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Tools for strengthening peer review in the Journal of the Faculty of Medicine, another step to increase its impact and visibility

The Journal of the Faculty of Medicine (*Revista de la Facultad de Medicina*) of the Universidad Nacional de Colombia, after being in the A2 category for ten years, was classified in the B category during the Call 768 of 2016 for Indexing Specialized Colombian Scientific Journals - Publindex (1), which is valid until September 15, 2019.

This new categorization occurred despite the notable evolution of the Journal in the past months, which aimed at increasing the visibility and impact of the published scientific production. To achieve this increase, the Journal migrated its editorial process to the Open Journal System (OJS) and implemented the progressive publication of articles in English starting with the coming issues (2). This is also consistent with its purpose: "to disseminate knowledge on various scientific, social and artistic fields related to health sciences, their professional practice and teaching processes."

These strategies have led to a significant increase in publication requests from different countries and the publication of original studies, which, in turn, generates the need to increase the number of members of the editorial committee and the peer review base (2), fundamental pillars for guaranteeing the quality of any scientific journal.

Peer review is essential for the editorial process in order to help publishers during the selection of research manuscripts whose results must have credibility and methodological quality, and should also be innovative and interesting for the scientific community. Peers collaborate in the detection of errors or weaknesses of the submitted articles (3), reason why the reviewer is expected to behave respectfully, timely, realistically, empathically, and impeccably from an ethical (4), scientific, professional, and constructive point of view at the moment of accepting, carrying out and filling out the format for reviewing a contribution to the journal. Additionally, a quality, relevance and importance assessment of the research is also expected, without replacing the editor (3).

To guide the work of authors and reviewers, the use of checklists is recommended to verify the quality of reports from the very beginning of the research process. The EQUATOR (Enhancing the QUAlity and Transparency of Health Research) Network is an international initiative, supported by the World Health Organization, that seeks to improve the reliability and relevance of the published literature resulting from health research (5). This strategy promotes transparency and precision in scientific reports by using publication guidelines in order to systematically counteract inadequate reporting of research.

The products generated by this initiative, available at http://www.equator-network.org (6), are a growing list of resources that, from the construction of the protocol and according to the type of study and methodological design, allow the researcher to prepare the final reports of their work, guaranteeing the transparency, veracity and reliability of the results to the final consumer to contribute effectively to the growth of scientific knowledge.

Out of the 386 checklists available to date, the following are the most relevant: the SPIRIT 2013 (Standard Protocol Items: Recommendations for Interventional Trials); the CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials; the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies; the Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement; the CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development; the Standards for Reporting Qualitative Research (SRQR); the COREQ (COnsolidated criteria for REporting Qualitative research) Checklist; the Standards for Reporting Diagnostic Accuracy (STARD) 2015; the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Initiative; the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement, and The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. The aforementioned are the most frequently used checklists based on the types of studies published more regularly in scientific journals.

The use of these checklists by authors, reviewers, editors and members of the editorial team will result in the strengthening of editorial quality by incorporating international publication parameters, which, together with the changes already implemented, will favor the international visibility of the published articles, since the submission, evaluation and final publication process will be optimized for the researchers who choose the Journal of the Faculty of Medicine as a platform to achieve the recognition and disclosure of their work.

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ORIGINAL RESEARCH

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Geographical distribution of centenarians in Colombia: An analysis of three databases

Distribución geográfica de los centenarios en Colombia: un análisis de tres bases de datos

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| Abstract |

Introduction: Individuals aged one hundred years or more are of interest for the study of the aging process, which has been scarcely addressed in Colombia.

Objective: To estimate the number and geographical distribution of centenarians in Colombia.

Materials and methods: Three sources of information were reviewed: the 2005 Census, the death certificates issued from 2010 to 2013, and the Individual Registries of Health Services Provision (RIPS in Spanish) of 2014.

Results: The census recorded data of 3 165 centenarians (1 972 women, 62.3%), finding the highest rates in La Guajira (2.23 x 10 000), Chocó (1.90) and Sucre (1.61). In the four-year period analyzed, 3 611 people died, with the highest proportions (for every 1 000 deaths) found in Chocó (10.4), La Guajira (9.4) and Sucre (6.5). RIPS identified 3 390 centenarians, with a higher frequency in Sucre (2.17 x 10000), Chocó (1.29) and Córdoba (1.11).

Conclusions: Although the results are consistent with the number and geographical distribution of centenarians, some errors may be found in the date of birth stated in the records, which is the basis for estimating age in the three sources. Other factors potentially involved in the results may be physical activity, family and community support, low stress and healthy diet in these regions.

Keywords: Age Distribution; Aged 80 and over; Demography; Gender Ratio (MeSH).

Rosselli D, Yucumá D, Polanía MJ, Machado JC. Geographical distribution of centenarians in Colombia: An analysis of three databases. Rev. Fac. Med. 2017;65(3):391-6. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.59505.

| Resumen |

Introducción. Las personas mayores de 100 años han sido poco estudiadas en Colombia, si bien son importantes para entender el envejecimiento.

Objetivo. Estimar el número y distribución geográfica de los centenarios en Colombia.

Materiales y métodos. Se revisaron tres fuentes de información: el Censo de 2005, los certificados de defunción de 2010 a 2013 y los Registros Individuales de Prestaciones de Servicios de Salud (RIPS) de 2014.

Resultados. En el censo, se identificaron 3 165 centenarios (1 972 mujeres, correspondientes al 62.3%) con las tasas más elevadas en La Guajira (2.23 x 10 000), Chocó (1.90) y Sucre (1.61). En el cuatrienio analizado fallecieron 3 611 y se hallaron sus mayores proporciones (por cada 1 000 fallecidos) en Chocó (10.4), La Guajira (9.4) y Sucre (6.5). Los RIPS identificaron 3 390 centenarios, cuyas tasas más altas se ubicaron en Sucre (2.17 x 10 000), Chocó (1.29) y Córdoba (1.11).

Conclusiones. Aunque los resultados de la investigación fueron consistentes en el número y la distribución geográfica de los individuos centenarios, pudo haber errores de registro de la fecha de nacimiento, que es la base para estimar la edad en las tres fuentes. Otra explicación de estos resultados podría involucrar la actividad física, el apoyo familiar y comunitario, el bajo nivel de estrés y la dieta saludable en estas regiones.

Palabras clave: Anciano de 80 o más años; Demografía; Distribución por edad; Razón de masculinidad (DeCS).

Rosselli D, Yucumá D, Polanía MJ, Machado JC. [Distribución geográfica de los centenarios en Colombia: un análisis de tres bases de datos]. Rev. Fac. Med. 2017;65(3):391-6. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.59505.

Introduction

Centenarians are individuals aged 100 years or older. This is a group of interest to geriatricians, demographers and epidemiologists concerned with the aging process (1-3). In Colombia, research on this age group is scarce, and its geographical distribution as well as other sociodemographic and clinical characteristics have not been analyzed. The only published Colombian study characterized 29 centenarian patients who consulted the emergency department of a university hospital in Bogotá during an eight-year period (4).

Current registration methods, particularly RIPS (which are completed every time a user of any of the health systems in Colombia has access to a health service), could help determining the number of centenarians in the country, their distribution by gender, the places where they live, and the types of diseases they suffer.

This paper describes the information collected from RIPS, together with the data obtained in the last national census of 2005 and the ages recorded in the death certificates that the National Administrative Department of Statistics (DANE in Spanish) records and summarizes every year.

Materials and methods

A descriptive study to review the information on centennial population was conducted in three different databases. First, data obtained from the 2005 census, referring to the population aged 100 or older and their characterization by gender and departmental distribution, were examined on the DANE webpage. Based on this census population, a rate was estimated for every 10 000 inhabitants per department that year.

Second, based on the DANE webpage as well, the data of centenarians who died between 2010 and 2013 were collected. At first, including data for 2014 was considered, but it was finally discarded since it had not been consolidated by the time this research was conducted. Subsequently, the number of deceased centenarians was correlated to the total number of deaths in the same departments during that period. This result was expressed in number of centenarians for every 1 000 deceased.

The third analysis was based on RIPS. These records were created in 2000 by the Ministry of Health to evaluate and monitor the Colombian health system and to support public health decisions. Although doubts about the quality of information are always mentioned, RIPS have been used in different fields of research, including a study of the economic impact of aging Colombian population (5). Information regarding the site of the query, gender and age could be considered reliable to some extent; even though RIPS records have missing and inconsistent data, with these records, it is possible to locate centenarians and determine their most common diagnoses.

Results

Census 2005

According to the 2005 national census, there were 50 077 people over 80 (213 734 men and 287 343 women) in Colombia, which is equivalent to 1.17% of the population. Out of this group of seniors, 3 165 were 100 years or older, 1 193 men and 1 972 women (62.3%). Given that the national population was 41 468 384 (20 336 117 men and 21 132 267 women) at the time, the national centenarian rate for 2005 was 0.76 per 10 000 Colombians (0.59 for men and 0.93 for women).

As Table 1 demonstrates, the rate of centenarians per 10 000 inhabitants presented a minimum value in Meta (0.32), Arauca (0.33), Quindío (0.35), and Casanare (0.36), while the highest values were recorded in La Guajira (2.23), Chocó (1.9), Sucre (1.61), and Córdoba (1.33). In the census, people were classified into ethnic groups. Thus, among those self-defined as indigenous, there were 73 255 over 60 years of age, of whom 467 (0.64%) were over 100. In the Afro-descendants group, 227 598 were over 60 and 1 425 were over 100 (0.63%). Furthermore, other groups had 3 190 262 people over 60 years, and 2 409 of them were over 100 years of age (0.08%).

Table 1. Geographical distribution of centenarians according to the 2005 census and rate per 10 000 inhabitants of each department.

	Total	Males	Females	Rate x 10 000
Amazon region	20	11	9	1.19
Antioquia	410	155	255	0.73
Arauca	5	1	4	0.33
Atlántico	177	49	128	0.84
Bogotá D.C.	314	164	150	0.46
Bolívar	161	50	111	0.88
Boyacá	77	35	42	0.64
Caldas	51	17	34	0.57
Caquetá	30	18	12	0.89
Casanare	10	3	7	0.36
Cauca	106	40	66	0.90
Cesar	54	18	36	0.61
Chocó	74	16	58	1.90
Córdoba	194	60	134	1.33
Cundinamarca	111	38	73	0.50
Guajira	146	48	98	2.23
Huila	55	31	24	0.55
Magdalena	115	59	56	1.01
Meta	23	10	13	0.32
Nariño	127	49	78	0.85
Norte de Santander	77	24	53	0.64
Putumayo	25	11	14	1.05
Quindío	18	7	11	0.35
Risaralda	59	22	37	0.69
San Andrés	6	1	5	1.01
Santander	140	47	93	0.73
Sucre	123	41	82	1.61
Tolima	99	44	55	0.75
Valle	358	124	234	0.88
Total	3 165	1 193	1 972	0.76

Source: Own elaboration based on (6).

Death Certificates 2010-2013

During this four-year period, 799 174 death certificates were issued in Colombia (200 524 in 2010, 195 823 in 2011, 199 756 in 2012 and 203 071 in 2013). 3 611 of them were for centenarians (832 in 2010, 857 in 2011, 897 in 2012 and 1 025 in 2013), of which 66.2% were equivalent to 2 390 women. The rate of centenarians per 1 000 deaths in that period was 4.52 (4.15 in 2010, 4.38 in 2011, 4.49 in 2012 and 5.05 in 2013).

Table 2 shows the total number of deaths and the respective proportion of centenarians per 1 000 deaths, per department. The highest values were observed in Chocó (10.4 per 1 000), La Guajira (9.4), Sucre (6.5) and Bolívar (6.2). The lowest rates were found in the Amazon region (which includes the Amazonas, Guainía, Guaviare, Vaupés and Vichada departments) with 2.3, and Meta with 2.6.

Table 2. Total deaths per department in the 2010-2013 period, and proportion of centenarians per thousand deaths.

Department	Deceased		Rate x 1 000
	Total	Centenarians	
Amazon region	2 592	6	2.31
Antioquia	117 625	604	5.13
Arauca	3 514	18	5.12
Atlántico	38 532	195	5.06
Bogotá D.C.	132 362	429	3.24
Bolívar	24 606	153	6.22
Boyacá	23 624	141	5.97
Caldas	21 871	95	4.34
Caquetá	6 373	32	5.02
Casanare	4 109	23	5.60
Cauca	17 376	96	5.52
Cesar	13 712	68	4.96
Chocó	3 851	40	10.39
Córdoba	23 347	126	5.40
Cundinamarca	35 931	119	3.31
Guajira	6 088	57	9.36
Huila	19 988	96	4.80
Magdalena	17 652	103	5.84
Meta	17 340	45	2.60
Nariño	25 609	108	4.22
Norte de Santander	25 418	125	4.92
Putumayo	2 973	13	4.37
Quindío	13 561	61	4.50
Risaralda	21 850	82	3.75
San Andrés	831	4	4.81
Santander	39 071	208	5.32
Sucre	10 856	70	6.45
Tolima	29 287	130	4.44
Valle	99 225	364	3.67
Total	799 174	3 611	4.52

Source: Own elaboration based on (7).

RIPS 2014

According to RIPS, 3 390 people aged between 100 and 109 years were attended in Colombia, of which 2 154 (63.5%) were women. Based on these records, the number of individuals is reduced every additional year, so that there are 1 270 people aged 100, 818 aged 101, 578 aged 102, and so on until having only 67 aged 109 (Figure 1).

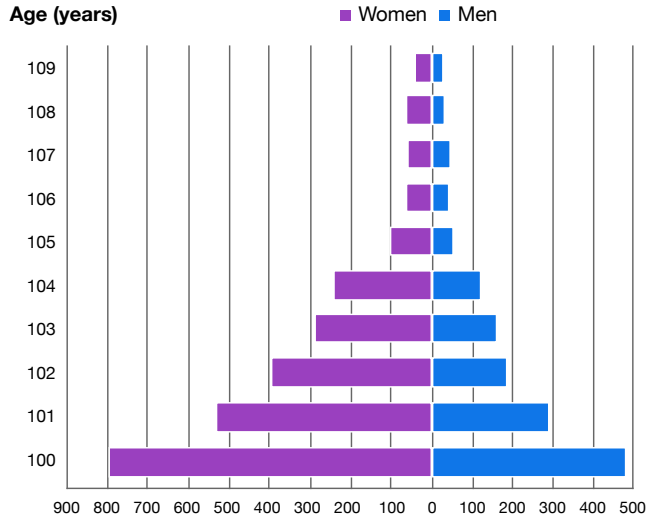

Figure 1. Centenarian population pyramid in Colombia according to RIPS 2014. Source: Own elaboration based on tne data obtained in the study.

