (18,19).
3. Erythrocytosis was established based on hematocrit values higher than 50% in women and 55% in men (18,19).

Patients with congenital heart disease, for whom diagnosis of exacerbation of lung disease was discarded at discharge, and those who did not wish to participate in the study were excluded from the study.

To define the entry of each individual to the study, the patient or caregiver was asked to sign an informed consent during the initial interview for authorization to collect data, accessing medical records, follow-up at 30 days and processing the information obtained.

Study assessments

After checking the study entry criteria and obtaining the authorization of the patients or caregiver for inclusion, we proceeded to collect information through a survey to patients during their hospital stay. Demographic and clinical data were obtained directly from patients or their relatives, and were verified using the medical records, from where information about paraclinical was also extracted. In the event that the patient underwent phlebotomy, blood count values at admission and the last blood count obtained after the last blood collection were taken for comparison.

The survey was completed by telephone at 30 days after admission to hospital in order to assess the outcome. Data were collected and tabulated in Microsoft Access 2010 and SPSS v19 was used for conducting statistical analysis. These information handling procedures were verified, each and in full, ensuring that no inconsistencies or missing data were found. At each step, the fulfillment of the criteria for inclusion and exclusion was verified.

Outcome measures

The outcome variable was a composite between death, length of hospital stay in floors, need for invasive or non-invasive ventilatory support, need to transfer to ICU and rehospitalization, provided that they were associated with chronic lung disease. The evaluation began the day of admission of the patient to the institution until day 30 of follow-up.

Statistical analysis

Knowing, based on the studies published in the literature, that patients with chronic lung diseases have an 11% rate of mortality, 11.6% probability of readmission, 25% probability of admission to ICU, and 3% probability of requiring mechanical ventilation due to exacerbation, the risk of a combined outcome for the study was defined in at least 25%.

Guided by the value of prognostic factors evaluated during exacerbations, it is assumed that the presence of erythrocytosis may increase or decrease the risk twice for the combined outcome.

A sample of 122 subjects was estimated at two tails in Stata 9.1, finding an expected risk difference of 25% and a power of 80%, assuming an error α of 5%.

In order to determine the normality assumption, the Kolmogorov-Smirnov test was performed for univariate analysis of quantitative variables. Depending on the outcome, the abnormally distributed variables were reported by their median and interquartile range, while those presenting normal distribution were reported by their mean and standard deviation. The qualitative variables were reported as absolute and relative frequencies.

In addition, the distribution of variables was stratified by sex and hematocrit value, which was categorized into three groups according to the 25th and 75th percentiles of the distribution.

For bivariate analysis, the Mann-Whitney U test was performed. It differentiates the medians of independent samples in the analysis of quantitative variables that do not follow a normal distribution with the dependent variable. To establish the association between the independent qualitative variables and the dependent or outcome variable, the Chi square test of independence (X^2) was used along with the Mantel-Haenszel method. If the expected frequencies were less than five cases, the Fisher's exact test was used. The odds ratio (OR) and confidence intervals were calculated through StatCal in EpiInfo 3.5.1.

To perform a multivariate analysis using the logistic regression method, those statistically significant variables associated with the outcome ($p \leq 0.25$) were selected, and the Hosmer and Lemeshow test was used as calibration criterion.

Results

Between March and October 2011, a cohort of 128 patients was selected, out of which 110 met the inclusion and follow-up criteria proposed for the study. The collection of the sample was interrupted between June and August 2011 due to issues in the attention of users in the institution, which affected the admission of patients.

The cohort was composed by subjects with a minimum age of 43 and a maximum age of 90, for a median of 73.5 years; the interquartile range was 62.5 to 84.5 years of age. 56.2% of the participants were female and the female:male:ratio was 5:4 (Table 1).

Table 1. Demographic, clinical and paraclinical characteristics of patients included in the study.

Variable		n (%)
Demographic characteristics		
Age		73.5 (11) *
Sex		
Female		62 (56.4)
Male		48 (43.6)
Type chronic lung disease		
Chronic obstructive pulmonary disease		95 (86.4)
Diffuse interstitial lung disease		3 (2.7)
Asthma		9 (8.2)
Do not know/no opinion		3 (2.7)
Comorbidities		
Arterial hypertension		76 (69.1)
Diabetes *mellitus* type 2		18 (16.4)
Heart failure		25 (22.7)
Ischemic heart disease		4 (3.6)
Cerebrovascular disease		3 (2.7)
Smoking		46 (41.8)
Use of medication		
Short-acting β-agonists		93 (84.5)
Long-acting β-agonists		5 (4.5)
Short-acting anticholinergic		80 (72.7)
Long-acting anticholinergic		3 (2.7)
Inhaled steroids		67 (60.9)
Chronic systemic steroid		17 (15.5)
Methylxanthines		26 (23.6)
Home oxygen		53 (48.2)
Clinical variables		
Functional class (NYHA)	I	36 (32.7)
	II	48 (43.6)
	III	22 (20)
	IV	3 (2.7)
History of phlebotomy		5 (4.5)
Anthonisen classification	1	54 (49.1)
	2	31 (28.2)
	3	25 (22.7)
Variable		**n (%)**
Paraclinical variables at admission		
PaO2/FiO2		218.45 (50) *
PaCO2 (mmHg)		35.65 (9.3) *
Hematocrit		45.15 (8.42) *
Hemoglobin (g/dL)		14.8 (2.7) *
Total erythrocyte count		4.910000 (1.010000) *
Complications during hospital stay		
Acute coronary syndrome		5 (4.5)
Nosocomial infection		1 (0.9)
Thromboembolism		1 (0.9)
Other		1 (0.9)
Length of hospital stay (days)		6.5 (4) *
Ventilatory support (invasive and/or non-invasive)		2 (1.8)
Transfer to intensive care unit		5 (4.5)
Re-hospitalization		11 (10)
Death		5 (4.5)

* Median (interquartile range). Source: Own elaboration based on the data obtained in the study.

The diagnosis of chronic lung disease was the most common chronic obstructive pulmonary disease (86.4% of the cohort) followed by asthma and interstitial lung disease. Asthma cases had an exclusive distribution in women. Overall, 3 out of 4 patients had NYHA functional class I or II, being the functional class IV the most uncommon.

The most frequently used medications were short-acting bronchodilators, and their combination was the most common association, followed by association with inhaled steroids. While the minority of patients had a severe functional class (IV), the use of long-acting bronchodilators was limited to only five cases, compared with the more extensive use of methylxanthines. There was no difference between sexes regarding the type of prescription medications. 48% of patients used home oxygen at the time of the study; indications for initiation and permanence with this treatment were not evaluated.

The presence of comorbidity was high, especially in women; among them, hypertension was the most prevalent comorbidity, followed by heart failure and diabetes *mellitus* type 2. Almost half of patients had a history of smoking and it was two times higher in men compared to women.

Regarding the severity of the exacerbation, all patients presented hypoxemia at admission, and the central tendency was no hypercapnia in accordance with the values of pCO2 accepted as normal for Bogotá. After assessment of the severity using Anthonisen criteria, 54% were classified in type 1.

During hospital stay, eight cases presented complications, four of them showed one of the outcomes assessed at 30 days, and only one included death. The most common outcome was rehospitalization, which occurred in 10% of the cohort; this coincides with data reported in the literature.

Erythrocyte parameters showed an overall predilection of being within normal values, with a median of 45.15% and an interquartile range of 8.42% for hematocrit. The frequency of anemia was 7.3%, while the presence of erythrocytosis was identified in 14.5% of the population, with a similar distribution between the sexes.

When assessing the data by dividing the sex distribution and the hematocrit levels in the 25th and 75th percentiles (Table 2) in order to debug the virtual relationships of the different levels of red cell parameters with the characteristics of the cohort, no relationship between hematocrit values and NYHA functional class of patients, nor between severity of exacerbation according to the criteria of Anthonisen was evident. Nevertheless, there was a tendency to lower PaO2/FiO2 and higher pCO2 in the presence of higher levels of hematocrit at admission.

No relationship between a history of use of home oxygen and hematocrit values was found.

At admission, five patients had a history of phlebotomy and hematocrits were located preferentially in the last interquartile or near this range. In only one case phlebotomy was repeated.

Regarding the outcomes, there was a predilection to higher length hospital stay in the presence of lower levels of hematocrit. Other outcomes did not appear to have any relation to hematocrit levels, although no deaths were recorded in the group of patients with the highest levels of hematocrit.

The variables in the bivariate analysis that were statistically significant to be included in the multivariate analysis were age, history of hypertension, history of heart failure, use of short-acting anticholinergics, home oxygen, type of Anthonisen and hematocrits at admission, being blood pressure the factor with the greatest weight (Table 3).

Regarding red blood cell parameters, a tendency to have a protective effect when located in the core values of hematocrit against extreme values, this difference did not show a statistical significance.

The multivariate analysis found an association with the development of the composite outcome in the Anthonisen classification, paradoxically, being the association with type 2 (OR=10.45, 95%CI: 1.11-98.48; p=0.04) higher when compared with other types. Hypertension continued to be the factor with the strongest association (OR=11.02, 95%CI: 1.32-91.75; p=0.026) and a history of heart failure acted as a protective factor (OR=0.09, 95%CI: 0.01-0.82; p=0.032) in an unexpected and difficult to understand association from the clinical and pathophysiological point of view (Table 4).

Only three of the patients underwent phlebotomy, and its indication included the hematocrit value in all cases, regardless of the clinical presentation. Blood volumes extracted and the number of sessions were variable in each of the procedures and did not correlate with the magnitude of change in the red blood cell values in the subsequent blood count control (Table 5). None of these patients presented any of the outcomes assessed at 30 days.

Discussion

This study attempted to establish the relationship between red blood cell parameters and the development of adverse outcomes at 30 days in patients with exacerbated chronic lung disease. The results showed that exacerbations of chronic lung diseases afflicted, with very little difference in frequency, both men and women and appeared at similar ages, without any difference in the severity of the disease, although comorbidities are more often associated with women. In Colombia, short-acting bronchodilator and inhaled steroids remain the mainstay of treatment; although, despite guideline recommendations for management of chronic obstructive pulmonary diseases, only a few cases of patients receive long-acting bronchodilator (20).

Of the outcomes assessed in this cohort at 30 days, mortality, the need for ventilatory support and transfer to ICU presented in a very low proportion to the expected compared to previously reported data; the only outcome that showed a similar frequency to that reported in the literature was rehospitalization in 10% of cases (5,21,22). Erythrocytosis frequency was 14.5%, being higher than that reported in other cohorts (8-10).

There are several observations that have found a worse prognosis of mortality and need for hospitalization in patients with lower red cell mass compared to those with higher values (9,10,12). The prognostic value of this variable in the exacerbation has not been evaluated to date.

Since the NYHA functional class and the use of medications did not differ due to hematocrit levels, erythrocyte parameters in this cohort did not appear to have any relation to the severity of chronic lung disease in patients. On the other hand, the presence of the exacerbation did not differ according to the Anthonisen criteria, but did show a trend to greater affectation of oxygenation and hypercapnia in the presence of higher hematocrit levels. Adverse outcomes were more likely to occur at the extremes of the distribution of hematocrit values, also with longer hospital stay when hematocrit values were lower.

The multivariate analysis did not include erythrocyte parameters given the lack of statistical significance of the data provided by these variables with the outcome.

The variables that were statistically significant showed some unusual associations, particularly with the Anthonisen classification and the presence of a history of heart failure, the latter being a protective factor, without defining a coherent explanation for this finding and without any publication report with a similar result that could be used to infer that protective effect. By contrast, other prognostic factors found to be related with exacerbations in other studies, such as age, use of home oxygen, the presence of signs of respiratory distress at admission, the number of Anthonisen criteria present and blood gases, could not be validated in this cohort (2,5,22,23,24).

Phlebotomy was performed in only three patients; indications focused on the hematocrit value and the technique used was variable in each case without having a direct relationship between the volume of blood extracted and the change of red cell values, in fact, in one patient no changes were seen. These data, although scarce, revalidated the limitation on the approach to a patient with erythrocytosis in the emergency room, as well as the absence of protocols that clarify the possible indications and phlebotomy techniques.

Table 2. Clinical and paraclinical characteristics of patients included in the study by sex and hematocrit levels in percentiles.

Characteristics		Hematocrit (women)			Hematocrit (men)		
		<40.96% (n=15)	40.96-46.63% (n=32)	>46.63% (n=15)	<43.78% (n=12)	43.78-54.23% (n=24)	>40% (n=12)
Age		75.47 (7.84) †	73 (19) *	70.73 (9.97) †	75.5 (7.18) †	70.83 (8.63) †	74 (9) *
Type of chronic lung disease							
Chronic obstructive pulmonary disease		12 (80)	26 (81.3)	12 (80)	11 (91.7)	22 (91.7)	12 (100)
Diffuse interstitial lung disease		1 (6.7)	-	-	-	2 (8.3)	-
Asthma		1 (6.7)	5 (15.6)	3 (20)	-	-	-
Comorbidities							
Arterial hypertension		13 (86.7)	25 (78.1)	10 (66.7)	6 (50)	14 (58.3)	8 (66.7)
Diabetes *mellitus* type 2		5 (33.3)	4 (12.5)	3 (20)	1 (8.3)	3 (12.5)	2 (16.7)
Heart failure		5 (33.3)	8 (25)	4 (26.7)	3 (25)	3 (12.5)	2 (16.7)
Ischemic heart disease		1 (6.7)	-	-	1 (8.3)	2 (8.3)	-
Cerebrovascular disease		1 (6.7)	2 (6.3)	-	-	-	-
Smoking		3 (20)	5 (15.6)	7 (46.7)	8 (66.7)	17 (70.8)	6 (50)
Use of medication							
Short-acting β-agonists		12 (80)	28 (87.5)	15 (100)	11 (91.7)	17 (70.8)	10 (83.3)
Long-acting β-agonists		1 (6.7)	2 (6.3)	-	-	2 (8.3)	-
Short-acting anticholinergic		10 (66.7)	22 (68.8)	14 (93.3)	9 (75)	16 (66.7)	9 (75)
Long-acting anticholinergic		-	1 (3.1)	-	-	2 (8.3)	-
Inhaled steroids		9 (60)	19 (59.4)	9 (60)	8 (66.7)	13 (54.2)	9 (75)
Systemic steroid		3 (20)	5 (15.6)	1 (6.7)	3 (25)	5 (20.8)	-
Methylxanthines		2 (13.3)	5 (15.6)	5 (33.3)	4 (33.3)	8 (33.3)	2 (16.7)
Home oxygen		5 (33.3)	11 (34.4)	8 (53.3)	9 (75)	13 (54.2)	7 (58.3)
Clinical variables							
Functional class (NYHA)	I	2 (13.3)	13 (40.6)	6 (40)	3 (25)	8 (33.3)	4 (33.3)
	II	8 (53.3)	12 (37.5)	4 (26.7)	8 (66.7)	12 (50)	4 (33.3)
	III	3 (20)	7 (21.9)	4 (26.7)	1 (8.3)	3 (12.5)	4 (33.3)
	IV	2 (13.3)	-	1 (6.7)	-	-	-
History of phlebotomy		-	-	1 (6.7)	-	2 (8.3)	2 (16.7)
Anthonisen classification	1	8 (53.3)	15 (46.9)	8 (53.3)	5 (41.7)	11 (45.8)	7 (58.3)
	2	6 (40)	11 (34.4)	3 (20)	3 (25)	7 (29.2)	1 (8.3)
	3	1 (6.7)	6 (18.8)	4 (26.7)	4 (33.3)	6 (25)	4 (33.3)
Paraclinical variables at admission							
PaO2/FiO2		228.57 (58.68) *	215.57 (36.61) *	214.29 (66.67) *	235.78 (88.09) †	225.22 (36.89) †	208.59 (40.06) †
PaCO2 (mmHg)		34 (5.3) *	34.27 (6.64) †	39.69 (5.85) †	35.9 (11.5) *	37.92 (9.04) †	40.72 (9.48) †
Hemoglobin (g/dL)		12.3 (2.1) *	14.23 (0.82) †	16.5 (3.1) *	13.32 (1.26) †	16.1 (1.12) †	19.21 (1.86) †
Total erythrocyte count		4.196666.67 (448117.75) †	4.764375 (288633.46) †	5.916000 (926882.64) †	4.483333.33 (316696.97) †	5.303333.33 (439066.86) †	6.150000 (922500) *
Length of hospital stay (days)		6 (4) *	7.06 (3.36) †	6.93 (2.94) †	8 (5) *	7.17 (3.42) †	7 (3.1) †
Ventilatory support (invasive and/or non-invasive)		-	-	-	1 (8.3)	1 (4.2)	-
Transfer to intensive care unit		-	-	2 (13.3)	1 (8.3)	2 (8.3)	-
Rehospitalization		-	2 (6.3)	2 (13.3)	2 (16.7)	2 (8.3)	3 (25)
Death		1 (6.7)	3 (9.4)	-	1 (8.3)	-	-

* Median (interquartile range)
† Mean (standard deviations)
Source: Own elaboration based on the data obtained in the study.

Table 3. Bivariate analysis of prognostic factors for the composite outcome.

Variables		OR (95%CI)	p
Sex		1.81 (0.56-5.99)	0.27 *
Age		NA	0.019 †
Use of short-acting β-agonists		1.33 (0.25-9.43)	1 ‡
Use of long-acting β-agonists		1.4 (0.23-8.59)	0.55 ‡
Use of short-acting anticholinergic		6.69 (0.85-142.12)	0.064 ‡
Use of long-acting anticholinergic		0.00 (0.00-14.2)	1 ‡
Use of inhaled steroids		0.59 (0.18-1.94)	0.335 *
Use of systemic steroids		1.32 (0.26-5.94)	0.71 ‡
Use of methylxanthines		1.58 (0.42-5.71)	0.52 ‡
Home oxygen use		2.72 (0.79-9.86)	0.076 *
History of hypertension		8.11 (1.04-171.86)	0.02 ‡
History of diabetes mellitus type 2		0.70 (0.1-3.73)	1 ‡
History of heart failure		0.19 (0.01-1.54)	0.1 ‡
History of ischemic heart disease		0.00 (0.00-9.68)	1 ‡
History of cerebrovascular disease		3.07 (0.00-47.79)	0.378 ‡
Smoking		1.10 (0.33-3.58)	0.866 *
Functional class	I	1.28 (0.37-4.31)	0.66 *
	II	0.99 (0.3-3.22)	0.98 *
	III	0.91 (0.18-3.95)	1 ‡
	IV	0.00 (0.00-14.22)	1 ‡
Anthonisen classification	1	0.74 (0.24-2.53)	0.64 *
	2	3.52 (1.05-11.84)	0.029 *
	3	0.22 (0.01-1.76)	0.18 ‡
History of phlebotomy		0.00 (0.00-7.29)	1 ‡
PaO2/FiO2		NA	0.274 †
PaCO2 (mmHg)		NA	0.321 †
Hematocrit		NA	0.219 †
25th percentile		1.03 (0.25-3.93)	1 ‡
25th-75th percentile		0.71 (0.22-2.32)	0.53 *
75th percentile		1.49 (0.40-5.35)	0.53 ‡
Hemoglobin (g/dL)		NA	0.458 †
Total erythrocyte count		NA	0.448 †

NA: Not applicable.
* X2 Mantel-Haenszel method
† Mann Whitney U test
‡ Fisher.
Source: Own elaboration based on the data obtained in the study.

Table 4. Multivariate analysis of prognostic factors for the composite outcome.

Variables		Crude OR (95CI%)	Adjusted OR (95%CI)	p
Anthonisen classification	3	0.22 (0.01-1.76)	1	0.054
	2	3.52 (1.05-11.84)	10.45 (1.11-98.48)	0.04
	1	0.74 (0.24-2.53)	3.19 (0.35-28.79)	0.301
Arterial hypertension		8.11 (1.04-171.86)	11.02 (1.32-91.75)	0.026
Heart failure		0.19 (0.01-1.54)	0.09 (0.01-0.82)	0.032

Hosmer and Lemeshow test: 0.948.
Source: Own elaboration based on the data obtained in the study.

Table 5. Erythrocyte parameters before and after performing phlebotomy in the recorded cases.

Case	1	2	3
Basal Ht (%)	62.2	70	62.5
Basal Hb (g/dL)	21.8	22.8	20.9
Basal erythrocyte count (/mm3)	7 140 000	8 080 000	7 040 000
Amount of blood collected (cc)	750	1000	150
Ht after phlebotomy (%)	55	70.4	56.2
Hb after phlebotomy (g/dL)	18.3	22.8	18.8
Erythrocyte count after phlebotomy (/mm3)	6 190 000	8 140 000	6 310 000
Composed outcome	No	No	No

Ht: hematocrit; Hb: hemoglobin. Source: Own elaboration based on the data obtained in the study.

The negative result of this study, regarding the influence of erythrocyte parameters in the prediction of exacerbations in chronic lung disease, may be caused by the statistical limitations of the study because the projected calculation of the sample was not obtained due to the difficulties for collecting data during the months in which the Fundación Hospital San Carlos was not fully functioning.

Also, fewer events than expected for the composite outcome presented, which could be explained by the fact that some of the included subjects were patients referred from other institutions in Bogotá, thus constituting a screened population for the hospitalization pavilions with minimum probabilities of requiring intensive care management or death, which implies a selection bias in the sample.

Since Fundación Hospital San Carlos did not have UCI service for most of the time when the sample collection was being performed, there is a possibility that patients admitted to the emergency room that required mechanical ventilation were sent to another institution before they could be included in the study. It is also probable that there were cases of patients with exacerbation who died during hours not available for sample collection and, therefore, could not be included.

Another limitation of the study was establishing definitions accepted for inclusion criteria and data analysis. The definition of chronic lung disease that was coined sought to be sensible, considering that few patients have pulmonary physiology studies and that some of those who actually had them were not available at the time of the survey or follow-up. This is why the diagnosis reported by the patient and relatives was chosen, making it difficult to determine which patients actually had a chronic lung disease and which type.

The difficulty in establishing the definition of hypoxemia, anemia and erythrocytosis is also relevant because normal values for Bogotá differ from those accepted at sea level, where most definitions are validated. For this, oxygen saturation was chosen considering the dissociation curve of hemoglobin and the values of red blood cell parameters of studies that have determined normal values in high altitudes (18,19).

Determining which patients had chronic hypoxemia at admission was difficult because, in most cases, there were no data, and for those who received home oxygen its indication was unknown.

The results suggest the need for further studies to clarify the relevance of erythrocyte parameters in exacerbations of chronic lung disease, both at sea level and in populations located at higher altitudes, as in this case.

The usefulness of phlebotomy in patients with erythrocytosis in this context remains uncertain, as well as the extrapolation of hematocrit values relevant to Bogotá. Studies that include phlebotomy in the prognosis of exacerbation should also evaluate the proper adherence to treatment, including supplemental oxygen as a primary factor to prevent recurrence of erythrocytosis.

In conclusion, this study could not determine a statistically significant association between red blood cell parameters and prognosis of patients with exacerbation of chronic lung disease; however, there is a tendency for extreme values to have adverse outcomes.

Conflict of interests

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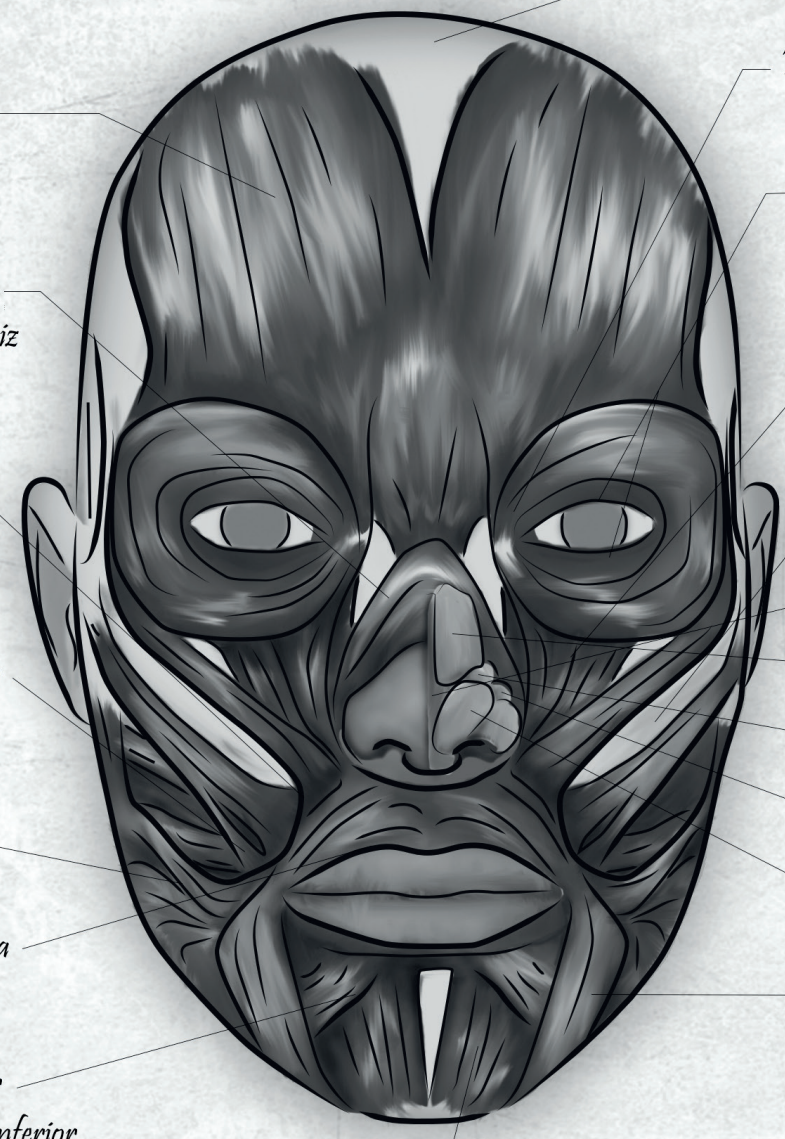
Miología Facial Frontal



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ORIGINAL RESEARCH

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Mortality in patients with esophageal and gastroesophageal tumors treated with self-expandable stents

Mortalidad en pacientes con tumores de esófago y en región gastroesofágica manejados con prótesis autoexpandibles

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| Abstract |

Introduction: Esophageal cancer is an aggressive disease and is the eighth cause of malignant tumors worldwide. To treat dysphagia, auto expandable prosthesis (AEP) are used in order to optimize the nutritional status and quality of life of the patients.

Objectives: To quantify patients' mortality and to evaluate variables related with this outcome.

Materials and methods: Retrospective cohort study that involved 135 patients with esophageal malignant obstruction that required AEP insertion. Survival and incidence density rates were estimated. The effect of these variables on the probability of death was assessed by using Cox models.

Results: Overall mortality rate was 13.7 deaths per 100 patients/month (95%CI: 10.9-17.1). Univariate analysis showed significant differences in survival functions according to pre-intervention albumin levels and the prosthesis size (>12cm). In the Cox model, albumin level (HR=0.53, 95%CI 0.31 to 0.89) was the only significant result.

Conclusions: AEP represent a therapeutic option to improve symptoms in patients with advanced esophageal and gastroesophageal junction tumors. This technique has few complications and its clinical success is around 90%. Patients' nutritional status and length of the stenosis caused by the tumor are variables that must be evaluated before performing a procedure as they seem to be related to mortality.

Keywords: Esophageal Neoplasms; Esophagogastric Junction; Esophageal Stenosis; Stents; Mortality (MeSH).

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| Resumen |

Introducción. El cáncer de esófago es una entidad agresiva y la octava causa de tumores malignos en el mundo. Para manejar la disfagia se insertan prótesis esofágicas autoexpandibles (PEA) que optimizan la ingesta y permiten mejorar el estado nutricional y la calidad de vida de los pacientes.

Objetivos. Cuantificar la mortalidad en los pacientes y evaluar las variables asociadas con este desenlace.

Materiales y métodos. Estudio de cohorte retrospectivo realizado en 135 pacientes con obstrucción esofágica maligna que requirieron inserción de PEA. Se estimó la función de supervivencia, se calcularon tasas de incidencia y se evaluó el efecto de las variables descritas sobre la probabilidad de morir utilizando modelos de Cox.

Resultados. La tasa de mortalidad fue de 13.7 muertes por 100 pacientes/mes (IC95%: 10.9-17.1). Los análisis univariados mostraron diferencias significativas en las funciones de supervivencia según niveles de albúmina previa y tamaño de la prótesis (>12cm). En el modelo de Cox solo resultó significativo el nivel de albúmina (HR=0.53, IC95%: 0.31-0.89).

Conclusiones. Las PEA representan una alternativa de mejoría de síntomas en pacientes con tumores esofágicos en estadios avanzados. Esta técnica presenta pocas complicaciones y tiene probabilidades de éxito técnico y clínico cercanas al 90%. El estado nutricional del paciente y la longitud de la estenosis producida por el tumor son variables que deben evaluarse antes de cada procedimiento ya que parecen relacionarse con la mortalidad.

Palabras claves: Cáncer esofágico; Unión esofagogástrica; Estenosis esofágica; Stents; Mortalidad (DeCS).

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Introduction

Esophageal cancer is one of the worst prognosis neoplasms: it is the eighth most common and holds the sixth place as a cause of death worldwide among other types of cancer (1). Its incidence varies; on the one hand, it is higher in Asian countries where rates range from 50 to 130 cases per 100 000 inhabitants (2) and, on the other hand, in countries like Colombia, the rate is much lower according to Globocan (3), since it is 1.2 cases per 100 000 inhabitants, with a mortality rate of 1.1 cases per 100 000 inhabitants.

The incidence of esophageal cancer has increased dramatically over the past three decades due to increased adenocarcinoma of the distal esophagus. The incidence of the disease increases with age —the average age of diagnosis is 68 years— and occurs more frequently in men (4:1). Squamous cell carcinoma is the most common esophageal malignant tumor —more common in the proximal and medial third— and its incidence has remained stable in the past years; however, the incidence of distal esophageal adenocarcinoma and gastroesophageal junction has increased substantially (4).

Most cases of this type of cancer are diagnosed in advanced stages, which is why the prognosis is poor. Clinical manifestations are dysphagia, weight loss, chest pain, malnutrition and anemia. All symptomatic patients should have a diagnostic evaluation to determine those who are candidates for a multimodal management, that is, who has the option of having the tumors resected with or without neoadjuvant management. Taking into account the stage of the disease, a large percentage of patients who are diagnosed undergo a merely palliative management; only 15% of patients with symptomatic esophageal tumors have a possibility of resection (5).

The placement of auto expandable esophageal prosthesis (AEP) before neoadjuvant therapy is a procedure that is used as a method to improve dysphagia, and to maximize nutritional supplementation and the response to treatment prior to surgical resection. Within the palliative treatment of patients with unresectable symptomatic esophageal tumors, AEP are highly effective for improving dysphagia by allowing swallowing food orally and improving the nutritional status and quality of life (6). The priority in the palliative treatment of unresectable esophageal and advanced gastroesophageal region tumors is to improve the quality of life rather than to prolong the survival period (7).

The management of this disease requires adequate staging, as this is a predictor of patient survival and allows selection of treatment (8). Although the variables that are part of the system of clinical and pathological staging can be considered predictors of survival, there are other variables related to tumor size and nutritional status that have not been sufficiently evaluated as predictors of mortality.

The aim of this paper is to show the experience with endoscopic insertion of the AEP for the management of patients with tumors in the esophagus and in the gastroesophageal region attended at a high complexity oncological management institution, and also to describe a group of socio-demographic and clinical variables, to set the frequency of mortality and to assess its association with the aforementioned variables.

Materials and methods

After a review of digital medical records, patients that had an AEP placed at Instituto Nacional de Cancerología in Bogotá between January 2010 and March 2012 were identified. Thus, 135 consecutive patients were found with AEP as a secondary treatment of malignant obstruction of the esophagus, gastroesophageal or chest junction that extrinsically occluded these structures. Since such treatment is directed at symptomatic management, cases of patients in advanced stage of the disease and patients with prolonged survival expectancy were included in the sample. These patients formed a cohort in which the follow-up start date was the date of AEP placement. The information was evaluated retrospectively, using the information provided by the institutional clinical records; the quality of the records of the variables considered in the study was supervised by an institutional monitoring team.

Each patient was monitored from the time of insertion of the prosthesis until death, until discharge from hospital or at maximum two years after the insertion of the AEP; the latter two events were censured for purposes of survival analysis, all cases were right censored.

The placement of the AEP was conducted by experienced endoscopists and the selection of the type of prosthesis was determined by the specialist in charge of each case. The prosthesis had to be 4cm longer than the tumor stenosis, ensuring that the 2cm proximal and distal segment would allow anchoring and impede their movement or migration.

For the analysis, socio-demographic variables (sex and age), clinical variables —main symptom, histological diagnosis, history of previous expansions, location and length of the stenosis— and variables related to the procedure of inserting the prosthesis —length and type of prostheses, technical and clinical success of the procedure, and immediate complications— were included. Technical success was defined as insertion or placement of the prosthesis in proper position with passage of the contrast medium. Clinical success was defined as the ability to swallow food after placement of the prosthesis, with improvement of the dysphagia score —Grade 0: normal ability to swallow; Grade 1: ability to swallow a semi-solid diet; Grade 2: ability to swallow a soft diet; Grade 3: ability to swallow a liquid diet; Grade 4: dysphagia—. The measurement of these variables was made based on what was written in the clinical records of the institution.

Regarding statistical analysis, continuous variables were summarized with means or medians, standard deviation (σ) and ranges according to the symmetry of the distributions. Descriptive statistics for categorical variables were reported as percentages. The difference between means was assessed using t-tests. To establish the frequency of the mortality rate, the survival function was estimated with the Kaplan-Meier method and incidence densities were calculated. Moreover, the difference between survival functions was assessed using the log-rank method and survival functions for variables sex, age (dichotomous at 65 years), length of the prosthesis (dichotomous at 12cm) and pre-dilations were compared.

On the other hand, the effect of the above variables was determined, including albumin levels over the risk of death during follow-up, estimating the hazard ratio with confidence interval at 95%; for this, Cox proportional hazards models were used. The model assumptions were evaluated for each of the independent variables using graphical tools (parallel cumulative risk) and a global test based on Schoenfeld residuals. Statistical analyzes were performed with the R version 3.1.1 program and two-tailed tests and significance levels of 5% were used.

The research that supports the results of this paper was approved by the ethics and research committee of Instituto Nacional de Cancerología.

Results

Out of 135 patients who underwent AEP insertion, 122 (90.4%) had esophageal tumors and esophagogastric junction, and 13 (9.6%) had mediastinal tumors causing extrinsic esophageal compression. 79.3% of patients of the cohort were male (n=107). The age of the patients had a mean of 63.7 years (σ=12.7), ranging between age 22 to 90; the average age for women was 64.3 (σ=3.4) and for men 63.5 (σ=1.1); the age difference between men and women was not significant.

Among non-mediastinal tumors (n=122), the most common histopathological diagnosis was adenocarcinoma in 84 patients (68.9%), which was located in the distal esophagus (n=8) and in the gastroesophageal region (n=6). Squamous cell carcinoma was reported in 38 patients (31.1%), and 15 of these tumors were located in the distal third of the esophagus, 16 in the middle third and 7 in the upper third.

The most common symptoms were dysphagia (n=91, 67.4%), vomiting (n=18, 13.3%) and aphagia (n=5, 3.7%). The serum albumin levels before insertion had an average of 3 (σ=0.7). The length of the stricture had a median of 6cm —range between 2 and 13cm— and the prostheses length of 12cm —range between 8 and 20 cm—. 60% of patients (n=81) required dilations before insertion; they were done ensuring no more than three dilators of ascending diameter per dilation session. The endoscopic insertion was performed without fluoroscopy to all patients.

Tecnostent prostheses were used in 126 patients, Micro-Tech in 8 and Boston in 1. The insertion of the prosthesis was performed in 78 hospitalized patients (57.7%) and 57 ambulatory patients (42.3%). Ambulatory patients received clear liquid diet within the first six hours after insertion, which was sustained for 24 hours in order to give time to the full radial expansion of the prosthesis to allow the intake of a semi-soft diet. Hospitalized patients received clear liquid diet between 6 hours and 24 hours after insertion of the prosthesis. Feeding was enteral for patients who received the prosthesis in surgery, through advanced probe, as some of them were in the intensive care unit with ventilatory support.

The technical and clinical success for insertion of the prosthesis was 85.9% (n=116). There were 13 complications in total, which corresponds to less than 10%. Major complications included chest pain in eight patients (5.9%), bleeding in four patients (3%) and perforation in one patient who died later (0.74%).

Each of the patients in the cohort provided between 1 and 757 days of follow-up (25.2 months) and all patients provided a total of 556 months. The median survival rate was 146 days (4.9 months). In the follow-up period, 76 deaths occurred (56.3%), and the estimated mortality rate was 13.7 deaths per 100 patients/month (95%CI: 10.9-17.1). The survival function estimated by the Kaplan-Meier method is presented in Figure 1. It shows that the probability of survival presents a sustained reduction at 10 months and that, after that period, it tends to be more stable. When comparing survival functions according to the strata of variables such as sex (male-female), age (under or over 65) and previous dilations (yes or not), no significant differences were found (log-rank test, p>0.05).

For the variable "prosthesis length" —longer or shorter than 12cm—, a significant difference in survival functions was found —log-rank test, X^2_{1gl}=5.5; p=0.019— (Figure 2). This variable was used as a substitute for the length of stenosis as only 79 patients were recorded and their incorporation into the models affected the accuracy of the estimates. The hazards ratio for serum albumin levels estimated using a Cox model, was 0.64 (95%CI: 0.41-0.90). Table 1 shows the raw hazards ratios, and it is possible to see that those patients with higher albumin levels had a lower risk of death during follow-up; it was also observed that the risk of dying during follow-up is almost double in patients whose prosthesis were longer than 12cm.

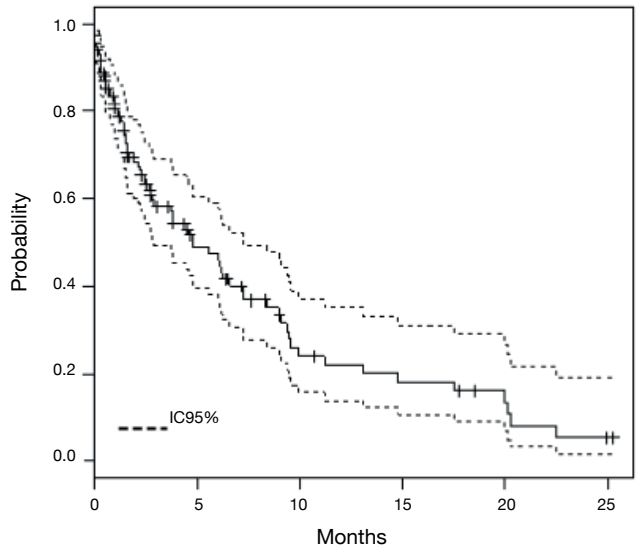

Figure 1. Kaplan Meier survival function with 95%CI. Source: Own elaboration based on the data obtained in the study.

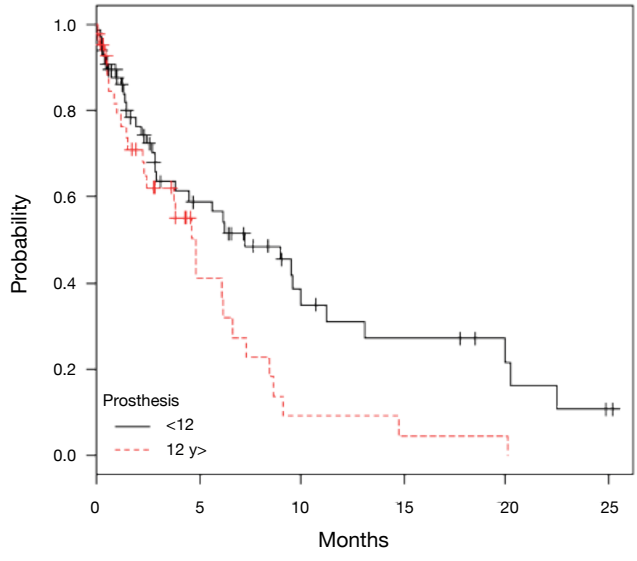

Figure 2. Survival functions depending on the size of the prosthesis. Source: Own elaboration based on the data obtained in the study.

When incorporating the above variables into a proportional hazards model and estimating the adjusted hazards ratios, it can be seen that the effect of the size of the prosthesis vanishes but the significant effect of serum albumin levels (Table 2) is maintained. As mentioned before, the proportional hazards assumption is verified using graphical tools.

Table 1. Raw ratios for mortality risk in patients with esophageal insertion of self-expandable prosthesis.

Variable	Hazards ratio	(95%CI)	
Albumin	0.6353	0.407	0.990
Sex (M)	0.831	0.489	1.42
Prosthesis length (≥12cm)	1.832	1.096	3.062
Age (≥65 years)	1.149	0.731	1.806
Previous dilations (Yes)	0.995	0.630	1.569

Source: Own elaboration based on the data obtained in the study.

Table 2. Adjusted hazard ratios for mortality in patients with esophageal insertion of self-expandable prosthesis.

Variable	Hazards ratio	(95%CI)	
Albumin	0.5311	0.3163	0.8919
Sex (M)	0.9485	0.4054	2.2192
Prosthesis length (≥12cm)	1.471	0.747	2.8966
Age (≥65 years)	0.8752	0.45	1.7022
Previous dilations (Yes)	1.0739	0.5415	2.1298

Source: Own elaboration based on the data obtained in the study.

Discussion

The most common tumors of the esophagus are squamous cell carcinoma and adenocarcinoma. While the treatment of these two histologic types is often the same, epidemiology is completely different (5). When the patient attends consultation due to dysphagia, the disease is locally advanced and more than 50% of patients present distant metastases (9).

Most patients are treated for palliation with surgery, chemotherapy, radiotherapy and/or endoscopic therapy. Given the high morbidity (13-22%) and mortality (36-71%) with palliative surgical procedures, surgery in these patients is not the best alternative, if we consider that these patients have a median survival rate longer than six months. A greater effort has been put into less invasive palliation methods, particularly during the insertion of AEP (9,10).

It is clear that the palliation of malignant esophageal obstruction should be based on the safety of the procedure, the restoration of swallowing, decreased hospital stay and reasonable costs (10).

Placing an AEP before surgery is a concept proposed and evaluated to improve swallowing, allowing the application of neoadjuvant therapy and maximizing the nutritional status (7). In general terms, AEP are reserved for patients with unresectable esophageal cancers (7).

Different studies have evaluated mortality in patients with this disease and its management. For two years, Gray (11) studied 53 patients, out of which 60.4% of cases corresponded to adenocarcinomas, 37.7% to squamous cell carcinoma and one a patient with undifferentiated lesion. He also found mortality at 30 days in 6 patients (11.3%), complications classified as major and minor —bleeding, perforation, pain, and aspiration pneumonia— in 23 (43.4%) and a median survival rate of 84 days (3 months) (11). Specifically, regarding patients treated with AEP, Eroglu *et al.* (12) reported 170 between 2000 and 2008, with a median survival rate of 177 days, being chest pain the most common complication in 31.7%. Stewart *et al.* (8) reported 138 between 1999 and 2009, with a median survival rate of three months, and also chest pain was the most frequent complication in 36% of cases. Dobrucali & Caglar (13) reported 90 cases between 2000 and 2009, with a median survival rate of 134 days. Finally, Castaño *et al.* (14) reported 99 cases between 1999 and 2004, with an average survival rate of 20 weeks, and technical and clinical success of 97%. The most common complication was chest pain in 12% of patients.

The findings of this study are consistent with the published series, where two thirds correspond to adenocarcinomas, with average survival rates of 53 to 139 days and mortality rates of 7.1% to 17% (11,15,16). Literature shows no difference in survival in relation to histological type (9): the reported estimates of mortality (11.3% mortality at 1 month and median survival rates between 53 and 177 days) are similar to those found here.

All patients were fitted with the prosthesis under direct endoscopic vision and without fluoroscopic support. The Wilkes series (16) confirms the results published by other groups and shows that the placement of the prosthesis under these circumstances, in the hands of experienced groups, can be safe and is comparable to the results published by institutions using fluoroscopic control. The question is whether fluoroscopy without endoscopy is better than endoscopy without fluoroscopy. There is no doubt that experienced groups with high volumes of patients may use endoscopy alone or fluoroscopy alone. In the clinical practice, management should be adapted to each case. Since fitting a prosthesis is not an innocuous procedure with enough complications, safety must come from experience. Endoscopy with fluoroscopy has advantages, for example, in the proximal esophagus. The use of both methods is recommended outside centers with extensive experience (17).

90.37% of the patients studied did not show complications with the insertion of the prosthesis. Chest pain within the first 48 hours was one of the most common issues (19).

Other complications described in the literature are tumor growth above the upper edge of the prosthesis, food impactions by obstruction, vomiting, migration —the most common phenomenon in closed prosthesis— aspiration of gastric contents —especially in prostheses that exceed the gastroesophageal region— incomplete expansion, bleeding and perforation, which is very rare. Usually none of the complications is associated with the type of prosthesis or insertion method (19).

It is important to note that there are different brands and different types of prosthesis, which can be coated or partially coated, and which differ in their structure and strength of radial expansion (19).

Na Kyu *et al.* evaluated the efficacy and safety of the prosthesis in patients with malignant esophageal strictures by reviewing 645 patients with different types of prostheses, classified from the first to the seventh generation, for 22 years. These authors found that the prostheses made from nitinol achieve greater adaptability and flexibility compared to those made with stainless steel, and that patients with nitinol prosthetics had significantly less chest pain compared with those with prostheses made with steel (4.1 vs .15.8; $p<0.001$) (20). Polyurethane-coated prosthesis showed increased tumor growth rate by degradation of the membrane compared to polytetrafluoroethylene-coated prosthesis. For these authors, the technical success rate was 99.4% and clinical success 95.5% (20).

The current staging system for the AJCC (American Joint Committee on Cancer) does not use the length of the tumor stenosis. Since 1987, the decision to use the deep invasion of the esophageal wall was taken, that is, the "T" more than the length of stenosis (8,21). In this paper, the length of the prosthesis is included as a substitute for the length of the stenosis because the latter was not found in all cases.