If the official population projections issued by DANE, which are based on the 2005 census, are taken as the denominator, there were about 47 661 787 inhabitants that year in Colombia, which means that for every 10 000 Colombians, there would be 0.71 centenarians. Most of these patients were attended in Bogotá (528), Antioquia (433), Valle del Cauca (410), Bolívar (222) and Santander (219). After adjusting the departmental population, however, the departments with the highest rates were Sucre with 183 (2.17 per 10 000), Chocó with 64 (1.29 per 10 000), Córdoba with 187 (1.11 per 10 000) and Bolívar and Santander (both with 1.07 per 10 000) (Table 3).

In the entire Caribbean Region, the centenarian population was 1 039, which is a somewhat higher proportion (1.01 per 10 000) than in the rest of the country, where the centenarian rate decreases (0.63 per 10 000) if the Caribbean Region is excluded. On the other hand, the departments with the lowest rates of centenarians were Guaviare with 2 (0.2 per 10 000 inhabitants), Vichada with 1 (0.14 per 10 000) and Casanare with 3 (0.09 per 10 000). The map shows the rates of centenarians by department (Figure 2).

Finally, Table 4 presents the list of the 40 Colombian municipalities with rates higher than 2.5 centenarians per 10 000 inhabitants. These include six municipalities of Chocó, six of Bolivar, four of Boyacá and four of Cauca. The capital city with the highest proportion of centenarians was Sincelejo, but Bucaramanga and Monteria also appeared on the top of the list.

Discussion

The results of this study showed, through three different sources of information, a similar pattern of the number and distribution of centenarians in Colombia. In terms of numbers, the 2005 census identified 3 165 centenarians, while the 2014 RIPS found 3 390 (corresponding to an annual growth rate of 0.8%).

Table 3. Number of centenarians registered in RIPS 2014. Population according to DANE estimates and centenarian rate per 10 000 inhabitants, having DANE projections for that year as denominator.

Department	Centenarians	Population	Rate x 10 000
Amazon region	2	75 388	0.27
Antioquia	433	6 378 132	0.68
Arauca	7	259 447	0.27
Atlántico	192	2 432 003	0.79
Bogotá D.C.	528	7 776 845	0.68
Bolívar	222	2 073 004	1.07
Boyacá	116	1 274 615	0.91
Caldas	51	986 042	0.52
Caquetá	15	471 541	0.32
Casanare	3	350 239	0.09
Cauca	130	1 366 984	0.95
Cesar	75	1 016 533	0.74
Chocó	64	495 151	1.29
Córdoba	187	1 683 782	1.11
Cundinamarca	100	2 639 059	0.38
Guainía	1	40 839	0.24
Guajira	61	930 143	0.66
Guaviare	2	109 490	0.18
Huila	61	1 140 539	0.53
Magdalena	92	1 247 514	0.74
Meta	32	943 072	0.34
Nariño	96	1 722 945	0.56
Norte de Santander	72	1 344 038	0.54
Putumayo	12	341 034	0.35
Quindío	33	562 114	0.59
Risaralda	67	946 632	0.71
San Andrés	5	75 801	0.66
Santander	219	2 051 022	1.07
Sucre	183	843 202	2.17
Tolima	92	1 404 262	0.66
Valle del Cauca	410	4 566 876	0.90
Vichada	1	70 260	0.14
TOTAL	3 390	47 661 787	0.72

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

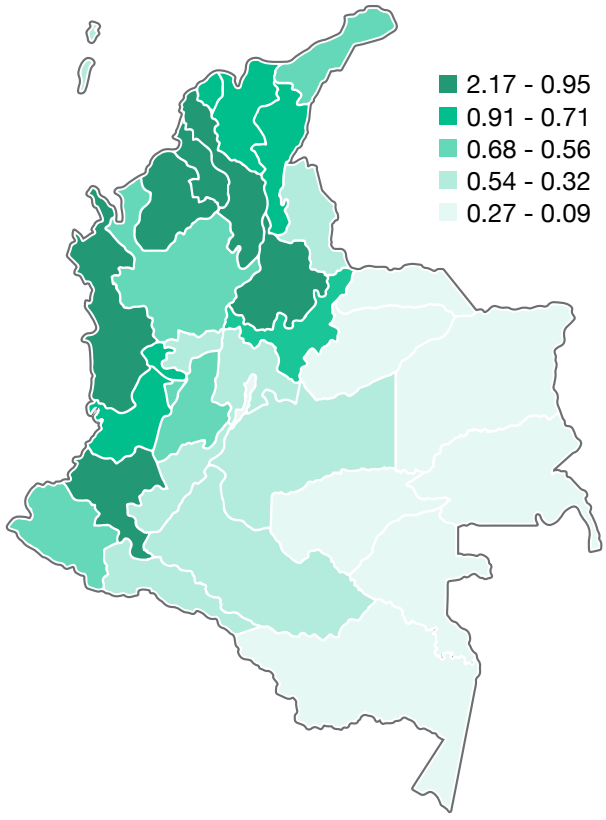

Figure 2. Rate of centenarians per 10 000 inhabitants in Colombia, according to RIPS 2014.
Source: Own elaboration based on data obtained in the study.

Furthermore, considering that 3 611 people aged 100 years or more died between 2010 and 2013, and estimating the death rate of Japanese centenarians aged between 100 and 104 years at 30% per year (35% for men and 27% for women) (8), it could be estimated that the average centenarian population for that period in Colombia was 3 009 people.

However, a common bias could be inherent in these records because of the process of obtaining the citizenship card and the date registered as birth date, which was the basis for age determination in the three databases. These official national citizen identification date back to 1952 (9), when current centenarians were around 30 years. It is possible that the age of birth, especially in the rural areas of Colombia, was imprecise, as was the case of the Ecuadorian population from Vilcabamba (10).

Moreover, there are methods to validate the age of people, as tested in Japanese (8), Chinese (11) and Caucasian (12) populations. These include interviews with relatives to confirm the birth dates, the age at marriage, and the birth date of children and grandchildren (13).

Even with these limitations, it is interesting to note the presence of a significant number of elderly people in some of the poorest areas of the country, such as Chocó and some departments of the Caribbean region. Certain characteristics of these inhabitants may be equated to those described in the so-called blue zones, which are sites of relatively large long-lived populations (14), such as Okinawa in Japan, Sardinia in Italy, Ikaria in Greece, Loma Linda in California, and the Nicoya peninsula in Costa Rica. Some of the characteristics described in these areas include a traditional lifestyle, intense physical activity even in seniors, reduced levels of stress, high family and community support, and consumption of locally produced foods (15,16).

Table 4. Colombian municipalities with the highest rate of centenarians according to RIPS 2014 (only those with three people older than 100 years or more were included). The population corresponds to the municipal projections of DANE for that year.

	Municipality	Centenarians	Population	Rate x 10 000
1	Iza, Boyacá	3	2 325	12.90
2	Soatá, Boyacá	9	7 446	12.09
3	Bajo Baudó, Chocó	16	17 290	9.25
4	Guateque, Boyacá	8	9 677	8.27
5	Pedraza, Magdalena	5	8 052	6.21
6	Colón, Putumayo	3	5 475	5.48
7	Tadó, Chocó	10	18 836	5.31
8	Caloto, Cauca	9	17 607	5.11
9	Sincelejo, Sucre	135	271 375	4.97
10	Condoto, Chocó	7	14 490	4.83
11	Vijes, Valle del Cauca	5	10 886	4.59
12	Mercaderes, Cauca	8	18 018	4.44
13	Arroyohondo, Bolívar	4	9 782	4.09
14	Arjona, Bolívar	29	71 180	4.07
15	Granada, Meta	4	9 855	4.06
16	Istmina, Chocó	9	25 183	3.57
17	Puerres, Nariño	3	8 449	3.55
18	San Juan del Cesar, La Guajira	12	36 851	3.26
19	Unión Panamericana, Chocó	3	9 447	3.18
20	Palmira, Valle del Cauca	96	302 727	3.17
21	Plato, Magdalena	18	56 894	3.16
22	Gómez Plata, Antioquia	4	12 662	3.16
23	Carmen de Bolívar, Bolívar	23	74 297	3.10
24	Tangua, Nariño	3	9 758	3.07
25	Miraflores, Boyacá	3	9 765	3.07
26	Linares, Nariño	3	10 225	2.93
27	Sampués, Sucre	11	37 787	2.91
28	El Carmen de Atrato, Chocó	4	13 819	2.89
29	Sasaima, Cundinamarca	3	10 632	2.82
30	Espinal, Tolima	21	76 291	2.75
31	Bucaramanga, Santander	143	527 451	2.71
32	Cicuco, Bolívar	3	11 110	2.70
33	Timbío, Cauca	9	33 467	2.69
34	Montería, Córdoba	116	434 950	2.67
35	Zambrano, Bolívar	3	11 525	2.60
36	Puerto Triunfo, Antioquia	5	19 656	2.54
37	Corinto, Cauca	8	31 485	2.54
38	Belén de Umbría, Risaralda	7	27 725	2.52
39	Galeras, Sucre	5	19 866	2.52
40	María la Baja, Bolívar	12	47 749	2.51

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

On the other hand, Colombia has no global indicators of healthy living by departments. Alcohol consumption represented by sales of alcohol in annual liters per capita has a national average of 4.15, which somewhat decreases in the departments of interest. Thus, in La Guajira, the average was 1.64, in Chocó 2.01, in Córdoba 3.20, and in Sucre 3.28 (17). However, these values do not consider the impact of contraband.

Regarding cigarette consumption, according to statistics from the Ministry of Health, in 2007, 3 of these 4 departments may have had a prevalence of tobacco consumption below the national average (12.8%), except for Chocó, which registered 15.9%. The other departments showed a prevalence of 7.8 in La Guajira, 10.5 in Córdoba and 11.9 in Sucre (18).

The 2005 census data allowed estimating life expectancy at birth in Colombia for the five-year period 2000-2005, with an average value for men and women equivalent to 72.8 years. This represented an increase of 2.5 years in relation to the previous 15 years. Some departments with high rates of centenarians, despite having a life expectancy at birth below the national average, showed higher increases when comparing the five-year period 1985-1990 to 2000-2005. Chocó was first with 5.4 years (going from 60.1 to 65.5), followed by Córdoba with 4.8 (from 65.8 to 70.6), and Sucre with 4.7 (from 67.0 to 71.7) (19).

By performing secondary analyzes of official databases (two from DANE and one from the Ministry of Health), this study intended to draw interest on the centenarian population in Colombia, and to continue with this the study, through other strategies, to know if there are regions in the country where longevity tends to concentrate.

Conflict of interest

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ORIGINAL RESEARCH

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Prevalence of defining malignancies in adult patients with HIV/AIDS in the National Cancer Institute of Colombia. 2007-2014

Prevalencia de neoplasias en pacientes adultos con VIH/sida del Instituto Nacional de Cancerología de Colombia. 2007-2014

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| Abstract |

Introduction: The widespread use of antiretroviral therapy has increased the survival rates of patients infected with human immunodeficiency virus (HIV) and, in consequence, the prevalence of both defining and non-defining cancers. In Colombia, information in this regard is unknown.

Objective: To determine the prevalence of defining malignancies in adult patients with HIV treated at the National Cancer Institute over a seven-year period.

Materials and methods: Descriptive study involving adult patients diagnosed with HIV and cancer. Sociodemographic variables, CD4 count, viral load and antiretroviral therapy were analyzed by establishing association measures with the presence of defining malignancies.

Results: 139 patients with confirmed HIV and cancer diagnosis were found; 84.2% were men. The age range was between 18 and 71 years, with a mean of 41.3±10.9 years. Defining cancers corresponded to 65.5% of the cases, the most frequent being non-Hodgkin lymphoma. The remaining percentage corresponded to non-defining cancers, mainly anal cancer and Hodgkin's lymphoma.

Conclusion: Despite the global trend, the population studied here shows predominance of defining cancers, which, like HIV, continue to be detected at a late stage.

Keywords: HIV; Acquired Immunodeficiency Syndrome; Malignances; Highly Active Antiretroviral Therapy; Colombia (MeSH).

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| Resumen |

Introducción. El uso de la terapia antirretroviral ha aumentado la supervivencia de los pacientes con virus de inmunodeficiencia humana (VIH) y, como consecuencia, la prevalencia de cánceres definitorios y no definitorios. En Colombia no se conoce información al respecto.

Objetivo. Determinar la prevalencia de neoplasias definitorias en pacientes adultos con VIH del Instituto Nacional de Cancerología en un período de 7 años.

Materiales y métodos. Se realizó un estudio descriptivo que incluyó pacientes adultos con diagnóstico de VIH y cáncer. Se analizaron variables sociodemográficas, conteo de CD4, carga viral y tratamiento antirretroviral. Se establecieron medidas de asociación entre las últimas tres variables y la aparición de neoplasias definitorias.

Resultados. Se estudiaron 139 pacientes con diagnóstico de VIH y cáncer, 84.2% de los cuales eran hombres. El rango de edad osciló entre 18 y 71 años con una media de 41.3±10.9 años. Las neoplasias definitorias se presentaron en 65.5% de los casos; la más frecuente fue el linfoma no Hodgkin. El porcentaje restante correspondió a neoplasias no definitorias, en su mayoría, cáncer anal y linfoma de Hodgkin.

Conclusión. Pese a la tendencia mundial, en la población evaluada hay preponderancia de neoplasias definitorias, las cuales —al igual que el VIH— siguen detectándose de forma tardía.

Palabras clave: VIH; Síndrome de inmunodeficiencia adquirida; Neoplasias; Terapia antirretroviral altamente activa; Colombia (DeCS).

Álvarez-Guevara D, Cuervo-Maldonado S, Sánchez R, Gómez-Rincón J, Ramírez N. [Prevalencia de neoplasias definitorias en pacientes adultos con VIH/sida del Instituto Nacional de Cancerología de Colombia. 2007-2014]. Rev. Fac. Med. 2017;65(3):397-402. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.56112.

Introduction

The world witnessed an HIV/AIDS epidemic for four decades, after the first case was reported back in the 1980s. Numbers are not encouraging; according to the report issued by the Joint United Nations Program on HIV/AIDS (UNAIDS) in 2014, 35 million people were infected around the world, with an incidence of 2.1 million new cases a year, in other words, about 6 000 new infections a day (1). In Colombia, the virus has a prevalence of 0.5-0.9% of the total population according to Unicef and UNAIDS reports (2). This, along with an average of 35% decrease in mortality rates observed during the past ten years, has caused an increase of the prevalence not only in relation to the number of new cases, but also to greater survival of infected individuals (1).

Regarding the association of HIV with cancer, between 6% and 49% of patients with retroviral infection develop some neoplasm during the course of the disease (3-5). Although a greater risk can be observed, there is no clarity about the direct pathophysiological role of the virus in the large group of tumors detected in this group of patients. Possible theories have considered the immunosuppressive role of the virus, coinfection with other oncogenic potential viruses such as Epstein Barr or hepatitis C, and the presence of common risk factors between both diseases (3,6,7).

Non-Hodgkin's lymphoma, Kaposi's sarcoma, and invasive cervical cancer report the highest relative risks, which are considered as the defining features of acquired human immunodeficiency syndrome (AIDS) (8). These neoplasms are usually observed in more than 70% of the cases worldwide (4,5). However, after the widespread introduction of the highly active anti-retroviral therapy (HAART) in the mid-1990s, a change in the distribution of neoplasms in this group of patients could be seen, in other words, the frequency of non-defining malignancies increased (6,9,10).

Considering the lack of studies on this condition in Colombia, this study intends to establish the prevalence of defining malignancies in adult patients with HIV/AIDS treated at the National Cancer Institute of Colombia (INC in Spanish) —national cancer reference center in the country— over a seven-year period. In addition, an evaluation was also performed on the association between the onset of defining neoplasms and the use of antiretroviral treatment, viral load and CD4 in the included patients. If the prevalence of defining malignancies in this group of patients is known, a hypothesis about the diagnostic opportunity of HIV/AIDS and the coverage of antiretroviral treatment in this population could be considered.

Materials and methods

Definition of study subjects

The study population included INC patients attended in the institution between 2007 and 2014, of legal age, with a confirmed HIV/AIDS diagnosis, whether or not they were taking antiretroviral therapy, a diagnosis of one or more solid organ or hematological malignancies confirmed by pathology, with or without specific treatment for them. Patients with benign neoplasms, in whom a malignant component was ruled out by pathology, were excluded.

Study design and stages

An observational, analytical, cross-sectional study was performed, in which patients were selected from the databases of the Epidemiological Research, Public Health, Systems and Clinical Laboratory groups, as well as from the data of consultations and inter-service consultations of the Infectious Diseases Group in the same institution between 2007 and 2014. This period was chosen since, as of June 2007, the clinical and laboratory reports of INC patients were available in the Systems, Applications & Products in Data Processing (SAP) software; this way, an adequate collection of information was guaranteed.

After obtaining a unified list, in April 2014, a review of the medical records was initiated, following approval (institutional registration INC-C410-3610-679) from the institutional Ethics Committees of the Faculty of Medicine of Universidad Nacional de Colombia and the INC. Then, the socio-demographic variables of the population were measured and the diagnoses were verified.

During the research, the INC Research Area Group supported the review of quality and veracity of the data provided in the registration forms. Furthermore, an adequate transcription of the information was verified in the database before the statistical analysis.

Definitions

The stage of retroviral infection was determined based on CD4 count, viral load and AIDS defining illnesses in each patient according to the 2008 classification issued by the Disease Control and Prevention Centers (CDC in Spanish) (11):

Stage 1: Non-defining condition, CD4>500 cells or CD4>29%.
Stage 2: Non-defining condition, CD4=200-499 cells or CD4=14-28%.
Stage 3: AIDS-defining condition regardless of CD4, CD4<200 cells or CD4<14% counts.
Stage 4: No information on CD4 count or AIDS defining conditions.

To establish the stage of the neoplasms, the medical records of the treating services were analyzed. These records were classified as defining and non-defining, taking into account the official definition of AIDS published by the CDC in 1992, which considers non-Hodgkin's lymphoma, Kaposi's sarcoma and invasive cervical cancer as defining malignancies (12).

Statistical analysis

A sample size of 126 patients was calculated with an expected difference between defining and non-defining malignancies of 20-

25% (4.9), 95% confidence interval (CI), and 7% accuracy around the estimator. A database was constructed based on the different variables, which served for conducting different analyzes using the statistical software R (R Core Team, New Zealand). A descriptive analysis was completed using means and standard deviations for numerical variables, and percentages for categorical variables. A 95% CI was calculated to establish the frequency estimators (prevalence of defining malignancies).

Taking into account the contingency tables, the Fisher's exact test was used to assess the association between the onset of defining malignancies and low CD4 count, high viral load and absence of antiretroviral treatment, which, according to the literature, happen to be associated with their development (4,13). Statistical significance levels of 5% with two-tailed hypotheses were used for this test.

Results

During the initial search in the databases of the participating services, 176 potential patients were identified. 37 patients were excluded since three were under 18 years of age, 12 did not have a confirmatory or negative test, seven had incomplete medical records, and 15 had a confirmed diagnosis of retroviral infection but cancer was ruled out during their stay in the institution due to the presence of benign neoplasms or opportunistic infections that mimicked malignant neoplasms.

In total, 139 patients that met the inclusion criteria and completed the data collection form were found. Of these, 84.2% were men (n=117) and 15.8% were women (n=22) whose ages ranged from 18 to 71 years, with an average of 41.3±10.9. Other characteristics of the population are summarized in Table 1.

Table 1. Socio-demographic characteristics of HIV and cancer patients of INC 2007-2014.

Variable		Frequency (n=139)	Percentage
Sex	Male	117	84.2%
	Female	22	15.8%
Schooling	None	1	0.7%
	Complete Primary school	17	12.2%
	Incomplete Primary school	8	5.8%
	Complete high school	24	17.3%
	Incomplete high school	17	12.2%
	Technical	8	5.8%
	University	26	18.7%
	Not reported	38	27.3%
Civil status	Single	82	58.9%
	Married	15	10.8%
	Widower	3	2.2%
	Separated	12	8.6%
	Common-law marriage	24	17.3%
	Not reported	3	2.2%

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

Likewise, other important variables for the diagnosis and follow-up of HIV and cancer were recorded for a complete characterization of the study population. Opportunistic infections were found in 35.9% of patients (n=50), the most frequent being *Pneumocystis jirovecii* pneumonia, followed by cryptococcosis, tuberculosis and esophageal candidiasis. These infections were found individually, combined with each other or with other high frequency infections in this population group such as herpes zoster.

Sex preference was only reported in 64.7% of the cases, being the man-man relationship the most frequent (18.7% of the patients). With respect to HIV infection, 86.3% of patients had continuous access to antiretroviral therapy, and the most frequent combination was protease inhibitors with nucleoside analogues (35.3% of subjects). Data on CD4 count, viral load and stage of retroviral infection are summarized in Table 2.

Table 2. Characteristics of retroviral infection in patients with HIV and cancer at INC 2007-2014.

Variable		Frequency (n=139)	Percentage
CD4 count	<200 cells	45	32.3%
	201-350 cells	29	21.0%
	351-499 cells	11	7.9%
	>500 cells	12	8.6%
	Not reported	42	30.2%
Viral load	Undetectable	54	38.8%
	1 000-250 000 copies	25	18.0%
	250 001-1 000 000 copies	6	4.3%
	>1 000 000 copies	4	2.9%
	Not reported	50	36.0%
Stage of retroviral infection by HIV*	Stage 1	6	4.3%
	Stage 2	16	11.5%
	Stage 3	108	77.7%
	Stage 4	9	6.5%

*According to Schneider *et al.* (11).
Source: Own elaboration based on the data obtained in the study.

Solid neoplasms predominated in 60.4% of the cases studied. At the time of inclusion, 12.2% of patients (n=17) were stage I, 10.8% (n=15) stage II and 45.3% (n=64) stages III and IV. For the remaining 31.7% (n=43), the stage was not recorded or the neoplasm was not stable. Although a high percentage of neoplasm diagnoses in advanced stages were observed, only three patients died within 30 days after diagnosis. 42.4% of subjects received anti-neoplastic chemotherapy (n=59), and the rest received combination therapy (23%), palliative care (18.7%), surgery (9.4%), antiretrovirals (4.3%) and radiotherapy (2.2%).

According to the main objective of this study, AIDS-defining malignancies were found in 91 patients, which correspond to 65.5% of the total sample (95%CI: 57.2-73.3). Non-Hodgkin's lymphoma was the predominant defining malignancy (n=46), followed by Kaposi's sarcoma (n=42) and invasive cervix cancer (n=3). Non-defining malignancies were found in 34.5% of the subjects (n=48), and the most frequent were anal cancer (n=7), Hodgkin's lymphoma (n=7) and non-invasive cervix cancer (n=6). The distribution of other neoplasms of this type was homogenous, and no hepatocellular carcinoma or lung cancer cases were reported in this series of patients (Figure 1).

Regarding HIV and cancer diagnosis, 56.8% of the patients were first diagnosed with the retroviral infection and then with the neoplasm. Diagnosis was simultaneous in 22.3% of the cases, cancer was first diagnosed in 16.6% (n=23), and data were incomplete in 4.3% (n=6). The initiation of HAART before cancer diagnosis occurred in 17.3% of the patients, was simultaneous in 14.4%, and subsequent in 18.7%. In 13.7% of cases, no antiretroviral management was initiated during institutional follow-up, and the remaining 35.9% (n=50) did not record the date of any of the two events, which prevented establishing a correlation.

Finally, Fisher's exact test evaluated the association between the presence of defining malignancies and the CD4 count, viral load and antiretroviral treatment variables. A statistically significant association was found only in CD4 count (p=0.034). There was a marginal correlation with the detectable or undetectable viral load (p=0.074), which may be influenced by the sample size (Table 3).

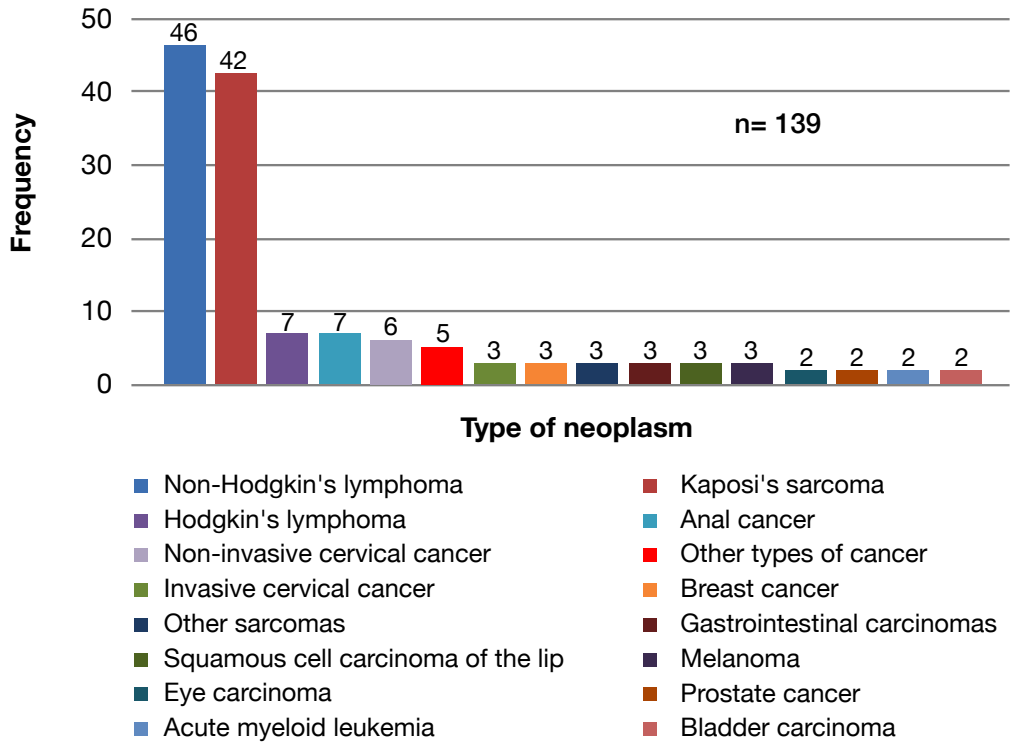

Figure 1. Distribution of neoplasms in the population of patients with HIV and cancer at INC 2007-2014.
Source: Own elaboration based on the data obtained in the study.

Table 3. Association between the development of defining malignancies and the CD4 count, viral load and antiretroviral treatment variables.

Type of neoplasm	CD4 count *†		Viral load ‡		Antiretroviral treatment	
	<350	>350	Detectable	Undetectable	Yes	No
Defining	53	11	29	26	81	10
Non-defining	21	12	25	9	39	9

* Fisher's exact test p=0.045.
† Patients without reported CD4 count = 42
‡ Patients without reported viral load = 50
Source: Own elaboration based on the data obtained in the study.

Discussion

The adult population treated at INC and recorded between 2007 and 2014 included 139 patients with HIV and cancer, of which 65.5% had AIDS defining malignancies as well. These results are similar to those found by Bedimo *et al.* (4), where 78% of cases had defining malignancies, and by Shiels *et al.* (14) who sub-analyzed the pre-HAART period and found that 64% of the cases had defining malignancies. However, these data have a lower percentage than the findings of Allardice *et al.* (5), who found 138 out of 162 patients with AIDS-defining malignancies (85.1%), and Fink *et al.* (15), who reported a prevalence of 82% of this type of cancer in the study population. The latter is the only work in Latin America with a population similar to the present study.

Such discrepancies are expected given the particular characteristics of the population, since INC, as a national reference center for cancer, selects patients after they have been evaluated and intervened in other institutions with a lower level of complexity. In addition, this study is descriptive and includes patients diagnosed with HIV before and after extensive use of HAART, thus it is not possible to establish changes in the epidemiological pattern of neoplasms related to this therapy since the 1990's. This prevents direct comparison with other international cohorts, but leaves open the possibility of further studies that show the chronological evolution of neoplasms in relation to the use of HAART. Currently, it can only be concluded that this population seems to behave similarly to others around the world before HAART. Differences should be further assessed in studies with a larger population.

Regarding sociodemographic characteristics, it is important to highlight the predominance of the male sex (84.2%), which coincides with the reports by national health entities (16) and other international studies (14). The age range of the patients was broad: three patients were older than 65 years, and working-age population was predominant, affecting not only their quality of life but also their social performance. The mean age was 41.3 years, similar to the findings of Shiels *et al.* (14) in the U.S. population, who reported that the diagnosis of both diseases occurs around age 38.

With reference to the variables for the diagnosis and follow-up of retroviral infection, HIV was mostly diagnosed at stage III, which implies that more than 76% of patients had CD4 counts lower than 200 or some AIDS-defining disease by the time of the study (11). This may occur due to failures in early detection or diagnoses at advanced stages of infection (4,17), considering that most patients of INC are referred from other cancer institutions with an initial diagnosis of retroviral infection for treatment and follow-up. This hypothesis is supported by the finding of more than 50% of subjects with an HIV diagnosis prior to cancer diagnosis.

Other relevant data on infection follow-up include viral load and treatment coverage. The viral load has a high underreporting rate (35.5%) despite its great impact on the follow-up of HIV-infected patients. This is one of the limitations of this study, because the lack

of this data prevents objectively determining the virologic response to antiretroviral treatment. Moreover, HAART coverage in this study was 86.3%, a positive figure compared to the 30% reported by the Ministry of Social Protection in 2012 (18).

Specifically for cancer, the diagnosis was made at advanced stages (stages III and IV) in 45.3% of the cases, which could be caused by two factors. First, late diagnosis could be related to a low suspicion index in patients with non-specific symptoms and findings in imaging studies. In some HIV patients, neoplasms are not detected early because of the absence of guiding symptoms or because they are mistaken for opportunistic infections (19). In this study, 15 of the HIV patients detected in the initial search were excluded from the study because opportunistic infections were found during follow-up and cancer was ruled out. Secondly, patients admitted at INC are carefully selected and admitted with more advanced neoplasms.