In literature, the length of the tumor is a significant predictor of survival, so it was measured at three and five years against an increase in the length of the tumor, with an interval of 1cm, showing a sharp drop in survival when surpassing 3cm. Patients with tumors <3cm had a median survival rate of 79.7% at three years and of 68.4% at five years compared to when the injury was >3cm, with a median survival rate of 23.3% at three years and of 10.6 % at five years ($p<0.0001$) (8,22). Similar results were seen in patients when the length of stenosis was associated with nodal spread N1 or N0, being the best survival rate in patients with lesions smaller than 3 cm and N0 (8).

When variables such as age, sex, histology, tumor location and type of surgery are reviewed, literature does not find a statistical association with survival. Eloubeidi (23) found that tumor length is significant in patients with localized disease, but not in patients with advanced disease.

Wang *et al*. (24) evaluated serum levels of C-reactive protein (CRP) and other variables like the number of white blood cells, alkaline phosphatase, transaminases, body mass index, platelet and albumin levels in patients with esophageal cancer taken to radiation therapy, A multivariate analysis of prognostic factors with statistical significance showed that only CRP and albumin were predictors of overall survival. The survival rates at two years, with and without, hypoalbuminemia were 58.5% and 0%, respectively ($p<0.001$) (24).

Some limitations of this study include the failure to analyze other variables related to mortality (clinical status, comorbidity), lack of measures of all clinically relevant outcomes —patient's perception, clinical response, quality of life, evolution of the nutritional state— and the failure to incorporate the size of the stenosis into the models —prosthesis length was used instead— due to the lack of registration in medical records. The latter is a common limitation of retrospective studies, especially those based on clinical records.

In conclusion, the results of this study suggest that AEP offer an alternative for improvement of symptoms in patients with esophageal tumors in advanced stages. This is a technique with few complications and probabilities of technical and clinical success at around 90%. The patient's nutritional status and the length of stenosis caused by the tumor are variables to be assessed before each procedure as they seem to be related to mortality.

Conflict of interests

None stated by the authors.

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ORIGINAL RESEARCH

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Recommendations on treatment of nail and fingertip injuries in children. Cases series and literature review

Recomendaciones de tratamiento en lesiones de la uña y punta de los dedos en la infancia. Serie de casos y revisión

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| Abstract |

Introduction: Nail and fingertip injuries in children are very frequent and may range from a simple nail or fingertip injury to amputations.

Objective: To present a series of cases with their clinical and demographic characteristics and to describe the current concepts for the treatment of these injuries.

Materials and methods: A series of cases presenting fingertip injuries was analyzed for six months. Epidemiology of injuries is described and the current concepts of their treatment are reviewed.

Results: 60% of the injuries analyzed in this study occurred in male subjects; 88% of patients suffered crush injuries, the nail was affected in 98% of the cases, sterile matrix damage was observed in 64% and germinal matrix damage was experienced in 34% of the cases. The soft tissue around the finger was affected in 40% of the cases and associated fractures were observed in 55% of the cases.

Conclusion: Fingertip crush caused by closing doors was the most frequent injury, which implied a higher involvement of the nail. An adequate treatment focused on the anatomic repair of the nail bed, the relocation of the nail plate and, in some cases, the use of flaps to cover defects in the soft tissue is ideal for this type of injuries, and must be provided as fast as possible to avoid secondary deformities.

Keywords: Hand Injuries; Hematoma; Paronychia; Wounds and Injuries; Nail Diseases (MeSH).

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| Resumen |

Introducción. En niños, son frecuentes las lesiones de la uña y de la punta de los dedos; estas varían desde traumas en la uña y el pulpejo hasta amputaciones.

Objetivos. Describir una serie de casos con sus características clínicas y demográficas y exponer el estado actual del tratamiento de estas lesiones.

Materiales y métodos. Se analiza una serie de casos con lesiones de punta de dedo durante seis meses. Se describe la epidemiología y se revisa el estado actual de tratamiento.

Resultados. El 60% de las lesiones evaluadas se presentaron en varones, 88% tuvieron trauma por aplastamiento, 98% compromiso de la uña, 64% afectación en la matriz estéril, 34% en la matriz germinal y 40% en el pulpejo; 55% de los casos sufrieron fracturas asociadas.

Conclusiones. La lesión por aplastamiento fue lo más frecuente, con mayor compromiso de la uña, predominando la contusión por cierre de puertas. Un buen tratamiento enfocado en la reparación anatómica de la matriz ungueal, reposición de la uña y, en algunos casos, uso de colgajos para cubrir los defectos en el pulpejo es el procedimiento ideal para este tipo de lesiones y debe hacerse rápidamente para evitar deformidades secundarias.

Palabras clave: Traumatismos de la mano; Hematoma; Paroniquia, Heridas y traumatismos; Enfermedades de la uña (DeCS).

Vergara-Amador E, Castillo-Pérez S, Tovar-Cuellar W. [Recomendaciones de tratamiento en lesiones de la uña y punta de los dedos en la infancia. Serie de casos y revisión]. Rev. Fac. Med. 2016;64(3):499-504. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.54201.

Introduction

Lesions of the nail and the fingertips are common in children and occur, mainly, due to home accidents with doors —for example, when closing doors or during games at school—. Crush traumas, puncture wounds and partial or total amputation of fingertip segments may occur with involvement of the nail, the soft tissue of the finger and the distal phalanx (1-6).

These lesions correspond to 2% of all accidents received in a pediatric emergency department (1). A good initial treatment prevents deformities that can affect positively function and aesthetics of the patient.

The objectives of this work are to analyze the results obtained in different cases related to injury to the nail and the fingertip and to review the current status of treatment.

Materials and methods

This is an observational and descriptive study of clinical cases of children assessed because of injuries to the nail and the fingertip for six months in a pediatric orthopedic service. Fingertip injuries included patients with trauma from the distal phalange to the distal interphalangeal joint.

Patient demographics, type of injury, the anatomical site affected and treatments were analyzed. Finally, literature was reviewed and recommendations were given for the treatment of nail injuries. Data were stored and analyzed using Microsoft Excel 2010. This was a minimal risk job, based on findings from patients, with informed consent and approved by the hospital ethics committee.

Results

66 children, with an average age of 4.6 (age ranged from 9 months to 17 years), who suffered from fingertip injury were studied. 60.3% were male, 55% of the cases occurred in the left hand and 29% in the third finger. 88% of cases were related to traumas caused by crushing (68% corresponded to closing doors), thus becoming the most frequent injury (Table 1).

The nail was compromised in 98% of cases, the soft tissue of the finger in 40%, and fractures of the distal phalanx were found in 55% of the cases, out of which 12 cases required osteosynthesis with 1.0 mm Kirschner Wire since there was a displaced fracture of the distal phalanx. The sterile matrix of 64% of patients was compromised and the germinal matrix, in 34%.

The most common surgical procedures were suture of the nail matrix (60.6%) and suture of the soft tissue (25.7%), with replacement of the same nail or using some substitute, all performed under general plus local anesthesia due to the type of population. Advancement flaps, such as VY, were required in 12 patients (18%).

Although no immediate complications occurred, we were unable to determine long term complications since many patients could not be monitored.

Discussion

The fingers of children are exposed to trauma, especially in the fingertips, which can be injured or amputated; the most vulnerable site is the nail and all its parts. The fingertip injury in children is described as the "door-smashed finger", since closing doors is the most common cause of these traumas (1-8), which is confirmed in this research after observing 45 cases (68%) with this type of injury.

Table 1. Overall results.

Variable		Quantity	
Age		9 months-17 years	
Median		3 years	
Average		4.6 years	
Mode		2 years	
Total Patients		**66**	**n (%)**
Sex		Male	40 (60%)
		Female	26 (30%)
Laterality		Right	30 (45%)
		Left	36 (55%)
Affected finger		First	13 (20%)
		Second	12 (18%)
		Third	19 (29%)
Affected finger		Fourth	18 (27%)
		Fifth	4 (6%)
Type of trauma	Crushing: 59 (88%)	Door	45 (68%)
		Bicycle	4 (6%)
		Rock	2 (3%)
		Unspecified	2 (3%)
		Window	1 (1.5%)
		Windmill	1 (1.5%)
		Toy	1 (1.5%)
		Wooden object	1 (1.5%)
		Chair	1 (1.5%)
		Car	1 (1.5%)
	Short blunt: 5 (8%)	Razor	2 (3%)
		Dog bite	2 (3%)
		Compressor	1 (1.5%)
	Penetrating: 2 (3%)	Sewing machine needle	2 (3%)
Injury type	Nail injury		65 (98%)
	Soft tissue around the fingers		26 (40%)
	Fracture		36 (54%)
Treatment	Nail replacement		48 (72%)
	Suture in the soft tissue of the finger		17 (25%)
	Suture of the nail matrix		40 (60%)
	Fixing the phalanx		12 (18%)

Source: Own elaboration based on the data obtained in the study.

Nails play several important roles in hand function: they protect the dorsal surface of the distal phalanges, increase the sensitivity of the fingertip, facilitate grabbing small objects and have an important aesthetic role. In order to plan appropriate treatment of traumatic lesions of the nails, thorough knowledge of their anatomy and physiology is required. Nails are composed of a nail plate structure, 0.5mm thick, and surrounding soft tissues (6,7,9-11); it is divided into the paronychium, the soft tissues on the sides of the nail, the eponychium —which is the soft tissue surrounding fingernails—, and the hyponychium, the area between the nail bed and the fingertip below the free edge of the nail, which functions as a waterproof seal that protects against infections (6,7,10) (Figure 1).

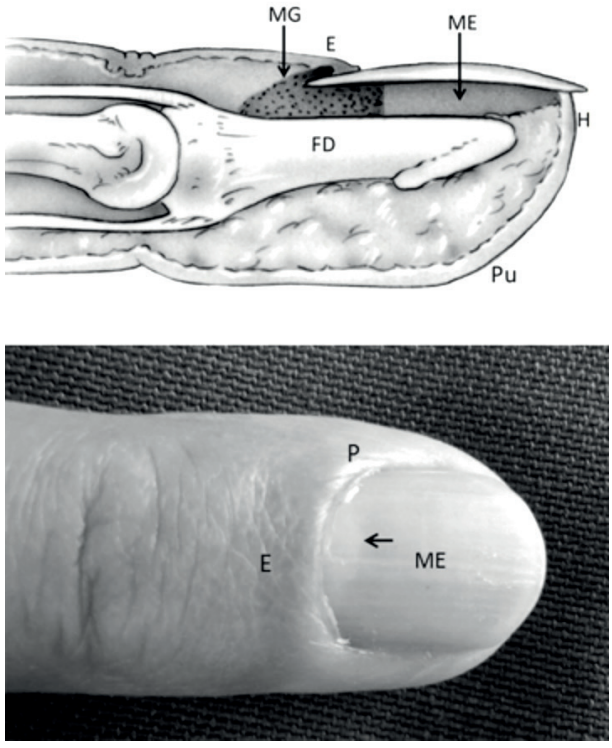

Figure 1. Normal anatomy of the nail and the fingertip. E: eponychium; H: hyponychium; P: paronychium; Pu: soft tissue; FD: distal phalanx; MG: germinal matrix; ME: sterile matrix; Black Arrow: lunula. Source: Own elaboration based on the data obtained in the study.

The nail bed is the place where the nail sticks and is divided into the proximal (germinal matrix), and the distal (sterile matrix); their union is known as lunula. The germinal matrix produces nail keratin and the sterile matrix provides adhesion. The nail bed is nurtured by a wide network of blood and lymph vessels, where many anastomoses occur, which allow using flaps in the bed or the matrix in any reconstruction surgery.

Nail growth depends on factors such as sex, age and habits; the growth rate is approximately 0.1 mm/day (0.5 mm/week) (1,6,11). Most nail injuries are caused by crushing trauma (2-4.11); in approximately 50% of cases, the lesions are associated with phalangeal fractures or damage of the soft tissue of the fingers. After a trauma, the nail stops growing for about three weeks, then an increase in the growth rate is seen over the next 50 days and, finally, a slow growth is observed for 30 days more; growth returns to normal 100 days after the trauma (1,6). During this period, a cross thickening of the nail represents signs of previous trauma (Beau's line).

Adequate primary care is of great importance to achieve a smooth nail, without scars. The wound should be sutured precisely to avoid secondary deformities: a scar on the dorsal roof (eponychium) leaves a line or stripe on the surface of the nail; a scar in the germinal matrix produces a slit or may prevent the growth of the nail, and a scar on the sterile matrix can cause a division of the nail or a distal detachment to the lesion (Figures 2 and 3). Only one year after the trauma and its treatment, the final outcome of the nail can be observed (2,11-14).

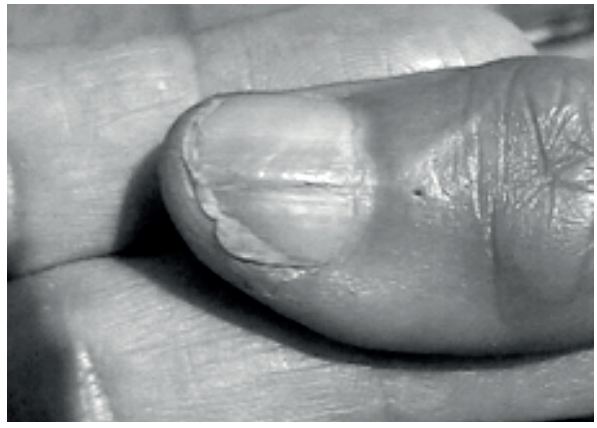

Figure 2. Outcome seen in the nail plate due to eponychium damage. Source: Own elaboration based on the data obtained in the study.

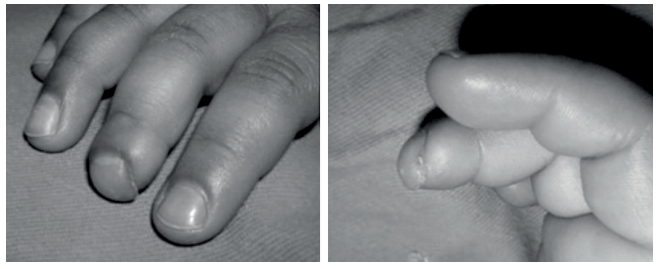

Figure 3. Hook nail tilted toward the palm due to the damage of soft tissues and the loss of the distal phalanx. Source: Document obtained during the course of the study.

Subungual hematoma

The subungual hematoma is a typical injury that occurs after a hammer blow, and its consequence is a subungual hematoma without exit, instead of losing the nail. Many of these hematomas do not increase in size and are confined under the nail, but in some cases, they grow and pain increases, behaving like a small compartment syndrome that requires prompt treatment.

Treatment of subungual hematomas depends on size and behavior; when they are small and the pain is minimal, no intervention is necessary since they incorporate into the nail and move towards the free edge as the nail grows. When they are small but cause pain or occupy up to 50% of the nail bed, it must be drained. An easy draining method implies drilling one or two holes on the surface of the nail with a hypodermic needle, in circular movements (Figure 4); hematoma pressure allows blood to flow out easily, quickly improving the patient's pain and allowing the nail to stick to its bed progressively (5-7,9,15).

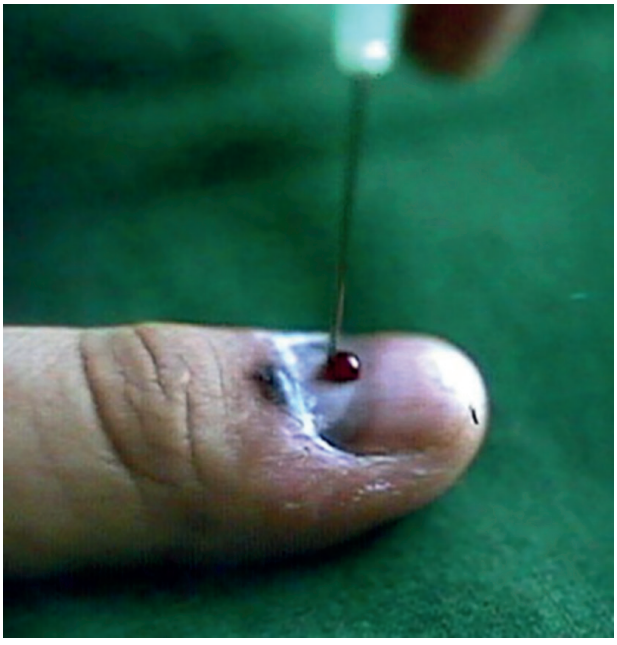

Figure 4. Maneuver with a hypodermic needle to remove a subungual hematoma. Source: Own elaboration based on the data obtained in the study.

In hematomas bigger than 50%, looking for an association of a fracture of the distal phalanx is mandatory, so lifting the nail and exploring the nail bed is recommended to verify the existence of an injury in the sterile or germinal matrix that requires suture (9,11,12).

For the scanning procedure of the nail bed, the nail is lifted with mosquito forceps or a small spatula, starting from the free edge, which is carefully separated from the bed and, depending on the type of lesion, completely removed with small rotating movements; it can also be left as a pedicle in some portion of the paronychia or eponychium (6,16). The suture matrix must be done with separate points of a resorbable monofilament 6/0 (Figure 5).

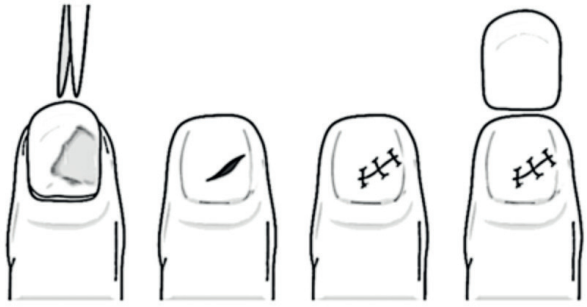

Figure 5. Removal of the nail to explore and suturing the sterile matrix. Source: Own elaboration based on the data obtained in the study.

The nail should be kept to be relocated, and can be used as a biological dressing during repair. In this way, it will fulfill the functions of shaping the nail bed, avoiding adhesions in the bottom of the nail between the eponychium and nail bed and, in the case of associated fractures in the distal phalanx, providing support as a splint and improving postoperative comfort.

When relocating the nail, making perforations is advisable in order to facilitate the process of draining the accumulated blood. The relocated nail must remain fixed in his bed and in the proximal bottom by a suture, preferably in the form of x, avoiding stitches through the nail bed (5,6,16-18).The new nail grows pushing the nail-ferrule, which is replaced in a period of 1 to 3 months.

Wounds and lacerations of the nail matrix and surrounding tissues

When avulsion or dislocation occur, the nail must be lifted to be replaced at the end of the procedure; if only sterile or germinal matrix are wounded, the nail must be sutured as indicated above (Figure 6 and 7).

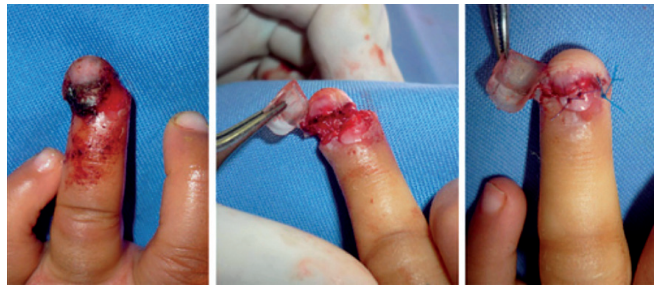

Figure 6. Crush injury of the tip of the fourth finger. The nail is lifted and an injury in the sterile matrix and paronychium is observed. The matrix is sutured with resorbable 6/0. Source: Own elaboration based on the data obtained in the study.

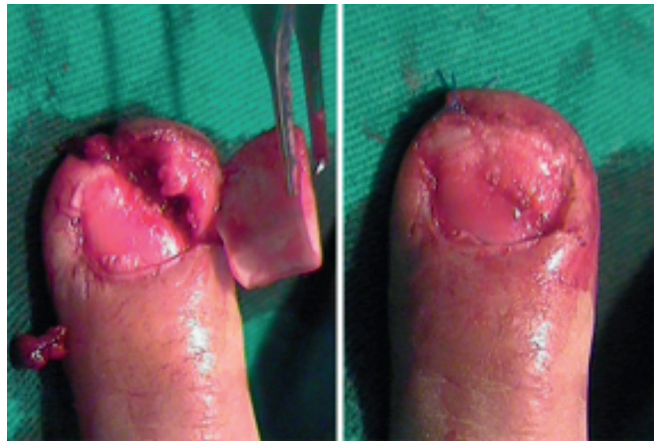

Figure 7. Crush injury. When the nail is lifted, hyponychium and sterile and germinal matrix damage is observed. It is approached with an initial suture in the hyponychium and then in the nail bed. Source: Own elaboration based on the data obtained in the study.

The loss of the nail bed may occasionally occur, which is solved through a flap in the matrix of the same finger, if necessary. Grafting from the nail matrix of the big toe or adipose flap rotation must be used when large losses occur (6,7,19-21).

The wounds that compromise the paronychium, the hyponychium or the eponychium should be sutured carefully. Sometimes, it is impossible to recover the nail, which makes a temporary replacement necessary for about two to three weeks, as it will prevent adhesions at the bottom of the eponychium and throughout the matrix during the healing process.

Soft and hard synthetic elements, such as pieces of x-ray film or the envelope of the suture, have been used in healing procedures, as well as non-adherent gauze, but these are easily contaminated and are hard to place on the nail bed. The most practical method used is a small flexible sheet removed from the sterile bag of the saline solution, which allows easy cutting and settles to the nail bed and the bottom of the nail (6,16,22-25).

In the case of deeper injuries associated with fracture of the distal phalanx, a fracture osteosynthesis with a nail, or alternatively a hypodermic needle, is recommendable.

Bandages are left in the nail or fingertip and must be replaced every three to five days for a period of 20 days, moment when the sheet that protects the nail bed is removed; then the area must be lubricated with petroleum jelly or cream. If the patient has his own nail-ferrule, it is allowed until new nail growth and falls by itself.

Wounds and lacerations of the nail with soft tissue damage

Besides the treatment described for lesions of the nail matrix and surrounding tissue of the nail, and according to the injury in the soft tissue, a simple suture should be done using local advancement flaps, such as VY, or a bit more complex flaps such as homodigital or heterodigital neurovascular island flaps (20,26-38) (Figure 8 and 9). This must be done by a specialist, but while the type of procedure is determined, the finger should be washed with a local anesthetic and covered with lubricated plasters.

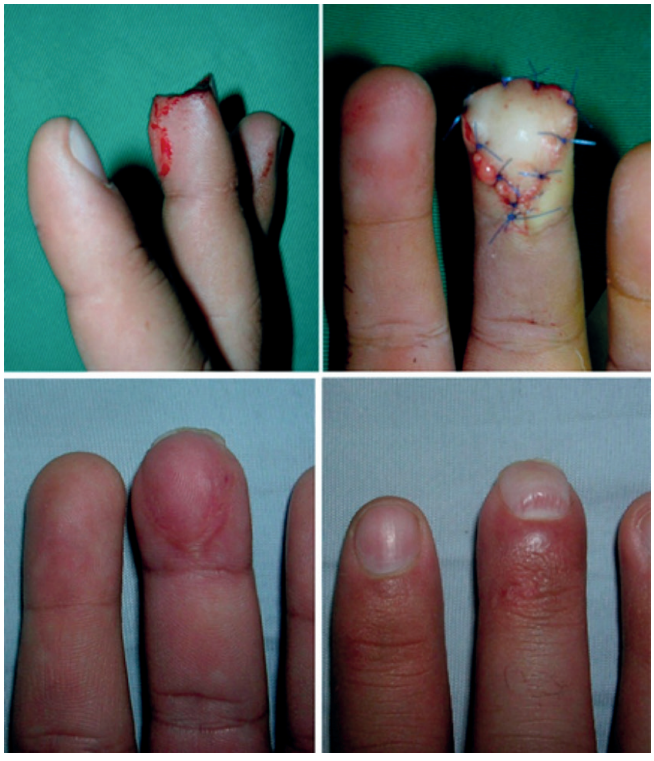

Figure 8. Loss of a fingertip that has been solved with VY advancement flap. Source: Own elaboration based on the data obtained in the study.

Conclusions

Nail lesions are the result of a contusion or compression against the underlying distal phalanx. The type of injury depends heavily on the energy and direction of the trauma. Different injuries can be observed as subungual hematomas, simple lesions of the nail and the nail bed, and more complex lesions with soft tissue or nail loss and associated fractures.

A proper anatomical knowledge and a good analysis of the type of injury and the compromised structures allow selecting an appropriate treatment, which, in turn, prevents secondary deformities with decreased secondary reconstructions of the nail that are more complicated and have unpredictable results.

Finally, promoting accident prevention programs at home and in schools, aimed at parents and teachers, is recommended.

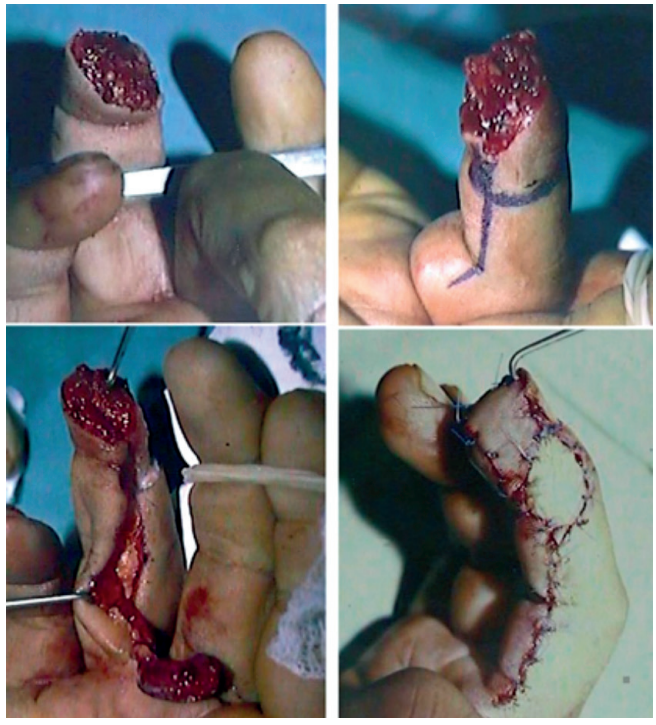

Figure 9. Amputation of fingertip that has been covered with a dorsal homodigital flap. The deformation of the site was covered with a total skin graft obtained from a donor. Source: Own elaboration based on the data obtained in the study.

Conflicts of interest

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ORIGNAL RESEARCH

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Functional assessment of muscle response in lower limbs of tumbling gymnasts through tensiomyography

Evaluación funcional de la respuesta muscular de miembros inferiores en gimnastas de tumbling mediante tensiomiografía

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| Abstract |

Introduction: Jumping capacity, a distinctive technical skill of tumbling gymnasts, is associated to a successful performance in training and competition; hence the need for an individualized, precise and localized assessment of the most demanded muscle structures.

Objective: To assess muscle response of the flexo-extension structure in the knee joint and the extension of the ankle joint in a sample of 12 high-performance male gymnasts.

Materials and methods: An acrobatic training protocol including sets of forward somersault in tumbling track was conducted. The contraction time, delay time and deformation of muscle belly were evaluated, and the muscular response speed was calculated using tensiomyography before and after the training intervention in different periods of time.

Results: Significant differences were found ($p<0.05$) according to the muscle group involved, where rectus femoris and biceps femoris presented greater enhancement and shortening of the contraction and delay time. Major differences appeared between agonist-antagonist muscles (vastus lateralis-biceps femoris) ($p<0.05$) due to a decrease in the contraction and delay speed in vastus medialis ($p<0.001$).

Conclusions: Tensiomyography allows estimating the states of activation-enhancing of the musculature responsible of jumping in tumblers, as well as planning the training based on the state of muscle fatigue.

Keywords: Gymnastics; Athletes; Athlete Performance; Muscle fatigue (MeSH).

| Resumen |

Introducción. La capacidad de salto, gesto técnico característico en gimnastas de *tumbling*, está vinculada al desempeño exitoso en entrenamiento y competición, de ahí la necesidad de una evaluación individualizada, precisa y localizada de aquellas estructuras musculares más solicitadas.

Objetivo. Evaluar la respuesta muscular de la estructura flexo-extensora de la rodilla y extensora del tobillo en una muestra de 12 gimnastas masculinos de *tumbling* de alto rendimiento.

Materiales y métodos. Se realizó un protocolo de entrenamiento acrobático con series de saltos mortales adelante en pista de *tumbling*. Se evaluaron tiempo de contracción, tiempo de activación y deformación radial del vientre muscular y se calculó la velocidad de respuesta normalizada mediante tensiomiografía antes y después de la intervención del entrenamiento.

Resultados. Se observaron diferencias significativas ($p<0.05$) según el grupo muscular implicado, siendo el recto femoral y el bíceps femoral los que presentaron mayor potenciación al reducir el tiempo de contracción y activación. Aparecieron diferencias entre musculatura agonista-antagonista —vasto lateral-bíceps femoral— ($p<0.05$), respaldadas por una disminución de la velocidad de activación y contracción en el vasto medial ($p<0.001$).

Conclusiones. La tensiomiografía permite estimar los estados de activación-potenciación de la musculatura responsable del salto en gimnastas de *tumbling*, así como planificar el entrenamiento según el estado de fatiga muscular.

Palabras Clave: Gimnasia; Atletas; Rendimiento atlético; Fatiga muscular (DeCS).

Rojas-Barrionuevo N, Vernetta-Santana M, López-Bedoya J. Functional assessment of muscle response in lower limbs of tumbling gymnasts through tensiomyography. Rev. Fac. Med. 2016;64(3):505-12. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.54004.

Rojas-Barrionuevo N, Vernetta-Santana M, López-Bedoya J. [Evaluación funcional de la respuesta muscular de miembros inferiores en gimnastas de *tumbling* mediante tensiomiografía]. Rev. Fac. Med. 2016;64(3):505-12. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.54004.

Introduction

Since its appearance as a demonstration sport during the Olympic Games of Atlanta 1996 and Sydney 2000, tumbling has increased its recognition worldwide. However, taking into account the intrinsic characteristics and the set of technical, physical and conditional factors, this gymnastic modality requires a detailed study to establish its basis in relation to injury prevention (1).

High performance gymnasts are exposed to demanding training programs, a large number of hours per session and a high volume of repetition of high intensity exercises, causing overload on certain systems and muscle groups (2). The jumping capacity of a gymnast, along with successful performance in floor and jump routines, is considered as an expression of dynamic and isoinertial force, which is essential not only in sports but also in acrobatic gymnastics (3). Reviews on this capacity in aerobic gymnastics, artistic gymnastics and rhythmic gymnastics (4,3,5) have been found, but they are rare in disciplines such as trampoline and tumbling (2,6).

The analysis of injuries related to the technical requirements and distribution of training loads was observed with attention to prevent injuries in a previous study with tumbling gymnasts. This study shows a higher percentage of lesions in lower limbs (72%), presenting the ankles (30%) and knees (10%) as the most affected areas mostly by tears or sprains of moderate severity, and related to tendinous-ligamentous (44%), muscle (32%), bone (16%) and articular (8%) issues (1). These facts demonstrate the need for an individualized, precise and localized, assessment of those muscular structures more frequently required for tumbling practice.

Tensiomyography (TMG) is a non-invasive tool to assess neuromuscular response, muscle stiffness, mechanical characteristics and contractile capabilities of muscle surface, using a bipolar electrical stimulation, and controlled and variable intensity. This tool allows to measure radial displacement of muscle belly (Dm), contraction time (Tc), activation time, latency or reactivity (Td), relaxation time (Tr), contraction holding time (Ts) (7) and, indirectly, the normalized response speed (Vrn) (8).

The purpose of this study was to evaluate neuromuscular response in male elite tumbling gymnasts through TMG and, through the analysis of the time of contraction and activation, the radial displacement of muscle belly and the normalized response rate in the musculature responsible for flexo-extension of knees (9) and extending ankles (10). Likewise, an analysis of the recovery time for each muscle group after the training intervention was attempted.

Materials and methods

Sample

This study involved 12 male tumbling gymnasts with the following characteristics: age 20.6±2.6, weight 67.2±5.5kg and height 173.4±3.2cm (mean ($\bar{x}$) ± standard deviation (σ)). Participants had more than five years of experience in training, and trained for ±3 hours/day, 4-5 times a week and competed exclusively in national events.

All participants were previously informed about the potential risk of the study and signed a written consent approved by the Ethics Committee of Universidad de Granada, following the criteria set out in the Declaration of Helsinki of the World Medical Association for medical research involving human subjects.

Measurement procedure

For evaluation through TMG, a TMG-S1 accuracy sensor (Furlan & Co., Ltd.) was used and placed perpendicularly on the point with greatest muscle diameter of the muscles responsible for flexion-extension in the knee joint and the medial gastrocnemius (MG) for the extension of the ankle (11): vastus lateralis (VL), rectus femoris (RF), vastus medialis (VM) and biceps femoris (BF). These muscle groups were selected as they are the most relevant for capacity jump (9).

An anatomical knee flexion cushion was used at 30° for evaluations in supine position, considering 0° as the maximum joint extension and 5° as flexion with pronation (9). Measuring points were noted with a dermatologic pencil (7,12) (Figure 1).

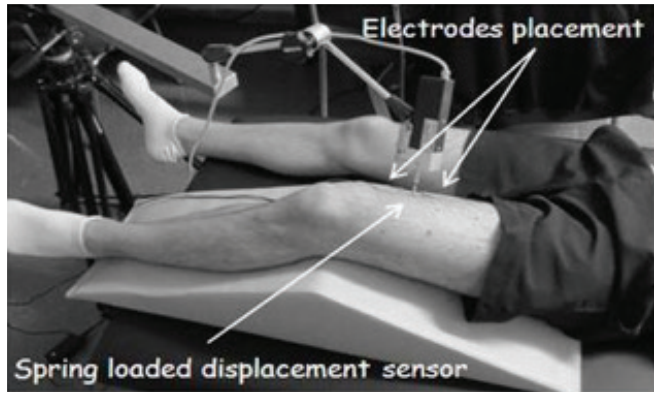

Figure 1. Placing the sensor and electrodes for measurements of the vastus medialis (VM). Source: Own elaboration based on the data obtained in the study.

To cause stimulation and consequent contraction, a bipolar electrical discharge of 100mA in one millisecond was applied with an initial plunger pressure of 1.5x10-2 N/mm-2 (8) and through two electrodes placed at the proximal and distal muscle ends, separated by 2-5cm as indicated by the sensor (13). To avoid post-tetanic activation, each stimulation was performed with sufficient pause between stimuli (8,13-15). The validity of the protocol used with TMG and the reproducibility of the method show that this is a highly accurate tool for this type of work (8).

The parameters measured were Dm, which assesses muscle stiffness; Tc, which is obtained by determining the time between 10% and 90% of the maximum radial displacement; Td, which represents the time it takes for the analyzed muscle to reach 10% of its maximum radial displacement, and Vrn, which shows the relation between the difference of displacement between 10% and 90%, exactly at 80%, and increased time of contraction for the same values in seconds (16).

Training protocol

At the beginning of the protocol, a standard warm-up and smooth running stretching was performed individually: five minutes of continuous running at 8 km/h —controlled by the Sigma Sport RC 1209® heart rate monitor— and four minutes for preset stretching exercises. The tumbling training protocol consisted of 12 sets of 6 repetitions of somersault to front landing from a raised platform with a height of 60cm through a plyometric rebound (3). Performing jumps from this height was determined following Marina (3), who pointed that the Drop Jump (DJ) from 60cm requires more stiffness from gymnasts.

An interval of two minute breaks between sets and five seconds between repetitions was established. The estimated duration of the protocol was about 1 hour and 30 minutes, which included two days off, compared to their weekly workout routine, to prevent influence of fatigue on the data. Participants were always convened at the same range of time (from 10 am to 12 m).

Three days were established to implement data collection and four subjects were individually evaluated each day; they were summoned every 40 minutes. All participants performed the same protocol under the same conditions (exercise room with a room temperature of 21-22°C).

Evaluations were performed by the same evaluator at the end of the warm-up, after the protocol and after 5, 15 and 30 minute-rest intervals as shown in Figure 2.

Statistical analysis

A Shapiro-Wilk Test was performed to verify the normality of distribution and the intraclass correlation coefficient (ICC) for TMG parameters was calculated using two measures per participant, as well as the confidence interval (CI) at 95%. As a rule, ICC below 0.5, between 0.5 and 0.7, and above 0.7 were interpreted as poor, moderate or good reliability, respectively (10). For the analysis of variance (ANOVA), repeated measures of data obtained for VM, RF, VL, BF and intra-protocol GM test were taken into account, through multiple comparison testing using the Bonferroni method and a significance level $p \leq 0.05$. The effect size (ES) (Cohen's d) was calculated through the formula: ($\mu 1$- $\mu 2$)/(pooled standard deviation)

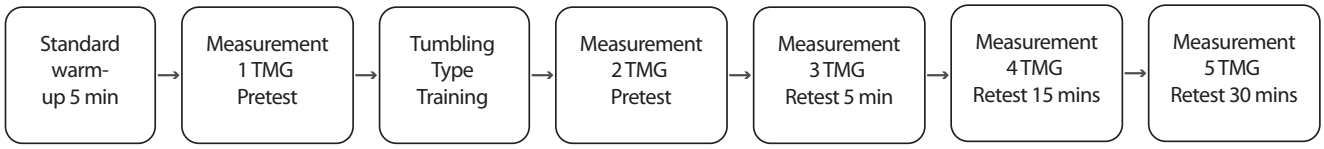

Figure 2. Tumbling measurement protocol design and rest periods between measurements. TU: tumbling; TMG: Tensiomyography. Source: Own elaboration based on the data obtained in the study.

Where $\mu 1$ and $\mu 2$ represent the mean in each condition and the pooled standard deviation was calculated using $[(\sigma 12+\sigma 22)/2]$ (17).

The effect size with values of 0.2, 0.5 and 0.8 were considered to represent small, medium or large differences, respectively (18).

Limitations of the study

The main limitations of this study are determined by a low sample size, exclusively male, so increasing the sample size and establishing the existence of sex differences is considered as useful.

When extrapolating the results the recommendation is to be cautious since these results were obtained through a specific gymnastic training protocol and a type of jump that involves only plyometrics as impulsion means. Therefore, although TMG is shown as a valid and reliable tool, it is necessary to standardize the measurement protocol to avoid possible errors when interpreting results.

Results

Descriptive statistics for each of the evaluated parameters (Tc, Td, Dm and Vrn) shown in Table 1.

Data obtained showed a good or very good reliability for 9 of the 15 values (0.74 to 0.95) and intermediate reliability the other (0.54 to 0.68), except for Td in the RF evaluation, which showed a lower ICC value (0.386) (Table 2).

To test the effects of training on muscles evaluated according to the selected parameters and the rest time, Table 3 shows the results of repeated measures ANOVA between each of the interventions of the evaluation: pretest, posttest, retest 5 minutes, retest 15 min and retest 30 min.

A greater number of significant differences ($p \leq 0.001$) was established for VM to show more variability in all parameters depending on the recovery time, followed by RF and VL ($p \leq 0.05$). By contrast, BF and GM showed less differences ($p \leq 0.05$). Comparison by pairs specifies where these significant differences are found regarding recovery time and muscle group ($p \leq 0.05$) (Table 4).

Data obtained through repeated measures ANOVA and Bonferroni post hoc adjustment for Vrn per muscle group are shown in Figure 3. The normalized response speed (Vrn) of the muscle in VL and VM are higher, followed by GM. The lowest values are found in RF and BF. Statistically significant differences ($p \leq 0.05$) are found in VL after 15 and 30 min rest, in RF at 30 min, in VM at 5, 15 and 30 min, and in BF at 15 min.

The relationship between agonist-antagonist muscle pairs was analyzed according to the time of evaluation, based on the Vrn values obtained and the consequent post hoc adjustment (Bonferroni). It should be noted that this was not a detailed and conclusive analysis of the potential existence of asymmetries or muscle instability, since determining such dysfunctionality should be done based on the muscle set in symmetry expressed as a percentage. Statistical significance between BF-VL and BF-VM ($p \leq 0.05$) muscles was obtained. No significant differences between BF-VM at 0, 5 and 30 minutes, between BF-VM at 30 minutes, nor between BF-RF were found (Table 5).

Discussion

The main findings of this study show that this training caused different tendencies to fatigue depending on the involved muscle group, being RF and BF the most enhanced muscles following the protocol based on the values obtained between pretest-posttest for Tc and Td parameters, highlighting statistical significance in RF, Tc: p=0.040, TE=0.73, td: p=0.006 and TE=0.82. On the other hand, VL, VM and GM experienced no significant changes in these parameters, but showed tendency to fatigue due to the progressive increase over time.

Thus, major differences appear between agonist (VL) and antagonist (BF) muscles, fact that is backed by a decrease in the rate of activation and contraction speed in the VM responsible for stabilizing the knee (9), muscle that causes rapid adaptation contractions to movement in small amplitudes of the knee extension (15). In parallel, the effect of a longer contact time is added during the jump causing a sustained isometric contraction that increases muscle and tendon structures stiffness, muscle volume and strength (19).

Table 1. Results of the descriptive statistics of each parameter according to muscle group and assessment time.

Muscle	Measure	Tc (ms)		Td (ms)		Dm (mm)		Vrn (mm/s)	
		x̄±σ	Min-Max	x̄±σ	Min-Max	x̄± σ	Min-Max	x̄±σ	Min-Max
VL	Pr	22.94±5.15	18.14-34.00	22.11±1.90	19.04-25.95	7.38±2.34	3.86-12.68	36.31±7.18	23.52-44.08
	P0	22.89±4.35	18.12-30.76	22.29±2.57	18.80-27.90	7.19±2.17	4.14-10.77	36.04±6.37	26.00-44.13
	P1	23.79±4.53	19.16-31.53	22.88±2.34	18.75-26.24	7.04±2.13	3.94-10.47	34.67±6.11	25.36-41.74
	P2	24.95±6.51	18.00-41.22	23.30±2.32	20.92-27.23	7.22±2.10	4.16-10.60	33.72±7.18	19.40-44.44
	P3	25.27±5.66	19.84-38.67	23.37±2.55	19.58-28.47	7.12±2.51	3.41-11.19	32.87±6.06	20.68-40.32
RF	Pr	31.39±6.05	24.05-44.18	25.74±3.20	22.76-33.50	10.11±1.61	5.85-12.05	26.29±4.70	18.10-33.26
	P0	29.05±5.37	22.38-40.23	23.52±1.85	20.68-27.75	10.04±1.64	7.16-13.82	28.33±4.80	19.88-35.74
	P1	30.76±5.76	22.14-40.18	24.36±1.91	21.87-28.39	9.82±1.64	6.36-12.00	26.85±5.01	19.90-36.12
	P2	32.69±9.19	23.75-52.85	24.19±2.16	19.86-28.08	8.67±1.60	6.12-10.74	25.99±6.03	15.13-33.67
	P3	34.60±9.04	27.44-53.30	25.37±2.17	22.06-28.64	10.24±2.11	6.52-13.94	24.31±5.04	15.00-29.14
VM	Pr	22.71±2.50	19.06-27.70	21.18±1.51	18.77-23.88	9.17±1.39	7.24-11.71	35.60±3.83	28.87-41.96
	P0	23.10±3.49	19.02-27.70	20.88±1.43	18.52-23.80	10.01±1.57	8.21-14.28	35.25±4.61	25.33-42.04
	P1	25.50±4.19	20.55-34.42	21.78±1.66	19.26-24.32	8.42±1.37	6.36-11.26	32.08±4.83	23.23-38.91
VM	P2	26.63±4.79	20.42-36.28	22.36±1.75	19.72-25.86	7.98±1.97	5.68-12.53	30.84±4.96	22.04-39.17
	P3	26.29±3.85	20.15-33.45	22.66±2.31	19.97-28.35	8.63±1.85	5.87-12.39	31.00±4.44	23.91-39.17
	Pr	34.14±14.34	17.85-63.06	23.69±2.87	19.88-30.45	8.18±2.54	4.93-12.66	26.92±9.77	12.68-44.80
	P0	32.59±12.67	21.31-62.97	22.76±1.89	20.21-26.34	7.39±2.59	3.28-12.13	27.40±8.45	12.70-37.52
	P1	35.66±13.97	21.78-65.99	23.86±2.22	19.52-27.33	8.05±2.72	4.19-11.97	25.29±8.34	12.12-36.71
	P2	40.72±12.52	20.77-66.63	25.34±2.94	20.55-29.54	9.04±3.27	4.28-14.28	22.03±7.81	12.00-38.51
	P3	37.35±13.29	16.12-61.58	24.62±2.64	19.47-28.45	8.14±2.17	3.83-11.69	24.45±10.18	12.98-49.62
GM	Pr	28.43±10.64	15.74-49.80	19.89±1.65	17.57-23.03	3.95±1.12	2.09-5.63	31.27±10.75	16.06-50.81
	P0	28.43±10.26	18.47-46.60	20.69±2.33	17.85-24.38	4.35±1.02	3.31-6.21	30.98±9.53	17.14-43.29
	P1	26.86±4.84	20.94-33.03	20.95±1.49	19.04-23.27	3.85±0.92	2.49-4.94	30.64±5.65	24.21-38.19
	P2	35.57±16.67	21.86-64.94	23.11±2.96	19.55-27.99	4.75±1.79	3.25-8.25	26.16±9.47	12.31-36.59
	P3	27.67±6.16	21.07-38.43	21.71±2.15	18.23-24.15	3.83±1.01	1.75-4.52	30.07±6.20	20.81-37.95

VL: vastus lateralis; RF: rectus femoris; VM: vastus medialis; BF: biceps femoris; GM: medial gastrocnemius; Tc: contraction time; Td: activation time; Dm: radial displacement; Vrn: normalized response speed; Pr: pretest; P0: posttest 0 min; P1: posttest 5 minutes; P2: postest 15 min; P3: postest 30 min; x̄: average; σ: standard deviation; Min-Max: minimum-maximum. Source: Own elaboration based on the data obtained in the study.

Table 2. Intraclass correlation analysis in vastus lateralis, rectus femoris, vastus medialis, biceps femoris and medial gastrocnemius.