Regarding cancer, the most frequent type of neoplasm was non-Hodgkin's lymphoma, followed closely by Kaposi's sarcoma and, less frequently, by invasive cervical cancer. These data are similar to those reported by Allardice *et al.* (5) in Scottish population, who found 2 574 HIV-infected patients between 1981 and 1996, of which 6.3% developed some neoplasm, non-Hodgkin's lymphoma being the most frequent (n=82). These results differ from the American populations, where Kaposi's sarcoma predominates (4,9,15). As mentioned above, the only known Latin American study was made by Fink *et al.* (15), who found 406 patients with HIV and cancer, in which Kaposi's sarcoma predominated with 225 cases (15).

In line with national and international studies, the most frequent non-AIDS defining malignancies are Hodgkin's lymphoma and anal cancer (4,9,15,20). As in cervical cancer, early detection through anal cytology in high-risk population could be a public health strategy for this population group. On the other hand, this study did not find hepatocellular carcinoma or lung cancer cases, which are the next more frequent neoplasms according to the existing literature (5,14,21).

Consistent with the findings of other studies (4,13,17,22-24), establishing non-causal associations between defining malignancies and low CD4 count, high viral load and no antiretroviral treatment was intended. When excluding unreported data, association was only found at the limit of the statistical significance between a higher viral load and the development of defining neoplasms. The lack of association with the other variables may be related to a lower number of patients compared to the American and European series, which opens the possibility for further research.

This work has some limitations, which include its retrospective character considering that the records are made by different health professionals and, as mentioned before, the under-registration of some data that may compromise interpretation. Similarly, the number of patients included is low in relation to other studies reviewed. In spite of this, according to the methodological design, the minimum number of patients was achieved for an adequate inference of the results. Finally, since this is a cross-sectional study, it was not possible to establish causality between the onset of HIV and cancer. These limitations are common in other studies with a similar design, and should be considered when generating strategies for quality research.

In conclusion, a predominance of defining malignancies was observed in the group of patients with HIV and cancer at INC, as reported by other studies worldwide in the pre-HAART period. The HIV infection diagnosis continues to be made at late stages; thus, strengthening strategies for early detection of HIV in the population is strongly advised. In view of the impact that the association between HIV and cancer may have in the short term for the health system, more studies with a larger population should be carried out to generate a national picture of this correlation.

Conflict of interests

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ORIGINAL RESEARCH

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Adherence to antiretroviral treatment and associated factors in people living with HIV/AIDS in Quindío, Colombia

Adhesión al tratamiento antirretroviral y factores asociados en personas viviendo con VIH/sida en Quindío, Colombia

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| Abstract |

Introduction: HIV/AIDS is a chronic disease; therefore, recognizing which factors favor adherence to antiretroviral treatment is necessary.

Objective: To determine the association between adherence to antiretroviral treatment and depression, anxiety, perception of social support and sociodemographic variables in people living with HIV/AIDS in Quindío, Colombia.

Materials and methods: An observational, cross-sectional study was performed in an intentional sample of 70 adults, who were applied the Morisky-Green questionnaire, the Beck Depression Inventory, the Beck Anxiety Inventory, the Medical Outcomes Study (MOS) Social Support Survey, and a sociodemographic survey. Univariate and bivariate analyzes were performed by calculating the odds ratio to determine association ($p<0.05$).

Results: 57.1% of the participants reported low adherence to treatment, 30% had moderate or severe depressive symptoms, 71.4% scored minimal or mild anxiety levels, and 77.1% had a low perception of social support. A statistical association between depression (high levels tripled the risk of non-adherence) and self-report on how treatment is followed (excellent or good self-report increased by five times the probability of adherence) was found.

Conclusion: Depression and self-report on compliance were associated with adherence to antiretroviral therapy. A comprehensive study on the perception of social support and cognitive variables, such as self-efficacy and risk perception, is highly recommended for people living with HIV/AIDS.

Keywords: HIV; Antiretroviral Therapy Highly Active; Medication Adherence; Depression; Anxiety; Social Support (MeSH).

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| Resumen |

Introducción. El VIH/sida es una enfermedad crónica, por ello es necesario reconocer qué factores favorecen la adhesión al tratamiento antirretroviral.

Objetivo. Determinar la asociación entre adhesión al tratamiento antirretroviral y depresión, ansiedad, percepción de apoyo social y variables sociodemográficas en personas viviendo con VIH/sida en Quindío, Colombia.

Materiales y métodos. Se realizó un estudio observacional analítico de tipo transversal en una muestra intencional de 70 adultos, a quienes se les aplicó el cuestionario autorreferido de Morisky-Green, el Inventario de Depresión de Beck, el Inventario de Ansiedad de Beck, el cuestionario MOS (Medical Outcomes Study) de Apoyo Social y una encuesta sociodemográfica. Se realizaron análisis univariados y bivariados calculando Odds Ratio para determinar asociación ($p<0.05$).

Resultados. 57.1% de los participantes reportó poca adhesión al tratamiento, 30% presentó síntomas depresivos moderados o graves, 71.4% puntuó niveles mínimos o leves de ansiedad y 77.1% tuvo baja percepción de apoyo social. Se encontró asociación estadística entre depresión —niveles altos triplicaron el riesgo de no adhesión— y autoevaluación de la manera como se sigue el tratamiento —excelente o buena aumentó cinco veces la probabilidad de adhesión—.

Conclusión. La depresión y la autoevaluación del cumplimiento se asociaron con adhesión al tratamiento antirretroviral. Se sugiere

profundizar el estudio de la percepción de apoyo social y variables cognitivas, como la autoeficacia y percepción de riesgo, en personas que viven con VIH/sida.

Palabras clave: VIH; Terapia antirretroviral altamente activa; Adhesión al tratamiento; Depresión; Ansiedad; Apoyo social (DeCS).

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Introduction

HIV is a public health concern worldwide. Since 2000, 38.1 million people have acquired the virus and 25.3 million have died from AIDS-related illnesses (1). In 2015, UNAIDS (2) reported an average of 34 to 39.8 million people living with HIV/AIDS (PLWHA) in the world; in Latin America, the figure ranges between 1.7 and 2.3 million. According to the same report, 17 million people had access to antiretroviral therapy (ART) in December 2015, while about 22 million people did not have access to treatment at all. About 28 million new cases could be avoided, if response to AIDS in low- and middle-income countries increases (3).

The Colombian Public Health Surveillance System reported 8 196 new PLWHA cases in 2012 (4), with the highest incidence in Barranquilla (50.6 cases per 100 000 inhabitants), Quindío (28.4 cases per 100 000 inhabitants), and Cartagena (37.6 cases per 100 000 inhabitants). In addition, 2 216 deaths associated with HIV/AIDS and a mortality rate of 4.76 per 100 000 inhabitants were reported. Quindío was one of the most affected departments by this epidemic (5).

HIV/AIDS is considered a chronic disease that involves multiple factors, since it has an impact on physical and mental functioning (6) and may affect self-concept and sense of life (7). This condition is a stressor that implicates psychological, physiological, social and economic aspects, therefore, it demands strategies that favor treatment and reduce threats to health. In this regard, the patient's attitudes and coping techniques can influence the HIV infection process (8), which, in turn, demands changes in lifestyle to comply with therapeutic indications. This is known as adherence to treatment, and indicates the commitment and participation of the individual in self-care (9,10).

Although no consensus in the definition of treatment adherence has been achieved (also known as cooperation or therapeutic compliance), it is generally understood as a complex and multifactorial problem that transcends following closely medical instructions or prescriptions (9,11). As proposed by DiMatteo & DiNicola, and accepted by other researchers, adherence is an active process of voluntary collaboration established between the patient and the health personnel to carry out mutually agreed upon behaviors, in order to generate the desired therapeutic effect (10,12,13).

Piña-López & Sánchez-Sosa (14) suggest that adherence in PLWHA is determined by the frequency with which subjects develop behaviors to comply with the instructions provided by health personnel based on their own skills. Adherence behaviors are a consequence of the interaction between biological variables (HIV disease and other conditions) and psychological variables (interaction styles related to stress, abilities, motives and emotional states), which have effects on health, control and course of infection with HIV (11,14).

Different situations may affect adherence to treatment in chronic diseases, for example, the nature of the disease, the time of evolution, the expectation of treatment outcomes, the characteristics of the treatment, the habits and customs of the patient (15,16), the interaction with health professionals, the characteristics of the health institution (9), and psychological and social aspects such as coping strategies (6). Other important factors in HIV infection include its asymptomatic character in most cases, the amount of drugs supplied (antiretrovirals and those necessary for opportunistic diseases), social stigmatization, side effects of certain drugs, patient's beliefs, affective states, perception of control over stressful life events, and the disease, among others (17,18).

Following the model of Sánchez-Sosa *et al.* (19), psychological variables such as depression, stress, anxiety, low motivation and lack of social support can contribute to the progression of the disease and reduce the quality of life of the affected patients.

Remor (20) reports low adherence in the presence of high levels of anxiety, stress, depression and poor social support. Piña-López *et al.* (21) and Piña-López *et al.* (22) report competencies, stress, motives, frustration, tolerance and ambiguity as predictors of adherence, which may vary according to the time of infection; also, Piña-López *et al.* (23) proposed that intermediate levels of stress and low levels of depression are favorable, and, finally, Piña-López *et al.* (24) add that associated psychological variables are affected by self-report on social competences.

Arrivillaga *et al.* have identified a correlation between anxiety and depression, as well as a perception of poor control over health and stressful life events in women living with HIV/AIDS, which affect their adherence and quality of life. Likewise, Arrivillaga *et al.* (26), Arrivillaga *et al.* (27) y Arrivillaga *et al.* (28) stress the role played by social and economic factors in the adherence to antiretroviral treatment (ART) by women. Social support is another key factor associated with better health results, adherence and quality of life in PLWHA (7,25,29-31).

In this regard, adherence to ART is a complex process, permeated by psychological and social factors of great relevance for the evolution, treatment and quality of life of PLWHA. These factors need to be further analyzed given the implications for public health that the lack of adherence to ART have, and to contribute to the enrichment of intervention programs. It is, therefore, pertinent to generate knowledge in this field, and specifically in one of the leading departments of morbidity and mortality caused by HIV/AIDS in Colombia. The aim of this study was to establish the association between adherence to antiretroviral therapy and depression, anxiety, perception of social support and sociodemographic variables in a group of PLWHA in Quindío, Colombia during 2015.

Methodology

This is an observational and analytical cross-sectional study, in which 70 PLWHA participated —men and women enrolled in an accompaniment program offered by a health institution in Quindío (Colombia). Some of them were hospitalized and others were attending medical and psychological follow-ups. Sampling was non-probabilistic, intentional, and selected taking into account as inclusion criteria HIV diagnosis, ART, being of legal age, no physical or mental conditions that would hinder understanding the instruments, will to participate in the study, and a signed informed consent.

A socio-demographic data survey was used for collecting information regarding age, sex, marital status, schooling, socioeconomic stratum and religion. In addition, variables related to the disease such as diagnosis time, perception of family support and understanding during the treatment, consumption of psychoactive substances (cigarettes, coca paste and/or marihuana), frequency of psychological therapy, and self-report on how treatment was followed were also investigated.

Adherence to ART was assessed using the Morisky-Green Scale (32), which reflects patient compliance with medication and has been used in different studies (33-36). This instrument consists of four questions with two response options (Yes/No); if the answer for any of these items is Yes, it means that the patient has failed and is reported as non-adherent.

To identify depressive symptoms and their severity, the Beck Depression Inventory (BDI) was applied; this is a 21-item scale that considers psychological-cognitive and somatic-vegetative aspects, which are evaluated based on affirmations selected by the individual. The scores range from 0 to 3, yielding a total number between 0 and 63. A score of 0 to 9 indicates absence of depression; 10 to 18, mild depression; 19 to 29, moderate depression, and from 30 onwards, severe depression (37,38).

On the other hand, the Beck Anxiety Inventory (BAI) was used to evaluate anxiety symptoms when investigating subjective, neurophysiological, autonomic and panic factors. This inventory is made up of 21 items, each with the following response options: 0-not at all; 1-slightly, it does not bother me much; 2-moderately, it was very unpleasant but I could bear it, and 3-severely, I could hardly bear it. In the Spanish version, the cut-off points are 0 to 7 for minimal anxiety, 8 to 15 for mild anxiety, 16 to 25 for moderate anxiety, and 26 to 63 for severe anxiety (39).

Perceived social support was assessed using the Medical Outcomes Study (MOS) questionnaire designed by Sherbourne and Stewart in 1991, and adapted to the Colombian population (40), which assesses structural support or size of the social network (item 1) and functional support (perception of support, items 2-19). Functional support is independent and multidimensional, and is composed of emotional/informative, tangible and affective social support and positive social interaction. The first question inquiries into the number of close friends and relatives. The remaining questions have answering options from 1 to 5 (never, rarely, sometimes, most of the time, always). The raw scores range from 19 to 95, and a higher score indicates greater perceived social support.

The study was supported by the Bioethics Committee of the Universidad de San Buenaventura Medellín. The instruments were codified and a route was established for channeling severe depression and anxiety cases or suicidal ideation in order to refer patients to specialists or appropriate care centers. Subsequently, the participants were contacted to be informed about the objectives and procedures of the study, and to request voluntary participation. An appointment was coordinated with those who accepted under certain conditions to ensure confidentiality.

The instruments were applied through an individual interview; prior informed consent was signed and participants were informed about the purpose of the study, voluntariness, confidentiality and non-remuneration, as well as about their right to abandon the study at any time. Individual results were returned to participants, and general results to the health institution. Lastly, the channeling route was activated in the necessary cases.

Data tabulation was performed in Microsoft Excel 2013, and the statistical analysis was made through SPSS version 21. Univariate and bivariate analyzes were performed. Central tendency, dispersion and position were evaluated as quantitative variables and, on the other hand, qualitative variables included absolute and relative frequencies. To determine the existence or non-existence of statistical association, the odds ratio (OR) was calculated and its confidence intervals and p values were deemed as significant when they were <0.05.

It should be noted that depression and anxiety variables were dichotomized for the analysis, and were reported as absent/mild depression, moderate/severe depression, and minimal/mild anxiety, moderate/severe anxiety. Regarding social support perception, the scores found in the first three quartiles were taken as low, and the ones in the last quartile were considered high. The socioeconomic stratum variable was analyzed based on the Colombian stratification, and was grouped into three categories: 0, 1 and 2, which included homeless population, low-low and low strata, and 3, 4 and 5 strata gathering middle-low, medium and medium-high strata.

Results

70 people, aged between 18 and 66 years, answered the survey; the average age was 38, with a standard deviation of 12 years. The highest age in 50% of the participants was 38, and the most frequent was 28. The highest proportions were found among men (64.5%), patients of socioeconomic strata 0, 1 and 2 (82.3%), catholics or protestants (82.9%), high school graduates (43.9%), and single (44.9%). 38.2% of the subjects were diagnosed two years or less before they participated in the study. Most of them (71.4%) reported feeling supported and understood by their relatives, and affirmed that they were receiving psychological therapy on a regular basis. 30% of the patients reported that they are currently using psychoactive substances.