Muscle	Variables	ICC (95%)	σ	Sig
Vastus lateralis	Tc	0.818	0.366; 0.983	0.007
	Td	0.909	-0.049; 0.985	0.001
	Dm	0.952	0.848; 0.992	0.000
Femoral rectus	Tc	0.770	0.145; 0.956	0.015
	Td	0.386	0.024; 0.729	0.305
	Dm	0.945	0.911; 0.992	0.000
Vastus medialis	Tc	0.565	-0.196; 0.945	0.113
	Td	0.684	0.212; 0.939	0.042
	Dm	0.748	0.344; 0.947	0.021
Biceps femoris	Tc	0.935	0.880; 0.996	0.000
	Td	0.787	0.373; 0.993	0.012
	Dm	0.660	-0.648-0.983	0.053
Gastrocnemius muscle	Tc	0.776	-0.222; 0.971	0.014
	Td	0.575	-0.603; 0.924	0.105
	Dm	0.545	-0.242; 0.898	0.129

Tc: contraction time; Td: activation time; Dm: radial displacement; ICC: intraclass correlation coefficient; σ: standard deviation; Sig: significance (p≤0.05). Source: Own elaboration based on the data obtained in the study.

Table 3. Results of the analysis of variance for repeated measures per muscle group in Tumbling.

Muscle	Variables	F (gl) P	
VL	Tc (ms)	5.96 (1.63;17.94)	0.014
	Td (ms)	4.22 (4;44)	0.006
	Dm (mm)	0.24 (4;44)	0.911
	Vrn (mm/s)	8.38 (4;44)	0.000
RF	Tc (ms)	3.74 (2.11;23.27)	0.037
	Td (ms)	9.69 (2.01;22.14)	0.001
	Dm (mm)	3.18 (4;44)	0.022
	Vrn (mm/s)	4.62 (4;44)	0.003
VM	Tc (ms)	11.81 (4;44)	0.000
	Td (ms)	13.68 (1.83;20.22)	0.000
	Dm (mm)	9.35 (4;44)	0.000
	Vrn (mm/s)	18.41 (4;44)	0.000
BF	Tc (ms)	2.35 (1.53;16.85)	0.135
	Td (ms)	5.57 (4;44)	0.001
	Dm (mm)	2.12 (4;44)	0.094
	Vrn (mm/s)	3.20 (2.01;22.16)	0.060
GM	Tc (ms)	1.46 (1.84;11.08)	0.271
	Td (ms)	6.23 (4;44)	0.001
GM	Dm (mm)	1.43 (1.92;11.58)	0.277
	Vrn (mm/s)	1.13 (4;44)	0.365

VL: vastus lateralis; RF: rectus femoris; VM: vastus medialis; BF: biceps femoris; GM: medial gastrocnemius; Tc: contraction time; Td: activation time; Dm: radial displacement; Vrn: normalized response speed; F (gl): population variance estimate (degrees of freedom); P: significance value (p≤0.05). Source: Own elaboration based on the data obtained in the study.

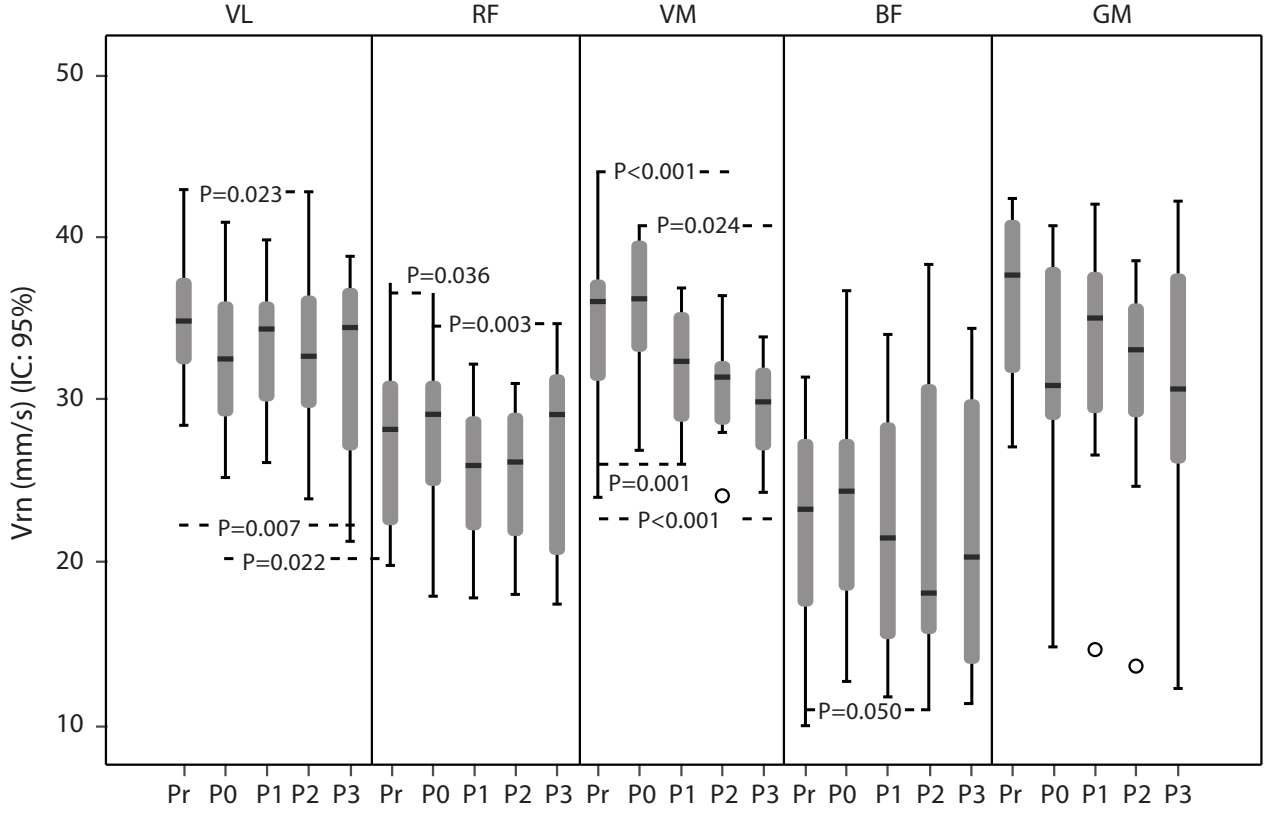

Figure 3. Box plot of normalized response speed (Vrn) in mm/s (CI:95%). VL: vastus lateralis; RF: rectus femoris; VM: vastus medialis; BF: biceps femoris; GM: medial gastrocnemius; Pr: pretest; P0: postest 0 min; P1: postest 5 min; P2: postest 15 min; P3: postest 30 min; P: significance value (p≤0.05). Source: Own elaboration based on the data obtained in the study.

Table 4. Comparison by pairs of the factorial analysis of repeated measures per muscle group in tumbling and post hoc adjustment through Bonferroni.

Muscle	Variance analysis of repeated measures				
	Variables	Comparison by pairs	t(gl) P		ES
VL	Tc (ms)	Pr-P3	-4.69(11)	0.007	0.81
	Td (ms)	Pr-P3 P0-P3	-3.73(11) -3.91(11)	0.033 0.024	0.74 0.76
	Vrn (mm/s)	Pr-P2 Pr-P3 P0-P3	3.95(11) 4.63(11) 3.95(11)	0.023 0.007 0.022	0.76 0.81 0.76
RF	Tc (ms)	Pr-P0	3.62(11)	0.040	0.73
	Td (ms)	Pr-P0 P0-P1 P0-P3 P2-P3	4.78(11) -3.96(11) -6.65(11) -3.69(11)	0.006 0.022 0.001 0.035	0.82 0.76 0.89 0.74
	Dm (mm)	P1-P2 P2-P3	4.23(11) -3.79(11)	0.014 0.030	0.78 0.75
	Vrn (mm/s)	Pr-P0 P0-P3	-3.68(11) 5.14(11)	0.036 0.003	0.74 0.84
VM	Tc (ms)	Pr-P1 Pr-P2 Pr-P3 P0-P2	-4.15(11) -4.78(11) -5.51(11) -3.93(11)	0.016 0.006 0.002 0.023	0.78 0.82 0.85 0.76
	Td (ms)	Pr-P2 P0-P1 P0-P2 P0-P3 P1-P2	-4.74(11) -4.33(11) -7.30(11) -4.26(11) -3,55(11)	0.006 0.012 0.000 0.014 0.045	0.81 0.79 0.91 0.78 0.73
	Dm (mm)	P0-P1 P0-P2 P0-P3	5.33(11) 7.01(11) 3.72(11)	0.002 0.000 0.034	0.84 0.90 0.74
	Vrn (mm/s)	Pr-P1 Pr-P2 Pr-P3 P0-P3	5.93(11) 7.21(11) 6.48(11) 3.92(11)	0.001 0.000 0.000 0.024	0.87 0.90 0.89 0.76
BF	Tc (ms) Td (ms) Vrn (mm/s) Td (ms)	Pr-P2 P0-P2 Pr-P2 P0-P2	-3.63(11) -4.47(11) 3.50(11) -4.54(11)	0.039 0.009 0.050 0.039	0.73 0.80 0.72 0.80

VL: vastus lateralis; RF: rectus femoris; VM: vastus medialis; BF: biceps femoris; GM: medial gastrocnemius; Tc: contraction time; Td: activation time; Dm: radial displacement; Pr: pretest; P0: postest 0 min; P1: postest 5 min; P2: postest 15 min; P3: postest 30 min; t (gl): t-Student (degrees of freedom); P: significance value (p≤0.05); ES: Cohen's d effect size. Source: Own elaboration based on the data obtained in the study.

Table 5. Differences between agonist and antagonist muscles through variance analysis for repeated measures and post hoc Bonferroni adjustment.

Variance analysis Functionality knee joint		VL RF VM				
		F (gl)	p	PH (p)	PH (p)	PH (p)
BF	Pretest	12.42(1.63;18.01)	0.001	0.050	1.000	0.036
	Posttest 0'	8.03(1.92;21.16)	0.003	0.041	1.000	0.090
	Posttest 5'	8.92(1.48;16.30)	0.004	0.026	1.000	0.143
	Posttest 15'	19.08(3;33)	0.000	0.001	0.453	0.006
	Posttest 30'	9.49(1.44;15.92)	0.004	0.067	1.000	0.124

VL: vastus lateralis; RF: rectus femoris; VM: vastus medialis; BF: biceps femoris; F (gl): estimate of the population variance (degrees of freedom); P: significance value (p≤0.05); PH (p): *post hoc* (significance) (p≤0.05). Source: Own elaboration based on the data obtained in the study.

As mentioned above, the protocol focused on plyometric jumping, predominant in training and competition in gymnastics (20). Marina (3) emphasizes on the high volume of plyometric jumps that gymnasts perform during their sporting life, resulting in greater stability in the implementation of vertical jumps, and suggests to perform these type of jumps preferably on elastic surfaces similar to those used in competition.

According to Rodríguez-Matoso *et al.* (23), stiffness determines motor efficiency depending on the sport; this is a quality of gymnasts for achieving high performance in plyometric jumps, and was determined

through DJ from 60cm and 90cm drop (20). Since stiffness requires the first value, this is the starting height for jumps.

Contrary to experiences in VL and GM, after completing the training protocol, Td and Tc values decreased and enhancement was indicated in all muscle groups. Such decrease in Td and Tc is due to high tension and explosiveness actions (9), and workload (21).

In this regard, Šimunič *et al.* (22) emphasize that knowing the exact point where fatigue process overcomes enhancement would be crucial; this is a key aspect to plan training since a brief prolonged exercise generates fatigue as a parallel process to empowerment, first by overcoming it, and then appearing in the end. Dm seems to be affected, to a lesser extent, in the absence of significant changes, except for VM ($p<0.001$), which reaches its greatest stiffness at 15 minutes ($p<0.001$; TE=0.90) and RF ($p<0.05$), which, similarly, achieves maximum stiffness also at around 15 minutes ($p=0.014$; TE=0.78). In both cases the values decrease gradually, indicating a trend toward muscle strengthening.

It has been estimated that certain situations of fatigue or stress, as well as of enhancement, influence greatly on the parameters evaluated since, on the one hand, an enhanced muscle has low values of Dm, Ts and Tr and a decrease in Tc and, on the other, a fatigued muscle has high values of Dm, Td, Ts and Tr as well as an increasing trend towards Tc (23). However, if Dm increases excessively, this may indicate muscle weakness, high fatigue or adaptive response to resistance training according to the literature (24).

VM recovers its initial Td values after five minutes of rest ($p=0.012$; TE=0.79), while Tc indicates fatigue by progressively increasing even 30 minutes after these explosive force actions ($p=0.002$; TE=0.85) (25). Similarly, BF reestablishes these parameters within five minutes of rest ($p<0.05$), while RF needs 15 minutes for both (Tc: $p=0.039$; Td TE=0.73 and $p=0.009$; TE=0.80). VL and GM show a slight increase, but progressive, of fatigue as Td increases ($p<0.05$), while enhancement is seen through Tc, being more evident in VL ($p=0.007$; TE=0.81).

In contrast, a study on cyclical sports showed that most neural fatigue was reached during the eccentric contraction phase, with Tc recovery after 15 minutes of completion of the test (26).

Gastrocnemius, along with the soleus and plantar flexors of the foot, is one of the extensors of the foot causing significant improvement in jumping ability, as they contribute in the transmission of the lifting power to the trunk in the last 20% of the impulsion (27). In this study, low values of Dm in GM are reported, which indicates an enhanced muscle and stiffness that allows greater efficiency in the actions of an explosive nature (23).

Starting levels in the normalized response speed (Vrn) for VL, VM and GM are higher than for RF and BF, hence the significant differences found in the speed of contraction between BF-VL and BF-VM, in both cases, reaching the biggest differences within 15 minutes after completion of the protocol ($p=0.001$ and $p=0.006$, respectively). These results can be compared with those by Heredia *et al.* (28), who got a greater Vrn in the muscles of the quadriceps in the presence of a higher percentage of fast fibers, as well as higher values of VL and BF in former players. In another study with volleyball players on jumping ability, a higher Vrn was estimated for VL and VM in relation to RF and BF (16). In this manner, excessive muscle tone can generate decompensation, resulting in functional asymmetries in the flexo-extensor muscles of the knee, where these values are lower than 65% (22,23).

Upon completion of the training, VL, VM and GM values decrease gradually during the first 30 minutes, but the latter tends to restore its starting values after 15 minutes. On the contrary, a gain of Vrn for RF and BF is obtained, causing greater joint instability right before the end of the training takes place, but the initial values quickly recover after five minutes.

Several studies considered Vrn relevant as an indicator of functional instability and influence on the ability to jump (29), when estimating the loss of muscle mass and the decreased contractile elements when there is deterioration in the rate of contraction (28).

Practical applications

TMG is presented as a valuable tool for estimating the threshold at which muscle strengthening reaches levels of unwanted fatigue, so changes in training sessions designed to meet muscle deficiencies that create potential instabilities are recommended, especially in the ankle and knee joints; the latter are the main involved in the successful performance of the jump and optimal athletic performance and prevent, therefore, both lateral and functional instability. Also, implementing a longer recovery time of the muscles responsible for flexion and extension of the knee is suggested in order to prevent such instability and possible risk of injury when plyometrics are included in the same training session.

Conclusions

The major muscle groups boosted following the Tumbling track protocol (RF and BF) show greater activation and enhancement as a result of explosive actions arising from plyometric jump, even the recovery time, regarding activation and consequent contraction, is smaller and allows that fatigue does not interfere with the mentioned functional balance. Likewise, RF and BF require more time to cause neural activation and generate a stronger contraction.

Greater involvement in contraction time and contact with the surface implied an increase in the level of enhancement, which was held for the first five minutes and gradually disappeared. The decrease in the rate of contraction, as occurred between BF-VM and BF-VL, increased agonist-antagonist functional differences in the plyometric co-contraction, generating higher levels of joint instability, estimating that VL and VM are the muscle groups with the highest percentage of fast fibers and showing great involvement in this type of characteristic jump in tumbling.

Conflicts of interest

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REFLECTION PAPER

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Airway management by the general practitioner in trauma patients. Technical and non-technical skills

Manejo de la vía aérea por el médico general en paciente traumatizado. Habilidades técnicas y no técnicas

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| Abstract |

General practitioners must constantly face challenges imposed by their profession when performing interventions that are necessary for their patients. Many of these interventions not only require proper use of theoretical knowledge, but also putting into practice non-technical and psychomotor skills developed through professional training. Given the specific characteristics of each patient, the clinical setting in the which procedure takes place and the limited skills of the professional, the management of the airway of a patient with trauma injuries in the emergency room represents a major challenge for physicians.

Keywords: Physician; Trauma; Primary Health Care; Learning; Complications (MesH).

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| Resumen |

El médico general con frecuencia debe enfrentarse a los retos impuestos por su profesión realizando de manera efectiva intervenciones vitales para los pacientes. Muchas de estas intervenciones requieren no solo del uso de conocimientos teóricos sino también de la puesta en práctica de habilidades psicomotoras y no técnicas desarrolladas a lo largo de la formación profesional. Debido a las características particulares de cada caso, al escenario clínico en el cual se debe realizar el procedimiento y a las habilidades limitadas del profesional, el manejo de la vía aérea en el paciente en urgencias (traumatizado) representa un gran reto para los médicos.

Palabras clave: Trauma; Atención primaria; Aprendizaje (DeCS).

Domínguez-Sánchez JD, Sánchez-García L, Navarro-Vargas JR. [Manejo de la vía aérea por el médico general en paciente traumatizado. Habilidades técnicas y no técnicas]. Rev. Fac. Med. 2016;64(3):513-5. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.53937.

Introduction

A general practitioner must be able to perform complex procedures in critical situations, since this is crucial for saving the lives of patients in chronic state. A timely and effective intervention in these situations increases patient survival rates, reduces the consequences and represents a profit on the economic burden to the health system (1).

Given its importance in the initial approach to the trauma patient, management of the airway is presented as one of the critical challenges for both pre-hospital care and primary emergency care. Management of airways corresponds to letters A and B of the initial assessment and treatment approach (ABCDE) to a politraumatized patient.

Permeabilizing and securing the airway allows protection and control of ventilation assistance, which becomes the main issue in most trauma patients (2,3). Thus, the physician should not be an inexperienced professional and, instead, must have the relevant knowledge and skills required to perform a complete, faster, timely and appropriate management of the airway in these patients.

Airway management

Managing the airway became highly important in the clinical practice in the early twentieth century, when the American Society of Anesthesiologists (ASA) showed that adverse events associated with its mishandling were the main cause of morbidity and mortality during anesthesia (4). Surprisingly, it was established that most adverse events and complications (75%) were caused by poor procedures and that a large number of them (70%) were considered preventable (5).

Practices in the major in Medicine

The skills required for good management of the airway are based on the acquisition of declarative (knowing why) and procedural knowledge or training knowledge (knowing how) and on familiarity with different devices, techniques and algorithms for the

procedure; psychomotor skills can be acquired in simulation labs and the competences in hospitals directly with patients.

Students must carry out clinical practice in the hospital context, where their integration with the medical team is tested and have to gradually show a proper and comprehensive performance (6). The type of training received in the academy and the progressive delegation under close monitoring of these clinical activities are crucial for quality and sufficient clinical performance, while they contribute to reduce complications of cases by more than 50% (1,5,7,8).

Importance of airway management in critically ill patients

Securing the airway and monitoring ventilatory patterns in critically ill patients are determining factors for patient recovery and for the decrease of inpatient stay time in critical care units. During this procedure, tracheal intubation is the Gold Standard, which is why knowing how to do it and previous experience in simulation laboratories and hospital environment is essential for the professional, so that he has enough competence to practice it. There is evidence that multiple attempts or failures when performing this procedure lead to extended periods of apnea, making the patient undergo hypoxia, hypoventilation and trauma of the pharyngo-laryngeal tissues, which can further compromise survival (8).

The NAP (National Audit Project) report by the Royal College of Anesthetists and the Difficult Airway Society from the United Kingdom 2011 (9) showed that 23% of deaths are related to failure in recognizing esophageal intubation in the emergency room and in the intensive care unit (ICU), and also that physicians with limited experience in managing the airway are involved.

The study by Mort (10), with more than 10 000 emergency intubations outside the operating room performed by doctors who were not anesthesiologists, found multiple intubation attempts associated with morbidity and mortality; the following figures were obtained when such attempts were compared against successful intubations: high rates of hypoxemia (70% vs. 11.8%), regurgitation of gastric contents (22% vs. 1.9%), aspiration (13% vs. 0.8%), bradycardia (21% vs. 1.6%) and cardiac arrest (11% vs. 0.7%). These data led to conclude that airway management requires not only knowledge, but also appropriate devices and alternative techniques, which include plans and handling algorithms, and a health team with optimal non-technical skills.

The difficulties and complications (Figure 1) occur more frequently with emergency intubation, which occurs in 20% of interventions performed. In addition, patients with severe trauma have a higher incidence of adverse events and more severe complications. The conditions that can aggravate these probabilities include environmental factors (context), intrinsic patient factors, lack of instrumentation (devices) proper materials and difficulties for monitoring (8).

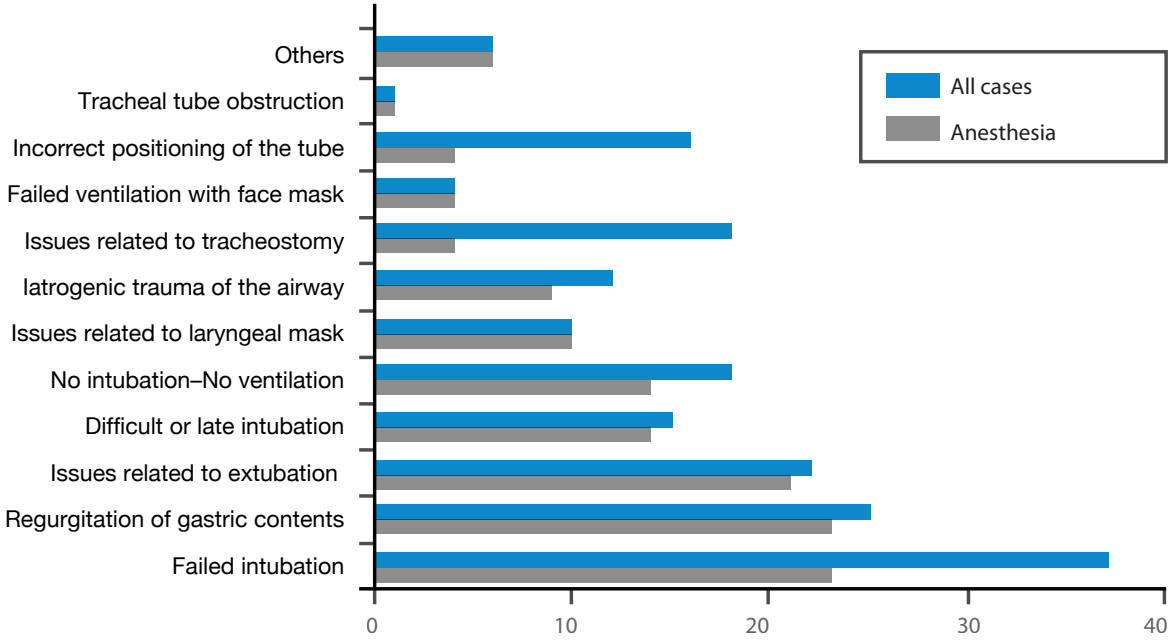

Figure 1. Main problems found when managing airway reported in the NAP4 2011 study. Source: Own elaboration based on Cook *et al.* (11).

Human errors (including misjudgment, lack of use of the check list, technical failures, negligence, rush, inexperience, and communication and equipment problems) were determined as the cause of more than 80% of critical incidents. It is relevant to highlight that miscommunication and poor performance in teamwork (11) are skills that are not considered technical but cognitive, social and personal resources that complement the technical skills and contribute to the correct execution of a task safely and efficiently; these skills are not taught or reinforced in the educational environment (12).

In the NAP5 report, Tim and Pandit attributed adverse events during anesthesia practice to preventable errors (75-90% of cases) due to problems of education and lack of training (13). It has been observed that, when handling the airway, serious complications have been judged in retrospect as suboptimal or poor quality in over 75% of cases; similarly, poor communication and the difficulty of teamwork contribute greatly to the poor results obtained (11).

Training in technical and non-technical skills

Current workshops on airway management have focused on theoretical knowledge and technical skills, with few hours of practice, ignoring non-technical skills which are key for the organization, leadership, successful team behavior, handling of

stressful situations, among others. These non-technical skills allow integrating medical knowledge with what is currently known as acquisition of skills; therefore, performing additional procedures and having an appropriate interaction with the environment and other actors who are in the environment can be achieved (5,14).

Enough practice time should be scheduled for acquiring the necessary skills for airway management. On average, more than 50 interventions or practices are required to achieve a success rate of 90% (15), of which 18% requires expert assistance after 80 intubations; this depends on the difficulty that securing the airway represents due to the characteristics of the patient (obesity, micrognathia, scars on the neck, limited mouth opening, difficult head extension, etc.) (15).

The learning process should consider all available resources throughout medical training, so that the student can obtain knowledge and technical and non-technical skills. Kennedy *et al.* (16) analyzed education based on the use of simulators for learning technical skills to manage the airway, finding that the simulation, as a learning method, was superior to "no intervention" to acquire skills and knowledge, and greater than "no intervention simulation" to learn skills but not to gain a comprehensive understanding. However, despite improvements and continuous studies like this, intended to optimize simulation-based training, no consistent results have been obtained so far (15,17).

Given these findings, new models of medical education should be developed to allow students to acquire, from their early stages of training, technical and non-technical knowledge through case discussions (clinical reasoning) or actual situations in which they must face, not only the clinical problem, but also the environment and teamwork (18,19). This practice-based model (demonstrative interventions) can also help achieve and maintain in force the objective of managing the airway efficiently by the health care professional (6,20).

In conclusion, medical schools must rethink the role of doctors when providing training on primary care of patients requiring critical interventions. Safe approach to the airway and tracheal intubation (gold pattern) are situations for which the future professional must be trained, not only for acquiring technical skills but also non-technical skills, since this theoretical and practical knowledge allows interventions, first, in a simulation lab and then in a clinical setting, to acquire skills and achieve optimal clinical performance with patients.

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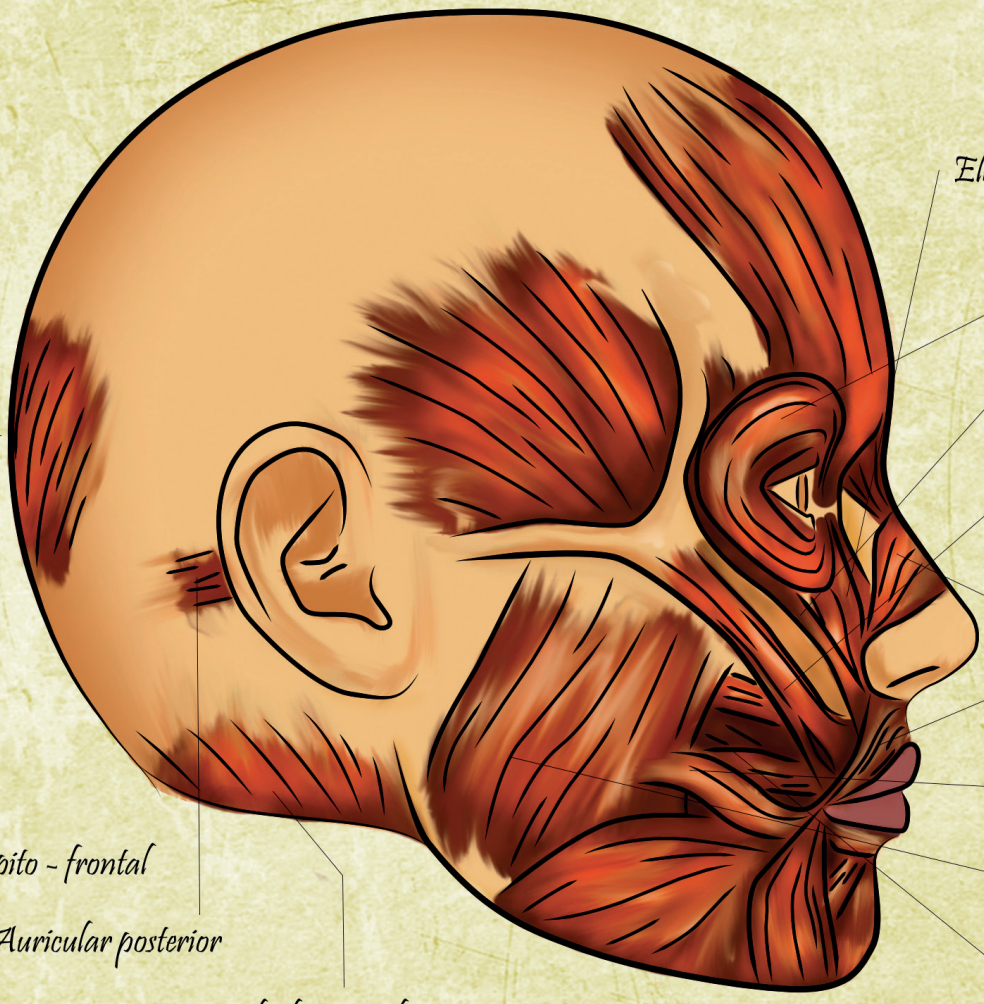
Miología Facial Lateral



Elevador común del ala de la nariz y el labio superior

Músculo orbicular de l ojo

Cigomático menor

Cigomático mayor

Músculo nasal

Músculo orbicular de los labios

Músculo risorio

Masetero

Bucinador

Músculo occipito - frontal

Auricular posterior

Esternocleidomastoideo

César Alexander Eslava Franco
"Mapas anatómicos"
Universidad Nacional de Colombia

REFLECTION PAPER

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One hundred years after the expedition by Harvard University to Peru to investigate Carrion's disease. Lessons for science

Cien años de la expedición de Harvard a Perú para investigar la enfermedad de Carrión. Lecciones para la ciencia

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| Abstract |

In 1913, around 100 years ago, the Harvard University sent an expedition to Peru, led by Richard Strong, to investigate Carrion's disease. This paper provides a critical review of the scientific research carried out in this expedition.

Richard Strong was a physician who performed unethical human experimentation in the Philippines and China. In Peru, Strong conducted experiments on humans to inoculate wart secretions to a psychiatric patient, which led him to replicate the Peruvian wart in this individual, although he could not replicate Oroya fever. Based on this experiment, and without taking into account epidemiological and clinical evidence, the Harvard expedition erroneously concluded that Oroya fever and Peruvian wart were two different diseases.

A retrospective review of the scientific work conducted by the expedition in Peru allows drawing the following lessons for science: a) disapproving unethical human experimentation conducted by the expedition; b) to determine the cause of infectious diseases, it is necessary to obtain the best scientific, experimental and observational evidence, and c) to acknowledge that, despite the poor infrastructure, researchers in developing countries are able to produce high-quality scientific knowledge that may surpass the knowledge generated by researchers in developed countries

Keywords: Carrion's Disease; Bartonella Infections; Oroya Fever; Bioethics (MeSH).

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| Resumen |

Hace poco se cumplieron 100 años de la expedición de la Universidad de Harvard a Perú, liderada por Richard Strong, para investigar la enfermedad de Carrion. El presente estudio realizó una revisión crítica de la investigación científica de dicha expedición.

Richard Strong era un médico con antecedentes relacionados con la realización de experimentaciones humanas antiéticas en Filipinas y China. En Perú, Strong realizó experimentación humana al inocular secreciones de verruga en un paciente psiquiátrico, logrando reproducir en este la verruga peruana, pero no la fiebre de la Oroya; con base en este experimento, y sin considerar la evidencia epidemiológica y clínica, la expedición de Harvard concluyó erróneamente que la fiebre de la Oroya y la verruga peruana eran dos enfermedades diferentes.
Una visión retrospectiva de la labor científica de la expedición de Harvard en Perú lleva a extraer las siguientes lecciones para la ciencia: a) se debe condenar la antiética experimentación humana realizada por la expedición de Harvard; b) es necesario obtener la mejor evidencia científica, experimental y observacional en la causalidad de las enfermedades infecciosas, y c) es necesario reconocer que en países subdesarrollados se puede generar conocimiento científico de alta calidad y que, pese a la escasa infraestructura, puede ser mejor al de los países desarrollados.

Palabras clave: Enfermedad de Carrion; Infecciones por Bartonella; Fiebre de Oroya; Verruga Peruana; Bioética (DeCS).

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Introduction

Carrion's disease or Bartonellosis by *Bartonella baciliformis*, also called Peruvian wart or Oroya fever, is a South American infection, scientifically reported only in Ecuador, Colombia and Perú, the latter being the most affected country, where it has been documented even in mummies from pre-Inca times (1).

This disease has two clinical stages: the stage known as Oroya fever, which is characterized by fever and severe hemolytic anemia type, and a later one, in which the patient develops the Peruvian wart. Common sense suggests that since these two phases are so dissimilar, they constitute two different diseases; however, it has

been proven that both conditions are part of the same pathology. This assumption was established by the unicist theory of bartonelosis by *B. bacilliformis* (2) (Figure 1). After quinine, this concept is considered the second most important contribution of the Peruvian medicine to the science community. In general terms, there is little information on the scientific achievements of Latin American science, so its actual history is unknown.

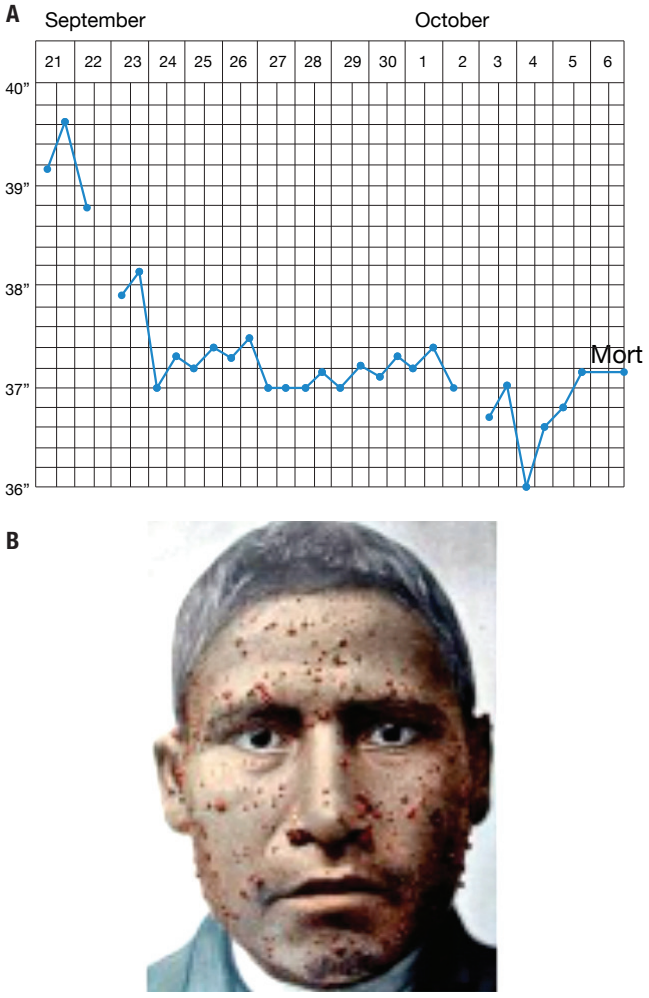


Figure 1. Unicist theory of Carrion's disease.
A) Febrile curve by Daniel Alcides Carrión, who suffered from Oroya fever; B) Patient with Peruvian wart. Source: (3).

Recently, the expedition to Perú by the School of Tropical Medicine of the Harvard University, headed by Richard Strong who was highly interested in Carrion's disease, celebrated its hundredth anniversary. This study provides a critical review of the scientific research conducted in this expedition.

Richard Strong

Richard Strong, American M.D, was born in Virginia in 1872, graduated from Yale University and John Hopkins University, and participated in the war between Spain and the US, which resulted in the transfer of several Spanish colonies, including the Philippines, to American dominance. After the war, Strong remained in the Philippines as the head of the biological laboratory of the Scientific Office (4,5); there, in 1906, he performed experimental inoculations with a vaccine for cholera in 24 men secluded in the Bilibid Prison, Manila, of which 13 died of the plague according to the autopsy. These vaccines may have been contaminated with *Yersinia pestis*.

Strong received harsh comments for his involvement in this event. The General Committee of the Philippines, in charge of the investigation, accused him of negligence; nonetheless, the prosecution exonerated him because his acts were informed to the US Congress and to the president, Theodore Roosevelt, who ordered not to conduct a research or a formal trial (6,7) against him. In 1911, with the support of the Red Cross and the U.S. War Department, Strong was sent by his government to China to investigate the bubonic plague in Manchuria (8); there, he relapsed into his unethical research practices when performing experiments with intravenous therapies. Chinese doctors suspected this behavior since patients who received his treatment died within the same day. This situation prompted the scientist to abandon his experimental therapeutic research, and work on etiological and anatomopathological research instead (8).

In 1912, Strong to returned the Philippines and performed illegal human experimentation on prisoners sentenced to death to determine whether a diet based on rice produced beriberi in them; as a reward, the 29 "volunteers" received all the cigarettes and cigars they wanted (7). It seems that this researcher was the first to use prisoners as subjects for large-scale unethical human experimentation (9). Decades later, during the Nuremberg trial, the defense of Nazi doctors —like Gerhard Rose, director of the Department of Tropical Medicine of the Robert Koch Institute in Germany and author of torture and experiments on Jews— cited that the experiments conducted by Strong were never sanctioned (10). Despite his unethical background in human experimentation, the Harvard University appointed him in 1913 as the first director of the newly established School of Tropical Medicine and appointed him to lead an expedition to Peru.

Harvard research expedition in Perú

In 1913, the School of Tropical Medicine Committee of the Harvard University traveled to Peru to obtain samples for the study of the Peruvian wart; this commission was headed by Richard Strong, with the collaboration of David Matto —Head of the Department of Bacteriology and Microscopic Techniques of the Faculty of Medicine from Universidad de San Marcos and director of Manicomio del Cercado (11-13)— and of Julio C. Tello, director of the Museum of Anthropology. In the final report of the expedition, the scientific community declared that the help of Julio C. Tello was indispensable, and he was appointed as delegate of the United States to the Fifth Latin American Medical Congress held in Lima. In this congress, held from November 9 to 16 in 1913, a preliminary report of the expedition was presented by the Peruvian microbiologist Gastiaburu, a member of the commission.

The national press covered the Fifth Latin American Medical Congress for a week, so the preliminary report of the Harvard expedition was exposed not only to the medical community, but to the general public; all activities performed by foreign delegations were published daily by the press, thus, the findings of the expedition were published in the social and scientific spheres (14-20).

After arriving in Peru, the expedition worked in the laboratory of the Municipal Institute of Hygiene, where experiments were performed on animal, as well as in a patient with a psychiatric disorder.

Bacteriology in Peru was just consolidating by the time when the Harvard expedition arrived. Ricardo Flores donated a bacteriology laboratory to the Faculty of Medicine and gave a free course on microscopic and bacteriology techniques for a year; then the course was assigned to David Matto, who was the main scientific collaborator of Richard Strong upon his arrival in Peru.

The textual conclusions by Harvard were:

> "From our research, we concluded that the eruptive Peruvian wart and the severe Oroya fever represent two different diseases; the first is caused by a virus, [...] while the latter is caused by a parasite organism located in the red blood cells [...]" (11, p5).

From a scientific point of view, there are four important facts in the report by the Harvard expedition:

1. It recognized the *B. baciliformis* as the etiologic agent of Oroya fever and its name was proposed in honor to Barton.
2. It wrongly raised the dualist theory, stating that the Oroya fever and the Peruvian wart were different diseases caused by different etiologic agents and ignoring the scientific conclusions of Carrion.
3. It acknowledged that bartonelosis by *B. baciliformis* begins in the endothelium; endothelial cells were named Strong cells for years after the expedition.
4. It carried out unethical human experimentation on a psychiatric patient.

Microbiological research on Peruvian wart was initiated by Vicente Izquierdo, Chilean, in 1885 (21); at the same time, a Peruvian medical student named Daniel Alcides Carrión, considering that a Chilean scientist was leading an investigation on this disease, decided to make a historic experiment with autoinoculation of secretions of Peruvian wart to further studies. The scientific interest that Carrión had was stimulated by a scientific nationalism since Peru had lost the war against Chile (22).

Harvard proposes the name of *Bartonella baciliformis*

Alberto Barton Thompson became a medical student at Universidad de San Marcos in 1894 and devoted his research to the microscopic observation of several samples of patients diagnosed with Peruvian wart since 1898. In 1899, he worked as a temporary intern at Hospital Italiano, where his main goal was to look for patients with suspected diagnosis of this disease in order to obtain blood samples and further research on his thesis project, which aimed to find the germ that killed Carrion (23,24).

Barton investigated and graduated as a doctor with the thesis "The pathogen of the Carrion disease" (25), study where a recurrent germ located in the spleens of five patients with severe Carrion fever was described; Barton was granted a scholarship and continued his studies in London due to his bacteriological findings. Meanwhile, in Lima, doctors Ugo Biffi, Manuel Tamayo and Julio César Gastiaburu reported that the germs found in his thesis were contaminating bacteria. Barton himself, after returning from Europe, acknowledged his mistake (26). Also by that time, Biffi observed the *B. bacilliformis*, but did not recognize it in the same way as done with photomicrographs (26).

In 1905, after conducting graduate studies at the School of Tropical Medicine in London, Barton specialized in the study of the Peruvian wart in the laboratory of Hospital Guadalupe del Callao. When evaluating the peripheral blood smears of two of his patients, structures that resembled bacilli in red blood cells drew his attention. In the meeting that commemorated Carrion's sacrifice, held in October 5, 1905, the researcher released these findings on a preliminary basis; then, on January 15, 1909, he published his full work entitled "Description of endoglobular elements found in patients with wart disease" in The Medical Chronicle (27), although, few Peruvian scientists believed in his discovery after its publication. During the Fifth Latin American Medical Congress held in Lima days before the Harvard report, Ernesto Odriozola and Julian Arce did not mention the discovery of Barton in their lectures, the most anticipated of the event (16,27). Furthermore, Julian Arce, the main witness of the Carrion's experiment, stated in this conference, in relation to the etiology of the Carrion's disease, that "this is not a bacterium [...] we can say that is a protozoan" (17)

The Harvard expedition recognized the *B. baciliformis* and proposed the genus name in honor to Barton. In the Fifth Latin American Medical Congress, Barton was invited to present the details of his discovery (19).

Harvard's dualist theory

Oroya fever and Peruvian wart are two different diseases

The Harvard commission conducted an experiment inoculating a wart exudate from the shoulder of a psychiatric patient; scientific findings included:

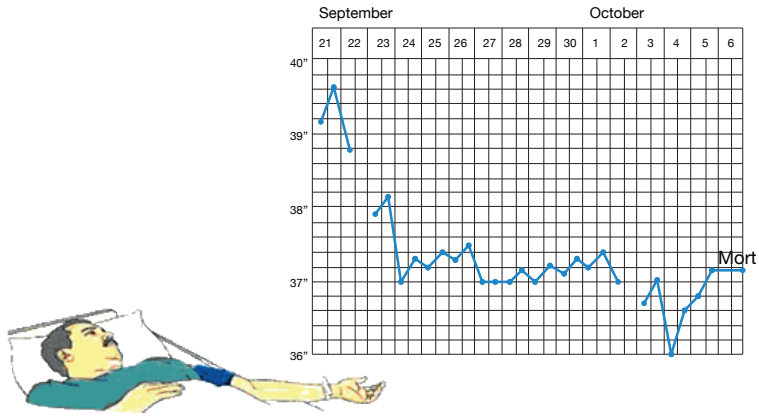
1. The patient did not reproduce Oroya fever, only the Peruvian wart.
2. No bacteria were found in histological sections of warts, and since warts resemble smallpox eruptions, a virus similar to this disease was proposed.

These two findings, along with the recognition of the *B. baciliformis* in the samples from patients with Oroya fever, caused the erroneous conclusion that the Peruvian wart and the Oroya fever were two different diseases caused by different germs: Peruvian wart was caused by a virus and Oroya fever by *B. baciliformis*; in this way, Harvard raised a dualist theory. The verbatim report of the findings of the commission stated:

> "After studying these conditions in Perú, we conclude that the Peruvian wart and the Oroya fever are two different diseases. We have been able to show that the first is caused by a virus, and the second by an organism that parasitizes erythrocytes and endothelial cells" (12, p14).

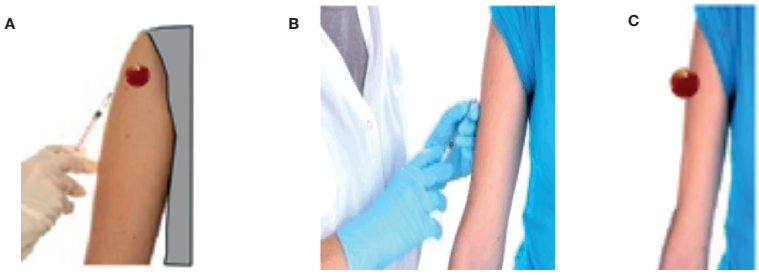
Given the prestige of Harvard University, the erroneous conclusions of the committee were disclosed and reached medical texts worldwide; for example, the Treaty of Tropical Diseases by Manson, at the time, exposed the Oroya fever and the Peruvian wart in different chapters, while various journals indicated that the wart was caused by a virus. (28,29) (Figure 2).

The expedition erroneously concluded that the Oroya fever and the Peruvian wart were different diseases based only on experimental evidence without considering observational, clinical and epidemiological facts. This conclusion was wrong because science must seek as much evidence as possible on the causality of an infectious disease.



First finding:
- *Bartonella baciliformis* was isolated in patients with Oroya fever.

First conclusion:
- Oroya fever is caused by Bartonella baciliformis.



Second finding:
- The Peruvian wart was experimentally reproduced.
- Oroya fever, previous to the Peruvian wart, is not reproduced.
- No Bartonella bacillifornis culture is achieved in the experimental wart.

Second conclusion:
- Oroya fever and Peruvian wart are different diseases; the Peruvian wart is caused by a virus.

Figure 2. Harvard report. a) A wart tissue is removed from a patient. b) wart secretions are inoculated from a experimental wart in a psychiatric patient. c) the patient develops a wart experimentally. Source: Own elaboration based on the data obtained in the study.