57.1% of the patients did not show adherence to the pharmacological treatment, although most of them state that they are following it with excellent outcomes (74.2%). Regarding the psychological variables, absent or mild levels of depression were found in most participants; 30% scored moderate or severe depression. Moderate or severe levels of anxiety were observed in 28.6% of the cases, and the perception of little social support in 77.1% (Table 1).

Bivariate analysis

In order to determine some associations that would indicate possible factors related to ART adherence, a bivariate analysis was performed. Two of the evaluated variables had a statistically significant association with adherence: self-report on the way in which treatment was followed (p=0.038, OR=5.385, 95%CI: 1.096-26.46) and depression (p=0.040, OR=3.33; 95%CI: 1.056-10.52). The p-value found in the remaining variables was >0.05, although a higher proportion of adherence was observed in women, in people from socioeconomic strata 3 to 5, in those who have more than 10 years of diagnosis, in those who do not profess any religion, are married or in some kind of relationship, have technical or professional studies, who frequently or always feel support and understanding from their families, those who attend therapy periodically, who are not currently using any type of illegal substance, and those who have low levels of anxiety and perceive high levels of social support (Table 2).

Discussion

This study identified adherence to treatment in a group of PLWHA in Quindío and its association with psychological and social variables that may play a fundamental role in interventions with this population. An outstanding percentage of subjects showed poor adherence (57.1%), which is highly relevant since this situation may indicate how patients are coping with their condition and, at the same time, how their quality of life and their relatives or closed ones are being affected by it.

Lack of adherence to long-term treatment leads to personal, social, health and economic issues, as it generates a greater risk to health (relapses, onset or worsening of symptoms, evolution to late or severe phases of the disease, adverse effects, and resistance to medication), lower quality of life and well-being; higher rates of stress, interference with lifestyle or alterations in performance areas of patients and their relatives, and greater probability of increasing the demand for hospital and pharmaceutical resources (41).

Table 1. Percentage distribution of sociodemographic, family, health and psychological variables evaluated in people living with HIV/AIDS by sex. Quindío, Colombia. 2015.

Characteristics		Men		Women		Total	
		n	%	n	%	n	%
Socioeconomic strata	0, 1 y 2	31	77.5	20	90.9	51	82.3
	3, 4 and 5	9	22.5	2	9.1	11	17.7
Religion	Believer (Catholicism, Protestantism)	36	81.8	22	84.6	58	82.9
	Non-believer/other	8	18.2	4	15.4	12	17.1
Education	Fifth grade	14	35	11	42.3	25	37.9
	Complete High school	17	42.5	12	46.2	29	43.9
	Professional or technical studies	9	22.5	3	11.5	12	18.2
Civil status	Married, domestic partnership, in a relationship	14	31.8	11	44	25	36.2
	Single	23	52.3	8	32	31	44.9
	Separated/Widowed	7	15.9	6	24	13	18.8
HIV diagnosis	≤2 years	19	44.2	7	28	26	38.2
	3-5 years	8	18.6	3	12	11	16.2
	6-10 years	9	20.9	6	24	15	22.1
	10-22 years	7	16.3	9	36	16	23.5
Support and understanding from relatives regarding treatment	Never/sometimes	4	9.1	4	15.4	8	11.4
	Many times/always	32	72.7	18	69.2	50	71.4
	They do not know about the diagnosis	8	18.2	4	15.4	12	17.2
Frequency of psychology counseling	Weekly or monthly	13	46.4	12	57.1	25	51
	Bimonthly, quarterly, other	15	53.6	9	42.9	24	49
Self-report on how treatment is followed	Excellent or good	28	75.7	18	72	46	74.2
	Fair, bad or terrible	9	24.3	7	28	16	25.8
Current consumption of psychoactive substances (cigarette, coca paste and/or marihuana)	Yes	17	38.6	4	15.4	21	30
	No	27	61.4	22	84.6	49	70
Adherence to treatment	No	26	65	14	35	40	57.1
	Yes	18	60	12	40	30	42.9
Depression	Absent/Mild	29	65.9	20	76.9	49	70
	Moderate/Severe	15	34.1	6	23.1	21	30
Anxiety	Minimal/Mild	30	68.2	20	76.9	50	71.4
	Moderate/Severe	14	31.8	6	23.1	20	28.6
Perceived social support	Low	37	84.1	17	65.4	54	77.1
	High	7	15.9	9	34.6	16	22.9

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

With this in mind, a public health problem is surfacing and demanding more attention, especially when it comes to low adherence to ART due to an increased probability of risk behaviors and possible reinfection and resistance to treatment, both in patients who have already been treated as in those who are just initiating a therapeutic regimen but have contracted a resistant virus (17,20). In addition, it causes a decrease in lymphocyte count and an increase in viral load, which facilitates the appearance of opportunistic diseases (21).

The findings in PLWHA from Quindío are not far removed from research in the field of adherence to treatment in Colombia, where Arrivillaga *et al.* (26) have indicated approximate figures (43%). In other countries, around 50% of patients with chronic diseases adhere, although this number can be between 37% and 83% in patients with HIV depending on the type of medication and population (42). Some studies show that about 50% of PLWHA fail to comply with medication intake and schedules, while 14% continue to maintain the risky behaviors that led them to become infected (17,43,44). It should be noted that adherence decreases as the complexity of the treatment increases, and that ART demands high compliance from the individual (more than 90-95%) to avoid resistance (21,45).

42.9% of patients in this study report being adherent. When comparing these results with other works, approximate figures can be found: in Spain reported adherence is 55% (45), in Venezuela 63.2% (46), and in Mexico between 31.9% (31), 57% (22), 65.6% (23) and 85.3%. This last indicator was not common when compared to most findings reporting a figure of about 50%, which may be explained by factors such as motivation and stress (19), particularly in Los Angeles, where the value reaches 63% (47).

However, differences with other studies were found: a study carried out in Madrid did not achieve strict therapeutic compliance not even in the third of the patients evaluated (20). In contrast, a longitudinal study in Italy reported a total of 81.4% of adherent patients (48). Comparative studies could help to reveal the contextual factors related to these differences.

Moreover, this research shows statistically significant differences that indicate greater adherence in those whose self-report is excellent when asked about the way they are following their treatment. However, despite the fact that 74.2% of PLWHA say that they have a good or excellent compliance with the treatment, only 42.9% adhered adequately according to the measurement instrument. The relevance of this aspect lies in the role of cognitive variables such as self-efficacy, locus of control, health beliefs, perception of vulnerability and treatment effectiveness in adherence behaviors (9-11), which require further research.

Similarly, there is a significant association between treatment adherence and depression. When depressive symptoms are absent or mild, the proportion of adherent and non-adherent patients does not differ. However, when these symptoms are moderate or severe, there is a significant difference, which indicates a greater probability of adherence among those with lower symptomatology. These findings coincide with reports in other countries such as Spain (20), Mexico (23) and Chile (49).

This situation is likely to be caused by the fact that HIV diagnosis and treatment generate distress (50), emotional alterations related to mourning due to the loss of health, and the assumption of a new role as a PLWHA, which can be more evident than in other diseases (e.g. cancer) (51). Likewise, patients may face discrimination and affective or economic losses given the social stigma that comes along with the disease, which in turn could generate alterations in their mood (12); furthermore, depressive symptoms may be a side effect of some transcriptase inhibitors (52,53).

Table 2. Association between sociodemographic, family, health and psychological variables, and adherence to treatment in people living with HIV/AIDS. Quindío, Colombia. 2015.

Characteristics		Adherence to treatment				p value	OR	95%CI	
		Yes		No					
		n	%	n	%			Lower	Upper
Sex	Men	18	40.9	26	59.1	-	1.000	-	-
	Women	12	46.2	14	53.8	0.669	1.238	0.466	3.291
Socioeconomic strata	0, 1 and 2	23	45.1	28	54.9	-	1.000	-	-
	3, 4 and 5	6	54.5	5	45.5	0.570	1.461	0.395	5.407
Religion	Believer (Catholicism, Protestantism)	22	37.9	36	62.1	-	1.000	-	-
	Non-believer/Other	8	66.7	4	33.3	0.077	3.273	0.881	12.156
Education	Fifth grade	10	40	15	60	-	1.000	-	-
	Complete High school	11	37.9	18	62.1	0.876	0.917	0.306	2.745
	Professional or technical studies	8	66.7	4	33.3	0.136	3.000	0.709	12.694
Civil status	Married, domestic partnership, in a relationship	13	52	12	48	0.430	1.733	0.443	6.789
	Single	11	35.5	20	64.5	0.851	0.880	0.231	3.353
	Separated/Widowed	5	38.5	8	61.5	-	1.000	-	-
HIV diagnosis	≤2 years	10	38.5	16	61.5	-	1.000	-	-
	3-5 years	5	45.5	6	54.5	0.692	1.333	0.320	5.548
	6-10 years	6	40	9	60	0.923	1.067	0.291	3.916
	10-22 years	8	50	8	50	0.464	1.600	0.454	5.634
Support and understanding from relatives regarding treatment	Never/sometimes	3	37.5	5	62.5	0.848	1.200	0.185	7.770
	Many times/always	23	46	27	54	0.430	1.704	0.454	6.396
	They do not know about the diagnosis	4	33.3	8	66.7	-	1.000	-	-
Frequency of psychology counseling	Weekly or monthly	11	44	14	56	-	1.000	-	-
	Bimonthly, quarterly, other	13	54.2	11	45.8	0.477	1.504	0.488	4.639
Self-report of how treatment is followed	Excellent or good	20	43.5	26	56.5	0.038 *	5.385	1.096	26.462
	Fair, bad or terrible	2	12.5	14	87.5	-	1.000	-	-
Current consumption of psychoactive substances (cigarette, coca paste and/or marihuana)	Yes	8	38.1	13	61.9	-	1.000	-	-
	No	22	44.9	27	55.1	0.599	1.324	0.466	3.766
Depression	Absent/Mild	25	51	24	49	0.040 *	3.333	1.056	10.525
	Moderate/Severe	5	23.8	16	76.2	-	1.000	-	-
Anxiety	Minimal/Mild	23	46	27	54	0.403	1.582	0.540	4.631
	Moderate/Severe	7	35	13	65	-		-	-
Perceived social support	Low	20	37	34	63	-	1.000	-	-
	High	10	62.5	6	37.5	0.077	2.833	0.894	8.975

* Statistically significant differences ($p<0.05$).
Source: Own elaboration based on the data obtained in the study.

The role of depression is fundamental to treatment, since negative thinking compromises the behavioral activity of those who present it at moderate and severe levels. Also, evidence shows that emotional states influence the functioning of the immune system and the evolution of HIV infection, particularly distress, depression and anxiety (18,44,54-56). The latter is identified in a higher proportion among non-adherents at moderate or severe levels, although no statistically significant differences have been observed.

Additionally, a higher proportion of adherence was found among those who scored higher in social support, even though no statistically significant differences were observed. This aspect has been studied extensively and is considered a factor that favors ART due to its buffering effect against stressful situations and depressive symptoms and, in general, its contribution to the process of adaptation to the new lifestyle.

There are many studies around the world that show social support as a protective factor related to adherence, well-being, perceived health and quality of life of PLWHA (18,29,31,57-59). This positive effect has also been confirmed in Colombia (7), where the search for professional support (6) and participation in support groups are also included (27). Similarly, the relationship between poor adherence to treatment, higher rates of emotional disturbances (distress and depression) and poor social support are clear (8,20,21,44); in spite of this, the fact that it can also become a source of conflict and stress must not be ignored (18).

In this particular sample, it is striking that when applying the MOS inventory, most participants perceived they were not socially supported, which is important for intervention in this context; however, when asked if they feel supported and understood by their relatives in relation to the treatment, most reported feeling it many times or always. This difference might suggest that, at first sight, although patients refer feeling supported, the way they receive such support is not perceived from an instrumental, affective, emotional or informational perspective in their daily lives, as the test indicates.

Further studies are required on what it means to provide and receive support, and to take a closer look at the different subtypes and their relationship to adherence. Likewise, it is important to delve into the role of social stigmatization, which can act to the detriment of seeking support, communicating the diagnosis, and deploying skills to obtain emotional and material support available in the surrounding environment.

Other results of this study indicate greater proportions of adherence in women (although not statistically significant), which requires more comparative research, and also among those who have higher levels of schooling and socioeconomic stratum, which is similar to the findings in other studies (26,60). Moreover, high adherence was also found in those who have a longer time of diagnosis, which positively interacts with the psychological variables that affect adherence (22), although its effects are inconclusive. In this regard, Levine *et al.* (47) observed that adherence seems to decline over time and Remor (20) identified greater adherence in patients with shorter infection times, since an increase in the probability of poor adherence when treatments involve several drugs for an indefinite period of time was observed. Finally, adherence was better in those who did not consume psychoactive substances, which is consistent with the literature presenting consumption as a problem in PLWHA (44,47). As for religion, studies are needed to elucidate its role as a coping strategy.

However, psychological and personal factors are not the only aspects implicated in adherence, since their effect may be influenced or mediated by aspects concerning the disease (symptoms and characteristics), treatment (secondary symptoms, therapeutic efficacy, doses, schedules, method of administration), the health system (characteristics of the system, barriers to medical care and accessibility to social and pharmaceutical services), the interaction of the patient with the health care team (relationship, communication, satisfaction, active involvement of staff and confidentiality) or social circumstances (educational level, social position, geographical and economic conditions, stigma and discrimination) (9,13,15,60-62). These aspects exceeded the objectives of this study, but the need for more research in this respect is emphasized to strengthen explanatory models.

In this sense, it is worth noting that research and work on adherence from a biopsychosocial perspective that considers all kinds of barriers and facilitators have a key role, so that people can exercise their duties and rights in health and follow their treatments adequately, particularly in developing countries (63). In Colombia, Arrivillaga *et al.* (26), Arrivillaga *et al.* (27), Arrivillaga *et al.* (28), and Arrivillaga *et al.* (62) report that the role of the health system, the socioeconomic position, gender role and other social aspects are some of the main obstacles to adherence to ART.

Finally, it is necessary to be cautious when interpreting the findings of this study due to the type and size of the sample and to the absence of validation measures in the Colombian population.

Conclusions

A high percentage of PLWHA did not report adequate adherence to ART (57.1%). A statistically significant association was found between adherence and depressive symptoms and self-assessment on the way treatment was followed. Low anxiety and high perception of social support did not represent statistically significant differences, but indicated higher proportions between adherents. The findings are related to global trends and some Colombian studies. There are no conclusive results on the association between diagnostic time, sociodemographic variables and adherence to treatment.