The rejection of the Harvard dualist theory in Peru

The publication of the report by the Harvard commission was criticized in various publications and conferences by various Peruvian researchers like Alberto Barton, Julián Arce, Ernesto Odriozola, Raúl Rebagliati, Oswaldo Hercelles, Carlos Monge, among others. (29-33). Oswaldo Hercelles, regarding the Harvard report, stated:

> "The American Commission of the Harvard School, headed by Dr. Strong, designated the disease with the name of *Bartonella baciliforme*, but this same commission made a mistake, [...] by concluding that the Peruvian doctors were making a mistake and that these were two different diseases [...] consequently, the clinical interpretation of all Peruvian doctors had been wrong for many years, which brought serious moral damage, as it was the equivalent to declaring to the world that the sacrifice of Daniel Alcides Carrión had been completely useless" (30, p240).

Odriozola proclaimed the unity of Oroya fever and Peruvian wart based on clinical and epidemiology data and describes that there are countless cases of Oroya fever during which wart rash appears; among these, several cases of patients who traveled to Europe and developed the wart stage on the continent were found (32). Carlos Monge Medrano, recognized for his studies in heights, also conducted a productive scientific work on this disease; at the School of Tropical Medicine in London, he studied and noted that the mistakes of the Harvard expedition were the consequence of its short stay in Peru (three months) and, therefore, its conclusions were premature (33) (Figure 3).

In 1926, Noguchi *et al.* (34) cultured and conducted serological cross-germs tests isolated from Oroya fever and Peruvian wart; these tests resulted in both diseases being caused by a single etiologic agent: *B. baciliformis* (34).The Harvard University conducted a second expedition confirming the findings of Noguchi (35-36) and concluding the following:

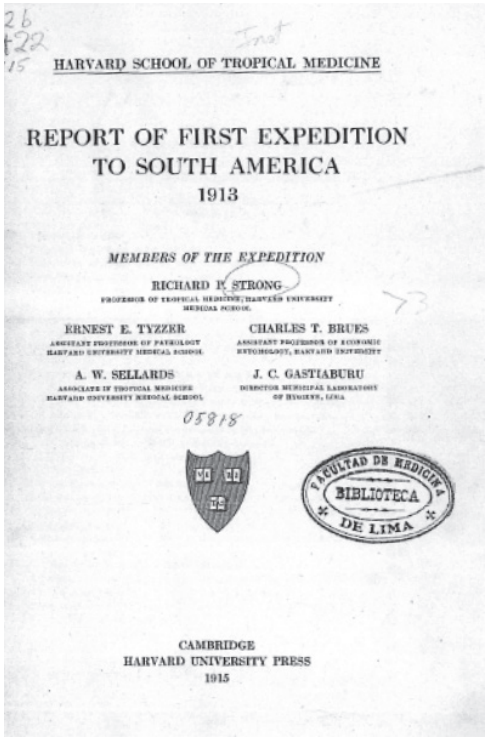
> "The Bartonella culture in both forms of the disease confirms the idea that the Peruvian wart and the severe Carrion fever are produced by the same microorganism.
>
> [...] Hopefully our studies will serve to correlate and complete the important work done by Peruvians and other researchers on this disease" (35, p41).

Even after the bacteriological demonstration of the unicist theory by Noguchi, French scientists at the Pasteur Institute (37) interpreted wrongly Noguchi's findings when two seeds were observed in photomicrographs and tried to revive the dualist theory, postulating again that different germs caused Oroya Fever and Peruvian wart; the main exponent of this position was the scientist André Lwoff, head of the laboratory at the Pasteur Institute and member of the French Society of Exotic Pathology.

Lwoff, Nobel Prize of Medicine in 1965 for his scientific contributions in microbiology (38), ignored the findings of the medical student Daniel Alcides Carrión and the Peruvian Medical School and persisted in the theory that the Oroya fever and the Peruvian wart were two different diseases. The main advocate of the unicist theory, before French scientists, was the Peruvian doctor Ramon Ribeyro. The Peruvian National Academy of Medicine, in response, issued a joint statement defending and consolidating the unicist theory to date (39).

The contrast between the two theories caused a broad scientific discussion between the Harvard University and the Peruvian Medical School and several hypotheses were proposed: on the one hand, the mistaken dualistic theory of Harvard (Figure 3), which stated that the Peruvian wart and the Oroya fever were two different

infections; on the other, the theory that stated that Oroya fever was caused by *B. baciliformis* and the Peruvian wart by a virus, and finally, the defense of the unicist theory (Figure 5), whose validity was demonstrated through subsequent bacteriological research.



HARVARD SCHOOL OF TROPICAL MEDICINE

REPORT OF FIRST EXPEDITION TO SOUTH AMERICA 1913

MEMBERS OF THE EXPEDITION

RICHARD P. STRONG

ERNEST E. TYZZER

CHARLES T. BRUES

A. W. SELLARDS

J. C. GASTIABURU

05818

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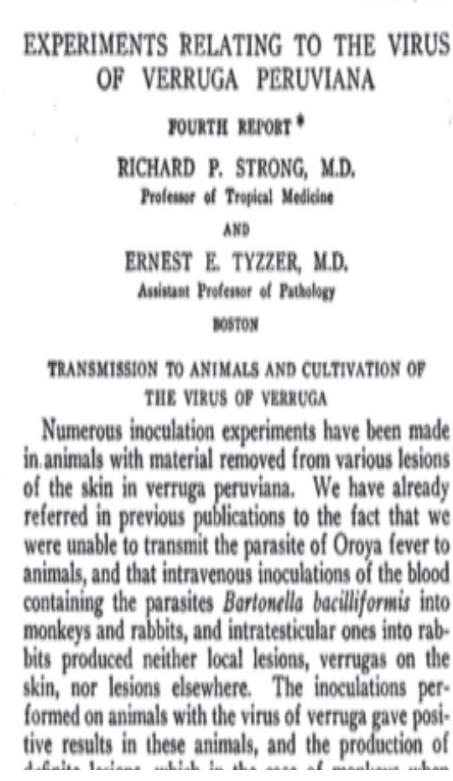
Figure 3. Scientific debate between the Harvard University and the Peruvian Medical School. Dualist theory. Source: (12).



EXPERIMENTS RELATING TO THE VIRUS OF VERRUGA PERUVIANA

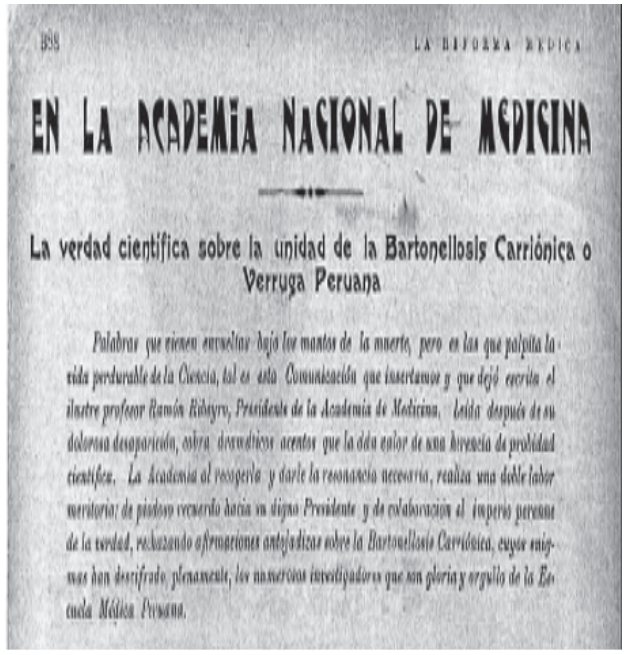
FOURTH REPORT *

RICHARD P. STRONG, M.D.
Professor of Tropical Medicine
AND
ERNEST E. TYZZER, M.D.
Assistant Professor of Pathology
BOSTON

TRANSMISSION TO ANIMALS AND CULTIVATION OF THE VIRUS OF VERRUGA

Numerous inoculation experiments have been made in animals with material removed from various lesions of the skin in verruga peruviana. We have already referred in previous publications to the fact that we were unable to transmit the parasite of Oroya fever to animals, and that intravenous inoculations of the blood containing the parasites *Bartonella bacilliformis* into monkeys and rabbits, and intratesticular ones into rabbits produced neither local lesions, verrugas on the skin, nor lesions elsewhere. The inoculations performed on animals with the virus of verruga gave positive results in these animals, and the production of

Figure 4. Scientific debate between the Harvard University and the Peruvian Medical School. Different causes of Oroya fever and Peruvian wart. Source: (28).



LA REFORMA MEDICA

EN LA ACADEMIA NACIONAL DE MEDICINA

La verdad científica sobre la unidad de la Bartonellosis Carriónica o Verruga Peruana

Palabras que vienen envueltas bajo los mantos de la muerte, pero en las que palpita la vida perdurable de la Ciencia, tal es esta Comunicación que insertamos y que dejó escrita el ilustre profesor Ramón Ribeyro, Presidente de la Academia de Medicina. Leída después de su dolorosa desaparición, sobre desconocidos acentos que la dan calor de una herencia de probidad científica. La Academia al recogerla y darle la resonancia necesaria, realiza una doble labor meritoria: de piadoso recuerdo hacia su digno Presidente y de colaboración al imperio perenne de la verdad, rechazando afirmaciones antojadizas sobre la Bartonellosis Carriónica, cuyos enigmas han descifrado plenamente, los numerosos investigadores que son gloria y orgullo de la Escuela Médica Peruana.

Figure 5. Scientific debate between Harvard University and the Peruvian Medical School. Unicist theory. Source: (39).

Strong cells

The Harvard committee identified only one case of an endothelial cell with abundant *B. baciliformis*; despite this being an isolated case, that the parasitized cells were the histobacteriological feature of Carrion's disease was declared. 14 years later, Aldana (40), based on findings from autopsies of patients with Carrion's disease, acknowledged the findings of Harvard and proposed the name Strong cells.

The probable vector of Carrion's disease, the *Lutzomyia verrucarrum* mosquito, inoculates the Bartonella with its sting in the endothelial cells of capillaries (Strong cells), which then release bartonellae in the blood "parasitizing" red blood cells; this stimulates macrophages and produces erythrophagocytosis and severe anemia.

The unethical human experimentation conducted by Harvard in Peru

Regarding human experimentation by the Harvard expedition in Peru, the report by Strong *et al.* argues that:

> "Inoculation was performed in a man with a warty product of two types of wart [...] 16 days later, on the site of scarification, two small groups of cherry-colored papules appeared. These small tumors gradually grew and were cut at 35 days, two of them to be studied [...]"
> [1] This inoculation was practiced on an insane and Dr. David Matto, director of Manicomio del Cercado and vice-president of the Fifth Latin American Medical Congress, was aware of it" (11, p10).

In the English version of the publication (12), the Harvard Commission changed the report and stated that the patient who was inoculated was a Chilean volunteer (4). Ironically, in the same Fifth Latin American Medical Congress, where Harvard confirmed the dualist theory based on human experimentation in a psychiatric

patient, the first motion of the members of Congress was to improve the health of psychiatric patients (20).

Lessons for science

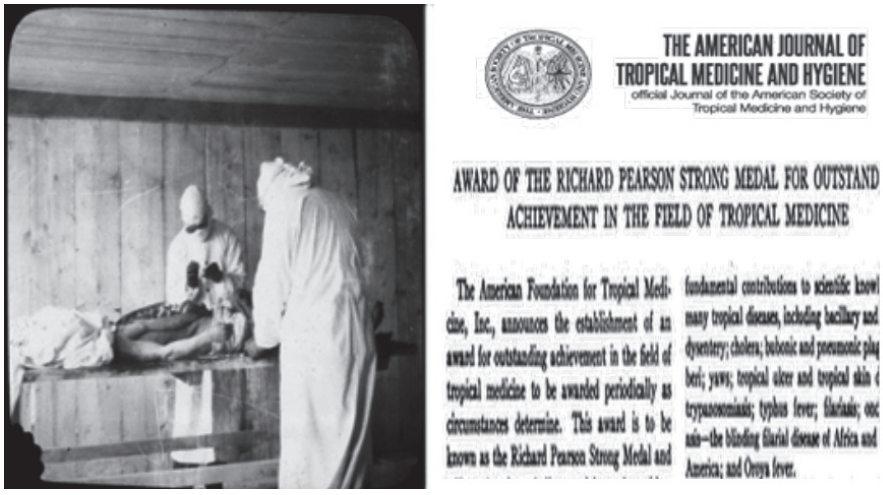
A retrospective view of what happened with the Harvard expedition in Peru leads to reflect and draw three lessons related to U.S. ethics on human experimentation, with the causality of an infectious agent and scientific ethnocentrism:

U.S. ethics on human experimentation in Latin America

For years the Peruvian Medical School criticized Strong for ignoring Carrion's finding, the unicist theory, however, there is no documentation of disapproval against his unethical experiment on a psychiatric patient. It is important to note that this procedure involved Dr. David Matto, a health authority who, taking advantage of his position as director of the mental hospital, allowed the experiment when he should have been the first to prevent or condemn it.

Strong was recognized for his work and was elected president of the American Society of Tropical Medicine, which publishes one of the most important journals worldwide to date: The American Journal of Tropical Medicine and Hygiene. It is noteworthy that this society was granted a palladium medal and a prize of thousands of dollars for the research conducted in honor to Strong (41,42).

Although American biographies describe him as a good Samaritan (41) and a friendly person (43), according to his team, Strong should have been given the nicknames "tourniquet" and "autopsy" (8); the American Society of Tropical Medicine created a medal of honor with his name and today, it is the symbol of American tropical medicine (Figure 6).



THE AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE
official Journal of the American Society of Tropical Medicine and Hygiene

AWARD OF THE RICHARD PEARSON STRONG MEDAL FOR OUTSTAND ACHIEVEMENT IN THE FIELD OF TROPICAL MEDICINE

The American Foundation for Tropical Medicine, Inc., announces the establishment of an award for outstanding achievement in the field of tropical medicine to be awarded periodically as circumstances determine. This award is to be known as the Richard Pearson Strong Medal and

fundamental contributions to scientific knowl
many tropical diseases, including bacillary and
dysentery; cholera; bubonic and pneumonic plag
beri; yaws; tropical ulcer and tropical skin
trypanosomiasis; typhus fever; filariasis; onc
sis—the blinding filarial disease of Africa and
America; and Oroya fever.

Figure 6. Richard Strong: scientific awards at the expense of unethical human experiments. Source: (44).

The scientific evidence on the causality of infectious diseases

The scientific evidence regarding the cause of infections is experimental and observational. Observational evidence does not determine causality, that is, an association between a particular infection and a particular infectious agent does not mean that the agent causes the disease.

In research on the Peruvian wart, the Harvard expedition, which traveled to Peru, and the scientists from the Pasteur Institute, determined the causation of this disease based on experimental evidence, ignoring the correlative clinical and epidemiological evidence previously obtained in Peru, which described several patients with Peruvian wart developing Oroya fever after its onset; this was a historical mistake. Critics by the Peruvian Medical School to the biased conclusions of Harvard and the Pasteur Institute, based only on experimental evidence, were not unfounded; Robert Koch himself recommended that, regarding the causality of infection, postulates should not be adopted rigidly, and that other aspects should also be considered.

Several scientific researchers say that there was a delay the studies of infectious diseases because of the adherence to Koch's postulates, which did not allow the identification of many infections. Science needs to base its findings on the best evidence and reasoning available (45,46).

Quality science can be generated in developing countries

Scientific ethnocentrism states that the ethnic group is superior and the most relevant. Although this ideology is based on the prejudices of developed countries (47,48), it is reinforced by the very underestimation of developing countries; this is known as inverted ethnocentrism and makes reference to local scientists who consider that they cannot achieve relevant scientific research because of the little advanced technology found in their countries (49).

Ethnocentrism can be fought by acknowledging that science can be developed in any country, culture or civilization; thus, it is necessary that medical students from developing countries know, objectively, scientific advances made in their countries, such as the one achieved by the Peruvian medical school with the unicist theory of Carrion's disease (50).

Conclusions

More than 100 years ago a Harvard expedition went to Peru to investigate Carrion's disease; although the expedition made a historical recognition of Barton's bacteriological findings by naming the bacteria *B. baciliformis* in his honor and by recognizing the role of endothelium in the onset of Carrion's disease, it also conducted unethical human experimentation practices on a psychiatric patient. In parallel, the findings of the expedition revealed the limitations of science to explain the causality of an infectious agent and the need to consider all the scientific evidence when building a scientific theory.

Conflict of interests

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REFLECTION PAPER

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Creation and initial development of the Radiology Service of the Faculty of Medicine from the Universidad Nacional de Colombia. One hundred years

Creación y desarrollo inicial del Servicio de Radiología de la Facultad de Medicina de la Universidad Nacional de Colombia. Primer centenario

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| Abstract |

The first X-rays laboratory of Hospital San Juan de Dios in Bogotá was acquired by the board of directors of the Faculty of Medicine and Natural Sciences of Universidad Nacional de Colombia, and was opened in September 1917. This laboratory was created in order to modernize the attention of patients and to promote medical education. Radiology, as a subject, was first introduced to the Medicine program curriculum of this university in 1928. It is important to note that before Gonzalo Gómez Esguerra became the first Colombian director of the laboratory, three radiologist from abroad had already taken this position.

Keywords: History; History of Medicine; Radiology; Colombia (MeSH).

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| Resumen |

El primer laboratorio de rayos X del Hospital San Juan de Dios de Bogotá fue adquirido por las directivas de, para ese entonces, la Facultad de Medicina y Ciencias Naturales de la Universidad Nacional de Colombia y se inauguró en septiembre de 1917; esta adquisición tuvo el propósito de modernizar la atención de los enfermos e impulsar la educación médica. La asignatura de radiología se introdujo por primera vez en el plan de estudios de la carrera de Medicina de esta misma universidad en el año de 1928. Cabe decir que antes de que Gonzalo Esguerra Gómez se convirtiera en el primer director colombiano del laboratorio, tres radiólogos extranjeros habían asumido este cargo.

Palabras clave: Historia; Historia de la Medicina; Radiología; Colombia (DeCS).

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Introduction

September 2017 will mark the hundredth anniversary of the opening of the Radiology Service of Universidad Nacional de Colombia in Hospital San Juan de Dios in Bogotá. This paper aims to describe and analyze the events leading the board of directors of the Faculty of Medicine to acquire the first X-ray equipment installed in Hospital San Juan de Dios, and hire foreign radiologists to operate the equipment and develop teaching activities.

Background

X-rays were discovered on November 8, 1895 by the German physicist Wilhelm Conrad Röntgen at the Institute of Physics of the University of Würzburg, Germany (1). Röntgen received numerous awards for his great discovery, the most important, the first Nobel Prize in Physics, awarded in 1901. The physicist, aware of the important applications of the new rays, decided to donate his discovery to the scientific world community to further progress in their study without patent limitations; this decision allowed a rapid dissemination of knowledge on X-rays and its applications, especially in medicine, throughout the world.

Arrival of X-rays to Colombia

The first record of an X-ray taken in Colombia dates back to 1902, and was taken by Juan Bautista Montoya y Flórez, surgeon from Medellin (2). Montoya y Flórez graduated from the medical school of Universidad Nacional de Colombia in 1892 with the thesis "Medical Electrology"; he traveled to Paris where he repeated his career in medicine. During his stay in Europe, he met the news of the discovery of X-rays and its novel applications in medicine. In 1901,

he decided to acquire an X-ray machine to be set up in Medellín, a task that began with the technical difficulties of the time (3-5).

In June 1912, the Society of Ophthalmology and Otolaryngology of Bogotá published in the journal Repertorio de Medicina y Cirugía (Medicine and Surgery Repertoire) the first medical case illustrated with X-ray photographs taken in Bogotá —obtained in Casa de Salud (Health House) owned by Dr. Manuel Peña— about radiographic follow-up of a foreign body (a ring) in the esophagus of a twelve-year-old patient (6).

Beginning of the Radiology Service at the Faculty of Medicine of Universidad Nacional de Colombia

In mid-1907, the Board of Directors of, by then, the Faculty of Natural and Medical Sciences of Universidad Nacional de Colombia, headed by its rector (a position equivalent to a dean today) Luis Felipe Calderón, made a first official call to the National Government for "the installation of a radiography, fluoroscopy and radiotherapy cabinet attached to the clinics of Hospital San Juan de Dios and directed by the professor of clinical dermatology" (7). The board of directors of the faculty, in the official letter sent to the Minister of Public Instruction, considered that "the growing importance of radiology and radiation therapy in diagnosis and treatment of many diseases motivates them to send their request" (7). Although the National Government decided to postpone the approval of such request, the following administrations of the Faculty of Medicine insisted on it (8).

Twenty years after the discovery of X-rays, the rector in charge of the Faculty of Medicine, Roberto Franco, informed the Minister of Public Instruction:

> "In order to make the observations of the clinics of Hospital San Juan de Dios more perfect and to use modern methods for the scientific study of surgical-medical conditions, the Board resolved to make the installation of a Cabinet of Radiology and Electrotherapy, and devote the sum of 5 000 pesos gold to these expenses, which were taken to the United States by the rector, Dr. Pompilio Martínez, to acquire the necessary elements for that installation. This implies progress that will translate into real benefit to clinical teaching and effective benefits for poor patients isolated in our hospital" (9).

Thus, Dr. Pompilio Martínez (Figure 1) acquired in 1915 the first X-ray equipment of the faculty, which was installed in Hospital San Juan de Dios.

Figure 1. Dr. Pompilio Martínez, rector of the Faculty of Medicine from 1914 to 1920. Source: Own elaboration based on the data obtained in the study.

Simultaneously, the Council of the Faculty of Medicine requested to the Congress of the Republic the approval of Act 48 of 1916, which ordered:

> "Article 1. The establishment, in the Faculty of Medicine of Bogotá, of the Radiology course.
> Article 2. The Government will proceed to hire a foreign radiologist to mount the Radiological Cabinet and teach radiology at the Faculty of Medicine. The necessary line item to meet this expenditure is deemed to be included in the budget of expenses (10)".

With the steps above, and in their eagerness to modernize patient care and promote teaching, the Council incorporated to the Faculty of Medicine a new diagnostic and therapeutic modality.

After facing numerous technical problems installing the equipment sent by the Inrok-Röentgen Manufacturing Co. in Philadelphia, on September 18, 1917 the Cabinet of X-rays was opened in the facilities of the old amphitheaters of Hospital San Juan de Dios in Street 12 with Avenue 10 in Bogotá (Figure 2) (11).

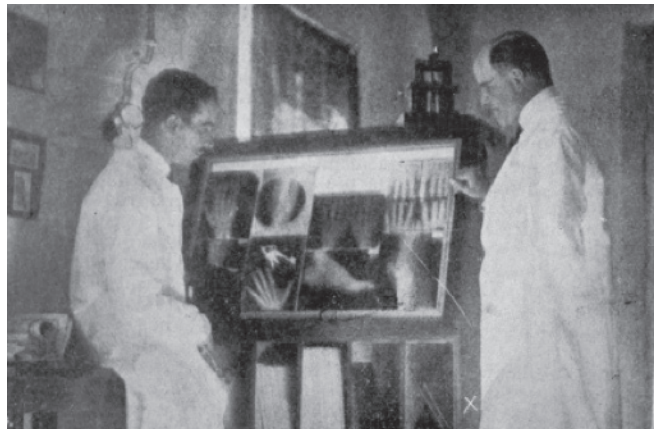

Figure 2. Opening of the first X-ray lab, Hospital San Juan de Dios. On the right, doctor Peer Martín Lund. Source: (18).

The first radiologist hired to manage the cabinet was the Danish Peer Martin Lund from New York, who arrived in the country in early 1917 (12). During his short stay in Colombia, he published three papers in the journal Repertorio de Medicina y Cirugía: "X-Ray diagnosis and treatment" (13), "Diagnosis of bone diseases by means of X-ray" (14) and "Value of X-rays in therapy and as diagnostic elements "(15). Due to the technical difficulties encountered, Dr. Lund was declared incompetent to continue managing the operation of the X-ray equipment, and after a few months, his contract was terminated and he left the country, forcing the rector of the faculty, Pompilio Martínez, to suspend the service cabinet the same year of its opening (16).

The forced resignation of the Danish radiologist forced the directors of the faculty to hire a new foreign radiologist and look for a new law with more demanding in terms for hiring (Act 8 of 1919):

> "Article 1. The Government shall hire a radiologist to assemble a Radiological Cabinet and to teach radiology at the Faculty of Medicine. Such professor must be skilled in the installation and operation of the radiology and X-ray devices, as well as of the latest developments on the subject (17)".

By mid-1919, the Faculty Council requested to the Ministry of Education the appointment of the French radiologist André J. Richard, also from New York, to head the radiology cabinet (19). His poor management of the Spanish language forced the recruitment of an interpreter who turned out to be the young bachelor Gonzalo Esguerra Gómez, who excited to observe the work of Richard, became his close collaborator and decided to study medicine at Universidad Nacional. This allowed him, over time, to become an eminent radiologist and to be appointed as the director of the Laboratory of Radiology at Hospital San Juan de Dios and as the first professor of the course, by competition, at the Faculty of Medicine of Universidad Nacional de Colombia (20).

Between 1919 and 1922, Richard demonstrated a remarkable knowledge of the matter that was affected by unjustified absenteeism. In May, 1922, he was commissioned to travel to the United States to purchase items needed for the radiology laboratory; the appliances arrived in December of that year, but Dr. Richard did not return (21).

This paralyzed the activities of the radiology service and forced the rector of the Faculty, Luis Felipe Calderón, to manage and bring from Hamburg a new radiologist, the German Professor Martin Weiser, who arrived in Bogotá by the end of February 1923 and succeeded in reopening the laboratory around mid-year (22).

During the time of his involvement as the director of the Radiology Service at Hospital San Juan de Dios, Weiser judiciously developed assistance work and urged improvements in the physical plant, modernization of X-ray equipment and acquisition of radiotherapy equipment (23); he also organized academic sessions of radiographs reading for students of internal clinic, external clinic and surgical clinic subjects (24).

Dr. Weiser had to transfer the Radiology Department of Hospital San Juan de Dios, located in the city center, to the new hospital facilities in Hortúa, Avenue 10 with Street 1, which was inaugurated on February 7, 1926. This dependence was located in the west wing of the second floor of the building originally intended for hospital administration (25).

Radiographic studies conducted from the beginning were mainly general radiology, digestive tract with barium under fluoroscopic control, excretory urography and cholecystogram. The quality of examinations increased with the introduction of intensifying screens for radiographic/film chassis, Coolidge X-ray tubes and Bucky-Potter grid. He also tried to use common X-ray tubes for radiotherapy but the obtained results were rated as mediocre (26).

The aforementioned Dr. Gonzalo Gómez Esguerra was privileged to spend considerable time of his training as a doctor accompanying and assisting doctors Richard and Weiser, which helped him in his training as a radiologist. In the sixth year of his career, during the temporary absence of Dr. Weiser, he had the opportunity to prepare projections of radiographic material which were presented to his fellow students and professors of Clinical Surgery, Pompilio Martínez and Juan N. Corpas (27). Dr. Weiser remained in the direction of the Radiology Service until 1927, year in which Gonzalo Esguerra Gómez received the degree of doctor of medicine and surgery, after defending the thesis "Radiological signs of chronic appendicitis" (28).

The year 1928 marked the most important period for the early development of Radiology at the Faculty of Medicine, and it was possible to begin with the training of Colombian medical staff in that area. Dr. Gonzalo Esguerra Gómez (Figure 3) was appointed in January of that year as the first director of the Radiology Service of Hospital San Juan de Dios and trained personnel in this laboratory, among them Dr. Carlos Trujillo Venegas, who became director of the service later (29). In addition, the course on Radiology was first incorporated into the curriculum of the medical career attached to the Surgical Clinic in the sixth year (30).

(Figure 2). Gonzalo Esguerra Gómez. Source: (32).

The appearance of the course on radiology in the Medicine curriculum, together with surgery under the name "Surgical Clinic and Radiology", marked the beginning of a new period in the history of this specialty in the faculty, where it gained recognition and expansion as an independent subject.

Dr. Alfonso Esguerra, brother of Dr. Gonzalo Esguerra, was a fellow of the Laboratory of Radiophysiology at the Radium Institute in Paris and managed to schedule a visit of the French physician and Professor Cladius Regaud to Colombia, and also motivated doctors and politicians to create the Instituto Nacional de Radium (Radium National Institute). The creation of this institution, known today as Instituto Nacional de Cancerología (National Cancer Institute), was approved by Act 81 of 1928 and was opened by President Olaya Herrera in 1934. This center was attached to Universidad Nacional de Colombia (31).

Conclusions

Since the first decade of the twentieth century, the board of directors of the Faculty of Medicine and Natural Sciences of Universidad Nacional de Colombia worked to organize a radiology service with the intention of modernizing patient care and strengthening medical education. Under the administration of Dean Pompilio Martínez, the radiological cabinet was inaugurated on September 18, 1917 in the premises of the old amphitheaters in Hospital San Juan de Dios, when it operated in Avenue 10 with Street 12 in Bogotá.

The Congress decreed Act 48 of 1916 and Act 8 of 1919, which had the purpose of organizing radiology at the Faculty of Medicine. The first law created the course of radiology and both ordered the hiring of a foreign radiologist for service management and radiology teaching.

The history of the Radiology Service at the Faculty of Medicine of Universidad Nacional de Colombia had a first period, between 1907 and 1928, characterized by the incorporation and initial development of a new diagnostic modality in which three foreign radiologists were hired (Lund, Richard y Weiser) for the organization of the radiological cabinet and the teaching of this discipline. Major technical difficulties were faced during the installation and operation of the equipment, while limitations caused by the language of the foreigners arose. Assistance overruled teaching; nonetheless, the training of Colombian personnel in this area, especially of Gonzalo Esguerra Gómez —first Colombian director of the Department of Radiology and future professor of the course— had great significance.

The formal inclusion of the radiology course in the curriculum of Medicine at Universidad Nacional de Colombia was done in 1928, alongside Surgical Clinic. This achievement was possible after a constant work begun in 1907 by the directors of the faculty, which included the organization of a radiology service in Hospital San Juan de Dios in Bogotá, the formulation of national laws, the recruitment of foreign radiologists and the training of Colombian personnel.

Part of the references listed here belong to the historical sources that the author of this paper found for the preparation of his Master's in Education thesis, at Universidad Pedagógica Nacional, entitled: "The teaching of Radiology at the School of Medicine of Universidad Nacional de Colombia 1915-1962". New historical sources and references were added to this paper (33).

Conflict of interests

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REVIEW ARTICLE

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Molecular mechanisms of autophagy and its role in cancer development

Mecanismos moleculares de la autofagia y su papel en el cáncer

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| Abstract |

Autophagy is an evolutionary process preserved in eukaryotes, which removes harmful components and maintains cell homeostasis in response to a variety of extracellular stimuli. It is involved in both physiological and pathological conditions, including cancer.

The role of autophagy in the treatment of cancer is described as a "double-edged sword", which reflects its involvement in tumor suppression, survival and subsequent proliferation of tumor cells. Recent advances are useful for planning appropriate adjustments to inhibit or promote autophagy in order to obtain therapeutic efficacy in cancer patients. The objectives of this review are to clarify the role of autophagy in cancer and to highlight the need for more research in the field.

Keywords: Autophagy; Cancer; Tumorigenesis; Proliferation (MeSH).

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| Resumen |

La autofagia es un proceso conservado evolutivamente en eucariotas que elimina componentes dañinos y mantiene la homeostasis celular en respuesta a una serie de estímulos extracelulares. Está implicada tanto en condiciones fisiológicas como patológicas, incluyendo el cáncer.

El papel de la autofagia en el tratamiento del cáncer se describe como un "arma de doble filo", un término que refleja su participación en la supresión tumoral, la supervivencia y la proliferación de células tumorales. Los avances recientes ayudan a proyectar los ajustes apropiados en la inhibición o la promoción de la autofagia con el objetivo de conferir eficacia terapéutica en los pacientes con cáncer. Esta revisión tiene como objetivo aclarar los roles de la autofagia en el cáncer y destacar la necesidad de una mayor investigación en el campo.

Palabras clave: Autofagia; Cáncer; Tumorigénesis; Proliferación (DeCS).

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Introduction

Tumorigenesis is a complex multistage process which involves tumor initiation, promotion, progression to malignancy and metastasis. Tumor cells are characterized mainly by the result of uncontrolled proliferation processes, where cell division occurs faster. In addition to proliferation, other affected molecular mechanisms are programmed cell death or apoptosis, and the cell cycle (1).

Autophagy plays an important role, not only in the different stages of tumorigenesis, but also in disease states that lead to a microenvironment that promotes tumorigenesis. The role of this process in pathological states associated with higher risk of cancer, such as chronic liver disease, obesity and inflammatory bowel disease, is increasingly clear (2-4).

Pharmacological management of autophagy, with the intention of preventing a favorable microenvironment for tumor initiation, may require an opposite approach to limit tumor progression once pre-malignant cells are established. In this review, the regulation of autophagy, types of autophagy, autophagy itself and its mechanism as tumor suppressor or inducer are addressed. Finally, autophagy as a therapy against cancer, mainly in tumor cells with competent autophagy and defective autophagy, and induction of cell death by autophagy as a therapeutic strategy are discussed.

Molecular regulation of autophagy

Autophagy is a mechanism essential for maintaining cellular homeostasis in the body in the absence of important nutrients that work as an energy source. This process begins with the retention of

cytoplasmic components, such as protein aggregates and damaged or aged organelles, through double-membrane vesicles called autophagosomes. The retentate is then transferred to degradation organelles such as lysosomes or vacuoles for destruction and eventual recycling of resulting macromolecules (5-7).

Although the study of the components of autophagy in mammalian cells was first performed in 1950, currently, it has been proved that there are studies performed in this population, and many others conducted using microorganisms such as yeast, where the existence of about 31 ATG genes has been observed; these genes are closely related to autophagy and the place where they are located in is known as perivacuolar site (PAS). The ongoing study of the nature of autophagy is becoming more important; here, the animal model in yeast is a powerful medium to decipher multiple concerns (8,9).

The molecular regulation of autophagy occurs in two different ways: a) through the activation of mTORC1 (mammalian Target of Rapamycin), in response to starvation or exhaustion of energy, and b) through energy detection, regulated by AMP-activated protein kinase (AMPK) (10). Autophagy could also be regulated by the Beclin 1 protein complex, consisting of the Beclin 1 (homolog Atg6) protein, phosphatidyl-inositol 3-kinase (PI3K) class III (PI3KC3/Vps34), p150, and Atg14L or UV radiation resistance-associated gene protein (UVRAG) (11,12). The intrinsic activation of the PI3KC3/Beclin 1 complex leads to the generation of phosphatidylinositol-3-phosphate (PI3P), which is required for the formation of the autophagosome. Moreover, there are several tumor suppressor proteins such as Atg4c, BAX-interacting factor-1 (Bif-1) homolog of phosphatase and tensin (PTEN) and UVRAG, which, besides inhibiting the growth of tumors, have common induction of autophagy (13) (Figure 1).

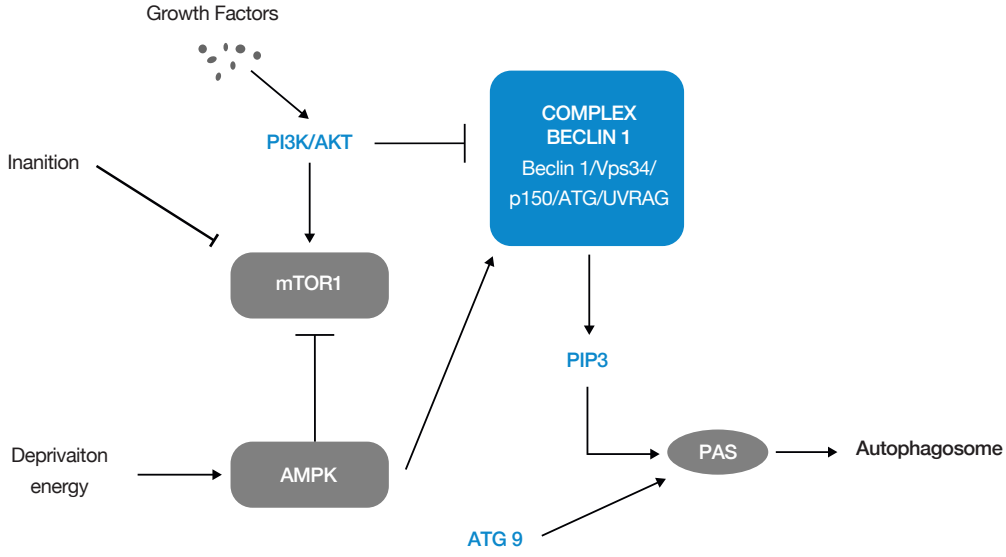

Figure 1. Molecular regulation of autophagy. Source: Own elaboration based on the data obtained in the study.

Autophagy responds to downregulation by stimuli of growth factors that regulate the phosphatidylinositol-3-kinase pathway (PI3K/AKT), which controls the activation of the mTOR pathway; the latter resides in a multi-protein and macromolecular (mTORC1) complex that is activated by signals associated with nutrients, including amino acids and growth factors, and downregulates autophagy by interacting with the complex Beclin 1.

Autophagy also responds to control due to cellular energy depletion through increased activity of protein kinase activated by AMP (AMPK). In response to elevated levels of 5'-monophosphate adenosine AMP, the inactive AMPK mTORC1 and active Beclin 1 promote Atg9 traffic. Beclin 1 is associated with a macromolecular complex, which includes hVps34, PI3KC3 class III, p150 and UVRAG. The Beclin 1 complex produces phosphatidylinositol-3-phosphate (PI3P), which recruits factors associated with autophagosome formation.

For inhibition of autophagy, the serine/threonine kinase mTOR protein is the most important in human cells; inhibition occurs through maintenance of hyper-phosphorylation of proteins that are needed for initiating the autophagy signaling pathway. mTORC1 promotes protein synthesis, cell division and metabolism in response to the availability of nutrients, growth factors and hormones, while suppressing autophagy. Mutations acquired in different regions of the mTOR C-terminal promote its hyperactivation, benefiting the uncontrolled growth of tumor cells (2).

Types of autophagy

There are three main types of autophagy that work for eukaryotic cells: macroautophagy, microautophagy and chaperone-mediated autophagy (CMA), which are all different in terms of the mechanics of the process (Table 1).

Autophagy and its mechanism as a tumor suppressor

Although autophagy is a survival pathway —used by both normal and tumor cells to survive hunger and stress— paradoxically, its defects are found in many types of human tumors. Allelic loss of gene Beclin 1, essential for autophagy, is common in human breast, ovarian and prostate cancer (16).

In early stages of the tumor, autophagy acts as a tumor suppressor process, since it is responsible for inhibiting the inflammatory events associated with cancer, and it also promotes genomic stability (17). Furthermore, the accumulation of reactive oxygen species (ROS) is one of the main consequences of metabolic stress, which can cause

damage to the structure of DNA through the induction of double strand breaks and change in the base sequence of the DNA, leading to activation of proto-oncogenes and, simultaneously, inactivation of tumor suppressor genes (18).

Table 1. Types of autophagy

Type	Mechanism
Macroautophagy	Dynamic reordering of the membrane: In this type of autophagy, specialized vacuoles serve for transportation purposes; these vacuoles are called autophagosomes and provide protein aggregation, lipids and damaged organelles to lysosomes for degradation.
Microautophagy	Dynamic reordering of the membrane: Direct introduction of the cytoplasm in the lysosomal surface is made by invagination and protrusion; consequently cells degrade through lysosomal hydrolases once the lysosome is completely closed.
Chaperone-mediated autophagy (CMA)	Kidnapping of proteins containing KFERQ substrate: This mechanism is mediated by the Hsc70 complex and the cytosolic chaperone protein recognition, which are responsible for the translocation of the substrates deployed across the lysosomal membrane; once inside the lysosome, proteins are degraded by lysosomal hydrolases action.

Source: Own elaboration based on Yorimitsu & Klionsky (14) y Chen & Klionsky (15).

For several years, ROS have been linked to cancer development in humans; after many studies, it has been concluded that autophagy plays an important role in reducing levels of ROS (19). The existence of high levels of ROS activates autophagy to eliminate these harmful compounds and, in consequence, prevent DNA damage and the development of tumorigenesis (18).

The study by Cao B *et al.* (20) shows that anti-microbial agents such as clioquinol, can induce tumor cell death; basically, its anti-tumor properties are given by their ability to activate autophagy in cancer cells by increasing the PI3KC3/Beclin 1 complex and disrupting the mTOR signaling pathway.

Autophagy and its mechanism as tumor inducer

One of the most remarkable abilities in the repertoire of tumor cells is the activation of autophagy in response to stress, which allows long-term survival, particularly when apoptosis is defective. Apoptosis might normally eliminate stress resistant tumor cells as a tumor suppressor mechanism; however, tumor cells often evolve to generate defects in this process, allowing activation of autophagy to sustain the survival under nutrient deprivation conditions. Tumor cells can digest themselves gradually under prolonged stress, becoming less than a third of normal size (Figure 2) (21).

Cellular stress activates autophagy in tumor cells, allowing survival by promoting selection of material for cell consumption. As a consequence, small cells that may remain in a dormant state in the presence of stress are generated, but these cells, capable to recover (complete cytogenetic response-CCR) regenerate and restore their cellular proliferation when stress disappears.

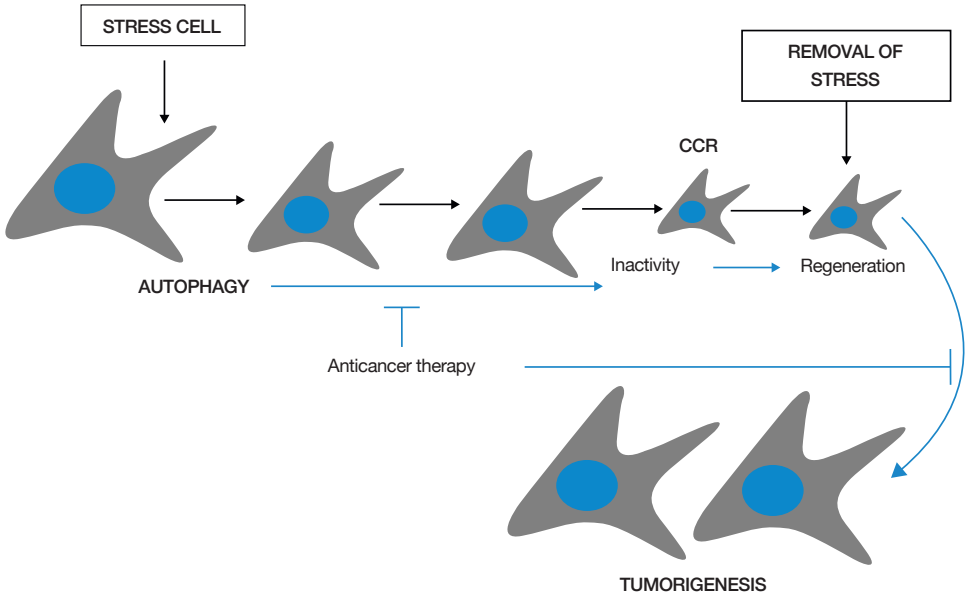

Figure 2. Survival and regeneration mediated by autophagy in tumor cells. Source: Own elaboration based on the data obtained in the study.

Establishing cell latency as a regenerative capacity is highly dependent on autophagy; in tumor cells with defects in autophagy, achieving latency and cell regeneration is less efficient. Therefore, autophagy confers tumor cells tolerance to cellular stress, limiting damage and maintaining cell viability (Figure 3) (22).

Although autophagy mitigates damage and promotes cellular senescence, inhibiting tumorigenesis by allowing tumor cells to survive cellular stress, remain dormant and regenerate with elimination of stress, it also promotes tumorigenesis.

Other factors that can originate and stimulate tumorigenesis are damaged tumor cells in tumors with defects in autophagy, particularly those with protein aggregates and genomic damage, and the presence of chronic inflammation, which generates a favorable microenvironment that alters cell death.

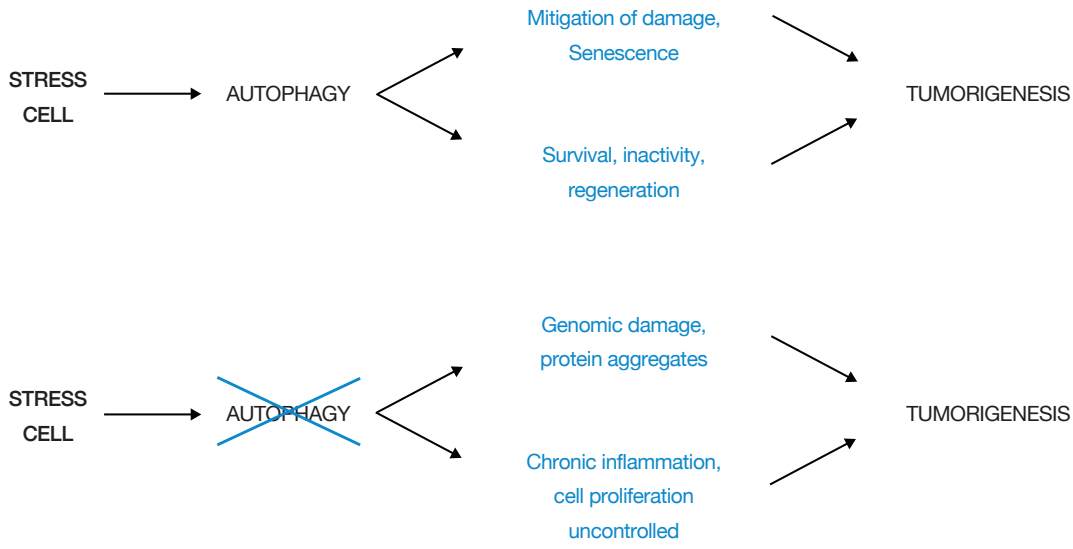

Figure 3. Two-way function of autophagy in tumorigenesis. Source: Own elaboration based on the data obtained in the study.

Targeting autophagy for cancer therapy

The role of autophagy in oncogenesis is variable, since it is a tumor suppressor during the early stages of the tumor and may contribute to their growth during their development (23). Autophagy, as a response to cancer therapy, can promote/suppress tumor development, for this reason, improving cancer therapy is considered an unusual goal.

Tumor cells with competent autophagy

This type of cells can activate autophagy as an adaptive response to therapeutic agents against cancer, therefore, autophagy could act as a resistance or survival mechanism of tumor cells in prolonged treatments. The absence of cancer cells in an essential mechanism for resistance, by specifically inhibiting autophagy, is expected to improve the efficacy of anticancer drugs (24). Cancer cells with defective apoptosis and low metabolic stress have been proved to establish autophagy activation as a survival mechanism; in contrast, tumor cells with competent apoptosis under stress may undergo rapid cell death following activation of apoptosis. Therefore, inhibition of autophagy is expected to be therapeutically more beneficial in the treatment of tumors that have defects in apoptosis (25).

Autophagy inhibition: therapeutic target against cancer

Inhibition of autophagy as a scenario to sensitize tumor cells to anti-neoplastic treatment has been validated in several studies. Inhibition of autophagy by chloroquine, a lysosomotropic agent which raises pH and interferes with autophagosome degradation within lysosomes, shows an improvement in anti-tumor activity of cyclophosphamide (alkylating agent) in a lymphoma induced model and colorectal cancer (26). Similarly, 3-methyladenine (3-MA), an autophagy inhibitor, allows sensitization in nasopharyngeal carcinoma cells (Hone-1) to treatment with cisplatin and radiotherapy, which relates to the prevention of endoplasmic reticulum stress induced by autophagy in such cells (27).

Several studies support the idea that autophagy, as a physiological process in response to treatments in cancer cells, can help tumors evade drug - induced cytotoxicity —as survival mechanism—.Thus, it was demonstrated in non-small cell lung cancer (NSCLC) that autophagy regulates their resistance to treatment with paclitaxel, mainly by decreasing microRNA-216b (miR-216b); therefore, strategies that increase levels of miR-216b or inhibit cell autophagy can improve the outcome of treatment with paclitaxel against NSCLC (28). Furthermore, it has been shown that chemoresistance of patients with hepatocellular carcinoma (HCC), compared to treatment with cisplatin, is the consequence of activation of autophagy by binding lectin beta-galactoside, and galectin-1 (29).

In order to determine the molecular mechanisms of the chemotherapeutic effect of chloroquine on malignant glioblastomas, recent studies have been devoted to probing the cytotoxicity of chloroquine in combination with temozolomide (TMZ), taking ROS as one of the main causes of dysfunctional mitochondria.

Hori YS *et al.* found that chloroquine increases cellular ROS and cytotoxicity of TMZ in glioma cells by inhibiting mitochondrial autophagy (30,31). Also, recent studies in patients with positive estrogen receptor (ER (+)) showed a significant increase in sensitivity to apoptosis in breast cancer induced by tamoxifen and fulvestrant after inhibition of autophagy induced by microRNA 214 (miR-214). These results support the regulation of autophagy as a new therapeutic strategy for overcoming endocrine resistance in breast cancers ER (+) (32).

Autophagy is commonly regulated in tumor and normal cells exposed to cancer therapies, but the greater dependence of tumor cells —compared with normal cells— on the cytoprotective effects of autophagy offers a new therapeutic opportunity. In fact, autophagy is induced as a strategy for survival in human tumor cells treated with histone deacetylase inhibitors (HDAC) (33), arsenic trioxide (34), tumor necrosis factor alpha (TNF α) (35), gamma interferon (IFN-γ) (36), rapamycin (37) and hormone therapy antiestrogen (38), suggesting that inhibition of autophagy could reduce resistance of cancer cells in these therapies.

Another strategy for inhibition of autophagy includes the use of siRNAs (small interfering RNA), which target autophagy essential genes and sensitize cancer cells to the induction of cell death by radiation cells (39), and a wide range of chemotherapeutic agents, including cyclophosphamide and N-(4-hydroxyphenyl) retinamide (40).

Tumor cells with defective autophagy

These tumors probably adapt to a state of defective autophagy over time and acquire compensatory mechanisms of cell survival. Hence, cancer cells with defects in autophagy are not expected to rely on this mechanism for cyto-protection during chemotherapy and radiotherapy; inhibition of autophagy cannot increase cytotoxicity by anti-neoplastic or irradiation drugs (41).

Moreover, tumor cells with defective autophagy probably have high susceptibility to metabolic stress, high levels of DNA damage and propensity to genomic instability, which are properties with different implications for responsiveness to anti-neoplastic treatments (42-43). Although, it is still poorly documented, tumor cells with defective autophagy may be particularly sensitive to metabolic stress induction regimens, such as anti-angiogenic pharmaceutical drugs, growth factors receptor inhibitors, glucose deprivation and agents that induce DNA damage, including platinum compounds and topoisomerase inhibitors (44).

Induction of autophagy: therapeutic target against cancer

Since defects in apoptosis are often observed in many tumor cells and may increase their resistance to several conventional therapies for carcinogenesis, targeting alternative pathways to cell death is an attractive strategy to improve anti-tumor therapy (45). Consequently, induction of autophagic cell death can serve as a novel therapeutic strategy to eliminate the development of various cancers, especially those with high thresholds of deficient apoptosis (46).

Several studies have reported that different agents, including arsenic trioxide (46) and the vitamin D analog EB1089 (47), induce autophagic cell death in tumor cells *in vitro*; unfortunately, in these cases, autophagic cell death was determined based on morphological characteristics, so the studies may not represent a true autophagic cell death (48,49). However, other reports have shown specific examples of autophagic cell death in response to certain agents.

Some tumor cells, especially those lacking essential modulators of apoptosis such as BAX, BAK or caspases, exhibit cell death autophagy *in vitro* when treated with certain chemotherapy drugs, such as etoposide, fenretinide and dexamethasone (50-52).

Also, other studies have shown that polyphenols activate autophagy, controlling cell regulator mechanisms; these results provide strong support to the idea that plant polyphenols are really useful in treating diseases such as cancer, where autophagy plays an important role (53).

Induction of autophagy, in response to nutrient starvation, is responsible for the beneficial effects on longevity in the presence of caloric restriction; at least in *Caenorhabditis elegans*, its activation slows aging and prolongs useful life (54).

It is tempting to speculate that periodic induction of autophagy may also be responsible for a preventive effect against the development of cancer processes in the presence of caloric restriction; if this were true, the pharmacological induction of autophagy could be used for chemoprevention of cancer. Future studies are needed to clarify whether the induction of autophagic cell death in cancer has a relevant clinical utility.

Conclusions

Autophagy can act in two ways during cancer development: as a mechanism of tumor suppression or as an adaptive response to stress to maintain cell survival. Nonetheless, the molecular mechanisms underlying the regulation of autophagy and the role of this process in tumor cells is not fully understood yet. For this reason, pharmacological modulation of autophagy may have significant clinical potential as a new therapeutic strategy for the eradication of cancer.

Induction of autophagy may be useful for cancer chemoprevention in normal cells or for triggering an alternative cell death mechanism in certain tumor cells, especially those with compromised apoptotic functions. Furthermore, deletion of autophagic pathways can be combined with conventional antitumor regimens to achieve greater efficiency, thereby, avoiding drug resistance in tumor cells, which represents a valuable therapeutic strategy for radio and chemo-sensitization.

On the other hand, additional questions and concerns arise, as it is known that autophagy inhibits oxidative stress, inflammation and genome instability, favoring tumor suppression in some models; it is still to determine whether these events contribute to the suppression of human cancer. If so, the essential autophagy gene should be represented among genes with recurrent mutations in the development of human cancers. Based on currently available data, this does not seem to be the case, but there is a possibility that the loss of tumor suppression by autophagy in cancer occurs indirectly.

The use of autophagy against cancer offers new opportunities for drug development, as more potent and specific inhibitors of this process are clearly needed to ensure the efficacy and safety of anti-tumor treatment. Future efforts should focus on the modulation of autophagy for maximum therapeutic benefit, as well as in elucidating the genetic and physiological conditions that determine the function of pro-survival or pro-death autophagy.

A major limitation of the research to date is that all models of cancer have addressed the role of autophagy only in tumors, leaving aside the direct comparison with this deficiency in normal tissues. Since, there is evidence that autophagy is important for some normal tissues, a critical question is whether the systemic inactivation of this process is selective enough to harm cancer growth without affecting normal tissues with harmful consequences.

Ultimately, the pharmacological manipulation of autophagy for prevention and treatment of cancer depends on the ability to correctly recognize the functional status of autophagy in tumors and the availability of specific modulators.

Conflict of interests

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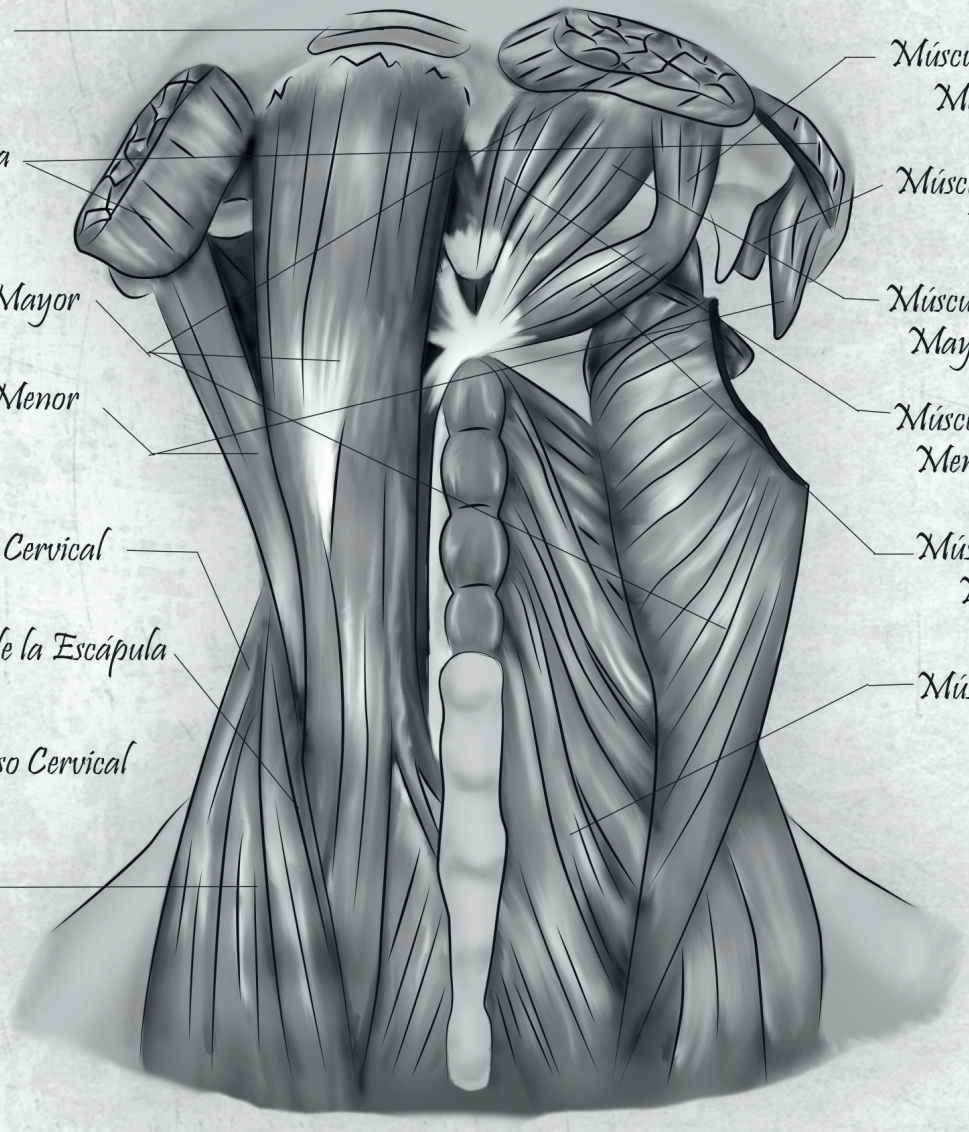
Miología de Cuello

Vista Posterior



César Alexander Eslava Franco
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Universidad Nacional de Colombia

REVIEW ARTICLE

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Molecular diagnosis of hereditary nonpolyposis colorectal cancer (Lynch syndrome)

Diagnóstico molecular del cáncer colorrectal no polipósico hereditario (síndrome de Lynch)

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| Abstract |

Lynch syndrome is the most common cause of inherited colorectal cancer, totaling 5 to 8% of all the cases with high susceptibility to this type of cancer and extracolonic cancer. It is related to germinal mutations taking place at mismatch repair genes. The diagnosis of Lynch syndrome is essential for both monitoring patients with this disease and detecting asymptomatic carriers, in order to establish appropriate clinical monitoring, preventive management and genetic counseling

Although clinical criteria have been standardized by implementing Amsterdam I and II, as well as Bethesda guidelines, the detection rate of mutations in these genes only varies between 20% and 60%.

The objective of this research was to review the state of the art regarding molecular diagnosis of Lynch syndrome; thus, a review of the literature published from 1995 to 2015 in PubMed database was performed by using the criteria "lynch syndrome molecular screening". 19 articles were selected and reviewed, and the relevant bibliography related to such articles was also reviewed.

This paper presents different approaches proposed by several researchers on molecular algorithms to improve the efficiency of Lynch syndrome diagnosis.

Keywords: Colorectal Cancer; Hereditary Cancer; Colorectal Neoplasms; Hereditary Nonpolyposis; Lynch Syndrome; Immunohistochemistry; Microsatellite Instability (MeSH).

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| Resumen |

El síndrome de Lynch es la causa más frecuente de cáncer colorectal (CCR) hereditario y representa el 5-8% de los casos con alta susceptibilidad a CCR y cánceres extracolónicos. Este síndrome se relaciona con mutaciones germinales en genes de reparación de malos apareamientos (MMR); su diagnóstico es fundamental, tanto para el seguimiento de los afectados como para la detección de portadores asintomáticos, y tiene el propósito de instaurar un adecuado seguimiento, un manejo preventivo y un asesoramiento genético. Si bien los criterios clínicos han sido estandarizados con la implementación de las guías de Amsterdam I y II y Bethesda, la tasa de detección de mutaciones en estos genes solo varía entre 20% y 60%.

El objetivo de esta investigación fue revisar el estado del arte con relación al diagnóstico molecular del síndrome de Lynch, para lo cual se realizó una revisión de la literatura publicada entre 1995 y 2015 en la base de datos PubMed usando como criterio de revisión: "Lynch syndrome molecular screening". Se escogieron y revisaron 19 artículos y además se revisó y escogió la bibliografía pertinente de los artículos.

Se presentan propuestas de varios autores sobre los algoritmos moleculares para mejorar la eficiencia del diagnóstico del síndrome de Lynch.

Palabras clave: Cáncer colorrectal; Síndrome de Lynch; Inmunohistoquímica (DeCS).

Serrano D, Arteaga CE. [Diagnóstico molecular del cáncer colorrectal no polipósico hereditario (síndrome de Lynch)]. Rev. Fac. Med. 2016;64(3):537-42. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.48458.

Introduction

With an incidence of 10.6 per 100 000 inhabitants and a mortality rate of 6 per 100 000 inhabitants, colorectal cancer (CRC) is currently the first or second leading cause of cancer-related deaths in Colombia. However, these statistics have increased; in 1997, CRC was considered as the fourth leading cause of cancer deaths and an estimated of about 75 people died from the disease. CRC is the third leading cause of cancer in men and the second in women, with a standardized incidence ratio (SIR) of 83 and 48, respectively, while in developing countries it is the sixth leading cause.

Lynch syndrome is the most common cause of inherited CRC and represents 5-8% of all cases (1-5); it is associated with

mutations in the germline of MMR genes including hMLH1, hMSH2, hMSH6, hPMS2, hPMS1 and hMLH3, which generate microsatellite instability in most cases. About 90% of the mutations identified in this group correspond to hMLH1 (50%) and hMSH2 (40%) genes (6).

In a previous study conducted to detect of mutations in MLH1 and MSH2 genes in Colombian families, the detection rate for this disease was 35% (7).

Clinical features

Lynch syndrome is a hereditary cancer syndrome with an autosomal dominant inheritance pattern. 40-60% of families who meet the clinical criteria for this disease have mutations in MMR genes. The risk of developing cancer among mutation carriers is 80% at age 70, and the average age for the onset of a neoplastic lesion, either in the colon or outside the colon, is 45, much earlier than in sporadic cancer; however, the risk of cancer and age of onset is different for each of the genes involved (8,9). Some studies suggest that mutations in MLH1 are at increased risk of CRC in MSH2, which have increased risk of extracolonic cancers. Mutations in MSH6, when compared to MLH1 and MSH2, show a lower expression of CRC, but an excess of endometrial cancer (10).

From the anatomopathological point of view, adenocarcinomas framed in this syndrome are characterized for being solid, poorly differentiated, mucinoide-like, with signet ring cells and peritumoral lymphocytic infiltration —similar to the infiltration observed in Crohn's disease—, which is currently considered as a prognostic marker. The most common site of lesion is the proximal colon and the number of adenomas varies slightly with villous growth (8,11).

Extracolonic malignancies that occur in Lynch syndrome include endometrial, stomach, ovary, ureter, renal pelvis, brain, small intestine, hepatobiliary and skin (sebaceous adenoma) cancers. These tumors can be synchronous or metachronous. Regarding extracolonic tumors, endometrial cancer predominates in Western countries and gastric cancer in Eastern countries (12); less frequently, cases of breast cancer have also been reported (13).

Classification of clinical criteria

In clinical practice, the diagnosis of Lynch syndrome is mainly based on Amsterdam I criteria. Selecting families using these criteria allows a mutation detection rate of about 60% (14) (Table 1).

Table 1. Amsterdam I Criteria.

At least three members of the family should be affected with CRC and the following criteria must be met:	First degree of consanguinity in at least two affected individuals
	At least two consecutive generations should be affected
	At least one diagnosed case of CRC before age 50
	Discarded familial adenomatosis polyposis
	Tumor verification through pathology tests

CRC: colorectal cancer.
Source: Own elaboration based on data obtained from Lynch *et al.* (11).

Amsterdam II criteria were proposed later, in 1999, because the first classification did not include extracolonic tumors, which are part of the phenotype of hereditary nonpolyposis colorectal cancer (HNPCC) (Table 2). Today, the revised Bethesda criteria, established by the US National Cancer Institute, are also taken into account, which allows selection of patients by determining the microsatellite instability (15) (Table 3).

Table 2. Amsterdam II criteria.

At least three members of a family with hereditary nonpolyposis or associated (endometrial, small bowel, ureter or renal pelvis cancer) colorectal cancer and the following criteria must be met:	First degree of consanguinity in at least two of the affected members
	Clinical presentation in at least two consecutive generations
	Diagnosis of at least one case of CRC or associated cancers before age 50
	Discarded familial adenomatous polyposis
	Tumors verification through histopathology tests

CRC: colorectal cancer.
Source: Own elaboration based on data obtained from Allen *et al.* (18).

Table 3. Revised Bethesda criteria (Asad Umar).

Tumors of individuals should be screened for microsatellite instability in the following situations:	CRC in a patient diagnosed before age 50
	Presence of synchronous, metachronous or other HNPCC-associated tumors regardless of the age
	CRC with high microsatellite instability (MSI-H) in a patient diagnosed before age 60
	CRC in one or more first-degree relatives with HNPCC or HNPCC-related tumor diagnosed before age 50
	CRC diagnosed in two or more of first or second degree relatives with HNPCC-related tumor regardless of age

CRC: colorectal cancer; HNPCC: hereditary nonpolyposis colorectal cancer; MSI: Microsatellite instability.
Source: Own elaboration based on data obtained from Asad Umar (15).

Repair systems

Repair systems are crucial for maintaining the integrity of the genome. The mismatch system repair increases fidelity of replication by a factor of 1 000 correcting errors generated during this event. The process begins by recognizing the alteration of DNA and continues with the repair of the defect. The mismatches are caused by errors during replication and recombination, through the generation of small insertions or deletions or physical damage of DNA caused by deamination or cytosine methylation. The best studied system is mutHLS in Escherichia coli; here, mismatch recognition is performed by the MutS protein with ATPase function (16-19).

MMR system in humans

The MMR has evolved to correct errors that are beyond 3'→ 5' exonuclease correction activity of DNA polymerases. The process begins with the recognition of the mismatch caused by the binding of the hMSH2/hMSH6 heterodimer, also known as hMutSa; this complex undergoes a conformational change promoted by ATP which turns it into a clamp, which is displaceable through the DNA strand and, then, recruits the hMLH1 / hPMS2 heterodimer, also known as hMuLa.

This ternary complex can move in any direction along DNA, and when it encounters the broken chain that is subjected to PCNA loading an exonuclease 5 '→ 3' (EXO1), degradation of the thread starts towards the site where the mismatch is located. The chain that is not degraded, is stabilized by replication protein A (RPA) preventing the action of EXO1. When the lesion is removed, the

degraded region is again synthetized by DNA polymerase then the ends are joined by DNA ligase action (20,21) (Figure 1).

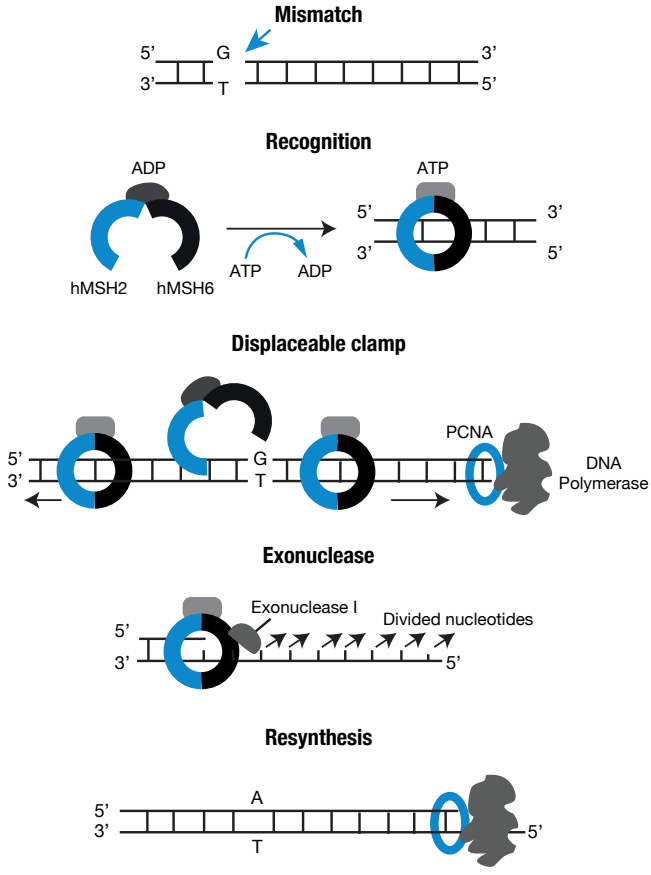

Figure 1. Mismatch repair process. Source: Own elaboration based on data obtained from Boland *et al.* (25).

MLH1 gene is located in the chromosomal region 3p21.3, with a length of 2752pb and 19 exons, and encodes a protein of 756 amino acids with a conserved region of 300 amino acids in its N-terminal end and 27 splicing variants. Location of protein is intranuclear (17,22).

MutL and hMLH1 are members of the GHKL ATPase/kinase superfamily including gyrase, type II topoisomerase, Hsp90 and histidine kinase. The hMLH1 protein has three domains of importance: a ATPase domain at the N-terminal region, an interaction domain with MutS that has another flexible and poorly preserved hinge region, and a domain in the C-terminal region (CTD) involved in homo- and heterodimerization (17). Protein produces heterodimers with hPMS2 proteins, forming the MutLa and hMLH3 complex, and also the MutLb complex which interacts with PCNA.

The hMLH1 protein is part of the surveillance genome complex known as BASC, which includes BRCA1, BLM and ATM proteins, and RAD50-MRE-NBS1, MSH2, MSH6 and MLH1 complexes. They intervene as control points during the cell cycle in the presence of DNA damage (23).

MSH2 gene is located in the region 2p21, is 3307pb long and has 16 exons, encodes a protein of 934 amino acids and has 13 splicing variants. The localization of the protein is intranuclear (22) and contains five domains: domain I DNA binding, domain II interaction with hMSH3 and hMSH6, domain III of ATP binding, domain IV of interaction with homologous MutL, and domain V of ATPase function (24). The protein forms two heterodimers: MutSa, consisting of MSH2/MSH6, which is more involved in the repair process, and MutSb, consisting of MSH2/MSH3.

As mentioned above, the MSH2 protein is also part of the genome surveillance complex and acts as a potential damage sensor in recombination and replication (23).

Microsatellite instability

Microsatellites correspond to short repetitive sequences of 1-4 nucleotides, generally adjacent to coding regions; they are also known as short tandem repeats (STR). Microsatellite instability (MSI) is defined as a change in length of the repeat units due to an insertion/deletion of one or more of these units. This can occur in a microsatellite tumor tissue when compared to normal tissue from the same patient (25). When there is damage in MMR, microsatellites tend to change the number of repetitions. About 70-90% of cases of HNPCC show positive MSI, which is even higher in families with mutation in any of the MMR genes, whereas, in sporadic colorectal tumors, it is only observed in 10-15% of cases (26); therefore, instability is a relatively sensitive but nonspecific marker for HNPCC (25).

In 1998, the National Cancer Institute of the United States proposed a panel of five markers for MSI analysis: mononucleotide in repeats BAT25 and BAT26 and dinucleotide repeats in D2S123, D5S346 and D17S250. A tumor is graded as high MSI (MSI-H), if two or more markers are altered; mild or low microsatellite instability (MSI-L), if a marker is altered, and stability (MSS) if markers are not altered (Table 4).

Table 4. Criteria interpretation of microsatellite instability.

Number of unstable markers	Percentage of unstable markers	Interpretation
2 or more	>40%	MSI-H
1	20%	MSI-L
0	0%	MSS

Source: Own elaboration based on data obtained from Boland *et al.* (25).

BAT26 is extremely sensitive for detecting tumors with instability and shows an insignificant size variation, either between two alleles of an individual or between individuals (25).

Colorectal tumors with MSI-H are found predominantly in the proximal colon, have histopathologically mucinous appearance and may be resistant to cytotoxicity induced by chemotherapeutic agents. Microsatellite instability varies from adenoma to adenocarcinoma and, then, to metastatic tumor.

MSI testing has 80-91% sensitivity in patients with mutations in the MLH1 or MSH2 gene and of 55-77% in MSH6 or PMS2; nevertheless, specificity is similar (27).

MMR gene and somatic mutations in Lynch syndrome

The MMR genes have a role in genome maintenance. The presence of a mutation in some of these genes, mainly MLH1 or MSH2, triggers a cascade of events that affect genes with tandem repeats in their sequence. The repetitive sequences are highly susceptible to misalignment during the replication process, resulting in an increase of 100 times their mutation rate.

Repetitive sequences are dispersed throughout the genome; a large number of human genes have mononucleotide repeats, therefore, they are possible targets of change in the frameshif during replication, which, in turn, generates truncated proteins. These genes,

which include MMR, MED-1 and RAD50, are usually involved in signal transduction (TGFβ-RII, IGFIIR, PTEN), apoptosis and inflammation (BAX, caspase-5), transcription regulation (E2F4, TCF-4) and repair (19).

Among the most important genes susceptible to mutations, gene TGFβRII (receptor II transformer of growth factor β) is found, which contains an adenine (A) repetition tract (7) found in 75-90% of patients with MSI, for both HNPCC and sporadic colon cancer. If the inactivation of one of the receptors occurs, the cells lose their responsiveness to TGFβ and cell growth, which represents an important milestone in tumorigenesis of various cancers such as stomach, neck and prostate. In colon cancer, this inactivation corresponds to an event that occurs early during the transition from adenoma to carcinoma. The inactivation of TGFβRII occurs frequently in MSI+ gastric tumors, but is rare in MSI+ endometrial tumors.

Insertion/deletion mutations in repetitive mononucleotide regions are located in BAX (G8), TCF-4 (A9), IGFIIR (G8) and hMSH6 (C8) genes. Such mutations also occur at a significant rate in MSI+ colorectal tumors. Other genes such as caspase-5 (A10), hMSH3 (A8) and RAD50 (A9) are inactivated, with a lower frequency, in primary tumors, but show a high incidence of frameshift mutations in CRC cell lines (19).

In a study by Yamaguchi *et al.*, the frequency of frameshift mutations in genes ACVR2 (activin receptor 2) and TGFβ -RII was between 70-95% for HNPCC. The signaling pathway of TGFβRII downstream includes Smad 2, 3 and 4 proteins, with subsequent inhibition of cell growth; this pathway may be disrupted by mutations in ACVR2. The Wnt pathway is also affected by disruption caused by mutations in APC. Other genes less involved in the early stages of tumor development are PTHLH, MARCKS, hMSH3, TCF4, CASP5, RIZ and RAD50 (28).

Molecular analysis for the diagnosis of Lynch syndrome

Studies have been performed worldwide to determine the presence of mutations that predispose to Lynch syndrome, and about 400 genes in all MMR have been identified; 90% are in MLH1 and MSH2. The first publications about Lynch syndrome indicate that age 44 to 45 is the average for CRC installation. However, it is now clear that not all cases appear at such a young age and this can vary according to the type of mutation which may not differ from sporadic cases, and could explain the lack of sensitivity of Amsterdam and Bethesda criteria (29).

The most frequent mutations in MLH1 and MSH2 genes are nonsense, missense, frameshift and splicing site changes, while the proportion of genome rearrangements varies in each population from 5% to 20% on average; there are also low frequency cases (1.5%) and, others with higher frequency due to a founder effect (12,31,32), like the results obtained from a study of Spanish population (30).

Conventional methods have been used for detecting mutations as single stranded conformational polymorphism (SCPP), denaturing gradient gel electrophoresis (DGGE), conformation sensitive gel electrophoresis (CSGE), denaturing high performance liquid chromatography (DHPLC) and direct sequencing of the gene. Since large genome rearrangements are not detected by these methods, the analysis by MLPA (Multiplex Ligation-Dependent Probe Amplification) is used, which allows semi-quantitatively assess the change number of copies in a specific region of the gene. The combination of techniques allows a better characterization of the mutational spectrum in a population study (12,29,33-36).

Given the high cost of molecular screening for all MMR genes in suspected families for Lynch syndrome, several pretest strategies, such as determining the degree of instability in tumors, have been suggested. The MSI phenotype is a specific marker useful in HNPCC. However, this can also be observed in sporadic cancers, since about 15% of them are caused by somatic mutations, loss of heterozygosity of MMR genes and promoter methylation of the gene MLH1; this situation is also observed in a study of hypermethylation of MLH1 promoter, predominantly in women over 40 with CRC (37).

The promoter methylation status is suggested as a marker to distinguish sporadic tumors from hereditary tumors. The discrimination of these two subtypes may improve detection strategy, therapy and prevention. In order to standardize the MSI tests, a working group from the National Cancer Institute in the United States recommended the use of the Bethesda panel with five markers, two single nucleotide and three dinucleotide (38,39). In this regard, Pedroni *et al.* (40) demonstrate that a two mononucleotide markers panel (BAT 25 and BAT 26) is more efficient in detecting tumors with high MSI in the absence of MMR proteins compared with the Bethesda panel (93% vs. 54%).

Another initial approach method is the demonstration of the absence of MMR protein expression through immunohistochemical staining (IHC). It has been proved that IHC for MMR proteins (MLH1, PMS2, MSH2 y MSH6) provides a faster, cost-effective, sensitive and very specific screening technique for MSI. Some studies compare methods for determining MSI based on PCR and IHC, showing high concordance (97.8%) (41-43).

IHC assessment for MMR protein expression is performed on tissue sections containing both tumor tissue and normal colonic mucosa. Monoclonal antibodies of mice are used in different dilutions for the total length of proteins. Normal tissue and lymphocytes adjacent to the respective tumor are used as positive internal controls and the loss of protein expression is defined as the complete absence of nuclear staining in tumor cells, but maintained in epithelial and normal stromal cells (40).

Stojic *et al.* (20) described a group of patients with symptoms compatible with Lynch syndrome in absence of IHC expression of the MSH2 protein and had no detectable mutations in this gene; individuals had deletion *of epithelial cell adhesion molecule gene* (EpCAM) located upstream of MSH2. In this study, it was also established that this deletion leads to somatic hypermethylation of MSH2 and loss of protein expression. The silencing of MSH2 gene promoter by deletions of gene EPCAM causes Lynch syndrome in 20-25% of patients with IHC negative for MSH2 and in whom no mutation is found in the germline, which corresponds to 2-3% of all patients with this syndrome (20). Studies have shown that a negative IHC for EpCAM with negative MSH2 indicates deletion of EpCAM with 100% specificity (44,45).

Lynch *et al.* (46) suggest that patients with suspected Lynch syndrome should initially have a test for MSI and then immunohistochemistry tests for MMR proteins, and molecular tests for the negative gene of IHC. In addition, the authors recommend that patients with clinical criteria for Lynch syndrome, even in the absence of germinal mutations for MMR, should be monitored and followed just like molecularly similar patients.

In 2011, a survey conducted by the National Society of Genetic Counselors to evaluate screening programs for Lynch syndrome and barriers for their implementation showed that more than 50% of respondents had been subjected to a screening protocol once the first case of colon or endometrial cancer in the family appeared. Screening methods in tumor tissue varied in 64.2% when the study initiated with IHC testing, 20.8% with MSI testing and 15% with both tests simultaneously. Also, with the results of the survey, the cost of testing and the lack of medical information were deemed as the most important barriers to screening (29).

Moreover, taking into account that only up to 80% of germline mutations are detected in despite of the Amsterdam and Bethesda clinical criteria, there are increasingly strong trends that support universal screening of all newly diagnosed cases with CRC and endometrial cancer (29,48,49).

The debate still lingers regarding the methods used to start screening for Lynch syndrome, as several authors propose IHC as the first test due to its cost-effectiveness and because the absence of protein expression can be detected in both CRC as endometrial cancer. However, as mentioned above, a percentage of tumors with absence of MLH1 and MSH2 expression may relate to somatic events such as promoter hypermethylation or BRAF V600E mutation. Cost-effectiveness data suggest that the best strategy for these cases is to follow IHC test with BRAF mutation or hypermethylation of MLH1 promoter test (48).

Shi *et al.* (49) suggest that, for patients with high microsatellite instability, somatic BRAF V600E mutation should be considered as a pre-molecular study of MMR genes, because this alteration is much more related to sporadic tumors and, thus, Lynch syndrome can be discarded. Similarly, the use of multiplex ligation-dependent probe amplification (MLPA) to detect large rearrangements corresponding to 20% of the mutations is suggested (49).

Liu *et al.* (50) propose a diagnostic strategy for Lynch syndrome that starts with finding MSI, uses the panel of five mononucleotide markers, and searches for specific high prevalence mutations, comprehensive determination of mutations in the MLH1 and MSH2 by sequencing and techniques for large MLPA rearrangements. All of this should be done before searching in other genes, including MSH6 and PMS2, through the MLPA technique (50).

Conclusions

The molecular diagnosis of Lynch syndrome is essential to locate affected individuals and carriers in families and to provide adequate monitoring and genetic counseling. It is necessary to gather evidence on the cost-effectiveness of making universal screening on CRC or to start the process with the use of clinical guidelines, determining the degree of microsatellite instability and IHC, and with this result, determining the next step for sequencing and search of large rearrangements in the MLH1 and MSH2 genes, and subsequently in MSH6, PMS2 and EpCAM.

Conflict of interests

None stated by the authors.

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REVIEW ARTICLE

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Isoinertial technology for rehabilitation and prevention of muscle injuries of soccer players: literature review

Tecnología isoinercial para la rehabilitación y prevención de lesiones musculares en futbolistas: revisión de la literatura

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| Abstract |

Introduction: Soccer is the sport with the highest risk of muscle injury for players. Eccentric exercise is fundamental for reducing injury rates and isoinertial technology devices cause an increase in eccentric demands after a concentric contraction.

Objective: To identify the use of isoinertial technology in the fields of physical activity and sports for rehabilitation and prevention of muscle injuries reported in scientific literature.

Materials and methods: A search of scientific papers in PubMed, Google Scholar, EMBASE and Science Direct data base was performed by using the following MeSH medical terms and search equations: [isoinertial AND technology AND flywheels] and [free weight AND sport AND humans AND soccer].

Results: 23 references, classified into three approaches, were selected: isoinertial technology for rehabilitation, fitness and injury prevention. The use of this technology is fundamental due to the increase of the eccentric demand in muscle groups.

Conclusions: Isoinertial technology is a useful tool for treating and preventing injuries, as well as for the development of physical qualities. However, it is necessary to work on protocols that allow unifying its usage parameters so that it can be included in prevention programs.

Keywords: Injuries; Athletes; Prevention; Exercise; Soccer (MeSH).

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| Resumen |

Introducción. El fútbol presenta el mayor riesgo de lesión muscular en la práctica deportiva. El ejercicio excéntrico es clave en la reducción de las tasas de lesiones donde los dispositivos con tecnología isoinercial generan un aumento en las demandas excéntricas.

Objetivo. Identificar el uso de la tecnología isoinercial en el ámbito de la actividad física y el deporte para la rehabilitación y prevención de lesiones musculares reportadas en la literatura científica.

Materiales y métodos. Se realizó una búsqueda de artículos científicos en las bases de datos PubMed, Google Scholar, EMBASE y Science Direct utilizando los términos MeSH y las ecuaciones de búsqueda [isoinertial AND technology AND flywheels] y [free weight And sport And humans and soccer].

Resultados. Se seleccionaron 23 referencias, las cuales fueron clasificadas en tres enfoques: tecnología isoinercial en rehabilitación, en condición física y en prevención de lesiones. El uso de esta tecnología es fundamental por el aumento en la carga excéntrica en los grupos musculares.

Conclusiones. La tecnología isoinercial es una herramienta útil para el tratamiento de lesiones, su prevención y el desarrollo de cualidades físicas; sin embargo, es necesario que para su inclusión dentro de los programas de prevención se construyan protocolos que permitan unificar los parámetros de uso.

Palabras clave: Traumatismos en atletas; Rehabilitación; Ejercicio; Fútbol (DeCS).

Prieto-Mondragón LP, Camargo-Rojas DA, Quiceno CA. [Tecnología isoinercial para la rehabilitación y prevención de lesiones musculares en futbolistas: revisión de la literatura]. Rev. Fac. Med. 2016;64(3): 543-50. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.47701.

Introduction

Compared to other team sports, soccer has the highest risk of injury; 70% of them are located in the lower extremities and muscle injuries are the most frequent (1). Ekstrand (2) states that 92% of

muscle injuries affect the four major muscle groups of the lower limbs: hamstring (37%), adductors (23%), quadriceps (19%) and calf muscles (13%). 16% of muscle injuries reported are repeated injuries, which cause longer absences. In particular, and because of its two-joint design, hamstring and quadriceps rectus femoris present a significant risk of injury during rapid movements, that is, sprint, stopping, acceleration, change of direction, kicking, landing, etc.

According to Jesper *et al.* (3), the incidence of hamstring injuries is 0.5 to 1.5 injuries per 1 000 hours of exposure during matches and trainings. Besides the high incidence, a common problem related to this injury is the risk of recurrence; the rate reported is 22% of players in the first two months after the injury.

Woods *et al.* (4) state that rectus femoris injuries are frequent in professional soccer, especially during the preseason. Barcelona Club reports that strain injuries in this muscle had an incidence of 6% in 2009. However, due to the shortage of literature on this type of injury, little is known about risk factors, time lost or recurrence rates (5).

These injuries are a serious danger to athletes because they cause long absences from training and competitions, affect their quality of life and generate enormous costs for teams and players (2). Regarding this issue, Gianotti & Hume (6) report the cost-effectiveness of sports injuries and protection elements prevention programs, highlighting cost reduction by using appropriate sports equipment and prevention programs that include balance and proprioceptive exercises.

Apart from considering costs, location and prevalence, it is essential to determine the risk factors that favor the lesion in order to address the issue of prevention of injury among soccer players (7,8).

Muscle injuries can occur due to the interaction of several factors, including intrinsic-internal and extrinsic-external factors. The former refers specifically to athlete factors that may be modifiable and non-modifiable; non-modifiable internal factors include age, since risk of injury increases over time, and gender, since women have higher risk of injury due to increased knee valgus.

The internal modifiable factors include previous history of similar injuries (previous injuries is the main risk factor for a new one) and physical conditions determined by the development of physical skills such as flexibility, aerobic capacity, strength and speed (2,9). Scientific literature establishes that muscle imbalance caused by strength deficit is the second most important factor of risk, because muscle or strength imbalance between agonists and antagonists, that is, between the tendons of the hamstring and quadriceps and/or lack of strength of the bilateral hamstring, is one of the most common factors (7,10,13).

According to Tais (14), further development of muscle strength occurs when an external force is greater than that produced by the muscle and it stretches while maintaining the contraction, thus creating a negative work called eccentric contraction. It has been suggested that eccentric exercise can reduce injury rates because muscle strain injuries occur when activated muscles lengthen over optimal lengths; therefore, injuries can be reduced, if the optimal length can be increased. Studies have shown that this length increases consistently due to eccentric exercise (15).

Authors like McHugh *et al.* (16,17) conducted a study to establish the adaptations generated in the muscle through eccentric exercise, which found that there are neural, mechanical and cellular adaptations. Meanwhile, Nosaka & Aoki (18) stated that, due to neural adaptations, recruitment of motor units is improved, motor unit trigger synchrony increases and a better load distribution between the fibers occurs. Other studies by Nosaka *et al.* (19) and Souza & Paz (20) state that eccentric training substantially increases muscular strength when the skeletal muscle lengthens at higher speeds, that is, with eccentric contractions, so that the production of strength is five times greater in the eccentric muscle actions compared to exercises that generate concentric contractions (19).

Regardless the size of the muscle mass of the tissues involved and despite a greater force production during muscle lengthening, eccentric exercise has a metabolic cost lower than concentric contractions. According to Roig *et al.*, eccentric contractions during low utilization of ATP (adenosine triphosphate) and a reduced concentration of metabolites such as ammonium and lactate (21) is generated.

In a study by Miller *et al.* (22), an analysis made using electromyography (EMG) shows that muscle activity during muscle actions with eccentric contractions is lower than during isometric or concentric contractions; also, the perception of fatigue is generally lower after eccentric exercise than after combining the concentric/eccentric exercise (22). Therefore, the special characteristics of eccentric actions are becoming an important research field, in which attempts to increase positive results of strength training as a protective method against injuries are sought (23).

Previously, the eccentric exercise had been excluded from training programs because such work produces greater damage and muscle inflammation compared to concentric work. Nevertheless, a review by Tous *et al.* (24) states that this type of training increases the size, strength and spring quality of the muscle fiber, so muscle-tendon structure responds favorably to eccentric exercise with a protective effect in the connective tissue; this plays an important role in improving high power sports activities, so it has been successfully incorporated into athletic performance, health, prevention and rehabilitation of sports injuries programs (24).

Thus, isoinertial technology devices become important tools for preventing injuries by allowing the increase of demands of eccentric action after a concentric action because of the inertial load caused during the return movement. Although these machines are isoinertial trends in the field of strength training (25), they are not used frequently in injury prevention programs and have little scientific evidence proven in research. That is why it is necessary to conduct a review to identify the use of isoinertial technology from the scientific literature.

Isoinertial technology

This type of technology can be considered one of the latest trends, as well as a pioneer in strength training. The increase of the eccentric demand produced through isoinertial technology is based on the use of wheels to provide independent inertial resistance to gravity (26).

This technology uses the inertia of a wheel instead of the potential energy obtained by the position of an external object. In the concentric phase, the individual generates kinetic energy through the rotation of the wheel, which is braked during the eccentric phase, where increased recruitment of motor units is required to stop the inertia of the wheel during the return movement.

In this system, resistance force is dynamic and proportional to that generated by the subject. Several studies conducted with isoinertial technology have shown that it enables the development of forces similar or superior to the same exercise done with traditional weights. This technology is currently being used with excellent results in the areas of training, rehabilitation and retraining (27,28).

Although this methodology is not new, interest in eccentric work has led to a more pronounced use of this technology in the

last decade, highlighting the use of machines as the yo-yo and the conical pulleys (27). It is important to stress the work with versapulley isoinertial machines when it comes to obtaining not only eccentric overload, but simulation of the movement in the three dimensions of space, as in the sport event, which does not occur during trainings with conventional overload.

The versapulley isoinertial machines (conical pulley) and the yo-yo develop strength/power and allow generating concretic, eccentric and plyometrics workout, causing a high rate of development of explosive strength and load deceleration required for all multidirectional sports (28,29). The differences between the two training systems is that, while the versapulley allows the development of high eccentric speed with moderate to high strength levels, the YoYo Technology™ enables the development of high levels of force with moderate to low speeds. Therefore, both training systems are necessary and complementary to completely cover the spectrum of force-velocity (27).

Materials and methods

An exploratory-descriptive study was conducted in two phases: the first consisted of a review of the literature and the second in its classification and analysis.

Literature review

A search of scientific literature was performed by consulting the PubMed, Google Scholar, EMBASE and Science Direct databases. The search was conducted between February and December 2014, taking into account the Medical Subject Headings (MESH) and search equations [Isoinertial AND technology AND flywheels] and [Free weight AND sport and humans AND soccer].

Inclusion criteria

The criteria for study inclusion were: papers related to isoinertial technology published between 1998 and 2014 —considering that the first study performed using isoinertial technology was published in 1998—, review articles, cohort and cross-sectional studies, and controlled and uncontrolled clinical trials available in full text.

For the selection of papers, a bibliometric analysis, which allowed defining and applying filters by title and abstract to determine the items to be reviewed in full text, was made.

Classification and analysis of studies

Systematization was conducted through a matrix describing the characteristics and contributions of each paper to the research objective. Such matrix allowed to classify the papers according to the topics addressed —isoinertial technology in rehabilitation, isoinertial technology in fitness and isoinertial technology in injury prevention— to perform content analysis afterwards.

Results

In the four analyzed databases, 64 references related to the topic of isoinertial technology were found with access to full text documents, of which 23 that met the inclusion criteria set forth above were selected after performing a detailed review by two researchers, of both title and abstract (Figure 1).

In a second phase, the 23 references based on three approaches were distributed as follows: isoinertial technology rehabilitation (nine papers), isoinertial technology in fitness (ten papers) and isoinertial technology in injury prevention (four papers) (Table 1).