Research on this topic has not discriminated some physiological symptoms that are typical of the infection, and those provoked by mood disorders; in addition, knowing the mental health history of the patients influences manifestation and coping methods, and would require further research on mediating variables and moderators of the relationship between depression and adherence.

In conclusion, longitudinal and mixed studies are recommended, as well as model proposals that include the analysis of the role of social and health barriers in adherence. The validation of interdisciplinary intervention programs contextualized to each region is pertinent in order to give effective answers to this situation that compromises public health.

Conflict of interests

None stated by the authors.

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ORIGINAL RESEARCH

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Off-label use of psychotropic drugs beyond officially approved indications in Colombia

Uso de psicofármacos en indicaciones no aprobadas por la agencia regulatoria nacional de Colombia

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| Abstract |

Introduction: Off-label use of psychotropic drugs is a common practice. In Colombia, no information is available in this regard.

Objective: To describe off-label use of psychoactive drugs in a health promoting entity (EPS in Spanish) in Bogotá D.C.

Materials and methods: Cross sectional, observational study (prescription-indication), including a random sample of patients prescribed with psychotropic drugs between January and June 2010. Sociodemographic, clinical, pharmacological and concordance variables were evaluated (correlation between use indication and approved indication). Multivariate analyzes were performed looking for an association with off-label prescriptions.

Results: 420 evaluated patients had a mean age of 44.2±18.8 years, with female predominance (67.9%). Off-label prescription was found in 58.6-59.8% of cases. 84.3% of the prescriptions were delivered by general practitioners. The main psychoactive drugs prescribed for conditions such as tension headaches and insomnia were amitriptyline (n=128, 86.7% of off-label use), trazodone (n=93, 88.2%) and fluoxetine (n=66, 36.4%). The multivariate analysis found that being a young adult (OR=1.99, 95%CI: 1.06-3.70; p=0.030), being treated by general medicine (OR=3.40, 95%CI: 1.50-7.67; p=0.003) and being prescribed with amitriptyline (OR=11.38; 95%CI: 5.06-25.58; p<0.001) or trazodone (OR = 13.08; 95%CI: 5.23-32.68; p<0.001) increased the likelihood of receiving an off-label prescription.

Conclusions: Psychotropic drugs in Bogotá are used, to a great extent, as off-label in indications other than those officially approved. Thus, it is important to strengthen education and control to achieve a rational, effective and safe use of drugs.

Keywords: Off-Label Use; Psychotropic Drugs; Pharmacoepidemiology; Colombia (MeSH).

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| Resumen |

Introducción. El uso de psicofármacos por fuera de las indicaciones aprobadas (*off-label*) es una práctica común, de la cual no se tiene información en Colombia.

Objetivo. Describir el uso *off-label* de psicofármacos en una entidad promotora de salud de Bogotá D.C.

Materiales y métodos. Estudio observacional de prescripción-indicación con una muestra aleatoria de pacientes prescritos con psicofármacos entre enero y junio de 2010. Se evaluaron variables sociodemográficas, clínicas, farmacológicas y de concordancia y se realizaron análisis multivariados buscando asociación con prescripciones no aprobadas.

Resultados. Los 420 pacientes evaluados tenían una edad promedio de 44.2±18.8 años, con predominio femenino (67.9%). Se encontró prescripción no aprobada en 58.6-59.8% de los casos; el 84.3% de las formulas fueron hechas por medicina general. Los principales psicofármacos en indicaciones como cefalea tensional e insomnio fueron amitriptilina (n=128; 86.7% de uso no aprobado), trazodona (n=93; 88.2%) y fluoxetina (n=66; 36.4%). En el análisis multivariado se halló que ser un adulto joven (OR=1.99; IC95%: 1.06-3.70; p=0.030), ser tratado por medicina general (OR=3.40; IC95%: 1.50-7.67; p=0.003) y ser formulado con amitriptilina (OR=11.38; IC95%: 5.06-25.58;

p<0.001) o trazodona (OR=13.08; IC95%: 5.23-32.68; p<0.001) aumentan la probabilidad de recibir una prescripción no aprobada.

Conclusiones. En la aseguradora estudiada, los psicofármacos son utilizados en una importante proporción de indicaciones no aprobadas por las autoridades regulatorias, por lo cual es importante fortalecer la educación y el control para el empleo de los medicamentos de manera racional, efectiva y segura.

Palabras clave: Uso fuera de lo indicado; Psicotrópicos; Farmacoepidemiología; Colombia (DeCS).

Fletscher-Covaleda PM, López-Gutiérrez JJ, Machado-Duque M, Machado-Alba J. [Uso de psicofármacos en indicaciones no aprobadas por la agencia regulatoria nacional de Colombia]. Rev. Fac. Med. 2017;65(3):411-5. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.57439.

Introduction

Drugs used in medical practice are effective and safe in specific indications. This is achieved through a long and rigorous study process that provides information about the specific population that can be benefited, as well as the use and appropriate dose. However, off-label use of drugs is based on the ability or freedom of physicians who prescribe them beyond approved indications when a therapeutic alternative is required.

Recently, the consumption of psychoactive drugs has increased in Colombia, which is one of the drug groups with the highest proportion of non-approved use, particularly antidepressants, antipsychotics, anxiolytics and sedatives (2-7).

Use beyond approved indications is an issue, and there is no unanimity in this regard among regulatory agencies. In fact, many of them do not even have a clear position. The US Food and Drug Administration (FDA), for example, defines off- label as the "use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling" (8).

Formulations different from the approved indication, according to a systematic review by Carton *et al.* (9) based on studies conducted around the world, show that they represent 40-75% of the total prescriptions of psychotropic drugs, mainly for mood, anxiety, insomnia and agitation disorders. Quetiapine is revealed as the main drug used off-label, especially for anxiety and insomnia. The Colombian Food and Drug Surveillance Institute (Invima in Spanish) established through Act 38 of December 13, 2006 (10) that "off-label" is a use different from that officially authorized by Invima"; therefore, it refers to unauthorized use and is "only acceptable if supported by clinical studies properly conducted."

In Colombia, little information is known on the unauthorized use of medications, and there is no clear regulation on this issue. For this reason, the following prescription-indication study is presented (11) with the purpose of describing the use of psychoactive drugs beyond the guidelines approved by the regulatory agencies in a health promoting entity (EPS) of Bogota D.C. during the first half of 2010. It is also intended to suggest tools for the regulation and control of medications based on evidence of risk of adverse reactions, lack of effectiveness and inappropriate use of resources.

Materials and methods

Cross-sectional study in which prescription-indication information was collected retrospectively. The sample was obtained from the databases of drugs dispensed by Audifarma S.A. in an EPS of Bogota D.C., as well as from the medical records of the patients included.

From a universe of 16 912 patients prescribed with a psychotropic drug for at least one month between January and June 2010, a random sample of 385 patients was classified based on the drugs to be evaluated (expected prevalence: 50%, alpha level: 5%, power: 80%) using the statistical package SPSS v22. Additionally, subjects with lower consumption requirements of diazepam, modafinil and zolpidem who were not included at first considering the classification criteria, were included later in the study, and, therefore, considered as mandatory, which increased the final size of the sample to 420 individuals.

A list of patients was obtained based on the records of Audifarma S.A. These patients were given one or more of the following psychotropic drugs: valproic acid, alprazolam, amitriptyline, bromazepam, carbamazepine, chlorpromazine, clozapine, diazepam, divalproate, fluoxetine, gabapentin, haloperidol, lamotrigine, lithium, methylphenidate, midazolam, modafinil, olanzapine, oxcarbazepine, pregabalin, risperidone, sertraline, trazodone, venlafaxine and zolpidem. During the same period, a chemist reviewed the medical records to know the medical reason for the prescription. When the drugs with the highest amount of prescriptions were determined, a bibliographical search of the clinical and academic support was made for the different unapproved indications that were found (12).

For the study the following variables were taken into account, and were recorded in a Microsoft Excel database:

Sociodemographic: age (infants <14 years, adolescents 14-18 years, young adults 19-45 years, and adults >45 years) and sex.
Clinical: diagnosis and indication for prescription.
Pharmacological: name of prescribed medication, route of administration, posology, pharmaceutical form and specialty of the prescribing physician.
Concordance: correlation between the use indication of the psychoactive drug and the indication approved by Invima and FDA (indication, dose, route of administration, contraindications).

Finally, each prescription was classified as a) *off-label*: use other than the approved by the regulatory agency; b) *approved use*: use under approved conditions; c) *no report*: use is not specified in the medical record, and d) *not evaluable*: no information that supports the use of the psychoactive drug and impossibility to evaluate whether the prescription is appropriate or not (this option was only applied for mandatory inclusion drugs because of the impossibility of replacing the information).

This study met the specifications of the category "research without risk" according to Resolution 8430 of 1993 of the Ministry of Health of Colombia (13), which establishes the scientific, technical and administrative standards for health research. The principles of beneficence and confidentiality of patients were preserved as established by the Declaration of Helsinki.

Analysis plan

Data were analyzed using the statistical package SPSS Statistics version 22.0 for Windows (IBM, U.S.A). A description of frequencies and proportions was made for categorical variables, and central tendency and dispersion measures for continuous variables. Chi-square tests were used for comparing categorical variables, using a variable dependent on off-label use of a drug. Binary logistic regression models were used based on the prescription not

approved by Invima as a dependent variable (because it was of greater local interest), and $p<0.05$ was determined as the level of statistical significance.

Results

420 clinical histories of patients prescribed with psychoactive drugs in Bogotá D.C were evaluated. The mean age was 44.2±18.8, and distribution was obtained with a female predominance of 67.9%.

Table 1 shows the distribution by sex, age group, specialty of the prescribing physician and method of use, as well as the proportion of off-label use.

Table 1. Socio-demographic variables, prescribing physician and off-label indications of psychoactive drugs in patients affiliated with a health promoting entity. Bogotá D.C. 2010.

Variables		n=420	(%)	Off-label use proportion	
				Invima %	FDA %
Sex	Male	135	32.1	50.4	53.3
	Female	285	67.9	62.5	62.8
Age group	Infants (<14 years)	20	4.8	10.0	15.0
	Adolescents (14-18 years)	35	8.3	48.6	45.7
	Young adult (19-45 years)	179	42.6	69.8	70.9
	Adult (>45 years)	186	44.3	54.8	56.5
Prescribing physician	General practitioner	355	84.3	62.8	63.9
	Neurology	15	3.6	40.0	40.0
	Psychiatry	12	2.9	8.3	25.0
General results of use	Off-label use			58.6	59.8
	Approved use			31.0	29.8
	No report			7.4	7.4
	Not evaluable			3.1	3.1

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

It was not possible to describe the use of drugs by route of administration different from that recommended by the health agency, because 31.4% of prescriptions did not report this variable for each psychoactive drug.

Table 2 lists the seven most frequent formulations of psychotropic drugs, and details the proportion of off-label prescriptions and the diagnostic reasons for off-label use.

Bivariate analysis

When comparing the dependent variable "off-label prescription not approved by Invima", the variables *prescribing a psychoactive drug as a painkiller* and *being treated for headache with psychoactive drugs* were found to be the most likely reasons for off-label indications. However, other variables such as prescription of amitriptyline or trazodone, receiving psychotropic drugs for migraine, being a young adult, and being formulated by general practitioners increased the probability of off-label prescriptions. Interestingly, the total number of patients treated for pain management (p=0.0001) and insomnia (p=0.0001) with psychotropic drugs were prescribed with drugs based on off-label indications.

It was also found that *the use of psychoactive drugs for the treatment of epilepsy* and *being treated by psychiatry* were the variables that further reduced the risk of unapproved use, although, prescription with fluoxetine or carbamazepine, depression and schizophrenia, being male and being an infant were associated with a lower probability of using psychoactive drugs with an off-label indication.

Table 3 presents the associated variables in relation to the decrease or increase of the risk of prescribing off-label indications of drugs.

Table 2. Psychopharmaceuticals most commonly used in off-label indications in patients affiliated with a health promoting entity. Bogotá D.C. 2010.

Drug	n	Invima %	Main off-label indications	FDA %	Main off-label indications
Amitriptyline	128	86.7	Tension headache	87.5	Tension headache
			Insomnia		Insomnia
Trazodone	93	88.2	Tension headache	88.2	Tension headache
			Insomnia		Insomnia
Fluoxetine	66	36.4	Other anxiety disorders	36.4	Other anxiety disorders
			Migraine without aura		Migraine without aura
Carbamazepine	30	13.3	Sleep disorders	16.7	Sleep disorders
			Myalgia		Myalgia
Valproic acid	28	3.6	Schizophrenia	3.6	Schizophrenia
Diazepam	23	43.5	Essential tremor	39.1	Essential tremor
			Myoclonus		Benign paroxysmal vertigo
Zolpidem	11	9.1	Depressive episode	9.1	Depressive episode

Invima: Food and Drug Surveillance Institute; FDA: Food and Drug Administration.
Source: Own elaboration based on data obtained in the study.

Table 3. Bivariate analysis of the variables associated with off-label prescription of psychotropic drugs in patients affiliated with a health promoting entity. Bogotá D.C. 2010.

Associated variable		OR	95%CI	p
Protective factors of use in approved indication	Being treated by psychiatry	0.06	0.08-0.47	<0.001
	Treatment with fluoxetine	0.34	0.19-0.58	<0.001
	Treatment with carbamazepine	0.12	0.04-0.33	<0.001
	Being used for epilepsy	0.02	0.006-0.09	<0.001
	Being used for depression	0.22	0.13-0.38	<0.001
	Being used for schizophrenia	0.22	0.13-0.38	<0.001
Risk factors of use in approved indication	Treatment with amitriptyline	7.59	4.33-13.29	<0.001
	Treatment with trazodone	7.40	3.80-14.41	<0.001
	Being used as a painkiller	41.9	5.72-307.04	<0.001
	Being used for headaches	23.6	5.67-98.36	<0.001
	Being used for migraine	6.44	1.91-21.71	0.001
	Adult (19-45 years)	2.29	1.52-3.44	<0.001
	Being treated by a general practitioner	3.08	1.77-5.35	<0.001

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

Multivariate analysis

By including the associated variables in a statistically significant manner, a binary logistic regression was performed. It is presented in Table 4, with the variables that were statistically associated with a higher risk of off-label prescriptions according to the approval of Invima.

Table 4. Multivariate analysis of the variables associated with off-label prescription of psychotropic drugs in patients affiliated with a health promoting entity. Bogotá D.C. 2010.

Variables	B	SE	Wald	DF	Sig	OR	95%CI	
							Lower	Higher
Young adult	0.688	0.317	4.717	1.000	0.030	1.990	1.069	3.703
Being treated by a general practitioner	1.224	0.415	8.682	1.000	0.003	3.401	1.507	7.677
Treatment with amitriptyline	2.432	0.413	34.611	1.000	<0.001	11.380	5.062	25.585
Treatment with trazodone	2.571	0.467	30.276	1.000	<0.001	13.080	5.234	32.685
Headache	2.057	0.851	5.848	1.000	0.016	7.823	1.477	41.446
Epilepsy	-2.720	0.829	10.765	1.000	0.001	0.066	0.013	0.334
Depression	-1.743	0.383	20.674	1.000	<0.001	0.175	0.083	0.371

B: Regression coefficient; SE: standard error; DF: degree of freedom; Sig: level of significance.
Source: Own elaboration based on data obtained in the study.