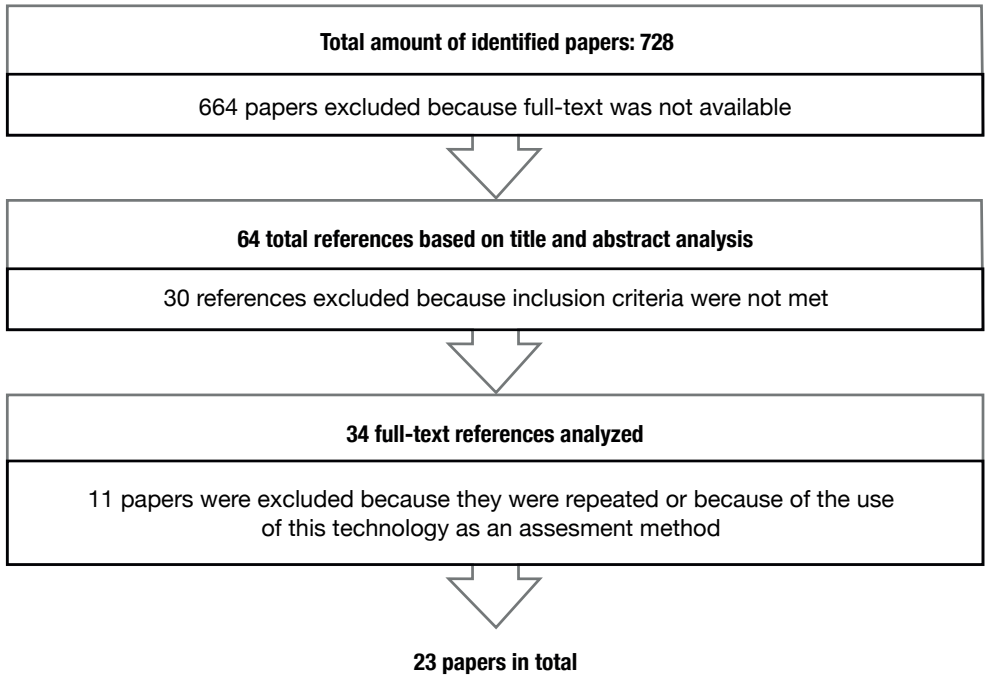

Figure 1. Flow chart of included papers. Source: Own elaboration based on the data obtained in the study.

Table 1. Paper analysis matrix.

Category	Author	Paper	Publication	Year
Isoinertial technology in rehabilitation	Romero-Rodríguez D, Gual D, Tesch PA.	Efficacy of an inertial resistance training paradigm in the treatment of patellar tendinopathy in athletes: A case-series study	Physical Therapy in Sport	2011
	Smith SM, Zwart SR, Heer M, Lee SM, Baecker N, Meuche S, Macias BR, Shackelford LC, Schneider S, Hargens AR.	WISE-2005: Supine treadmill exercise within lower body negative pressure and flywheel resistive exercise as a countermeasure to bed rest-induced bone loss in women during 60-day simulated microgravity	Bone	2008
	Rittweger J, Frost HM, Schiessld H, Ohshima H, Alkner B, Tesch P, Felsenberg D.	Muscle atrophy and bone loss after 90 days' bed rest and the effects of flywheel resistive exercise and pamidronate: Results from the LTBR study	Bone	2005
	Belavy DL, Ohshima H, Bareille MP, Rittweger J, Felsenberg D.	Limited effect of fly-wheel and spinal mobilization exercise countermeasures on lumbar spine deconditioning during 90d bed-rest in the Toulouse LTBR study	Acta Astronautica	2011
	Trappe S, Costill D, Gallagher P, Creer A, Peters JR, Evans H, Riley DA, Fitts RH.	Exercise in space: human skeletal muscle after 6 months aboard the International Space Station	Journal of Applied Physiology	2009
	Fernández-Gonzalo R, Nissemark C, Åslund B, Tesch PA, Sojka P.	Chronic stroke patients show early and robust improvements in muscle and functional performance in response to eccentric-over-load flywheel resistance training: a pilot study	Journal of NeuroEngineering and Rehabilitation	2014
	Brasileiro JS, Pinto OM, Avila MA, Salvini TF.	Functional and morphological changes in the quadriceps muscle induced by eccentric training after ACL reconstruction	Brazilian Journal of Physical Therapy	2011
	Croisier JL.	Muscular Imbalance And Acute Lower Extremity Muscle Injuries In Sport	International SportMed Journal	2004
Isoinertial technology in fitness	Volkers KM, de Kieviet JF, Wittingen HP, Scherder EJ.	Lower limb muscle strength (LLMS): Why sedentary life should never start? A review	Archives of Gerontology and Geriatrics	2012
	Tous-Fajardo J, Maldonado RA, Quintana JM, Pozzo M, Tesch PA.	The Flywheel Leg-Curl Machine: Offering Eccentric Overload for Hamstring Development	International Journal of Sports Physiology and Performance	2006
	Bara-Filho M, Manso JG, Sarmiento S, Medina G.	Hamstrings co-contraction in knee extension during isoinertial strength work	Revista Brasileira de Biomecânica	2008
	Tomberlin JP, Basford JR, Schwen EE, Orte PA, Scott SC, Laughman RK, Ilstrup DM.	Comparative study of isokinetic eccentric and concentric quadriceps training	Journal of Orthopaedic & Sports Physical Therapy	1991
	Norrbrand L, Tous-Fajardo J, Vargas R, Tesch PA.	Quadriceps muscle use in the flywheel and barbell squat	Aviation, Space, and Environmental Medicine	2011
	Norrbrand L	Acute and early chronic responses to resistance exercise using flyweel or weights	Department of Physiology and Pharmacology, Karolinska Institute.	2008
	Fry AC, Schilling BK, Lohnes CA.	Kinetic and Kinematic Comparison Between Versa-Pulley and Free-Weight Front Squats	The University of Memphis, Department of Health & Sport Sciences	2007
	Norrbrand L, Pozzo M, Tesch PA.	Flywheel resistance training calls for greater eccentric muscle activation than weight training.	European Journal of Applied Physiology	2010
	Onambélé GL, Maganaris CN, Mian OS, Tamd E, Rejc E, McEwan IM, Narici MV.	Neuromuscular and balance responses to flywheel inertial versus weight training in older persons	Journal of Biomechanics	2008
	Goldmana EF, Jones DE.	Interventions for preventing hamstring injuries: a systematic review	Physiotherapy	2011
Isoinertial technology in injury prevention	Hibbert O, Cheong K, Grant A, Beers A, Moizumi T.	A systematic review of the effectiveness of eccentric strength training in the prevention of hamstring muscle strains in otherwise healthy individuals	North American Journal Of Sports Physical Therapy	2008
	Askling C, karlsson J, Thorstensson A.	Hamstring injury ocurrence in elite soccer players after preseasons strength training with eccentric overload	Scandinavian Journal Medicine and Science in sport	2003

Source: Own elaboration based on the data obtained in the study.

Isoinertial technology in rehabilitation

Usage for skeletal muscle injury management

In the rehabilitation of anterior cruciate ligament (ACL) injury, the study of Brasileiro (29) reports that eccentric strength training in the quadriceps muscle generates important functional and morphological changes; also, it shows that eccentric training significantly increased isokinetic torque and quadriceps area with greater hypertrophy in the proximal region, showing that eccentric training proves to be a powerful resource for recovery and strengthening the quadriceps, both morphologically and functionally.

Likewise, at muscle level, Croisier (40) shows that muscle function abnormalities can lead to persistent recurrent lesions and discomfort when resuming an activity. A rehabilitation program based on muscle strength training leading to the standardization of specific isokinetic parameters, with specific exercises according to the deficits, contributes to a decrease in symptoms during the return to field. Similarly, Croisier states that "some prospective studies have shown that preseason isokinetic testing in risk sports is useful to identify strength variables like the predictors of strained muscle in hamstring or adductor" (40, p13). Therefore, it can be said that muscle strength and intra and intermuscular coordination play a key role in acute muscle injuries.

In tendon injuries, a case study conducted in 10 male athletes who had patellar tendinitis showed that exercises using inertial eccentric overload in the short term improved eccentric strength by 90% ($p=0.03$), as well as the maximum concentric strength by 70%, which was evident in the quadriceps muscle, specifically in the femoral rectum. Regarding pain in the patellar tendon, as measured by the visual analog scale, it decreased after training by 60% ($p<0.01$) (41).

Usage in induced immobilization or simulated microgravity

Exercise protocol was used in the study conducted by Smith & Rittweger with women who went through induced rest for 60 and 90 days; the protocol combined exercise in bed and resistance exercise with flywheels for four days a week, in order to prevent bone resorption and promote bone formation. After the simulated microgravity, it was evident that, although the protocol did not provide an optimal bone countermeasure, it promoted bone formation and helped mitigate the net bone loss (42,43).

The findings suggest that both measures are partially effective in preserving bone mineral content (BMC) and muscle cross-sectional area (MCSA) of the leg during bed rest. The partial effectiveness of exercise with the flywheel and the response of bones to discharge makes evident the importance of mechanical stimuli; however, the huge variability of BMC changes suggests that other factors affect changes in bone strength (43).

In another study related to prolonged immobilization, changes in the parameters of the spine and posterior lumbar disc morphology after 90 days of bed rest are found. These results indicate that countermeasures used (measures taken before immobilization) were not optimal for maintaining the integrity of the spine and the trunk musculature during bed rest (44).

On the other hand, Trappe *et al.* (45), in a study of a crew traveling into space concluded that the exercise program did not completely protect the calf muscles in the absence of gravitational stimulus; also, they observed a substantial decrease in muscle mass of the calf and performance, along with a type of transition from slow to fast fibers in the gastrocnemius and the soleus. These data suggest that changes in the program of countermeasures exercise are required to protect the skeletal muscle while the crew are in space for long periods.

Usage in neurological or central nervous system diseases

Research reporting the use of these devices in neurological diseases are scarce and, also, contradictory. The study by Fernández-Gonzalo *et al.* (46) states that eccentric exercises with isoinertial technology generate muscular adaptations and functional performance in patients with chronic cerebrovascular accident. In contrast, another study in patients with degenerative neurological diseases did not find positive effects of isoinertial technology and shows greater benefits caused by concentric exercise (47), perhaps due to the type of neurological disease and its particular neuromuscular features, which requires further study.

Isoinertial technology in fitness

Currently, several studies report that the eccentric workout generates rapid strength gains compared to concentric work, since it shows that more tension is developed by using less active motor units and, therefore, less energy; similarly, neuronal conduction is improved, recruitment is more effective and greater inhibition of protective mechanisms is found. These factors make the crossbridge of the sarcomere develop greater strength and quantitatively determine that workout with eccentric strength can generate an average gain of 498±336J compared against 273±196J of concentric work. Within eccentric workout methods, isoinertial technology generates more overload that enhances the effects of this type of contraction (29-31).

According to Filho (32), strength training with the use of isoinertial machines is one of the current methods being used to improve physical capacity. Specifically, physical activity establishes the importance of proper development of the hamstring muscles to ensure muscle balance between them and the extensor muscles of the knee (quadriceps) since hamstrings work as synergists for actions like running. Some researchers, in different areas related to physical activity, thoroughly study the process of co-contraction of the hamstring muscles (33). Bernardi (34) states that the main objectives of the co-activation are related to the regulation of joint movement and control of joint stability, thus, co-activation of the hamstrings is necessary to stabilize the knee joint, equal the tension distribution on the surface of the joint and prevent cartilage damage.

Squats are the most practiced exercise in training to improve performance due to the development of horizontal or vertical strength, power and speed; however, in this exercise, muscle activation and recruitment of motor units are not generated in most repetitions, on the contrary, resistance achieves maximum motor action from the first repetition of a series with flywheel machines with isoinertial technology. The comparison between these different training methods allows establishing resistance using the flywheel to generate the maximum voluntary force by the rectus femoris muscle through each repetition of a set, increasing muscle tropism (35-37). The study by Onambélé (38) reports that the burden of inertia of the flywheel on the quadriceps causes an increase in muscle strength of the gastrocnemius of 26%, which leads to increased stiffness of the tendon by 136% with isoinertial technology; the increased rigidity is associated with an improvement in postural balance.

According to Tous (39), learning is an essential component for the execution of these exercises; given their complexity, it is important to provide immediate visual feedback to further adjust performance and control to allow the individual to get used to a correct manipulation of the isoinertial machine.

Clearly, the use of a greater moment of inertia results in higher production adaptations of eccentric force; likewise, muscle, power and speed improvements are much more influenced by the reduction of the moment of inertia. Although the optimal condition for improving quality distinctly varies among individuals, the general guidelines regarding the configuration of the moment of inertia is still undefined (24).

Isoinertial technology in injury prevention

The effectiveness of interventions used to prevent hamstring injuries in soccer players or those involved in other high risk activities has been demonstrated in randomized controlled trials (48), which state that the use of the isoinertial technology device yo-yo, in particular, reports a reduction in the incidence of hamstring strains in soccer players because it generates a considerable increase in strength of the biceps femoris muscle for greater eccentric activation. The above statement could suggest that the biceps femoris plays a much more relevant role in braking than the semitendinosus as there are no specific differences in strength, power and speed profiles caused depending on the moment of inertia applied during the year (24,35).

The results of a systematic review suggest that eccentric training is effective in primary and secondary prevention of hamstring strains. However, the heterogeneity of the studies and the poor methodological rigor limit the ability to provide clinical recommendations. More randomized clinical trials (RCT) are required to support the use of eccentric training protocols in preventing hamstring strains (49).

These results indicate that adding preseason strength training, specific for hamstring —including eccentric overload— would be beneficial for elite soccer players, for both injury prevention and performance improvement (50).

Conclusions

According to the literature, isoinertial technology is an important tool for rehabilitation and prevention of injuries that allows further development of force during the concentric and eccentric phases due to the particular functioning mechanism (33). This technology offers superior eccentric loads compared to traditional methods, where the co-activation of the hamstring muscles is greater; most studies are performed on this musculature, given the high prevalence of injury in soccer players. Generating high eccentric loads provides improved power and speed in the muscles, which is potentiated by reducing the moment of inertia (24). These effects are achieved at the end of the concentric action and by allowing the player to slow down, thus increasing the eccentric overload by decreasing the angular displacement (29).

As for the benefits of using the isoincercial technology for the treatment or management of some pathologies, studies demonstrating its effectiveness in recovering from ACL (29), patellar tendinopathy (40), as well as muscle-tendon injuries generated by muscle imbalance are found. Similarly, the isoinertial technology has proven to be beneficial in bone formation and in the decrease bone loss, as well as for increasing of muscle cross-sectional area during prolonged immobilization, which is important for the mechanical stimulus generated (42). It is also important to note that no changes were obtained in the morphology of the intervertebral disc using this technology due to the characteristics of the cartilage (44).

Although positive effects on muscle adaptations and functional performance in patients with sequelae of cerebrovascular disease (46) are found, a greater effect of the concentric exercises than of eccentric load generated by such technology is evidenced in patients with degenerative neurological diseases (47).

Regarding the prevention of sports injuries, it is reported that the use of this technology reduces the incidence of injury in the hamstring muscles, specifically in the biceps femoris —muscle with the highest rates of injury— (24,35,51). These results indicate that eccentric overload is beneficial for elite players in both injury prevention and performance improvement. However, few studies have used isoinertial technology, which raises the need for generating further research in the field.

Isoinertial technology is an important tool for the prevention of sport injuries, as it allows functional movements related to the sporting context and an increase of eccentric load during the workout. Similarly, it is important for inclusion to promote the construction of a protocol using these machines, which will unify parameters and ensure optimal stimulus in the development of responses and musculoskeletal adaptations.

The scientific literature shows the benefits of isoinertial technology; nonetheless, there are few experimental studies to determine the effect of preventing musculoskeletal injuries in athletes, in controlling them and in pathological conditions caused by immobilization processes or alterations of the central nervous system.

This review opens a field of research in injury management, control and prevention, which must be explored from analytical and experimental studies to determine their effect and efficacy, while promoting rehabilitation processes and functional rehabilitation.

Conflict of interests

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CASE REPORT

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Autoimmune hemolytic anemia as an initial manifestation of Hodgkin's Disease: Case report

Anemia hemolítica como manifestación inicial de la enfermedad de Hodgkin. Reporte de caso

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| Abstract |

This paper presents the case of an 11 year-old male who attended the Internal Medicine Service at a high complexity pediatric hospital.

Initially, the patient attended due to a clinical profile consisting of autoimmune hemolytic anemia that was partially responsive to steroid treatment and, after exhaustive complimentary analysis, was associated to a Hodgkin lymphoma. Similar cases found in the scientific literature were reviewed in order to analyze this case.

Through this paper, the authors intend to remind the medical community about the importance of a prompt and deep study of all autoimmune hemolytic anemia cases found in pediatric patients, without overlooking possible malignant causes related to this condition such as a lymphoproliferative disorder. Thus, before diagnosing a hemolytic anemia as idiopathic, the practitioner must be certain that the condition is not a clinical manifestation of an underlying disease.

Keywords: Anemia; Hemolytic Anemia; Hodgkin Disease (MeSH).

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| Resumen |

Se presenta el caso de un niño de 11 años atendido en el servicio de Medicina Interna de una institución pediátrica de alto nivel de complejidad.

El paciente consultó por un cuadro de anemia hemolítica autoinmune que respondió parcialmente al tratamiento con esteroides y luego de los estudios complementarios se encontró asociada a un linfoma Hodgkin. Se revisaron casos similares en la literatura y se hizo un análisis al respecto.

A través de este artículo se recuerda e insiste en que toda anemia hemolítica en niños se debe estudiar de forma pronta, profunda y sin descuidar posibles causas malignas relacionadas como una enfermedad linfoproliferativa; por lo tanto, antes de declarar una anemia hemolítica como idiopática, se debe estar seguro de que no se trata de una expresión clínica de otra enfermedad de base.

Palabras clave: Anemia; Anemia hemolítica; Enfermedad de Hodgkin (DeCS).

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Introduction

Autoimmune hemolytic anemia (AHA) is a relatively rare disease with an annual incidence of 1 per 75 000 to 80 000 people. The average age of diagnosis is 3.8 years in the pediatric population (1). For decades, autoimmune entities such as hemolytic anemia, thrombocytopenic purpura, neutropenia and insulin receptor antibodies have been reported as paraneoplastic manifestations of Hodgkin's disease (HD) (1-4). Therefore, all patients with AHA should be studied to discover the cause and to discard the presence of neoplastic based entities such as HD and non-neoplastic entities such as infections, autoimmune diseases, drug intake, etc. (5).

The development of autoimmune hemolytic anemia in lymphoproliferative disorders is multifactorial and caused by disorders in regulatory and autoreactive LB and LT (6) cells. The Hodgkin lymphoma implies alterations in the immune system, which include abnormalities in the cytokine production and increased sensitivity to regulatory T cells, but with an overall decrease in the number and functional capacity of T cells (6-8). Thus, during a decrease of cytotoxic T lymphocytes, an increase in autoantibody production may occur; this is currently the most accepted mechanism to explain the appearance of AHA in some of these patients (9).

In the past, based on epidemiological studies, the hypothesis of a possible infectious etiology during HD that instigates the production of

antibodies that cross-react with antigens in the erythrocyte membrane (10,11) was proposed, however, this theory has not been proven yet.

This paper describes the case of a pediatric patient who developed hemolytic anemia as an initial manifestation of Hodgkin lymphoma; this finding is highlighted as a paraneoplastic manifestation of HD that should be taken into account when studying the causes of AHA.

Case presentation

Male patient, 11 years old, with a history of anemia of 10 months which was diagnosed in a control consultation, with unclear characteristics and etiology, and managed with ferrous sulfate.

On admission in hospital, the relatives referred fever peaks of up to 39°C, predominantly nocturnal, associated with asthenia, adynamia and unquantified weight loss. Physical examination showed a thin aspect and muco-cutaneous pallor. A complete blood count found hemoglobin at 7.4 g/dL, mean corpuscular volume of 77.7fl and mean corpuscular hemoglobin of 25.9pg; the blood smear showed moderate anisocytosis with presence of dacrocytes and codocytes. The patient was hospitalized under the diagnosis of normocytic normochromic anemia of unclear etiology; studies were extended and a direct Coombs test, with positive results (+++), and a high LDH were performed, which finale led to conclude that the patient presented immune hemolytic anemia.

The fever and weight loss manifestations suggested a neoplasm as the cause of the immune hemolytic anemia; therefore, further studies, such as chest radiography and abdominal ultrasound, were performed. The first exam showed no alterations and the second showed para-aortic lymphadenopathy and left iliac chain, as well as hypo-echoic images in the common left iliac artery. A biopsy and bone marrow aspiration were also performed, which reported no tumor infiltration. Due to the presence of an acute hemolytic picture, treatment with methylprednisolone 30 mg/kg/day for three days was ordered; after this, a control complete blood count was performed, in which an increase in the value of Hb 8.9g/dL was found. Treatment was continued with prednisone at 1 mg/kg/day.

The studies initially performed to find a possible infectious, tumor and autoimmune disease causes were negative. The patient persisted with spiking fevers and presented painful hepatomegaly during the clinical evolution, so a new abdominal ultrasound was requested, in which enlarged lymph nodes in the para-aortic region with involvement of the left iliac region were found. The child was further evaluated through pediatric surgery for lymph node biopsy; the pediatric surgeon ordered complementary studies including an abdominal computed tomography scan that reported lymphadenopathies in the left iliac chain with ipsilateral para-aortic region involvement. Based on these findings, a magnetic resonance imaging of the abdomen and pelvis was ordered, which showed splenomegaly, nodes in the para-aortic region, left infrarenal aortoiliac bifurcation and solid smooth masses accompanying the major vessels and the lower region of the renal hilum, compatible with neoplasia.

A biopsy of the retroperitoneal lymph node showed infiltration of Reed Stemberg cells with positive reactivity in immunohistochemistry for CD15, CD30, PAX-5 and LMP-1 studies, which confirmed the diagnosis of a mixed cellularity Hodgkin disease. The clinical status corresponded to stage IIB, for which chemotherapy with ABVD scheme was started.

The patient received six cycles of ABVD chemotherapy (doxorubicin, bleomycin, vinblastine and dacarbazine) and subsequent consolidation treatment with radiotherapy in sites involved at diagnosis.

At the end of the study, the child was in clinical remission for two years, with control blood counts within normal limits, and monitoring and control through the oncohematology service.

Discussion

Previously, prevalence of autoimmune hemolytic anemia has been reported in patients with Hodgkin's disease ranging between 0.2% and 2.7% (2,12); with the development of more sensitive immunoassays, it is likely that a larger number of HD patients are being diagnosed with AHA (13). However, this type of anemia as the first manifestation of this disease is even more unusual than their mere association (10,14).

Bowdler & Glick (15) first published about this relationship, stressing that the diagnosis of AHA preceded by three years the dignosis of HD, as in the case of this patient, who had anemia for 10 months before diagnosis of Hodgkin lymphoma.

The secondary AHA, besides presenting the characteristic clinic of hemolytic anemia such as dyspnea, fatigue, paleness or jaundice, among others, are presented along with the underlying disease clinic. In the case of a lymphoproliferative syndrome, associated manifestations usually include appetite and weight loss, night sweats, lymphadenopathy and hepatosplenomegaly; this clinic is important because it directs or allows suspecting a neoplastic entity (6,14,16), as in this patient. Moreover, even in the absence of clinical manifestations suggestive of a lymphoproliferative syndrome as the cause of autoimmune hemolytic anemia, this type of pathologies should always be sought once the diagnosis is made, as well as other possible causes (Table 1) (16,17).

Autoimmune hemolytic anemia may be present at any stage of Hodgkin's disease; although it is usually associated with the active or advanced disease, it can precede the diagnosis or be present in a relapse episode (1,10). A positive Coombs test can be an indicator to suspect possible relapses in patients with a history of HD in remission with or without AHA (6,10).

Currently, there are no studies of sufficient quality to establish appropriate protocols for the management of AHA, nor a consensus on what complete remission or partial remission of the disease means (19), therefore, the management of hemolytic autoimmune anemia is based on experience and individual clinical decisions.

It should be noted that the effectiveness of therapies for AHA is low when it is secondary to an underlying disease, this being especially true for autoimmune hemolytic anemias secondary to lymphoproliferative syndromes (6,13).

The above statement was evident in the case reported here, in which no adequate response to treatment with corticosteroids was obtained. Definitive therapy for autoimmune hemolytic anemia associated with Hodgkin's disease is the treatment of the underlying disease, through which there is a progressive decrease of antibody titers until reaching the eventual negativization of the Coombs test (20), the recovery of Hb values and the disappearance of hemolysis signs.

Conclusions

Autoimmune hemolytic anemia, although unusual, can be a paraneoplastic manifestation of a lymphoproliferative syndrome as Hodgkin's disease. The underlying cause of AHA must always be sought, even if it is refractory to treatment. Additionally, if there is an AHA in a patient with a history of HD in remission, HD should be suspected and a relapse should be discarded.

Table 1. Causes of AHA.

Autoimmune diseases	Evans syndrome
	Systemic lupus erythematosus
	Autoimmune thyroiditis
	Graves disease
	Vitiligo
	Giant cell hepatitis
	Rheumatic disease
	Type 1 diabetes
	Crohn's disease
	Ulcerative colitis
Immunodeficiency	Common variable immunodeficiency
	Combined immunodeficiency
	Adenosine deaminase deficiency
	HLA class II deficiency
	HIV
	Wiskott-Aldrich syndrome
Infections	Epstein-Barr virus
	Mycoplasma pneumoniae
	Parvovirus B19
	Cytomegalovirus
	Chickenpox
	Hepatitis C
	Rubella
Malignancy	Lymphoproliferative diseases
	Acute leukemia
	Lymphoma
	Myelodysplasia
Drugs	Piperacillin
	Ceftriaxone

Source: Own elaboration based on (18).

Conflicts of interest

None stated by the authors.

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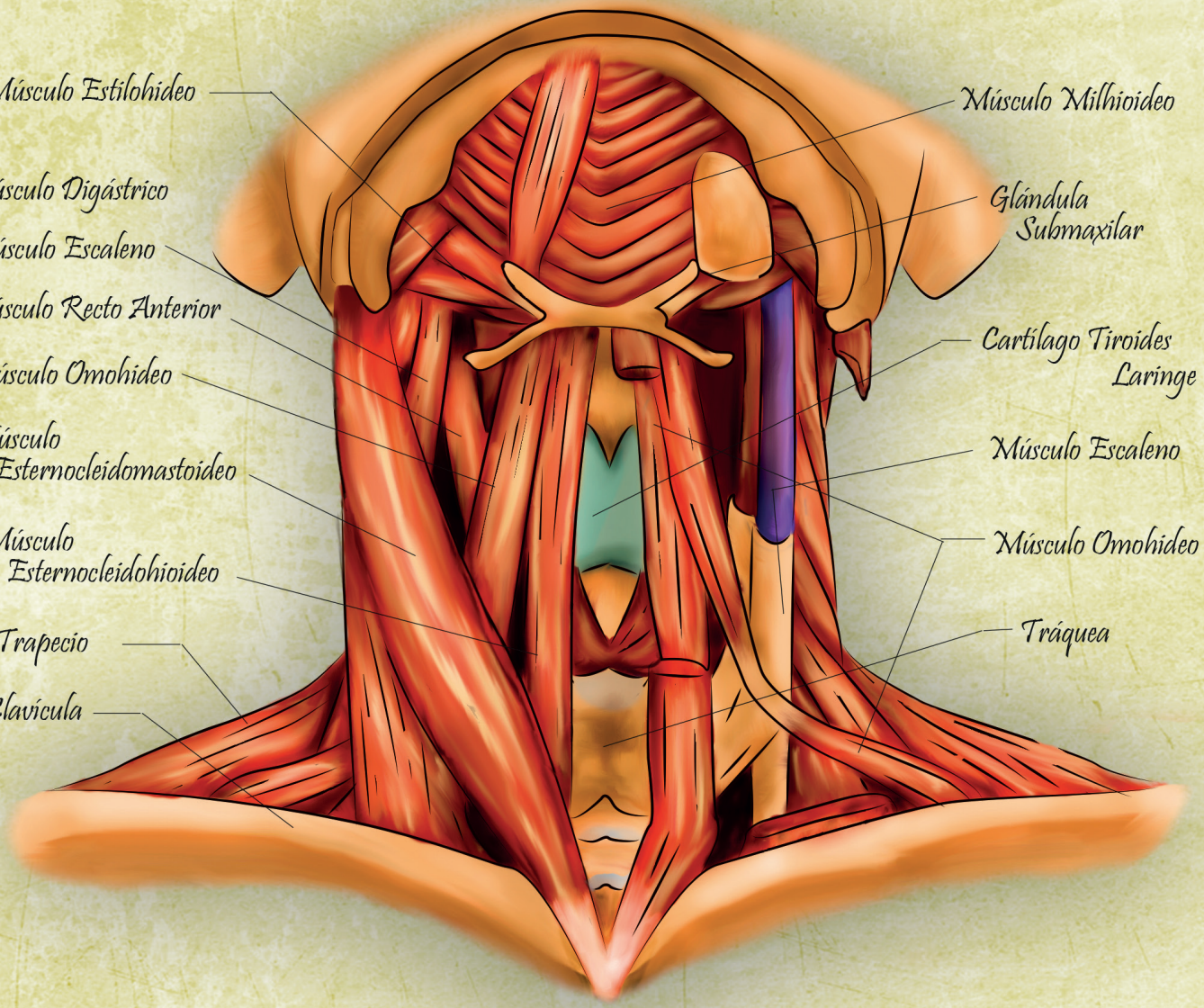
Miología de Cuello

Vista Anterior



Plano Superficial

Plano Profundo

César Alexander Eslava Franco
"Mapas anatómicos"
Universidad Nacional de Colombia

CASE REPORT

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Fulminant gas gangrene in an adolescent with immunodeficiency. Case report and literature review

Gangrena gaseosa fulminante en adolescente con inmunodeficiencia. Reporte de caso y revisión de la literatura

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| Abstract |

Immunity defects are important predisposing factors to aggressive infections with high risk of mortality. The case of a teenager with a history of immunodeficiency, who developed gas gangrene infection originated in the left lower limb is reported here. The disease progressed in less than 24 hours, developed systemic involvement and led to multiple organ failure and death. Pathophysiological aspects and features of the agent are reviewed here, highlighting the importance of high index of clinical suspicion and immediate handling.

Keywords: Gas Gangrene; Infection; Immunodeficiency; Subcutaneous Emphysema; Histiocytosis (MeSH).

García EK, Sierra PA, Quintero O, Jaramillo L. Fulminant gas gangrene in an adolescent with immunodeficiency. Case report and literature review. Rev. Fac. Med. 2016;64(3):555-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.49794.

| Resumen |

Los defectos de la inmunidad constituyen un importante factor predisponente a las infecciones agresivas de alto riesgo de mortalidad.

Se presenta el caso de un adolescente con antecedente de inmunodeficiencia, quien de forma rápida desarrolla infección del tipo gangrena gaseosa. La infección inicia en miembro inferior izquierdo y en menos de 24 horas desarrolla compromiso sistémico con falla orgánica múltiple y el paciente fallece.

Se revisan los aspectos fisiopatológicos y las características del agente causal, resaltando la importancia del diagnóstico y tratamiento oportuno y temprano.

Palabras clave: Gangrena gaseosa; Inmunodeficiencia; Histiocitosis; (DeCS).

García EK, Sierra PA, Quintero-Guevara O, Jaramillo L. [Gangrena gaseosa fulminante en adolescente con inmunodeficiencia. Reporte de caso y revisión de literatura]. Rev. Fac. Med. 2016;64(3):555-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.49794.

Introduction

Gangrene means cell necrosis (1) and may be caused by various microorganisms: *Pseudomonas aeruginosa, Estaphylococcus aureus, Streptococcus pyogenes* (2)*, Clostridium spp* and other anaerobic bacteria (3,4). When gas is present and evolution is fast, gangrene is caused by bacteria of the genus clostridium, whose spectrum of infection includes contamination and anaerobic cellulite before myonecrosis (5).

Clostridial myonecrosis or gas gangrene is very rare in pediatric population; its origin can be traumatic (6) due to the continuity to the inoculum, or spontaneous due to hematogenous spread from the gastrointestinal tract. The first is mainly caused by *Clostridium perfringens* (7) and the second usually by *Clostridium septicum* (8).

C.septicum is a Gram positive anaerobic bacillus that forms spores, found in 2% of healthy population at the cecum and the ileocecal area, where poor vascularization, pH and osmotic and electrolytic characteristics —associated with lymphocyte protection imbalance— (9) favor their proliferation (10). The microorganism has tolerance relative to oxygen, which facilitates its proliferation in healthy tissues, so that the inoculum required for infection is 300 times smaller than that for *C. perfringens* (11).

The proliferation of *Clostridium* produces large amounts of hydrogen and carbon dioxide; these gases are distributed in tissue planes, are dissected and generate palpable emphysema. The necrotic process extends to adjacent healthy tissue, causing massive necrotizing gangrene within hours (12).

The rapid proliferation and systemic toxicity generated by *C. septicum* is considered to be caused due to the production of four exotoxins —alpha toxin, cytolysin, β-toxin and neuraminidase —(13); alpha toxin (14), the most pathogenic of all, is responsible for intravascular hemolysis, tissue necrosis and increased capillary permeability —pore-forming cytolysin— (15). Other functions of this toxin include sphingomyelinase activity, favoring the increase of platelet aggregation, reducing the adhesion of polymorphonuclear (16) and suppressing muscle contraction (17).Tissue destruction results in edema

and ischemia, which consequently cause severe metabolic acidosis, fever, DIC and renal failure secondary to the effects of hypotension, myoglobinuria and direct toxin nephrotoxicity (10). Genomic studies of the bacterium show highly conserved nuclear sequences (18).

Case presentation

17 year old teenager with a history of Rosai-Dorfman histiocytosis, autoimmune lymphoproliferative syndrome, decreased T helper lymphocytes, with two episodes of febrile neutropenia, recurrent stomatitis and two episodes of pneumonia. The patient attended the emergency room due to a clinical picture of pain for 16 hours in the anterolateral side of the left leg, with limited mobility and gait; acetaminophen and optimal analgesia was administered for management of fever and pain at home. Two hours before consultation, a rapidly progressive edema had begun in the same location of the lower left limb. A diarrheal episode occurred a week before, which resolved spontaneously, and no traumas were referred.

On admission to the emergency room, the respiratory rate was 23 breaths/min, the heart rate of 112 beats/min, body temperature of 38°C and blood pressure of 105/74mmHg; the left inguinal region presented erythema, limbs with edema, cyanosis and erythema, crackles in the left lower limb in its entirety, capillary filling greater than three seconds, difficult palpation pulse and no other abnormalities on physical examination. Gas gangrene was considered and antibiotic treatment was administered with vancomycin and meropenem, as well as analgesia with morphine.

X-rays of the abdomen and left lower limbs showed subcutaneous emphysema in the thigh, leg and pelvis (Figure 1); a deep vein thrombosis with signs of gangrene and compartment syndrome was determined, so a fasciotomy was conducted as a vital urgency.

In the operating room, increased mottling purple coloring and extension to the lower abdomen and right thigh was observed, along with blebs of serohematic not fetid content in the inguinal region and presence of marked edema in the left scrotal sac (Figure 2); after examining the subcutaneous tissue and fascia, abundant gas production, thrombosed venous vessels of small caliber, marked tension in the lateral compartment of the left thigh with full pressure in the vastus lateralis when cutting the fasciae latae were found.

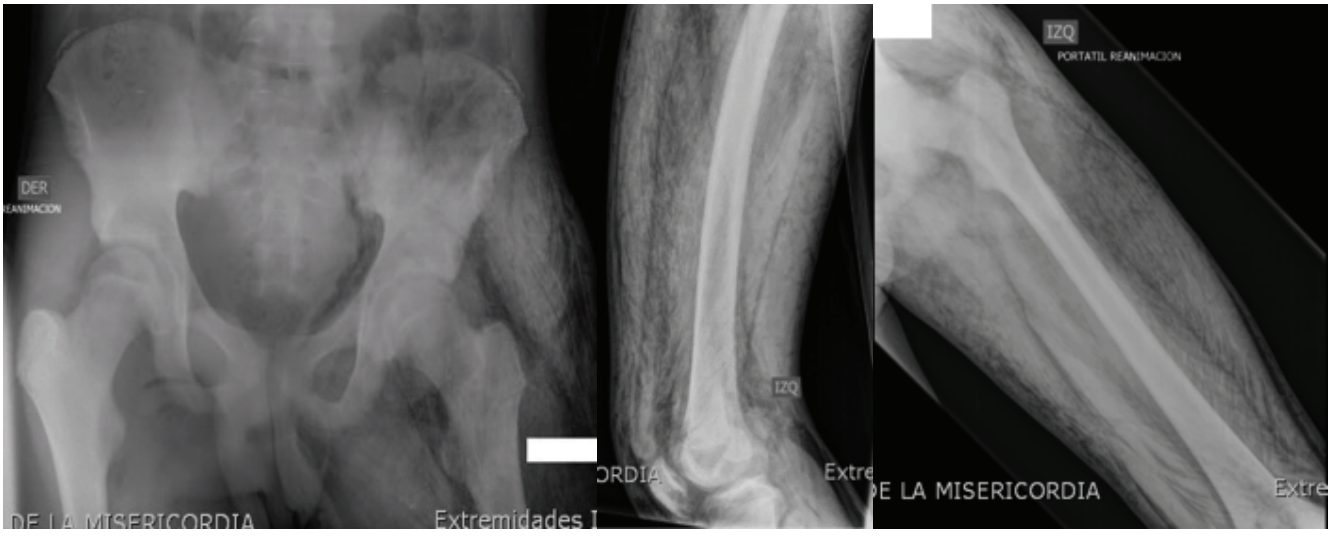

Figure 1. Radiographs of the left thigh in lateral projections, AP and hip, where the presence of gas dissecting the muscle planes and subcutaneous tissue is visible, with no evidence of bone involvement. Source: Own elaboration based on the data obtained in the study by the Radiology Service of Fundación Hospital de la Misericordia in Bogotá.

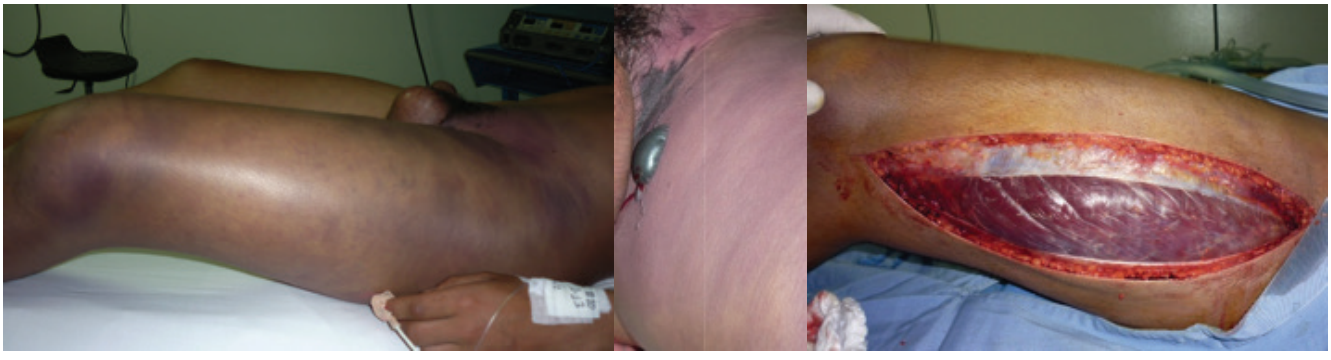

Figure 2. Pictures taken in the operating room previous and during fasciotomy, where purplish skin coloration, marked edema, blisters in the inner side of thigh and vastus lateralis pressure are observed. Source: Own elaboration based on the data obtained in the study by the Plastic Surgery Service of Fundación Hospital de la Misericordia in Bogotá.

By the end of the procedure, persistence of distal coldness and paleness of the left lower limb were observed; when removing surgical fields, violet color progression on the chest and ecchymosis in the left iliac fossa were found. Biopsies were taken to histopathology and penicillin and metronidazole (Figure 3) were administered. Laboratory results are shown in Table 1.

Immediately after the surgical procedure, the patient was transferred to the pediatric intensive care unit, where he was admitted hypoperfused with hemodynamic deterioration, requiring high ventilatory parameters and with diastolic hypotension; then, he suffered a cardiac arrest with asystole unresponsive to resuscitation and died.

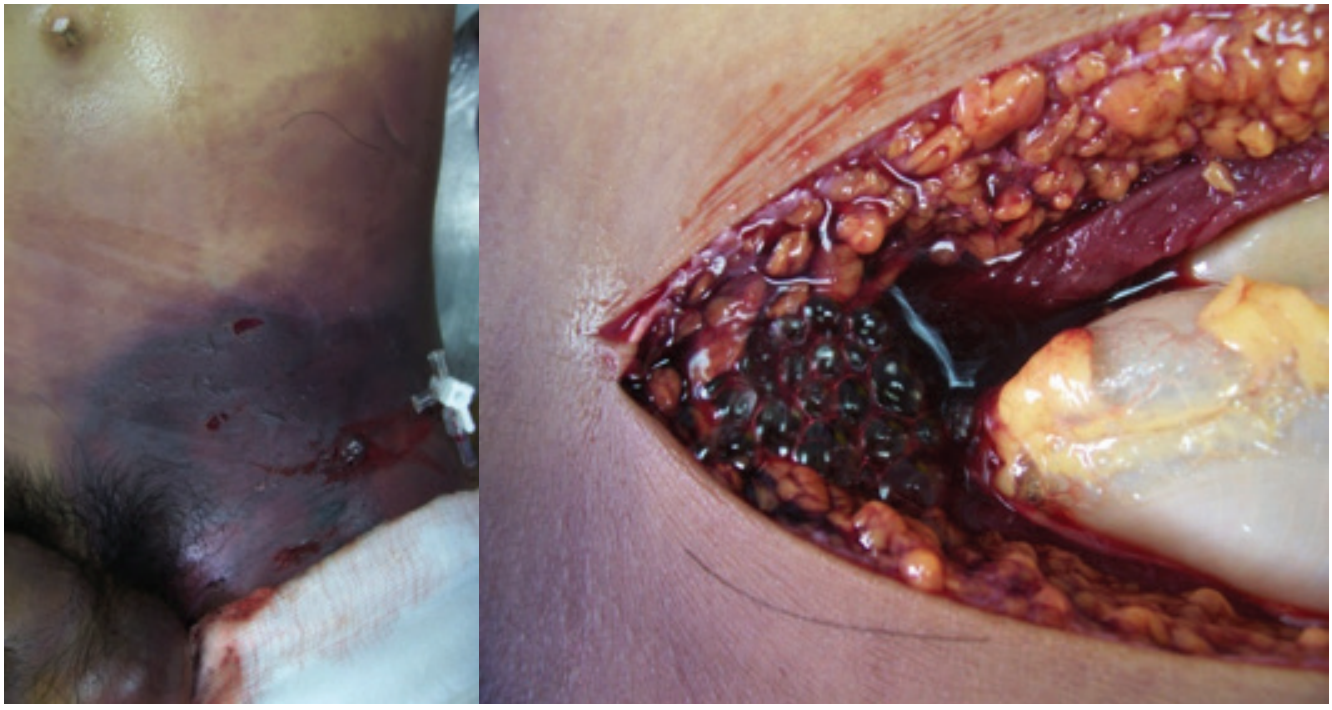

Figure 3. Postmortem picture where accentuation of violet color in the skin and scrotal edema are observed. Aspect after cutting the muscle and tissues where the expelling of bubbles caused by the gas that dissects the tissue are observed. Source: Own elaboration based on the data obtained in the study by the Pathology Service of Fundación Hospital de la Misericordia in Bogotá.

Table 1. Laboratory exams

Blood count	Leukocyte 1130, N 0%, L 97%, MONO 3%, HGB 12.2, HTO 37, PLT 153000 Leukopenia and absolute neutropenia	**Central venous gas**	PH 7.0, PCO2 50, PO2 50.6, SO2 63, HCO3 13, NA 129, CA 0.9, GLU 111, K 5.35, CL 95, LACT 8.0, HB 10.5. Metabolic acidosis+respiratory acidosis Increased lactate
Clotting times	PT 31.2, INR 2.43, PTT 33.4, CTRL 30.7 Normal		1.48
Procalcit/PCR	58.44-96 High	**Creatinine/BUN**	1.62
Blood culture 1	S. hominis 22.3, H Res. Oxacillin	**Blood culture 2**	1.77
Left vastus lateralis culture		**S. epidermis resistant to oxacillin**	
Pathology	Skin and tissue, IIM subcutaneous cells: changes of ischemia and bleeding. Skeletal muscle, IIM vastus externus negative for necrosis or inflammatory changes		

Source: Own elaboration based on data taken from the clinical profile of the patient.

Discussion

In recent decades, most cases of gas gangrene in adults have been associated with intestinal malignancy (19-22), recent surgery, trauma, diabetes or peripheral vascular disease (23); between 1 000 and 3 000 cases of this disease are reported per year in the United States (24,25).

In children, a prevalence of *Clostridium spp.* of 7% in all isolates of anaerobic bacteria has been reported (26); there is no difference in the distribution between genders and most cases of *C. septicum* are associated with leukemia, immunodeficiency (as in this case), cyclic neutropenia (27), hemolytic uremic syndrome, among others (28,29). In the case of this paper, there is no clear intestinal focus, but there is a history of diarrhea a week before.

The diagnosis of clostridial myonecrosis is difficult because it may be initially confused with cellulitis, pyoderma gangrenosum (30) or necrotizing fasciitis (31); however, unlike others, the clinical course is very fast (6 to 48 hours) and there are some more specific

symptoms that appear late. Thus, the presence of severe pain as the predominant symptom, as well as signs of systemic inflammatory response and gas (crepitation) should immediately lead to suspect this disease (32); progressive inflammation signs and blisters with brown liquid content appear subsequently (28).

Imaging studies like X-rays are useful since they help to identify gas in the deep tissues; similarly, computed tomography or magnetic resonance imaging can detect the spread of the infection along fascial planes.

The definitive diagnosis is made by determining the bacilli on the site of the lesion; bacteremia can be detected in up to 15% of cases and develops several hours before skin manifestations. To isolate the bacteria, special anaerobes culturing is required; the microorganism can also be found in the aspirate of the lesions or in the biopsy. Surgical findings show that the muscle does not contract with stimulus nor does it bleed, and edema and variable color are observed. Histopathology showed varying cell lysis —muscle, fascia, fat— and gas formation with absent inflammatory cells. In this particular case, the absence of necrosis signs under light microscopy can be explained by the rapid onset of the symptoms (5).

No procedure can delay or replace emergency surgical treatment and antibiotic treatment, accompanied by hemodynamic stabilization (1). Selected antibiotics include crystalline penicillin at high doses plus other antibiotics based on clinical suspicion, for example, clindamycin (33); another scheme includes administering broad spectrum antibiotics such as vancomycin, metronidazole or meropenem (34). Surgical intervention —fasciotomy, debridement, resection or amputation— determines survival since necrotic areas do not allow the arrival of the antibiotic (28).

There are no conclusive studies to recommend the use of hyperbaric oxygen in spontaneous gas gangrene; the study of immunoglobulin and granulocyte stimulating factor (9) in immunosuppressed children recently started (10) and the future of treatment leads to the inhibition of the alpha-toxin. Mortality varies between 67% and 100% (11), finding the highest values among immunodeficiency patients with underlying malignancy (35).

Gas gangrene is considered to be a fulminant disease, so initiating antibiotic therapy and surgery must not be delayed once the diagnosis is suspected. It is highly recommended to always handle these patients in pediatric intensive care units due to the high risk the disease represents.

Conflict of interests

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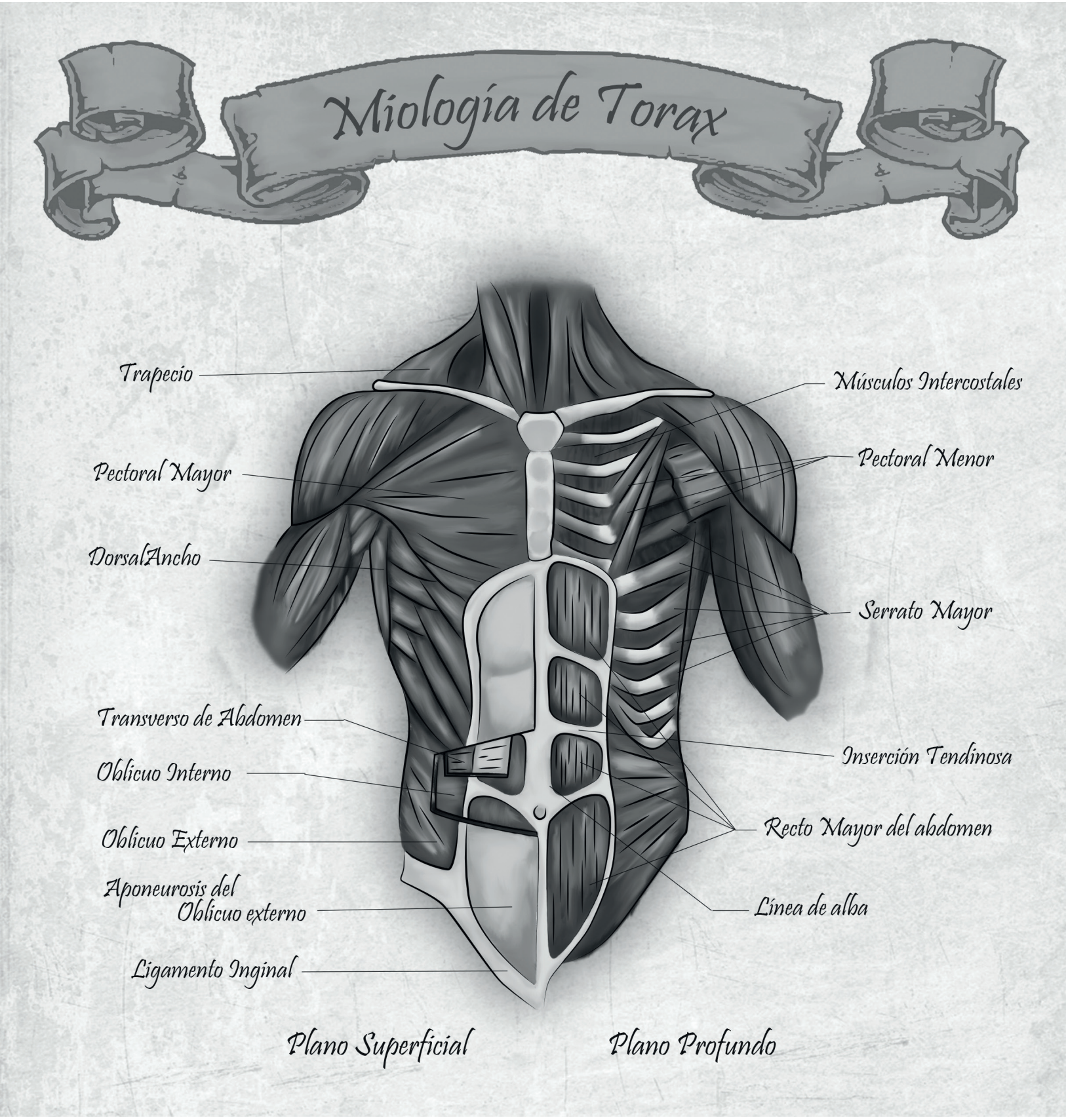
Miología de Torax



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CASE REPORT

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Neurocysticercosis, unusual manifestations

Neurocisticercosis, manifestaciones inusuales

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| Abstract |

Neurocysticercosis is the most common parasitic infection in the central nervous system. This disease is presented when a person ingests *Taenia solium* eggs excreted in feces from another individual infected with taeniasis. In 50% of the cases, neurocysticercosis takes place in the brain parenchyma, and its appearance is less frequent in the posterior fossa and the spinal cord.

The case of a patient with an atypical location of the parasite at the medulla oblongata, between parenchymal and spinal areas, is presented. The initial symptoms were common but its subsequent manifestations were similar to those of Bruns syndrome. Furthermore, the epidemiological profile of neurocysticercosis in Colombia, its control measures and prevention strategies were reviewed in this study.

Keywords: Neurocysticercosis; *Taenia solium*; Bruns; Syndrome; Medulla Oblongata (MeSH).

López-Valencia D, Medina-Ortega AP, Saavedra-Torres JS, Zúñiga-Cerón LF, Zamora-Bastidas TO. Neurocysticercosis, unusual manifestations. Rev. Fac. Med. 2016;64(3):561-4. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.53471.

| Resumen |

La neurocisticercosis es la infección parasitaria más frecuente en el sistema nervioso central; esta enfermedad se desarrolla cuando los huevos de *Taenia solium* excretados en heces de un individuo con teniasis son ingeridos por otra persona. La presentación de la neurocisticercosis tiene lugar en el parénquima cerebral en 50% de los casos, mientras que en la fosa posterior y en la médula espinal es menos frecuente.

Se presenta el caso de un paciente que tuvo una ubicación exótica del parásito a nivel del bulbo raquídeo concomitando con la forma parenquimatosa y medular; las manifestaciones clínicas iniciales fueron las comunes, pero sus síntomas posteriores se caracterizaron por el síndrome de Bruns. Además, durante la investigación se revisó el perfil epidemiológico de la neurocisticercosis en Colombia y las medidas de control y de prevención.

Palabras clave: Neurocisticercosis; *Taenia solium*; Síndrome; Bulbo raquídeo (DeCS).

López-Valencia D, Medina-Ortega AP, Saavedra-Torres JS, Zúñiga-Cerón LF, Zamora-Bastidas TO. [Neurocisticercosis, manifestaciones inusuales]. Rev. Fac. Med. 2016;64(3):561-4. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.53471.

Introduction

The most common parasitic infection of the central nervous system (CNS) is neurocysticercosis (NCC), caused by the larvae of the *Taenia solium* (1). In developing countries, there is a 90% prevalence of cases in which this disease is neglected (2), but due to the ease and accessibility of transportation and the large groups of migrant population, this disease can also be found in developed countries (3,4). The World Health Organization (WHO) considers cysticercosis as a serious public health issue (5,6). This infection appears in the brain parenchyma in 50% of cases, and less frequently, in intraventricular, subarachnoid, eye and cord areas (6).

The case described in this research presents an unusual appearance in the medulla oblongata, along with the parenchymal and spinal form. NCC symptoms are very diverse, including, among the most frequently observed and described by the authors, headaches and convulsions (7). 80% of infections are completely asymptomatic and when symptoms arise, they are non-specific depending on the number of injuries, the development stage of the cysticercus and the larval location (8). The presence of cysticerci in the brain may be prolonged —10 to 20 years in asymptomatic state— (9,10) although, in many occasions, when headaches occur, this symptom is not considered important. The diagnosis of NCC is often confused with incidentaloma.

The characterization of the patient was made based on neurological manifestations such as focal seizures and signs of intracranial hypertension. Neuroimaging, initially obtained through computerized axial tomography scan (CT scan) and head magnetic resonance imaging (HMRI), helped identifying different forms of NCC.

The objectives of this paper are to present an unusual form of neurocysticercosis in the medulla oblongata and, thus, to provide

the scientific community with information about the location and heterogeneous behavior of the larva of *T. solium*.

Case presentation

A male patient, 37 years old, from Popayán, Cauca, farmer without history of chronic non-communicable diseases, who denies prior neurological abnormalities and family history of importance, was admitted in Hospital Universitario San José from Popayán, on February 25, 2014, with an eight-month clinical history of neck pain treated with analgesics with partial response. The assessment by neurosurgery and pain medicine suggested that the patient had a chronic degenerative pain syndrome, with C5 and C6 discopathy. Algesiology delivers lumbar sympathetic block and epidural steroid; however, this procedure is not performed because the patient felt drowsy.

The neurological assessment found a patient with pain in the posterior cervical region, permanent headache, stiff neck, discreet meningeal stripe, hyperesthesia in eyeballs and drowsiness. ELISA technique was initially indicated for *T. solium*, as well as a complete blood count reporting reactivity and marked eosinophilia, respectively; also, a brain CT with contrast was requested, which showed a cystic image located in the left Sylvian fissure. Considering personal history and the regional epidemiology, in addition to the clinical manifestations and the report of the TAC, treatment against NCC with albendazole 200mg every 12 hours, dexamethasone 8mg every hour, and phenytoin 100mg every 12 hours was begun.

Eleven days after admission, a second brain CT showed supratentorial hydrocephalus, megacisterna magna and three scattered calcifications in both cerebral hemispheres (Figure 1 and 2).

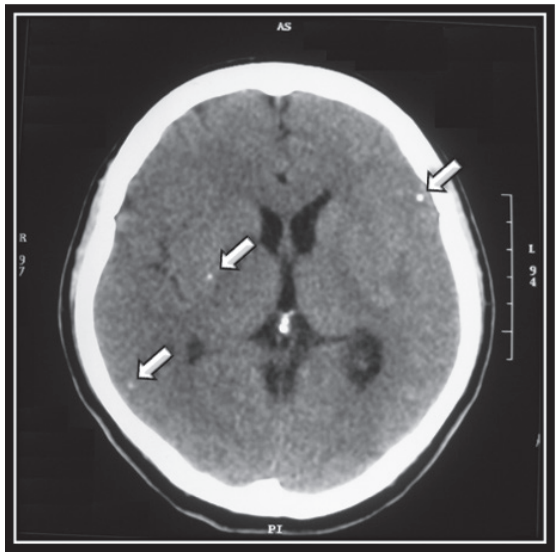

Figure 1. Computerized axial tomography scan which allows observing calcifications that suggest the effects of neurocysticercosis. Source: Own elaboration based on the data obtained in the study.

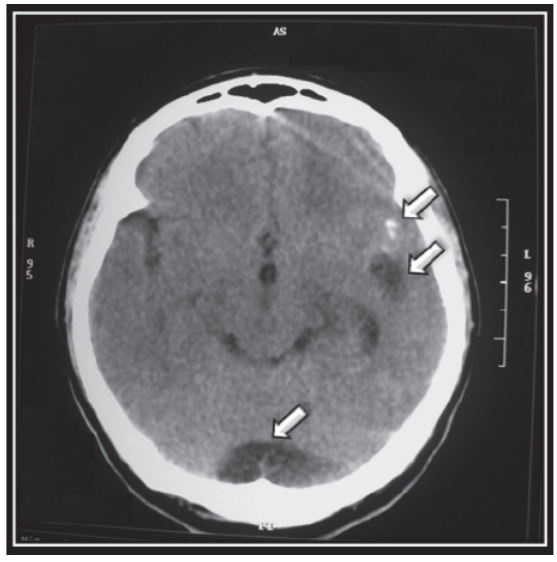

Figure 2. Computerized axial tomography scan which allows observing, from top to bottom, calcifications, cystic image located in the left Sylvian fissure compatible with neurocysticercosis in vesicular phase and megacisterna magna. Source: Own elaboration based on the data obtained in the study.

The patient reported improvement after 12 days of treatment with albendazole, however, he experienced sporadic crisis of headaches, vomiting and drowsiness. Neurological examination determined predominantly left hypotonia and muscle stretch reflexes showed hyperreflexia in lower extremities. Since the patient could not walk on his own, possibly due to subsequent involvement of the posterior cords, cysticercosis related injury in the posterior fossa is discarded and a simple and contrast HMRI was requested.

Deworming was completed after 26 days of admission in the service. Although the evolution of the patient indicated improvement, headaches did not diminish. Finally, a HMRI was taken, showing, on the one hand, two hyperintense punctiform images of corticosubcortical location in the left frontal region and towards the ipsilateral Sylvian fissure compatible with residual calcifications, and, on the other, a rounded cystic image, with intermediate signal intensity and hyperintense with walls that enhance the lateral contrast and apparent contact with the medulla oblongata on the left side, which was about 6x3mm long (Figure 3).

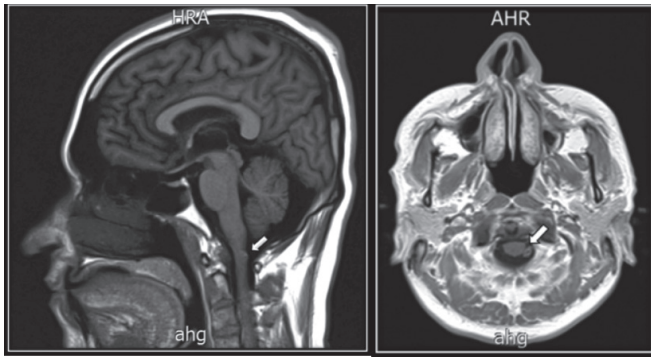

Figure 3. Head magnetic resonance imaging showing a cystic lesion adjacent to the medulla oblongata. Source: Own elaboration based on the data obtained in the study.

The results of the studies concluded a cystic lesion adjacent to the medulla oblongata and enhancement of the walls that, in association with chambered images of multicystic appearance in the subarachnoid space of the posterior fossa and cortico-subcortical calcifications, lead to discard NCC (Figure 3). The patient progressed satisfactorily with complete improvement of the symptoms and was discharged without complications.

Treatment

The patient was treated with cysticidal drugs that are currently recommended by experts in parasitology, infectious diseases and neurology. Epilepsy was controlled using phenytoin sodium, which allowed a gradual improvement.

Discussion

Finding neurocysticercosis manifestations in inhabitants of endemic areas consulting for severe headache and developing signs of intracranial hypertension is not uncommon taking into account that the highest national prevalence of this disease is found in the department of Cauca (55.2%) (11). The taeniasis-cysticercosis complex (CTC) is caused by the pork tapeworm known as *T. solium*, which affects humans after eating their eggs, while NCC is the most common CNS helminths and the leading cause of acquired epilepsy in the world (12). Hence the importance of recognizing the biology of CTC when applying control and prevention measures in the population.

The manifestations and findings of cerebellar dysfunction are the key factors of this case: the holocraneal headache with persistent (and occasional projectile) vomiting, alongside ataxia with lateropulsion to the left that compromised gait and resulted incapacitating —which constitutes the most frequent alteration that indicates cerebellar dysfunction— the initial hypotonia worsened to such an extent that supine position could not be sustained and the patient chose left lateral decubitus position, signs of leg length discrepancy, dysdiadochokinesia and non-fluid language.

All signs indicated that the patient suffered a supra and infratentorial lesion, therefore, a BMRI was required. An ELISA test for *T. solium* helped confirming the infection and neuroimaging was useful to classify various stages of cysticercosis: vesicular, colloidal, granular and nodular (calcification) (12).

During the course of the disease, the patient had critical days with acute headache, dizziness, complete abnormal gait due to ataxia and lateralization with compromised state of consciousness, manifestations explained by Bruns syndrome (13-15).

In 1902, Bruns described ataxia caused by frontal lesions, similar to what was observed in diseases of the cerebellum that fundamentally compromised statics, lateropulsion and retropulsion of gait originated by a malfunction of the fronto-ponto-cerebellar tract (16-19). Bruns syndrome is typically characterized by episodes of severe headache, vomiting and associated vertigo related to sudden changes in head position that may persist for a few minutes to an hour and, sometimes, cause sudden death.

Epidemiology

NCC is considered the leading cause of acquired epilepsy and hydrocephalus (15) in adults from countries in South Asia, Mexico, Colombia, Ecuador, Peru, among others (20-22). Colombia does not have clear studies for the whole country; there are reports by Universidad Industrial de Santander, Universidad de Caldas (23) and a study conducted in Boyacá (24), all of them showing different figures.

In 2004, in the Department of Cauca, an epidemiological profile of human cysticercosis in five first level hospitals reported a total of 55.2% in the department out of a population of 433 patients (11). This result surpassed the study conducted in Vaupés, whose figures are considered the highest in Colombia (38.7%) (25). Given this situation, it is necessary to conduct studies that are valid for the entire national territory.

Control measures and prevention

A disease like NCC involves cultural and socioeconomic aspects of human groups, especially when considering that mechanisms of propagation and perpetuation of infection are not overcome due to the customs of the people living in endemic areas. There is no doubt that proper handwashing before and after food consumption, control of environmental sanitation, proper disposal of feces, adequate water service to ensure potable water, among others, are the best means to prevent, control and cure patients with taeniasis-cysticercosis complex (26-28). Even though pork, when the animal is not raised with hygienic standards, is one of the main sources of *T. solium*, irrigation of vegetables and fruits with polluted water may also contribute to the development of CTC, hence the importance of knowing the life cycle of the parasite (12).

Conclusions

A comprehensive analysis of the patient is essential to establish an accurate diagnosis and determine treatment. The description of this case shows an atypical manifestation of the larva of *T. solium*, which should always be considered within the diagnostic possibilities currently obtained through the use of imaging tools such as CT or HMRI, the detection of antibodies and other laboratory tests. NCC requires immediate and complete cysticidal treatment managed at hospitals to achieve full eradication of the larvae and prevent future recurrences and/or sequelae.

NCC is a chronic disease of the CNS that deserves attention; the WHO considers this condition as a public health problem, reason why healthy habits that improve eating behaviors should be taught to avoid infection, since this is a completely preventable disease.

Conflict of interests

None stated by the authors.

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To Universidad del Cauca and the patient reported here.

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CASE REPORT

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Case report: sleep alterations associated with hypothyroidism

Reporte de un caso de alteraciones en el sueño asociadas a hipotiroidismo

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| Abstract |

This paper presents a case report of a perimenopausal woman who repeatedly attended health care institutions due to chronic insomnia, and underwent pharmacological treatments and psychiatric hospitalizations without achieving any positive result for nearly three years. After compiling all the information of the case, as well as analyzing previous and recent paraclinical studies, the patient was diagnosed with hypothyroidism.

The purpose of this paper is to draw attention on the adequate use of clinical diagnostic tools and processes to optimize the medical practice and to offer a better service to patients.

Keywords: Sleep Disorders; Hypothyroidism; Diagnosis; Sleep Iniciation and Maintenance Disorders (MeSH).

Chica-Urzola HL. Case report: sleep alterations associated with hypothyroidism. Rev. Fac. Med. 2016;64(3):565-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.53769.

| Resumen |

Se presenta el caso de una mujer adulta perimenopáusica quien consultó múltiples veces al sistema de salud por presentar insomnio crónico y, durante cerca de tres años, recibió tratamientos médicos farmacológicos e incluso hospitalizaciones psiquiátricas sin lograr mejoría. Tras la integración de la información de la cual se dispuso, así como la toma y revisión de paraclínicos previos, se documentó hipotiroidismo.

En este estudio se intenta hacer un llamado a la utilización de las herramientas clínicas y a la implementación de adecuados procesos diagnósticos con el fin de optimizar la práctica médica y ofrecer un mejor servicio a los pacientes.

Palabras clave: Trastornos del sueño; Hipotiroidismo; Diagnóstico; Trastornos del inicio y del mantenimiento del sueño (DeCS).

Chica-Urzola HL. [Reporte de un caso de alteraciones en el sueño asociadas a hipotiroidismo]. Rev. Fac. Med. 2016;64(3):565-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.53769.

Introduction

This paper presents the clinical case of a patient who had consulted general and specialized physicians, several times, for about three years, without obtaining an effective solution to her ailments. For this reason, the possibility of illustrating the process experienced by the patient was considered; the patient, ultimately, received a comorbid diagnosis of hypothyroidism and dyslipidemia, and was provided with a treatment that evidently improved her symptoms.

In this study, all relevant precautions to protect the identity of the patient and maintain the confidentiality were taken. This paper makes reference to the patient in terms of sex and age, but no specific personal or contact information is provided.

Case presentation

This case is about a 51-year-old woman who consulted different doctors during the span of three years and felt that could never sleep nor obtain any rest. When explaining her sleeping habits, she explained that she woke up at 4:30 am, but got up two or three hours later; she did not take naps despite feeling tired and fatigued during the day, and went to sleep at 9:30 pm. She did not mention any difficulty to fall asleep. Sometimes during the week, she exercised at 8:00 am for about an hour, but she felt without energy. In order to sleep, and by medical order, she took Lorazepam 2 mg/night and Levomepromazine 50 drops/night (50 mg/night) without improvement. No related triggers of the symptoms were described.

Previously, the patient was hospitalized in a psychiatric clinic with a diagnosis of depression, and was administered zolpidem, zopiclone, lorazepam, levomepromazina, clonazepam and valproic acid; however, she felt that the treatment did not represent any improvement, and then, decided to self-medicate with amitriptyline, without any change. Due to her sleep difficulties, she consulted a general physician, and was again referred to psychiatry and a polysomnography (PSG) was requested; according to the patient, the result was normal, so her treating psychiatrist decided to continue the treatment with benzodiazepines.

The patient also reported a history of irritable bowel syndrome, an asymptomatic pituitary adenoma and frequent consultation to hospital services due to gastrointestinal issues. She also reported that her mother had died from breast cancer and had some nephews with thyroid malignancies.

During medical examinations, possible thyroid nodules were found, therefore, she underwent FNAB (fine-needle aspiration biopsy), and the result was normal. The patient did not remember if other paraclinical examinations had been taken.

A systems enquiry found dry skin, hair loss, brittle nails, milk discharge from breasts, menstrual irregularities prone to oligomenorrea, frequent headaches treated with NSAIDs, nocturia and weight gain (about 10kg in two years).

Physical examination found a hemodynamically stable patient, with vital signs within normal limits, overweight, dry skin, dull and thin hair, brittle nails, acrocyanosis, non-visible thyroid and no other relevant findings.

Mental examination exposed hypoprosexia, bradypsychia and an overvalued somatic ideation related to the difficulty to sleep. After active exploration, no depressive overvalued ideation was found, but fatigability, constrained sadness and anxiety, lack of repairing sleep and preserved reality judgment were identified.

At the time, additional paraclinicals were requested. The gradual discontinuation of benzodiazepines and levomepromazine was indicated, and mirtazapine 15 mg/night during this period was prescribed. Sleep hygiene and habit structuring recommendations were given and the patient was scheduled for a control consultation with the paraclinical results requested, in addition to those previously taken.

Two weeks later, the patient attended consultation with the previous tests: a thyroid FNAB reporting goiter according to the Bethesta System category III and a PSG showing "no respiratory disorders during sleep" reported by a pneumologist; however, when reviewing other parameters and the hypnogram, a sleep destructuration was found along with a significant increase in the superficial slow wave sleep, and multiple alertness periods at the expense of deep slow wave sleep without significant disturbances in the percentage of rapid eye movement (REM) sleep. A total sleep time of more than 350 minutes was reported, without respiratory events.

Among the tests requested on the initial consultation, hypothyroidism associated with dyslipidemia was documented, for which treatment was initiated, obtaining progressive symptomatic remission and instructions on changing habits were given. Finally, the patient was recommended to continue in treatment with endocrinology and attend a psychiatry control for follow-up, which she attended three months later with her bedmate and both, patient and companion, spoke about the improvement of symptoms according to their perception of sleep quality, day performance and parallel symptoms. In the same consultation, psychoeducation was provided to the patient and her companion.

Topic review

The relevance of this case is based on two important topics: the impact of hypothyroidism on sleep from the psychiatric point of view, which is not uncommon, and the necessary wake-up call that must be made regarding the diagnosis process in medicine, leading to consider this case for illustration.

Hypothyroidism and its impact on sleep from a psychiatric point of view

Hypothyroidism is a syndrome caused by a qualitative or quantitative decrease of the thyroid hormone, usually by alteration in any of the links of the hypothalamic-pituitary-thyroid axis; rarely, it may also be caused peripherally (1). It usually has an insidious course, so it is uncommon to have patients consulting in the early stages of the disease. Diagnosis can take time and requires suspicion based on clinical and paraclinical confirmation.

This syndrome is characterized by metabolic, cardiovascular, reproductive, neurological, and osteotendinal alterations, and, in general, affects all bodily functions. Patients are more vulnerable to this disease at specific stages of life, like pregnancy or senior age (2-11).

Regarding the mental sphere, a slower course of thought, fatigability, asthenia, apathy, visuospatial construction skills and attention memory disorders are frequent, so the differential diagnosis often includes depression or dementia (2,12-16). However, although infrequent, there have been psychotic episodes called "malignant myxoedemas", so the study of this pathology has been proposed in conjunction with others such as sleep apnea (17).

With hypothyroidism, sleeping habits may be altered including daytime sleepiness and prolonged nighttime sleep (18) that improves with the administration of the thyroid hormone (19). In addition, subclinical hypothyroidism has been documented in 10-15% of patients with symptomatic hypothyroidism and obstructive sleep apnea (OSA) in 5% of them; the occurrence of snoring and sleepiness was also reported. These respiratory events during sleep are explained from a pathophysiological perspective based on reduced thyroid activity which, in turn, produces anatomical changes and increases airway resistance, compromising significantly REM sleep with the appearance of sleep apnea.

Moderate to severe hypothyroidism causes central respiratory rhythm disorders with secondary alveolar hypoventilation. This supports the idea of the relation between hypothyroidism and increased resistance syndrome of the upper airway.

A direct relationship between the severity of hypothyroidism, the presence of nocturnal snoring, daytime sleepiness and improvement after treatment with thyroid hormone was also documented (20-22).

Advanced hypothyroidism may lead to macroglossia, weight gain, muscle dysfunction or deposits of mucopolysaccharides in the upper respiratory tract and decreased ventilatory control, along with sleep apnea (23); however, no correlation was found between the severity of sleep apnea and thyroid hormone levels, so the recommendation for all patients with sleep apnea (24-27) or sleep disorders (28,29) is to undergo a thyroid study (30,31), even children (32), since the combination between hypothyroidism and sleep apnea is associated with pulmonary hypertension (33).

On the other hand, there have been studies on the quality of sleep of patients with thyroid disorders in which the measurement of objective (polysomnographic) and subjective (use of the Pittsburgh sleep quality index and Epworth Sleepiness Scale) parameters is included. Controversial results ranging from no correlation (34,35) to correlation between snoring and excessive daytime sleepiness with hypothyroidism, especially in the presence of obesity (28,36), were obtained.

Finally, some studies, such as Koehler *et al.* (38) have shown that acute and severe deficiencies of the thyroid hormone do not have a significant impact on the sleep architecture and no statistically relevant differences were found when comparing parameters such as the rate of apnea-hypopnea index (AHI), the average length of each of the stages of sleep, the duration of REM sleep, the latency of REM sleep, the total sleep time, the rate of leg movements and the alertness index in euthyroid persons. However, the effect of hypothyroidism on long-term sleep habits and structure was proven.

It is important to note that TSH is always high in primary hypothyroidism, but if tropine is within normal or low range, the existence of a sellar or suprasellar pathology should be considered; this may also correspond to the direct effect of a drug, usually a neuropsychiatric one, which prevents the rise of TSH levels.

Therefore, as a general recommendation in all cases, it is important to perform a complete clinical evaluation that includes paraclinical examination of the thyroid profile and taking into consideration the medical history.

Thus, from psychiatry, hypothyroidism is treated as a condition that often presents alterations in the sleep habits and sleep itself, and exploring and considering both conditions for diagnosis is advisable to provide a complete and appropriate treatment.

The diagnosis process in Medicine

Medicine is a probability science and an art for managing uncertainty (38), but it is also a discipline that follows the scientific method, described by The Real Academia Española (English: Royal Spanish Academy) as a "procedure followed by the sciences to find and teach the truth" (39).

The scientific method consists of several steps; the Oxford Dictionary defines it as "a method of procedure that has characterized natural science since the 17th century, consisting in systematic observation, measurement, and experiment, and the formulation, testing, and modification of hypotheses" (40). This means that, when facing a concern from a patient, the doctor makes a detailed study, formulates a hypothesis that is tested and acts accordingly, generally, proposing or offering treatment to seek relief or cure.

The "mechanics of clinical reasoning" or "intuition", named after Beltran (41), is based on factors specific to the doctor as experience, learning, inductive and deductive logical reasoning, interpretation of information and high diagnostic suspicion. The quality of this reasoning —validity and reliability—, regardless of the scientific and technological baggage related to medicine, is what makes a good clinician. However, it is necessary to consider the different individual variations among physicians as the ones mentioned above, the intellectual analysis and synthesis skills, as well as the accumulation of knowledge and experience.

In order to achieve this "clinical reasoning", which is the basis for the physician to start the research process and expand the information about the "history of the current illness", the practitioner can follow one of the two methodological trends: the traditional, in which a predominantly algorithmic interrogation is used, and that which develops iterative hypotheses (42).

The development of other aspects of the clinical history —as the medical history and the review by systems of the life history— as well as the physical and mental examination seeks further information to confirm, discard or expand the hypotheses.

The way how this information is processed relates to the diagnostic process and the way it is taught and developed in the academic context, performing syndromic, topographic and etiologic diagnosis, that is, starting from the general to the specific, which can be narrowed with the use of diagnostic aids according to each case.

Three strategies complementary to the development of the cognitive diagnostic process are proposed: the deterministic strategy, causal reasoning and the probabilistic strategy. Thus, when combining clinical and laboratory findings in the form of probabilities, a rigorous definition of the disease is required based on the diagnostic criteria, which usually include the gold standard, in addition to clinical or paraclinical diagnostic aids such as radiological, histological, biochemical tests, among others.

The diagnostic process is a probabilistic estimate that includes several sources of information, among them, the doctor-patient dyad; this means that it is a dynamic process that is adjusted from the start allowing the approach to diagnostic certainty.

Discussion

This clinical case takes into consideration the difficulties faced by patients who, for various reasons, have weakened the diagnostic processes based on clinical practice. This case references a person who consulted general and specialized practitioners that offered treatments that did not provide solutions. However, during the consultations, the information was not obtained in a complete, adequate and meaningful manner, therefore, conclusions, different from those initially considered, could not be reached.

This case included a more extensive medical history, which took into consideration anamnesis and heteroanamnesis; clinical and paraclinical diagnostic aids were also considered, and the patient and her partner received therapeutic and psychoeducational interventions, with the subsequent strengthening of the doctor-patient relationship.

After establishing the specific complaint of the patient, a detailed characterization showed that her main issue was the perception of poor sleep and rest more than the lack of it, was established in detail. After a review of other portions of the medical history, some general health difficulties surfaced, as well as relevant family and personal medical history; also, physical and mental examinations were performed. Based on this preliminary information, the diagnostic hypotheses considered possible affective disorders (depressive/anxious) and their related differential (metabolic, endocrinological or rheumatoid) somatic or psychiatric diagnoses. Because of this, the patient required other clinical and paraclinical assistance. Finally, additional information was integrated with available information, reaching the diagnostic conclusions described above, and a treatment plan was proposed, which eventually proved useful for the expressed complaint.

This is the time to recognize that hypothyroidism is a relatively common condition that affects physiologically all body systems, and can even induce anatomical changes in people with this condition; this is evident in the results of the corresponding paraclinical examinations, but, as in this case, FNAB and PSG may be unspecific, therefore, this is not to be considered a typical o illustrative case.

While psychiatry considers hypothyroidism as a differential diagnosis when facing the possibilities in any given case, it is interesting that, for this specific case, the main ailment of the patient consisted of sleep difficulties that were perpetuated in time, despite being accompanied by a parallel array of symptoms.

The review of the topic sought to illustrate that the association between hypothyroidism and sleep disturbances is not unusual and its manifestations are varied, so recognizing and identifying a relation or a simultaneous occurrence requires a high diagnostic suspicion, as well as complete medical history and the use of an appropriate diagnostic algorithm.

In addition, the case shows the need for integration and implementation of a diagnostic process that allows to offer an effective therapeutic approach as soon as possible, since, after a long journey, the end result is that after years of subjective insomnia, multiple consultations, psychiatric hospitalizations, pharmacotherapy and paraclinical examinations, the patient was diagnosed with hypothyroidism and dyslipidemia, and an improvement in the habit of sleep was obtained with the recommendations of sleep habits and hygiene, the prescription of antidepressants in hypnotic doses —indicated in chronic insomnia to preserve sleep architecture— and the initiation of hormone replacement therapy.

It is worth noting that the pathology related to sleep disorders is multiple, but it is not uncommon that the symptoms mentioned

in other pathologies involving qualitative or quantitative alterations in sleep, lead to consultations due to the discomfort or interference this causes in the patients' lives. The reason for consultation is not always the real reason of the discomfort, therefore, it is necessary to perform a complete medical history and examination before opting for a symptomatic treatment.

It is important to ask whether the patients are no longer seen as a whole, full of medical complexities because of the medical specialization and, hence, they are simplified according to each medical specialty.

Conclusion

This case serves to illustrate the close link between sleep disorders with other pathologies, as common as hypothyroidism that can manifest with symptoms ranging from the presence of unspecific sleep alterations to complex clinical entities related to breathing disorders during sleep or even with episodes of psychosis. In consequence, it is important to perform a complete diagnostic exercise, a process based on the scientific method in which the clinical skills are challenged for the sake of the welfare of patients.

Conflicts of interest

None stated by the author.

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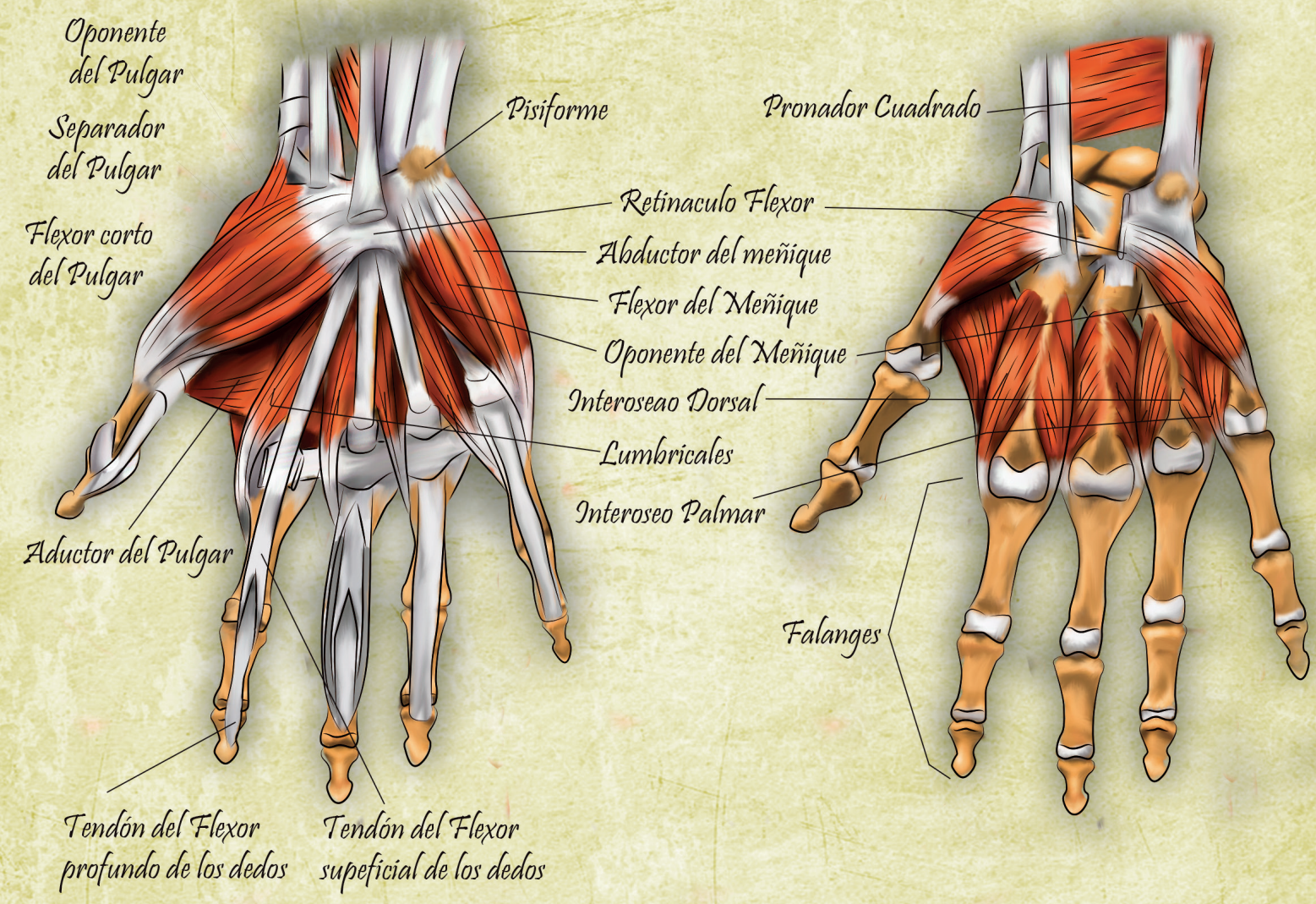
Miología de Mano

Vista Anterior



Plano Superficial

Plano Profundo

César Alexander Eslava Franco
"Mapas anatómicos"
Universidad Nacional de Colombia

CASE REPORT

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Bilateral testicular pain as an acute aortic dissection symptom

Dolor testicular bilateral como presentación de disección aórtica aguda

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| Abstract |

Acute aortic dissection is a serious cardiovascular event and the most common acute disease of the great vessels. According to the anatomical distribution of the compromised aorta, the Stanford Group classifies it into type A and type B. Its prognosis depends on its early identification and treatment, as the mortality rate in type A increases rapidly with each hour of delay of diagnosis.

Clinical manifestations of aortic dissection may be varied, which makes its early diagnosis difficult. Regarding its diagnosis, genital pain is one of the rarest symptoms. In this paper, the case of a patient who initially attended a health care institution due to acute bilateral testicular pain and was eventually diagnosed with acute aortic dissection is presented.

Keywords: Aortic Diseases; Dissection; Acute Pain; Referred Pain; Chest Pain; Testis (MeSH).

Guarín-Loaiza GM, Nocua-Baez LC, Alfonso-Hernández G. Bilateral testicular pain as an acute aortic dissection symptom. Rev. Fac. Med. 2016;64(3):571-4. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.53257.

| Resumen |

La disección aórtica aguda es un evento cardiovascular catastrófico que corresponde a la más común de las enfermedades agudas de los grandes vasos. Según la distribución anatómica de la aorta comprometida, el grupo de Stanford la clasifica en dos tipos: A y B. Su pronóstico depende de la identificación y manejo tempranos, siendo la tasa de mortalidad rápidamente creciente en el tipo A con cada hora que se retrasa el diagnóstico.

Las manifestaciones clínicas de la disección aórtica pueden ser múltiples, lo que dificulta su diagnóstico precoz. Dentro de las formas de presentación, una de las más infrecuentes es el dolor en los genitales. Se presenta el caso clínico de un paciente que consulta inicialmente por un dolor agudo testicular bilateral y que finalmente es diagnosticado con disección aórtica aguda.

Palabras clave: Enfermedades aórticas; Disección; Dolor agudo; Dolor referido; Dolor en el pecho; Testículo (DeCS).

Guarín-Loaiza GM, Nocua-Baez LC, Alfonso-Hernández G. [Dolor testicular bilateral como presentación de disección aórtica aguda]. Rev. Fac. Med. 2016;64(3):571-4. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.53257.

Introduction

Acute aortic dissection (AAD) is part of the acute aortic syndrome and is defined as an emergency condition involving the aorta, which can lead to rupture of the carotid intima and media (1). AAD occurs when an ulcer or a tear in the arterial intimal layer allows passage of blood and the appearance of a false light between this and the middle or muscular layer of the vessel (1); this break spreads and causes a catastrophic event, which corresponds to the most common acute diseases of large vessels.

This syndrome was described for the first time by Laennec in 1826 (2). In autopsy studies, a prevalence of 0.2% to 0.8% was determined, and in population works, an incidence of 0.5 to 4 cases per 100 000 inhabitants per year (3) is estimated. The most important risk factors include age, male gender —male: female ratio 2:1 to 5:1 according to the series— (3), poorly controlled hypertension (HTA) in 65-75% of patients and pre-existing aortic disease (1).

Different classifications of aortic dissection have been described; the Stanford group is currently used and describes two types: A, which corresponds to the originated in the ascending aorta and is extended at least to the aortic arch, and B, which begins in the descending aorta and usually is distal to the left subclavian artery (1).

The typical clinical manifestation of the disease is chest pain, heart failure, syncope, shock, paraplegia and even mesenteric commitment with bleeding in the gastrointestinal tract (4).

The AAD prognosis is bleak in the context of late identification and management, with the mortality rate as high as 1% per hour (1).

This study presents an AAD case with an atypical manifestation of the disease, corresponding to type B according to the Stanford group.

Case presentation

The case of a 49-year-old male, who consulted a second-level hospital due to a clinical picture of sudden bilateral testicular pain of 30 minutes of evolution, which began after trying to stand after being in squatting position, did not improve with rest, irradiated to

the lumbar region and prevented supine position. The intensity was rated 10/10 in the analog pain scale. 15 minutes after the patient had moderate intensity oppressive retrosternal chest pain with marked and intermittent 3/10 diaphoresis; there was persistence of severe back pain.

Medical history showed a patient with hypertension diagnosed eight years before, with poor adherence to treatment, obstructive sleep apnea hypopnea syndrome (OSAHS) which made the use of supplemental oxygen necessary, and morbid obesity with BMI of 35 kg/m2. In the review of systems, the patient was classified as class III in the New York Heart Association (NYHA) Functional classification scale and reported an episode of hematuria 15 days before admission.

Physical examination found an obese, alert, algic, diaphoretic patient, with high blood pressure, tachycardia and low oxygen saturation corrected by nasal cannula suplencia, and grade II jugular venous distention at 45 degrees. Cardiopulmonary, abdominal, urinary and genital examination had no apparent abnormalities. The pressure values of all four limbs were abnormal with marked decrease in the right leg, greater than 20 mmHg compared to the left leg. Table 1 summarizes the findings in the patient's vital signs.

Table 1. Patient's vital signs at the time of initial assessment.

Vital signs	-	Right upper limb	Left upper limb	Right lower limb	Left lower limb
BP Average initial BP	-	250/150 183	- -	- -	- -
BP after labetalol	- -	186/102 130	182/102 128.6	170/110 130	198/114 142
Heart rate beats/minute	100	-	-	-	-
Respiratory rate breaths/minute	20	-	-	-	-
Saturation with FiO2 0.24	92%	-	-	-	-

BP: blood pressure. Source: Own elaboration based on the data obtained in the study.

Paraclinical examinations showed polycythemia, positive troponin, microscopic hematuria, impaired renal function, arterial blood gases with chronic respiratory acidosis and moderate oxygenation disorder, electrocardiogram axis shifted to the right and signs of overload of the right ventricle with dynamic changes in the T wave in leads V4-V5. Chest radiography was performed with cardiomegaly at the expense of the right cavities and pre-capillary pulmonary hypertension without mediastinal widening.

Hypertensive emergency was considered with aorta or heart target organs, probable acute myocardial infarction (AMI) without ST-segment elevation, and electrocardiographic findings related to the axis and ventricular overload were correlated with his OSAHS history. Treatment was started with intravenous labetalol to control blood pressure and heart rate, pain was managed with opioids, oxygen therapy was administered through a nasal cannula, among others. A computed tomography (CT), with contrast material, of the chest and abdomen and protocol for the aorta were performed; CT showed AAD with extensive thoracoabdominal flap extending from the aortic arch, in antegrade direction, until the origin of the inferior mesenteric artery (Figure 1, 2 and 3).

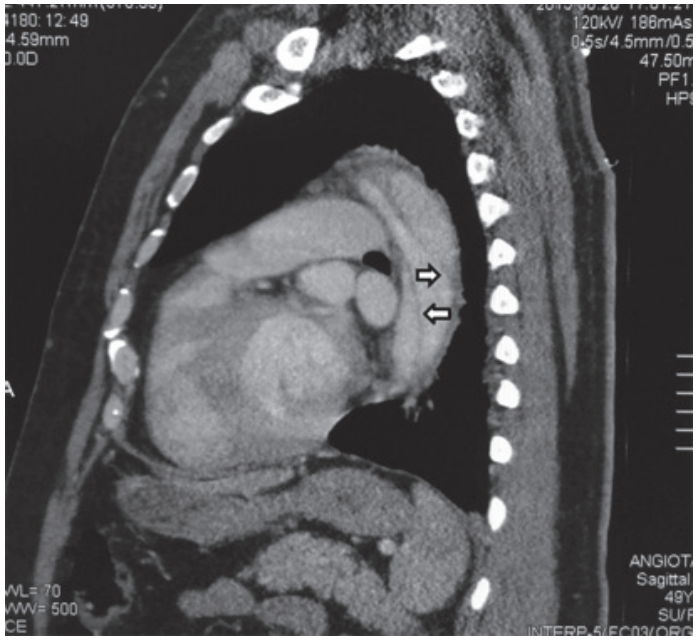

Figure 1. CT angiography of the chest. Arrows: extensive aortic dissection with inferiorly dissection flap from the aortic arch along the thoracic aorta. Source: Own elaboration based on the data obtained in the study.