Discussion

This study served to identify the most common use of psychoactive drugs used beyond the approval of regulatory agencies and the FDA, as well as the diagnostic reasons, the prescriptive specialty and the variables associated with this practice in an EPS of Bogotá D.C. This contribution is the first approach to information regarding the unapproved use of psychotropic drugs in Colombia.

The proportion of psychoactive drugs found in this study (58.6%), especially antidepressants in non-approved indications, is within the range published by other authors such as Kharadi *et al.* (14) (39.5%, predominantly benzodiazepines), Leslie *et al.* (7) (60.2%) and Chen *et al.* (15) (75.4% predominantly antidepressants).

As presented in the systematic review of Carton *et al.* (9), off-label prescriptions correspond to 40-75% of total prescriptions of psychotropic drugs worldwide according to the reviewed studies, which coincides with the data presented in this study. In this review, the most frequent uses of off-label medications are mood, anxiety and insomnia disorders. However, this research showed that they were almost always used for the management of tension headache and insomnia, being amitriptyline and trazodone the most used drugs, compared with quetiapine as the main drug in this systematic review (9). These differences may be explained by the access to medicines in the Colombian health system, where the prescription of many of these psychotropic drugs is restricted, although amitriptyline and trazodone are over-the-counter.

Off-label drug use may be justified in cases that require therapeutic alternatives, for example, in population groups with few investigations such as infants or pregnant women (1). However, statistical analyzes show that these prescriptions were more frequent in young adults, which may be related to the lack of knowledge by the general practitioner of the indications authorized for the drugs, the population that uses these type of drugs, and those easily related to diagnoses with other approved alternatives (1,2,8).

This scenario leads to reflect on whether the physician, when prescribing, makes an appropriate analysis of the risk-benefit balance based on available clinical evidence and on the Invima guidelines that establish that unauthorized use is acceptable only if it is supported by adequate clinical studies (10).

Amitriptyline and trazodone were frequently prescribed off-label to treat tension headache and insomnia. Regarding amitriptyline, some studies have reported its effectiveness in these two indications (14-17); however, regulatory agencies still do not approve these uses. Something similar occurs with trazodone when indicated to treat sleep disorders. Some reports show good results, but it has not been approved for it yet.

This situation creates a gap between the clinical practice guidelines that include it, and the surveillance and regulation measures that have not been updated. As a consequence, the responsibility of prescribing falls directly on physicians without the support of the drug regulatory agencies (17,18).

Amitriptyline, trazodone, fluoxetine, carbamazepine and valproic acid are less likely to be used without following the guidelines in patients with depression or epilepsy, but may increase the likelihood of unapproved use in different indications, although they may be effective (16,18).

Given the results presented in this paper, questions are raised about the relevance of unapproved prescriptions, since the panorama of off-label drug use does not offer conclusive answers. Perhaps, the best approach to a more rational use of drugs is based on the availability of resources —drugs and other technologies—, the robustness and availability of scientific evidence, the expertise of the physician, and the competence of the surveillance authorities (1).

Therefore, the efforts of all health professionals, regulatory agencies and the pharmaceutical industry should be focused on working together to ensure patient safety, the collection of scientific evidence and an informed prescription. This translates into a more rational use of drugs (16,17).

One of the limitations of this work is its results, which were obtained from a single health promoting institution and can be extrapolated to populations with similar characteristics. In addition, the information was collected from the clinical records and the drug dispensing database, but not through interviews with physicians who are the actual decision makers and are responsible of selecting the

most appropriate therapy for their patients. However, the rigor of data collection allows us approach the reality of the use of psychoactive drugs in indications not authorized by regulatory agencies.

In conclusion, psychoactive drugs, especially antidepressants and antiepileptics, are used in this cohort of patients in a high proportion in indications not approved by regulatory agencies such as Invima and FDA, and were mostly prescribed by general practitioners for treating headaches and insomnia. It is important to strengthen information and continuing education programs, as well as relevant updates of health records of some psychotropic drugs with precise indications that already have sufficient evidence. Similarly, surveillance and control strategies should be developed for these drugs or included in pharmacovigilance programs by regulatory agencies when their uses may compromise patient safety in order to minimize the risks related to incomplete or inadequate information that may lead to increased off-label use of medications (18).

Conflict of interest

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Iván "Ivanquio" Benavides
"El niño vacío" – 001
Técnica: tinta, color digital

ORIGINAL RESEARCH

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Clinical features of brain activation deficit in children

Características clínicas de niños con déficit de activación cerebral general

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| Abstract |

Introduction: Brain activation is considered as one of the mechanisms of the brain related to the functional state of deep subcortical structures. A deficit in this mechanism may be involved in behavioral disorders during development and school learning.

Objective: To identify the clinical features of Mexican schoolchildren with general brain activation deficit, and to determine the neuropsychological tasks that help to detect this syndrome.

Materials and methods: The sample included 20 Mexican schoolchildren attending regular schools and diagnosed with behavioral and/or learning disorders. The types of errors and performance in neuropsychological tasks were analyzed by categories.

Results: The results showed that there are common clinical features in schoolchildren, particularly, executive instability, fatigue and/or slow execution, and instability in memory and perceptive graphic tasks. These features can be demonstrated through the qualitative syndromic analysis of perceptive graphic tasks, retention tasks and manual praxis.

Conclusions: Qualitative assessment is effective to differentiate this type of cases from other possible neuropsychological conditions.

Keywords: Neuropsychology; Evaluation; Diagnosis (MeSH).

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| Resumen |

Introducción. La activación cerebral general se considera como un mecanismo de trabajo cerebral relacionado con el estado funcional de las estructuras subcorticales profundas; su déficit puede subyacer a los trastornos conductuales durante el desarrollo y el aprendizaje escolar.

Objetivos. Precisar las características clínicas de escolares mexicanos con déficit de activación cerebral general e identificar las tareas neuropsicológicas que ayudan a la detección de este síndrome.

Materiales y métodos. Se incluyeron 20 casos de escolares mexicanos: alumnos de escuelas regulares con problemas de conducta o aprendizaje que solicitaron apoyo de evaluación neuropsicológica. Se analizaron los tipos de error y la forma de ejecución de tareas neuropsicológicas por categorías.

Resultados. Se demostró que existen características clínicas comunes en los escolares evaluados. Como rasgos particulares se identificó inestabilidad en la ejecución de tareas neuropsicológicas, fatiga o lentificación e inestabilidad en el mantenimiento de huellas mnésicas y durante la realización de tareas gráfico-perceptivas. Estos rasgos se evidenciaron a través del análisis sindrómico cualitativo en tareas gráfico-perceptivas, de retención en diversas modalidades y de praxias manuales.

Conclusión. Se encontró eficacia clínica de diferenciación en este tipo de casos frente a otras posibles dificultades a nivel neuropsicológico.

Palabras clave: Neuropsicología; Evaluación; Diagnóstico (DeCS).

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Introduction

According to Luria (1), the brain has three functional blocks, one of which is related to subcortical regulation levels. The author named this unit first functional block of the brain.

From a structural point of view of the first functional block, most of them are nuclei of the reticular formation located in the central part of the brainstem and in diverse parts of the thalamus (2). These nuclei have ascending and descending connections that are in charge of regulating the cortical tone, sleep and consciousness states, orientation reflex, stability, and the course of the mental processes. The literature shows that these structures are related to emotional, vegetative and mnesic regulation (3), and several opinions about their correlation with cognitive functioning can be found (4). The projections of the ascending reticular system reach non-specific nuclei in the thalamus, from where projections

are sent to the cortex (2) to activate it and regulate the status of its activity.

As stated by Luria (1), the contribution of the first functional block is fundamental for maintaining the cortical tone necessary for performing any type of cognitive activity. This takes on a particular meaning in school age, when children invest most of their time in cognitive tasks that require executive stability, continuous attention and active stay during tasks. Thus, without a specific modal influence, the first functional block makes an uncertain but fundamental contribution to successful accomplishment of this type of tasks.

Accordingly, it is useful to consider deep subcortical structures as one of the fundamental neuropsychological factors involved in cognitive task performance at school age, which can be called general nonspecific activation factor (5). This factor is implicated in cortical energy activation and in general regulation of all mental processes (1); its functional weakness generates instability in the execution of cognitive actions. Such instability can be increased or expressed more clearly in fatigue states, loss of motivation, or increased complexity for executing an action (5).

Deep subcortical structures are particularly sensitive to adverse conditions in the perinatal and postnatal period. A deficient functional status of subcortical regulation levels is considered part of almost all immature syndromes or disorders in higher mental functions (6), preventing the nervous system from maintaining an adequate alert level and causing a general failure in information processing required to perform cognitive tasks (7).

At the neurophysiological level, several investigations have performed a qualitative analysis of electroencephalographic records in preschoolers (8-10) and schoolchildren (11-14) diagnosed with attention deficit hyperactivity disorder (ADHD) or learning problems (15-19). These works have identified a immaturity state in the non-specific activation system (20,21), which is especially relevant since attentional processes fundamentally depend on the reticular formation (22). In the field of qualitative neuropsychology, several clinical studies have been carried out to identify behavioral and cognitive traits in children with these deficits; from this perspective, a neuropsychologist can identify the altered factor to understand the syndrome and provide tools for its reorganization (23-26).

Studies on preschool children diagnosed with ADHD have established that the functional weakness of the general nonspecific activation factor is one of the responsible factors. Typical errors and difficulties are related to fatigue, latency, short latencies to initiate an activity, difficulties in motor coordination activities, and executive instability in the presence of micrographs and macrographs (8,10). At school age, trace interruption, task abandonment, weak tracing and simplification have also been found (13,14). Difficulties in concentration and disturbances in attention have been described; in addition, greater fatigue caused by hyperactivity has also been observed as a compensation for the lack of stimulation of the central nervous system (6,27).

Furthermore, difficulties to evoke verbal and visual information of material semantically unrelated have also been observed in 7- and 8-year-old schoolchildren with immaturity in the nonspecific regulation system (20). The same observations have been made in the neuropsychological clinic of adults with brain lesions in deep subcortical structures (28-30). In this regard, Glozman (6) reports that the acquired information is unstable or inhibited by the interference of various influences, especially homogeneous influences, even with sufficient memory capacity.

The deficit of this neuropsychological factor can alter the performance in tasks and activities assigned during school learning, manifesting fatigue states before the complexity or duration of an activity increase (6). However, it is still necessary to systematize behavioral and cognitive clinical evidence that may help to define the presence of non-specific brain activation in cases of students with behavioral and learning problems. In particular, there are few data on these difficulties in school age, which makes the work of specialists difficult and does not allow differentiating these cases from those with a predominance of regulation and control problems. Meanwhile, none of the neuropsychological factors mentioned above can be identified in cases with an ADHD diagnosis, which makes differential neuropsychological diagnosis difficult, as well as decision making on treatment.

The objectives of this study are to characterize the clinical performance of schoolchildren with learning or behavioral problems who present deficits in the nonspecific brain activation factor, and to identify the neuropsychological tasks that help detecting this syndrome.

Materials and methods

Subjects

Twenty records of schoolchildren between 6 and 12 years of age were selected out of 105 patients attended due to learning or behavior problems in the neuropsychology unit of the university hospital of Universidad Autónoma de Puebla, México, in the period 2012-2015. Similar clinical features were identified in the selected cases, which allowed diagnosing functional deficit of nonspecific cerebral activation.

Out of 20 cases analyzed, 18 corresponded to males and six had been previously diagnosed with ADHD. The mean age was 8, and problems in school learning or behavior were the main cause for consultation. All children were public school students in Puebla.

None of the selected cases was related to pathological history (trauma or brain tumor) or to the presence of primary hearing impairment, vision or motor problems.

Material

All the participants were given the qualitative neuropsychological evaluation protocols “Puebla-Sevilla Child Neuropsychological Evaluation” (31) and “Verification of School Success in Primary School” (32). For data analysis, the tasks of both protocols were systematized by categories: graphic-perceptive, retention in different modality, manual coordination and intellectual tasks (Table 1).

Procedure

The types of error observed were recorded per subject, as well as the characteristics and difficulties found by the evaluator at the time of the assessment.

For the qualitative analysis, the responses were recorded and the most frequent types of errors and executions were characterized in the neuropsychological evaluation tasks. In addition, a comparison between tasks that showed typical errors and those that did not show any error was made. The tasks were classified in verbal, graphic-perceptive, retention, motor coordination and intellectual tasks. For the quantitative analysis, the types of errors and the most frequent execution characteristics were determined in the whole sample and in the different tasks of neuropsychological evaluation.

Table 1. Neuropsychological and intellectual tasks analyzed.

Category	Tasks in the "Puebla-Sevilla" neuropsychological evaluation protocol
Verbal	Repetition of syllables, sounds and word pairs
Graphic-perceptive	Free animal drawing Copy of a house Copy and continuation of a graphic sequence
	Visual Retention
Retention in different modality	Reproduction of letters and figures and their evocation after homogeneous interference Reproduction of free animal drawing
	Auditory-verbal retention
	Involuntary/voluntary retention of two sets of three words and recalling them after heterogeneous interference Repetition of sentences
	Kinesthetic integration
	Reproduction and evocation of finger positions on the opposite hand
Manual coordination	Reciprocal coordination of hands Sequence of manual movements Swapping finger positions
Category	**Tasks of the "Verification of success in primary school" protocol**
Intellectual tasks	Writing
	Copy and dictation of sentences Independent writing
	Lecture
	Reading sentences and short texts
	Calculus
	Solving arithmetic problems

Source: Own elaboration based on Solovieva *et al.* (31) and Solovieva & Quintanar (32).

Results

A qualitative analysis of the clinical manifestations in neuropsychological tasks was performed. Table 2 shows the types of errors and the most common execution characteristics identified during the accomplishment of the tasks in each category.

The different neuropsychological tasks provided interesting data. First, perceptual graphs showed types of errors such as micrographs, macrographs and loss of horizontality that were also evident in writing. Retention tasks showed difficulties to retain visual and auditory-visual information. Manual coordination tasks showed poor fluency in the movements; however, in some cases, the help of the evaluator was important to fulfill the task with better fluency. Finally, the execution of the students' verbal tasks improved when the evaluator repeated the information, even in the presence of phonemic substitutions.

Figure 1 presents some examples of the most common error types identified in perceptual graphic tasks.

Table 2. Summary of the types of errors and execution in neuropsychological tasks.