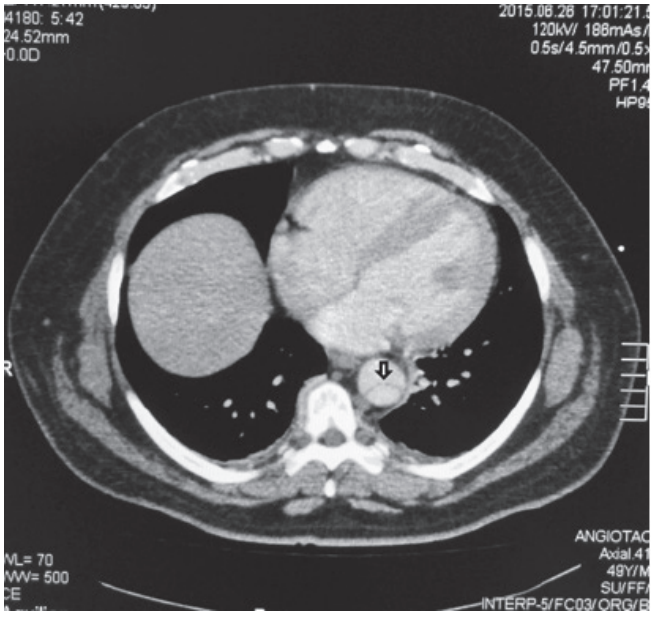

Figure 2. CT angiography of the chest. Arrow: aortic dissection from the middle third of the aortic arch, which is thick and has usual course without aneurysmal dilation inside. Source: Own elaboration based on the data obtained in the study.

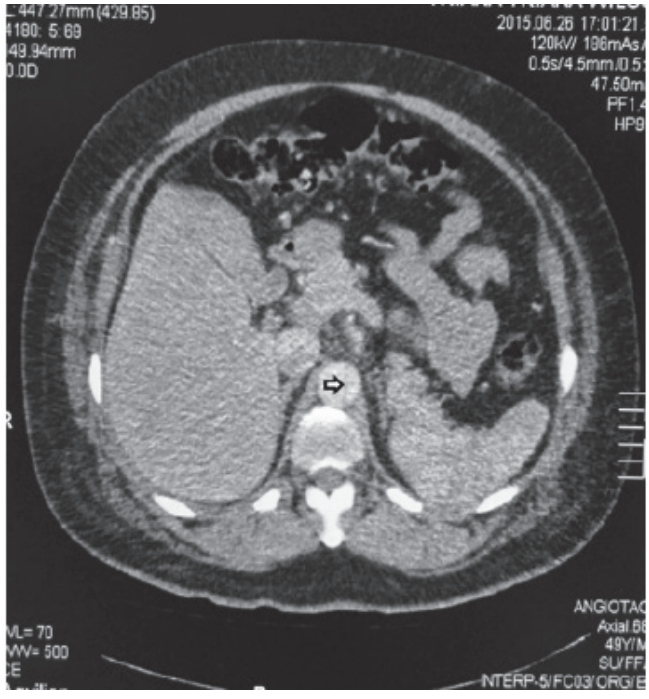

Figure 3. CT angiography of the abdomen. Arrow: aortic dissection that involves the abdominal aorta approximately to the origin of the inferior mesenteric artery. Source: Document obtained during the course of the study.

The patient was admitted to the intensive care unit, sent to an institution of higher complexity of care to be assessed by cardiovascular surgery physicians, who considered non-operative management, and discharged him from the institution with medical treatment and strict control of risk factors.

Both the patient and the health institution gave their consent to the publication of this case.

Discussion

AAD is a condition that can occur in clinical practice and is similar to other more common entities such as AMI and pulmonary thromboembolism. Its diagnosis requires high clinical suspicion, especially if, as in this case, there are risk factors such as hypertension, which is found in 75% of patients with this type of aortic dissection (5,6).

Although most patients present with acute and severe abdominal or chest pain, described as a "tearing sensation", this pain may spread to the back, gluteus, groin, legs, or lumbar region (1,5); in despite of this being the most common characteristic (7,8), some patients may be asymptomatic: chest pain may be absent in 10-33% of cases (1,4).

The first symptom of the evaluated patient was bilateral testicular pain as the predominant symptom. The patient was a young man with a rare age for infra-diaphragmatic or abdominal AAD, which, added to the previous history of hematuria (confirmed through urinalysis), raised the suspicion of urolithiasis. Given the coexistence of chest pain, persistent severe back pain and high blood pressure, with great difference in data between the legs, AAD diagnosis was suspected.

The presentation of hypertension in the emergency department can be found in 45% of patients (8) and abdominal and back pain have been previously reported as more frequent in patients with type B AAD (1,7,9).

Differential systolic blood pressure higher than 20 mmHg in both arms had been determined as an independent predictor of the presence of acute aortic syndrome, but some recent studies have reported this condition as a normal finding in patients without this diagnosis (9). In this case, high pressure values were seen in all four limbs and with very different data between the two lower limbs, which helped increase the suspicion of the diagnosis.

Additional studies, such as electrocardiogram and chest X-ray, may not show pathological findings (1). The dissection of the right coronary artery is associated with acute myocardial infarction with ST elevation in the lower face (10), which is not evident in this case, since AAD extended only until the arch, without involving the ascending aorta. 12% to 15% of patients have normal x

X-rays (6), especially if the damage is limited to the ascending aorta (1), so an X-ray with normal mediastinum does not rule out AAD; for example, radiological findings did not suggest the syndrome in this patient.

Renal failure can occur in 10% of patients with type B dissection, as in this case: creatinine 1.39 mg/dl, with estimated glomerular filtration rate of 50 ml/min. The cause of this situation is related to hypoperfusion and strokes when the renal arteries (7) are involved, which often requires additional studies to establish the AAD diagnosis. As to chest CT with aorta protocol, sensitivity of 99% and specificity 00% for this diagnosis was found (9). Similarly, determining the role of markers such as D-dimer, which, with a negative value in a low-risk patient, helps to exclude the diagnosis (11) has been attempted.

Moreover, within the atypical manifestations of AAD, bilateral testicular pain is described in few previous publications. Two cases in Europe are found: one patient in Italy, who was confirmed dissection of the abdominal aorta (12), and another in the UK, who presented a clinical picture of six months that was initially treated as pyelonephritis and epididymitis, but was diagnosed with type A AAD during the study of acute renal failure (13). There are also two reports in North America, both in the United States: the first related to a patient admitted with hypertension, who presented with cardiac arrest due to pulseless electrical activity and received type A AAD

diagnosis at necropsy (14); the second is related to a patient who, despite the history of nephrolithiasis and persistent hypertension, received type B AAD diagnosis (15). No cases have been reported in Colombia or in Latin America.

Regarding the clinical picture, differential diagnoses that may arise when a patient presents with scrotal pain localized in the testicular region are urolithiasis, orchitis, epididymitis, prostatitis, varicocele, spermatocele, hydrocele, strangulated hernia, acute appendicitis, vasculitis, testicular torsion, among others (13).

Although suspected aortic dissection is suggested in most previously reported clinical cases, it should be noted that usually these entities are not present with bilateral testicular pain (12-14), which is why the variability of the clinical picture may be secondary to the intrinsic anatomic structure of the aortic wall, and which may cause the patient to present with systemic symptoms or signs secondary to hypoperfusion (5). Bilateral testicular pain, such as in this patient, can be explained by an expanding aneurysm or hematoma that compresses ilioinguinal or genitofemoral nerves within the psoas muscle (13,14).

As to the procedure, the group of specialists of the institution chose a medical treatment according to the literature, where there is no conclusive data of a difference between mortality rates and optimal medical treatment or endovascular therapy, survival of 95.6% against 89.6%, respectively (1). In cases of uncomplicated type B AAD —absence of persistent or recurrent pain, difficulty controlling blood pressure values, progression of the dissection or poor perfusion with rupture and hemothorax, periaortic or mediastinal hematoma— considering surgical treatment is not necessary, since surgery can increase mortality rates up to 50% (1).

Conclusions

The clinical presentation of the AAD is variable, so it should be suspected in atypical clinical pictures such as bilateral testicular pain, especially if pathological findings are not present at physical examination, there is persistent pain, history and clinical hypertension and additional risk factors. Clinical suspicion is the most important fact for early diagnosis, since it is the main determinant of survival in these patients due to the high mortality of AAD.

This case is the first report made of AAD in Colombia and Latin America with clinical presentation of bilateral testicular pain, which helps broaden the spectrum of differential diagnosis in patients arriving in the emergency department with sudden, severe scrotal pain and that should raise the diagnostic suspicion of this disease.

Conflict of interests

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CASE REPORT

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Salmonella enteritidis meningitis in an infant: Case report and literature review

Meningitis por Salmonella enteritidis en un lactante menor: reporte de un caso y revisión de la literatura

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| Abstract |

Salmonella meningitis is an entity with relatively low incidence. In developed countries, it represents 1% of meningitis cases while in developing countries it may occur in up to 13%. Its treatment is difficult and there is no consensus about it.

This article presents the case of an infant with a clinical picture consisting of coughing, runny nose, fever, tachycardia, tachypnea, hyporexia and hypoactivity, with cerebrospinal fluid (CSF) test compatible with bacterial meningitis and common germs culture positive for *Salmonella spp*, which was finally typified as *Salmonella Enteritidis*. The patient was mainly treated with meropenem showing favorable results.

This case evidences the difficulty of antibiotic treatment for *Salmonella spp* meningitis, especially if it is taken into account that its management is based on case reports and expert recommendations due to the lack of randomized clinical trials.

Keywords: Meningitis; Salmonella; Therapeutic; Antibiotics (MeSH).

Cedeno-Burbano AA, Galeano-Trivino GA, Manquillo-Arias WA, Muñoz-García DA. *Salmonella enteritidis* meningitis in an infant: Case report and literature review. Rev. Fac. Med. 2016;64(3):575-80. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.54613.

| Resumen |

La meningitis por *Salmonella* es una entidad de incidencia relativamente baja; en los países desarrollados apenas alcanza el 1% del total de los casos, mientras que en los países en vías de desarrollo puede llegar hasta 13%. Su tratamiento es difícil y no existe consenso al respecto.

El presente artículo presenta el caso de una lactante menor con cuadro clínico consistente en tos, rinorrea, fiebre, taquicardia, taquipnea, hiporexia e hipoactividad; con estudio de líquido cefalorraquídeo (LCR) compatible con meningitis bacteriana y cultivo para gérmenes comunes compatible con *Salmonella spp*, la cual se tipificó finalmente como *Salmonella enteritidis*. La paciente fue tratada principalmente con meropenem con resultados favorables.

El caso pone en consideración lo difícil que resulta el tratamiento antibiótico de la meningitis por *Salmonella spp*, en especial si se tiene en cuenta que, en ausencia de ensayos clínicos aleatorizados, las pautas para su manejo se basan en reportes de caso y recomendaciones de expertos.

Palabras clave: Meningitis; *Salmonella*; Terapéutica, Antibacterianos (DeCS).

Cedeño-Burbano AA, Galeano-Triviño GA, Manquillo-Arias WA, Muñoz-García DA. [Meningitis por *Salmonella enteritidis* en un lactante menor: reporte de un caso y revisión de la literatura]. Rev. Fac. Med. 2016;64(3):575-80. English. doi:http://dx.doi.org/10.15446/revfacmed.v64n3.54613.

Introduction

Salmonella genus microorganisms are gram-negative bacilli of the Enterobacteriaceae family. The most recent classification of Salmonella includes only two species: *Salmonella enterica* and *Salmonella bongori*. *S. enterica* consists of six subspecies subdivided into different serotypes based on somatic antigenic factors O, flagellar H and capsular Vi. According to the Kauffmann-White scheme, recommended by the Collaborating Centre of the World Health Organization for Reference and Research on Salmonella, there are plenty of somatic and flagellar antigens, so serovars can be classified into serogroups based on the type of antiserum-O which causes agglutination in the laboratory. In this regard, *Salmonella enteritidis* belongs to serogroup D and corresponds to *S. enterica*, subspecies *enterica*, *serovar enteritidis*, a name that is ignored for practical purposes.

Salmonellosis is a global public health problem (1,2); it is an infection acquired orally and the following are considered risk factors for the development of the gastrointestinal infection in children: contact with another household member infected with the

bacteria, consumption of infant formula, visits to health centers and consumption of untreated water (3). Breast milk decreases the risk of sporadic salmonellosis in infants (4,5), although there are reports that suggest that this may favor the transmission of some serovars of *Salmonella* that colonize the mammary glands (6).

The incubation period for the gastrointestinal infection is 6-72 hours (7) and, despite the usual self-limitation of the infection, between 1% and 5.7% of patients may develop bacteremia, which is mostly benign, although ocasional osteoarticular or meningeal secondary outbreaks (8,9) may appear. Invasive infection occurs due to the distortion of local enteric immunity and is particularly seen in the extremes of life or in individuals with predisposing conditions, particularly in immunosuppressed patients. The disseminated form is frequent in infants under two years of age and is much more common in the neonatal period, becoming an important cause of morbidity and mortality in this age group (11-14).

In developed countries, *Salmonella* meningitis represents less than 1% of cases of bacterial meningitis confirmed in infants and children. In contrast, the incidence reported in developing countries reaches 13% (15-21). The clinical implications of *Salmonella* meningitis are serious, with a mortality rate that can reach up to 89% in underdeveloped countries (22-24). In an observational study, 13% of the patients died, 75% had at least one complication during the acute phase —hidrocefalia 50%, subdural collection 42%, stroke 33%, ventriculitis 25%, empyema cerebral 13%, and brain abscess 8 %— and 71% of patients developed motor sequelae, epilepsy, language delay or cognitive delay in long-term follow-up (25). The prognosis is poor, especially, due to complications inherent to the infection, so early diagnosis is crucial to achieve a favorable outcome (26-28).

Gastrointestinal infections are usually self-limiting diseases and rarely require antibiotic treatment (29,30). A meta-analysis proved that there are no benefits in using antibiotics to treat gastrointestinal infections caused by *Salmonella* (31); however, this is mandatory for invasive complications such as sepsis and meningitis. Broad-spectrum cephalosporins, such as cefotaxime and ceftriaxone, are preferably used in the treatment of salmonellosis in children, since fluoroquinolones are not clearly marked and the evidence for carbapenems is still insufficient (1,32).

This paper aims to present the clinical case of an infant with *Salmonella enteritidis* meningitis successfully treated with meropenem.

Case presentation

The patient was a two month-old infant, admitted in the pediatric emergency department of a level III hospital in Popayán, Cauca, who came from the rural area, daughter of a 31 year-old mother as a result of a second pregnancy, born by Caesarean section at 37 weeks due to hypertensive disorder during pregnancy and weight of 2 550g at birth.

At birth, the patient received BCG and hepatitis b vaccines, but was not administered rotavirus, polio, pneumococcus nor pentavalent (DPT, *haemophilus influenzae* type b and hepatitis b) vaccines at two months of age, which are included in the expanded immunization program for Colombia; until then, she had been fed exclusively on breast milk.

The infant had a clinical picture that started the same day of admission, consisting of a runny nose, coughing without cyanosis nor associated vomiting, fever, hyporexia and hypoactivity; she entered in the hospital in poor general condition, with 4.2kg weight, afebrile, heart rate of 145 beats/min and respiratory rate of 45 breaths/min, peripheral oxygen saturation equal to 88%, intercostal runs, pushing and staring episodes that suggested absences. No aggregated noises were found in lung auscultation and, apart from what has been described, the rest of the physical examination was normal, including fontanelar tone and consciousness. Paraclinical studies documented at admission are detailed in Table 1.

Table 1. Paraclinical results of studies on admission to the emergency room.

Paraclinical		Result
Hemogram	Leucocytes	3 300 /mm^3
	Neutrophils	1 800 /mm^3
	Lymphocytes	1 300 /mm^3
	Hemoglobin	9.6 g/dl
	Hematocrit	29.9%
	Platelet count	330 000 /mm^3
	Band neutrophils	2%
	Metamyelocytes	2%
ABG		Severe metabolic acidosis
Prothrombin time		10.6 seconds
Thromboplastin time		35 seconds
Creatinine		0.3 mg/dl
BUN		6 mg/dl
Serum electrolytes (sodium, chlorine, potassium, magnesium, phosphorus, calcium)		Normal
Glycemia		92 mg/dl
Urinalysis		Negative for urinary tract infection
Viral panel	Type A	Negative
	Type B	Negative
	A H_1N_1	Negative
Chest X-ray		No positive findings for pneumonic infection

Source: Own elaboration based on the data obtained in the study.

Based on these findings, diagnosis of unknown origin sepsis was established; empirical antibiotic treatment with ceftriaxone was initiated at a dose of 100 mg/kg/day and urine and blood cultures 1 and 2 were ordered, as well as a lumbar puncture for cerebrospinal fluid studies (CSF). The CSF cytochemical reported hypoglycorrhachia, hyperproteinorrachia and neutrophilic pleocytosis, which suggested bacterial meningitis. The Gram staining showed moderate gram-negative bacilli and scarce gram-negative coccobacillary, confirming the diagnosis (Table 2); for this reason, suspending ceftriaxone was determined and meropenem antibiotic treatment was started at a dose of 120 mg/kg/day and the patient was admitted in the Pediatric Intensive Care Unit. Preliminary reports from blood cultures 1 and 2 confirmed the presence of concomitant gram-negative bacilli in blood.

In the critical care unit, evolution was torpid since a septic shock requiring inotropic support with milrinone at a maintenance dose of 0.4 mcg/kg/min was documented. After a CSF study report, a stool culture was performed, in which enteric pathogens compatible with Salmonella or Shigella were not isolated. However, two days later, isolation of Salmonella spp was reported in cultures of cerebrospinal fluid and blood, of a strain sensitive to ampicillin, ceftriaxone, imipenem, meropenem and trimethoprim-sulfamethoxazole, so meropenem was suspended after two days of treatment and antibiotic treatment was readjusted to ceftriaxone dose of 100 mg/kg/day.

Table 2. CSF diagnostic and control analysis.

Parameter		Diagnostic studies	Follow-up 1	Follow-up 2	Follow-up 3
Physical exam	Color	Yellow	Colorless	Amber	Colorless
	Aspect	Turbid	Transparent	Slightly turbid	Transparent
Cell count	Red blood cells	275 /mm³	43 /mm³	730 /mm³	30 /mm³
	White blood cells	327 /mm³	10 /mm³	0 /mm³	127 /mm³
	Neutrophils	255 /mm³	5 /mm³	0 /mm³	25 /mm³
	Lymphocytes	72 /mm³	5 /mm³	0 /mm³	102 /mm³
Chemical test	Glucose	2 mg/dl	25 mg/dl	5 mg/dl	13 mg/dl
	Proteins	513.5 mg/dl	114.4 mg/dl	416.9 mg/dl	236.9 mg/dl
	LDH	189 UI/L	66 UI/L	--	--
Microbiological examination	Gram	Moderate gram-negative bacilli Moderate PMN leukocytes	Scarce PMN leukocytes No bateria observed	PMN leukocytes No bacteria observed	Scarce PMN leukocytes No bateria observed
	Cultures	*Salmonella spp* was isolated	Negative after 72 hours of incubation	Negative after 72 hours of incubation.	Negative after 72 hours of incubation.
Salmonella spp classification.		*Salmonella enterica*, subspecies *enterica*, *serovar enteritidis*			

Source: Own elaboration based on the data obtained in the study.

In the critical care unit, evolution was torpid since a septic shock requiring inotropic support with milrinone at a maintenance dose of 0.4 mcg/kg/min was documented. After a CSF study report, a stool culture was performed, in which enteric pathogens compatible with *Salmonella* or *Shigella* were not isolated. However, two days later, isolation of *Salmonella spp* was reported in cultures of cerebrospinal fluid and blood, of a strain sensitive to ampicillin, ceftriaxone, imipenem, meropenem and trimethoprim-sulfamethoxazole, so meropenem was suspended after two days of treatment and antibiotic treatment was readjusted to ceftriaxone dose of 100 mg/kg/day.

Isolated *Salmonella spp*. was sent to an external laboratory for classification and was reported as *Salmonella enteritidis*. Meanwhile, a first simple and contrasting computerized axial tomography (CAT) was performed, concluding that it was normal. The patient remained hypotensive, with inotropic, tachycardia and tachypnea requirement, with metabolic acidosis evidenced in arterial blood gases and fever peaks; a five day course of antibiotic treatment with ceftriaxone was concluded with stationary evolution, period in which the patient also had seizures characterized by isolated episodes of gaze deviation, tachycardia and associated peripheral oxygen desaturation, initially managed with phenobarbital at a dose of 7 mg/kg/day without adequate clinical response.

Based on this situation, concomitant treatment with phenytoin at a dose of 5 mg/kg/day was indicated; meropenem was restarted and control cultures in blood, CSF and urine were taken. CSF control studies reported hypoglycorrhachia and hyperproteinorrachia within the ranges of bacterial meningitis, with fluctuating values of polymorphonuclear and leukocytes (Table 2). After 10 days of antibiotic treatment, a control simple and contrastig brain CT was performed, which reported meningeal vascular reinforcement and right frontotemporal and left frontal subdural effusions, consistent with clinical findings of acute meningitis (Figure 1). Nevertheless, due to clinical deterioration, the possibility of nosocomial gram-positive bacterial coinfection by germs was considered, so vancomycin was added to the antibiotic treatment at a dose of 60 mg/kg/day. Vancomycin was suspended five days later, after 72 hours without fever, within th context of negative control blood cultures, urine culture and CSF culture.

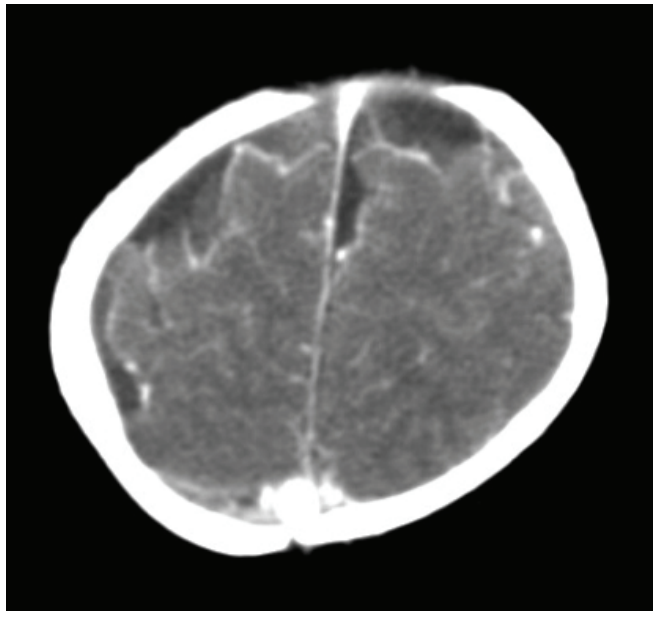

Figure 1. Simple and contrasting control CAT scan on the 10th day of antibiotic treatment. Source: Own elaboration based on the data obtained in the study.

Another simple and contrasting control brain CT scan performed at day 12 of treatment reported bilateral frontoparietal subdural collections, which suggested subdural empyema (Figure 2). A transfontanelar ultrasound was performed and then reported as normal. For this reason, performing a transfontanelar puncture was suggested by neurosurgery, but it was not performed due to favorable evolution.

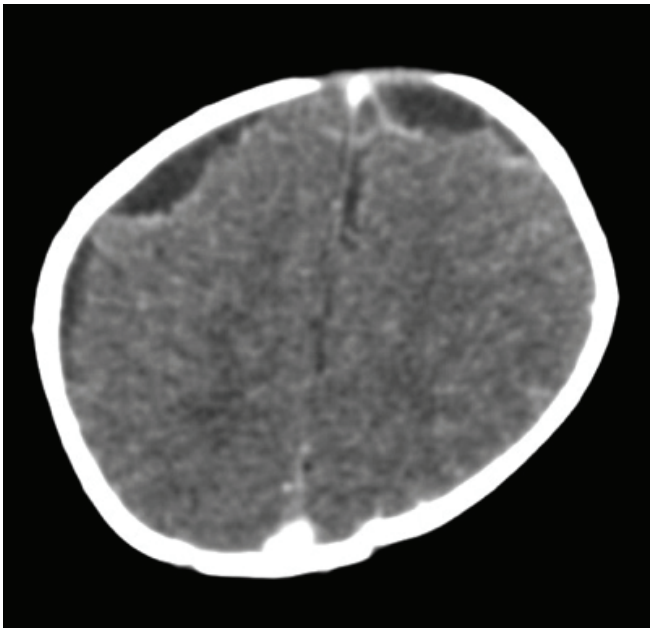

Figure 2. Simple and contrasting control CAT scan on the 12th day of antibiotic treatment. Source: Own elaboration based on the data obtained in the study.

After 19 days of combined antibiotic treatment that included ceftriaxone, meropenem and vancomycin, the infant gained clinical improvement obtained by limiting the convulsive episodes, as well as reaching hemodynamic and ventilatory compensation, and was transferred from the critical care unit to pediatrics hospitalization rooms with the aim of completing 21 days of antibiotic treatment with meropenem, which ended satisfactorily, without recurrence until discharge or after it. Three months after the acute event was solved, the patient returned to neurodevelopmental physical therapy and psychomotor prognosis was reserved, therefore, if neurodevelopmental goals are reached or if, instead, definitive neurologic sequelae are in place, can only be determined in the long-term.

Discussion

There are no case reports about *Salmonella* meningitis in the department of Cauca; epidemiological data are inconclusive and may be underreported. This clinical case is about a patient from the countryside, where pigs and chickens are raised in her home. It is known that *Salmonella enteritidis* colonizes the gastrointestinal tract of poultry and can be found on the surface of their eggs, so it is presumed that the transmission occurred through contact of the child with their caregivers. It should also be noted that the patient had no prior gastrointestinal conditions and the microorganism was not isolated in any stool sample. The literature has emphatically mentioned that the enteric picture precedes disseminated forms, so there are no reports about primary meningitis caused by *Salmonella spp*.

Given the difficulty in the design, there are no controlled clinical trials to consider antibiotic treatment of meningitis by *Salmonella spp*. and a consensus about treatment has not been reached (33), in consequence, its management is based on information documented by case reports or expert recommendations (8,34).

In the past, ampicillin, chloramphenicol and cotrimoxazole were used alone or combined for treatment, with not always favorable outcomes and a reported mortality rate associated to the treatment with ampicillin and/or chloramphenicol of up to 30% (6,35,39). With the arrival of third-generation cephalosporins, mortality rates and relapse of *Salmonella meningitis* have considerably decreased taking into account that *Salmonella spp. meningitis* resistance to these drugs is uncommon (35), but are occasionally reported (16,40).

Although ceftriaxone is an antibiotic with poor intracellular fluid penetration, its concentration in the cell is directly related to the concentration on the outside, so the effectiveness of the treatment depends on the time and the dose employed. Therefore, an intravenous treatment at high doses for at least four weeks must be assured (35). Currently, the American Academy of Pediatrics recommends the use of ceftriaxone or cefotaxime for four weeks or more, as lower courses of treatment have been associated with higher recurrence rates (16,41,42).

The resistance of *Salmonella spp.* to third-generation cephalosporins is rare, but the general resistance of *Salmonella* to antimicrobial begins to be a global problem in public health (43).

A descriptive study, which evaluated the susceptibility of 739 strains of *Salmonella* showed that serogroups A and D were sensitive to all drugs used (ampicillin, cotrimoxazole, chloramphenicol, ofloxacin, pefloxacin, norfloxacin, ciprofloxacin, ceftriaxone and cefotaxime). Serogroup B was sensitive to quinolones but resistant to ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole in 78%, 83% and 54% of cases, respectively. Serogroup C had a resistance sensitivity profile similar to that of serogroup B. Finally, serogroup E was 100% sensitive to quinolones, but less sensitive to ampicillin, cotrimoxazole, ceftriaxone and cefotaxime at a 67-82% range (44). In this case report, although *Salmonella* strain was sensitive to third-generation cephalosporins in the antibiogram, clinical response using ceftriaxone was erratic, therefore, antibiotic treatment with meropenem was preferred.

On the other hand, the combination of third-generation cephalosporins with gentamicin, used in the initial treatment of gram-negative meningitis, may not be appropriate when it comes to intracellular facultative as *Salmonella* because gentamicin has poor penetration into intracellular fluids and does not penetrate the blood brain barrier well enough (16,45).The evidence of the use of carbapenems is insufficient, although satisfactory results have been reported in individual cases (16,38,39,41).

In the absence of pharmacological alternatives, the combination of ceftriaxone and ciprofloxacin, or ceftriaxone plus cefotaxime (if ciprofloxacin is contraindicated as in cases of newborn jaundice) can be considered for a minimum period of three weeks (16), even though that association has not been correlated to clear indications. This combination is not synergistic, but there is no evidence that pharmacological antagonism occurs between molecules (16,46). While the use of ciprofloxacin in children has been limited due to the possibility of arthropathy, the overall experience indicates that this is a rare event (47-49). There are reports that indicate the successful use of ciprofloxacin as monotherapy for *Salmonella* meningitis, but its combined use is suggested given the likelihood of resistance (16,40,50).

Conclusions

There is no consensus about antibiotic treatment of *Salmonella* meningitis. In the absence of clinical trials, cohort studies, and cases and controls, all recommendations come from case reports or advice from experts, models that have very low levels of evidence. Despite this, it is well recognized that ceftriaxone and cefotaxime are suitable alternatives, since the doses used have good penetration into the central nervous system and *Salmonella* resistance to these drugs is uncommon; therefore, they should be considered as the first choice of management.

The evidence on carbapenems is even more insufficient to recommend routine use; nonetheless, the case presented here suggests that meropenem can be an alternative to third-generation cephalosporins for the treatment of *Salmonella spp* meningitis.

Albeit with a low level of evidence, the available literature suggests that ampicillin should not be used empirically given the high rate of treatment failure. Similarly, fluoroquinolones, with no clear indication in the pediatric population, can be considered as pharmacological alternatives, especially in patients who do not have favorable clinical response or in relapse cases, but more studies with appropriate epidemiological design to support such recommendation are needed.

Finally, all isolation of *Salmonella spp.* in the cerebrospinal fluid requires antibiotic sensitivity studies that allow an adequate treatment.

Conflict of interests

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Acknowledgements

To Uriel Alfonso Palta Velasco.

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LETTER TO THE EDITOR

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Analysis of individual records of health services provision related to oral cancer in Colombia

Análisis de los registros individuales de la prestación de servicios de salud del cáncer bucal en Colombia

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Aristizabal-Mayor JD, Rosselli D. Analysis of individual records of health services provision related to oral cancer in Colombia. Rev. Fac. Med. 2016;64(3):581. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.56973.

Aristizabal-Mayor JD, Rosselli D. [Análisis de los registros individuales de la prestación de servicios de salud del cáncer bucal en Colombia]. Rev. Fac. Med. 2016;64(3):581. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.56973.

We have carefully reviewed the paper entitled "Epidemiological study of oral cancer in Colombia 1989-2008" (1) and would like to make some comments about it. While the author estimates incidence rates of oral cancer in Colombia during that period based on the data from the Instituto Nacional de Cancerología (INC), the denominator used to calculate the frequency, either incidence or prevalence, is not provided; this makes the comparison with the published literature difficult. Motivated by this work, we conducted an analysis of the Individual Records of Health Services Provision (RIPS by its acronym in Spanish) obtained from the Sispro database between 2010 and 2014, using the same ICD-10 codes of the aforementioned study and the denominator population projections of the National Administrative Department of Statistics (DANE) for the middle term (that is 2012). The results were classified by age in five-year periods and gender.

According to RIPS, during those five years, 57 657 people were diagnosed, 31 435 women (53.7%), with some malignant disease in the oral cavity, with an average rate of patients seen per year of 26.7 per 100 000, with a progressive increase during life span, most dramatically manifested after age 50. The highest prevalence is found in the senior group (80 years or more), where incidence reaches 123 per 100 000.

During the five-year period analyzed, there does not seem to be a trend toward increasing or decreasing frequency, although it is an inadequate lapse of time to draw conclusions. According to the records of the INC presented in the study, a progressive reduction appears to be seen in the incidence of oral cancer, so it is not clear why the author begins his discussion declaring a "dramatic increase". Bernal also suggested that oral cancer associated with human papillomavirus (HPV) could be increasing, while associated smoking would be decreasing (2); however, the overall incidence reported in the literature has not shown variations in the last two decades (3).

Although the literature and the study by Bernal have in common that males are more affected by oral and oropharyngeal cancer (1,4,5), according to the Colombian RIPS, this would only be true in patients younger than 14 years, where the male:female ratio was 1.21. In all older age groups, we found an inverse ratio of 1.28 women for every affected man. This epidemiological finding is certainly interesting and should encourage new research on the particularities of oral cancer in Colombia.

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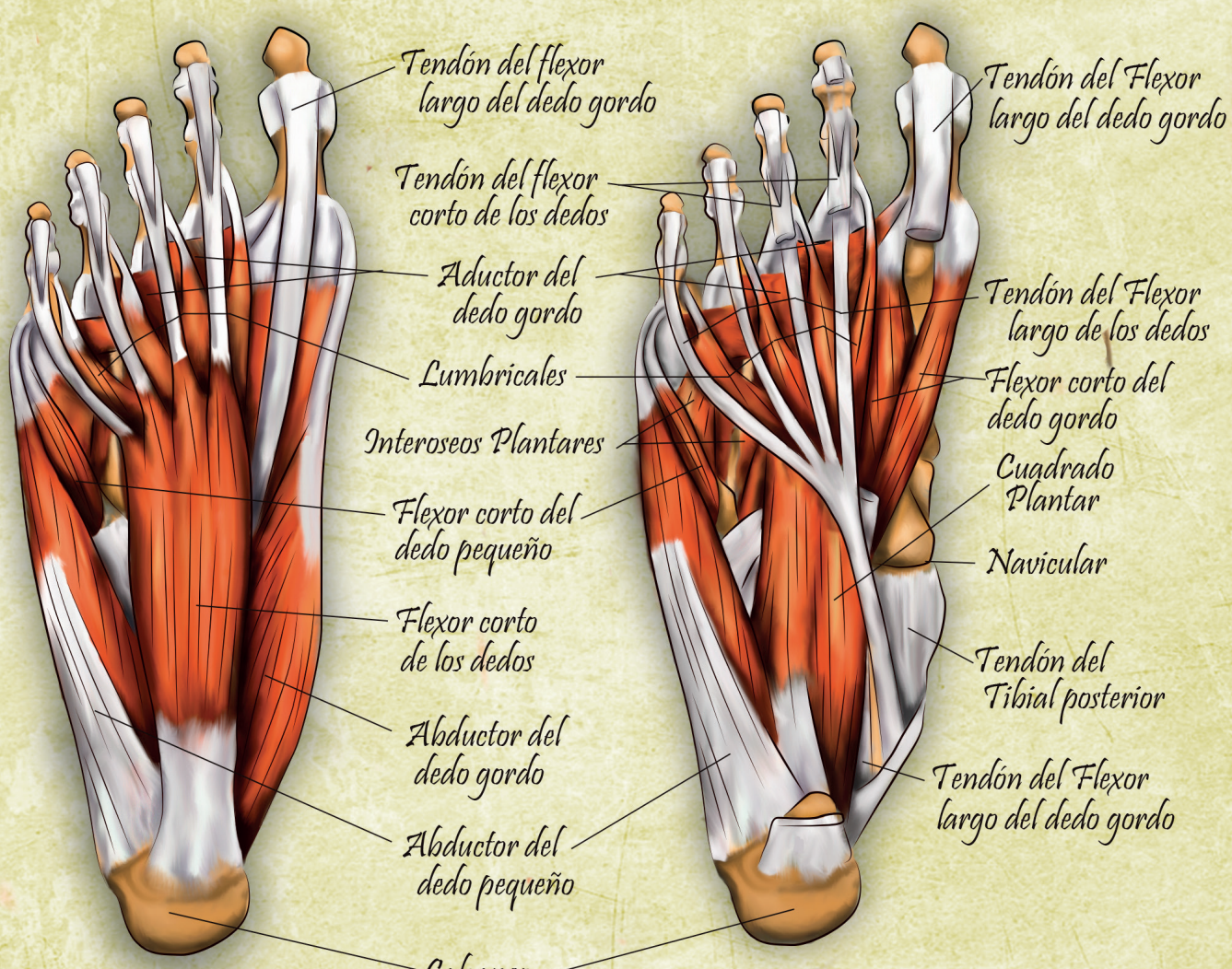
Miología de Pie

Vista Plantar



Plano Superficial

Plano Profundo

César Alexander Eslava Franco
"Mapas anatómicos"
Universidad Nacional de Colombia

LETTER TO THE EDITOR

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Response to "Analysis of individual records of health services provision related to oral cancer in Colombia"

Respuesta a "Análisis de los registros individuales de la prestación de servicios de salud del cáncer bucal en Colombia"

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Bernal-Baláez AE. Response to "Analysis of individual records of health services provision related to oral cancer in Colombia". Rev. Fac. Med. 2016;64(3):583. English. doi: http://dx.doi.org/10.15446/revfacmed.v64n3.59632.

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Dear Editor

Dr. Franklin Escobar

In response to the document written by Aristizabal & Roselli (1), referred to the section Letter to the Editor and related to the already published paper entitled "Epidemiological study of oral cancer in Colombia 1989-2008" (2), which I authored, I present the following considerations:

Sirs Aristizabal & Roselli, I appreciate your interest in approaching a health issue as complex as oral cavity cancer, which has personal and social consequences, and to which I have devoted a lifetime of work from the most diverse points of view in relation to Oral and Maxillofacial Pathology. You are always welcome to provide constructive comments and critics. However, my recommendation, from a scientific and academic perspective, is to have the research findings assessed and analyzed by academic peers, experts in the field, to prevent that eventual doubtful products may be disclosed in prestigious journals.

Regarding the text discussed in the aforementioned letter to the editor, I find remarkable contradictions, since the authors report having "reviewed carefully" the text, and question that it begins citing a "dramatic increase", which is not mentioned in any part of the description; this casts doubt on the proper reading of the document.

Those who have worked for more than 30 years in this field of action do not doubt that the male sex has historically been the most affected by these malignant and even premalignant lesions (correct term to use instead of pathology).

Similarly, considering the possibility of oral cancer in children under 14 drifts the attention apart from the morbidity of this serious disease. At such age, this type of cancer is very rare and primary malignant lesions correspond with lymphoreticular tumors.

Exploring into a field of work requires adequate experience to interpret correctly epidemiological reports and records without making mistakes and inappropriate assertions. That is why I recommend young researchers to define a line of research since the beginning, in order to address any topic with respect, soundness and humility, after obtaining enough expertise over time.

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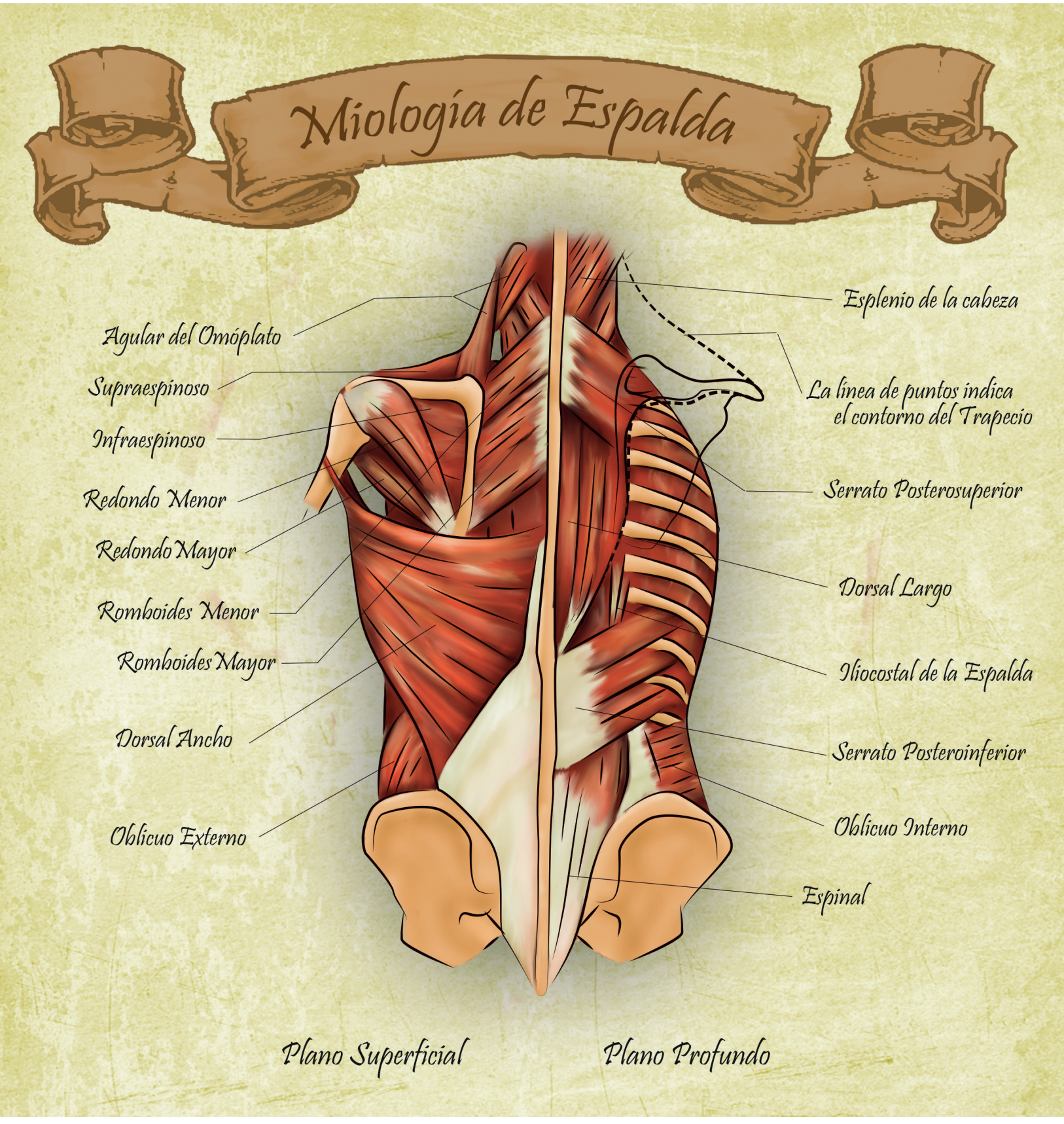
Miología de Espalda



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Universidad Nacional de Colombia

Authors' Guidelines

Scope and Editorial Policy

The Revista de la Facultad de Medicina (Journal of the Faculty of Medicine) first appeared in June 1932; it is an official publication of the Universidad Nacional de Colombia (National University of Colombia) and its purpose is the dissemination of knowledge in the scientific, social and artistic fields related to those professions found in the Health sphere, its practice and teaching. In particular, it is aimed at professionals and students who belong to the area of Health, as well as those who are involved in the social and human sciences related to this professional field.

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Papers that meet the formal requirements will be submitted to an academic peer review process. The list of consulted peers is published once a year in the last issue of the year.

Form and preparation of manuscripts

1. **General requirements:**

Papers submitted to the Revista de la Facultad de Medicina must be adjusted to "Uniform requirements for manuscripts submitted to biomedical journals", established by the International Committee of Medical Journal Editors (ICMJE), available at the following website: https://goo.gl/GzWnk8

The article must be submitted in a Word type document, letter-sized paper format, (21.5 x 27.5 cm), leaving a margin of at least 2.5 cm on all four edges, Verdana font, size 12, double spaced. Pages must be numbered in the upper right, beginning with the title page. The articles sent to the journal are only received through the Open Journal System Platform of the Universidad Nacional de Colombia's Journals Portal: http://www.revistas.unal.edu.co/index.php/revfacmed, or through the following direct link: http://goo.gl/rsVzGU. The Journal accepts manuscripts written both in English, Spanish and Portuguese.

When submitting the article through the Rev Fac Med OJS portal the following steps must be taken into account: 1) all the items included in the requirements checklist in step 1 and in the end of this document must be met. 2) The article must be submitted in step 2 of the process. 3) Article metadata must be included in step 3, namely: authors' data, affiliation and e-mail; title, abstract, keywords and references. 4) Additional files (such as copyright transfer format or Authorship responsibility format) must be uploaded in step 4. These files can be downloaded from the following links: https://goo.gl/VpSel7 and https://goo.gl/8CoLhL, respectively.

2. **Types of article and general structure:**

"Original Papers" must be divided into the following sections: Introduction, Objective, Materials and Methods, Results, Discussion, and Conclusions. Other types of articles, such as "Case Report", "Reflection Paper", "Update Paper" and "Review Paper" can be adjusted to more flexible formats, but must be approved by the editors.

3. **Papers structure and order:**

3.1. Title page: The first page of the manuscript must contain: 1) Title of the article, both in Spanish and English, which have to be concise but informative on the central content of the publication. It also must have a 40 characters maximum short title, including spaces between words. 2) The author or authors of the article, identified with their full names. After each author's name there must be superscript numbers in order to identify their affiliation. 3) Author's affiliation: name of the area or areas, departments, services and institutions to which this author belonged during the realization of the paper. 4) Full name, address, phone, plus the indicative or related codes, city, country and email of the main author or the author with which the Journal should establish communication. 5) Any source of financial support, if there is any, received in the following ways: a research grant (scholarship), equipment, drugs, or all of the above. Authors must state any financial aid received, specifying whether the organizations that provided financial aid had or had not any influence on the study design; the collection, analysis or interpretation of data, and on the preparation, review or approval of the manuscript.

3.2. Summary: summarize, in no more than 200 words, the purpose of the study or research, the materials and methods that were used, the main results obtained and the most important conclusions, with its respective Spanish version. Similarly, use the structured summary model and don't use non-standard abbreviations.

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