Category	Type of error	Characteristics of execution
Verbal	Phonemic substitution	Correct execution or error overcome with the help of the evaluator Impossibility even with help Help: repetition of the series by the evaluator
Graphic-perceptive	Micrographs/macrographs Instability or interruption in trace Loss of horizontality Lack of characteristic traits	Slowing down Latency
Retention in different modality	**Visual retention**	
	Loss of elements Micrographs/macrography Recovery of disorder elements Lack of characteristic traits Trace instability	Slowing down Latency
	Auditory-visual retention	
	Phonemic or semantic substitution Partial loss of elements Total loss of elements Recovery of disorder elements	Correct execution Latency Help: repetition of the sentence to improve execution
	Kinesthetic retention	
	Impossibility to perform the posture	Correct execution with or without active search for posture Impossibility to perform the posture even with active search
Manual coordination	Poor fluency or impossibility even with the help of the evaluator	Correct execution Auto-correction or error overcome with the help of the evaluator Help: verbal regulation "I close the right hand and I open the left one" and slow execution of the movements

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

Intellectual tasks included writing, reading and calculation. The qualitative analysis established types of errors such as substitution or omission in writing and reading tasks that arose after feeling fatigue, and improvement in the execution with the aid of the evaluator (Table 3). In addition, about 50% of the sample did not consolidate literacy and calculation processes.

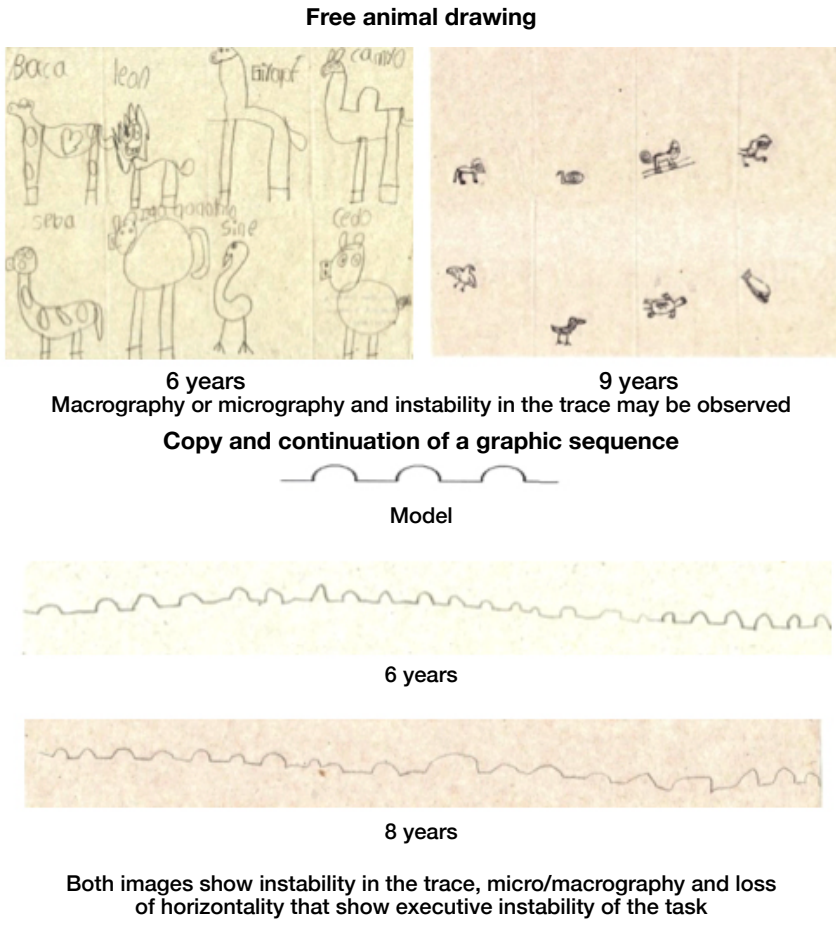


Figure 1. Examples of common error types in perceptual graphic tasks.
Source: Own elaboration based on the data obtained in the study.

Table 3. Summary of the types of errors and execution in intellectual tasks.

Category	Types of error	Execution characteristics
Intellectual tasks	**Writing**	
	Loss of horizontality Omission/substitution Micro/macrography Instability in trace	Unbound process Latency/slowing down Help: repetition of the sentence at dictation
	Reading	
	Substitution/omission	Unbound process Poor fluency
	Calculus	
	Rotation of a number	Unbound process Correction with the help of the evaluator Help: the operation is repeated Difficulties when the task becomes more complex

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

Figure 2 presents examples of the writing task and the most representative error types in schoolchildren of different ages.

For the clinical characterization, the most frequent types of error and execution were identified in all sample individuals, which allowed obtaining a deficiency table of non-specific cerebral activation in Mexican schoolchildren. Table 4 shows the frequency of the types of error committed in the different neuropsychological tasks.

In general, qualitative characteristics were observed during the execution of the proposed tasks. In most cases, children accepted the help provided by the evaluator to improve task execution; sometimes they requested help in order to repeat the instruction or to perform the task. A slow performance was observed during task execution, as well as distraction to various stimuli, restlessness or fatigue.

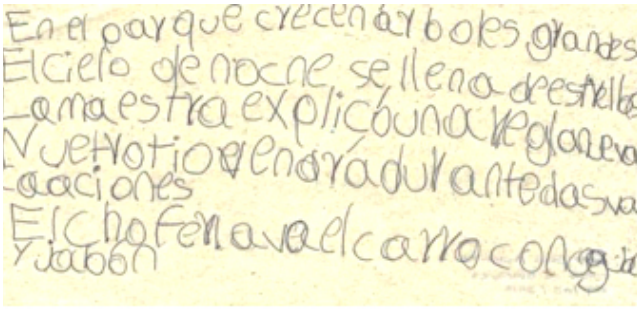
Furthermore, 10 types of errors were identified in more than 50% of the sample, mostly related to visual and auditory-verbal retention tasks, as well as graphic-perceptive, manual, verbal, reading and writing coordination tasks (Table 4).

It is important to specify that each child of the sample always presented more than one type of error in the tasks. For example, it was possible to see micrographs/macrographs in graphic tasks and instability in the trace (Figure 1).

Discussion

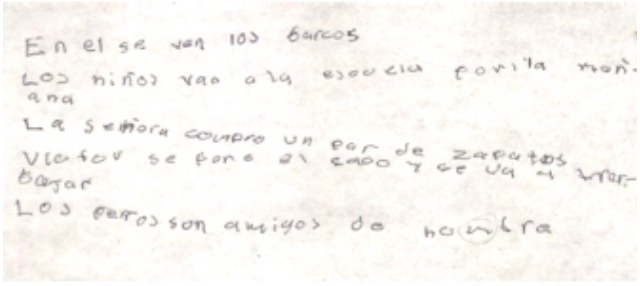
According to Fishman (33), several causes that affect the brain in the prenatal or postnatal period may delay the maturation of brain structures and their connections, which are manifested through the discordance between the social demands on the activity and the neurophysiological possibility to guarantee an adequate level of nonspecific regulation (10). In these cases, difficulties in development and school learning can be expected, based on the non-optimal functional state of the first brain unit according to Luria's conception (1,34).

Typing based on another text



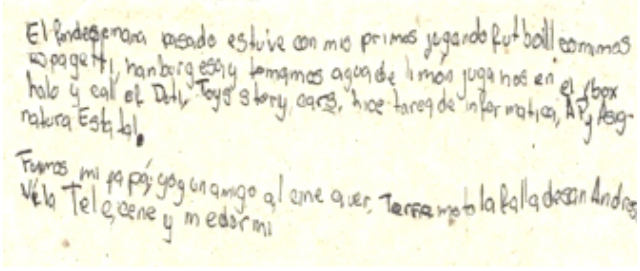
6 years
Macrographs, block writing, and spelling errors

Dictation



7 years
Loss of horizontality and omissions

Independent writing



12 years
Loss of horizontality, instability in the trace and block writing

Figure 2. Examples of the most common types of typing errors.
Source: Own elaboration based on the data obtained in the study.

The results showed that there are common clinical features in schoolchildren with functional deficits in the nonspecific brain activation factor during neuropsychological assessment, regardless of the initial reason for consultation (learning or behavior problems). Moreover, it was possible to identify sensitive tasks that help detecting this syndrome during the neuropsychological assessment based on instability, fatigue or latency during the assessment, as well as to differentiate these features from other types of errors related to functional weakness of other neuropsychological factors. In this work, such tasks were graphic-perceptive, retention in visual and auditory-verbal modality, manual coordination and writing.

The absence of these tasks in common psychometric evaluation protocols or quantitative cutoff tests, as well as the inability of specialists to detect the corresponding errors and differentiate them from other types of errors, makes it difficult to identify the state of nonspecific cerebral activation. These difficulties may be unnoticed or mistaken with problems in regulation and control factors, while ADHD (35,36) or problems in executive functions (25) may be suspected from traditional diagnosis.

Table 4. Most frequent types of error and execution in the sample throughout the neuropsychological evaluation.

Tasks	Types of error	Frequency (cases)
General characteristic during evaluation	Accepting adult support	17
	Slowing down	15
	Requiring repetition by the evaluator	13
	Distraction to various stimuli/ restlessness	13
	Fatigue	11
Graphic-perceptive	Instability in trace	19
	Micro/macrographs	19
Auditory-verbal retention	Loss of elements in at least one mode	20
Visual retention	Loss of elements	19
Graphic sequence	Trace interruption	18
Graphic sequence and writing	Loss of horizontality	18
Verbal tasks, reading and repetition of sentences	Phonetic or semantic substitutions after fatigue	18
Writing	Slight substitutions and omissions in some of the writing tasks	15
Manual coordination	Poor fluidity in movements	11
Drawing animals	Lack of characteristic traits found in children between 6 and 8 years of age as they draw	10

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

Data indicate latency and fatigue as the main characteristics, both in children with a previous ADHD diagnosis (13,14) and in cases in which a formal diagnosis is missing, only mentioning learning or behavior problems. Distraction before various stimuli and restlessness in the presence of fatigue was identified as a behavioral characteristic. In the literature, these behavioral characteristics are included under the term "hyperactivity" (35,36). In addition, it was observed that children accept the help of adults to improve their performance, as opposed to cases with primary affectation of other brain mechanisms in which the external assistance is not effective (9).

Results showed that executive instability during the evaluation allowed identifying insufficiency of the activation tone of the cerebral work. Therefore, in graphic-perceptive tasks, there is instability in the trace, as well as micrographs and macrographs. These types of errors have been identified in preschoolers and school children with ADHD in which functional weakness underlies the non-specific activation factor (8-10,13,14). Furthermore, Machinskaya & Semenova (20) identified difficulties in visual and auditory-verbal retention in schoolchildren aged between 7 and 8 years. These difficulties were related to information evocation without finding variability with age, which implies instability before the deficit (6).

It is important to note that results indicated that almost 50% of the children did not consolidate school skills, which may be related to the use of pedagogical strategies in primary school in general. At the same time, it can be assumed that the lack of nonspecific activation prevents evaluated children from properly consolidating

school habits, turning them into children who manifest learning problems. The qualitative analysis of the types of errors presented by students allowed to identify phonemic substitutions that appeared due to tiredness during reading tasks (18 cases), as well as loss of horizontality and, sometimes, substitutions and omissions of consonants in writing tasks (15 cases). These characteristics imply that the deficit of this neuropsychological factor prevents adequate performance and the acquisition of the required abilities for literacy.

These data coincide with the latest publications that point out the need to consider the functionality of the first brain block during the neuropsychological evaluation and the presence of particular characteristics in the school activity, as well as the evidences during the neuropsychological evaluation. Future studies dedicated to the detailed analysis of errors in the literacy process will allow clarifying the errors related to the use of pedagogical strategies and cerebral functional weakness during the neuropsychological evaluation (37).

The obtained results may indicate a way for identifying difficulties related to the functional deficit of the first brain block, which has not been a frequent topic in neuropsychology so far. The possibility of correlating neuropsychological assessment data with electroencephalographic recordings can provide valuable information about the involvement of subcortical regulation levels at school age (38).

It is worth noting that qualitative neuropsychological evaluation and syndromic analysis allow the detection of objective clinical features. The first is a very useful tool for differential diagnosis and for the treatment of cases with learning problems and difficulties in development.

Conclusions

Qualitative neuropsychological assessment in Mexican schoolchildren provided relevant information for the detection of nonspecific cerebral activation syndrome. The syndrome was characterized by instability in the performance of neuropsychological tasks, fatigue, latency or short latencies at the beginning of an activity. Typical errors included micrographs/macrographs, loss of horizontality and instability in traces during graphical tasks, poor fluidity of the movements during motor tasks, as well as instability in the maintenance of the mnesic traces in visual and auditory-verbal retention tasks. The data obtained can be useful to generate intervention strategies and neuropsychological correction of children with this neuropsychological syndrome.

Conflict of interests

None declared by the authors.

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Iván "Ivanquio" Benavides
"El niño vacío" – 002
Técnica: tinta, color digital

ORIGINAL RESEARCH

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Prevalence and variables associated with pediculosis capitis in kindergarten children from Popayán, Colombia

Prevalencia y variables asociadas a la pediculosis capitis en un hogar infantil de Popayán, Colombia

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| Abstract |

Introduction: *Pediculosis capitis* is a skin disease that affects the hair and scalp, and is caused by the *Pediculus humanus capitis* ectoparasite. High levels of infestation are reported worldwide, affecting especially children.

Objectives: To determine the prevalence and the variables that are associated with *pediculosis capitis* in kindergarten children in Popayán, Colombia.

Materials and methods: Cross-sectional descriptive study based on a sample of 148 children aged between 1 and 5 years of age. Only the head was examined. Nits, nymphs and adult lice were mechanically removed using lice combs and wetting the hair, covering the frontotemporal, parietooccipital, mastoid and nuchal regions. An informed consent and a structured survey were filled out by each parent or guardian.

Results: The prevalence of *pediculosis capitis* in the studied population was 11.5%. The variables associated with ectoparasitosis were female sex, long hair (>3 cm) and scalp pruritus.

Conclusions: *Pediculosis capitis* is present and perpetuated in children from Popayán. Promotion, prevention and pediculicide treatment campaigns are strongly recommended.

Keywords: Pediculosis; Lice; Children; Prevalence (MeSH).

López-Valencia D, Medina-Ortega A, Vásquez-Arteaga LR. Prevalence and variables associated with pediculosis capitis in kindergarten children from Popayán, Colombia. Rev. Fac. Med. 2017;65(3):425-8. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.58812.

| Resumen |

Introducción. La pediculosis capitis es una dermatosis que afecta el pelo y el cuero cabelludo; esta es causada por el ectoparásito *Pediculus humanus capitis*. La infestación presenta una distribución mundial y en su mayoría afecta a la población infantil.

Objetivos. Determinar la prevalencia y las variables asociadas a la pediculosis capitis en un hogar infantil de Popayán, Colombia.

Materiales y métodos. Estudio descriptivo de corte transversal. La muestra estuvo compuesta por 148 niños entre 1 y 5 años. Solo se examinó la cabeza y se realizó la remoción mecánica de liendres, ninfas y piojos adultos por medio de peines liendrera con el pelo húmedo siguiendo las áreas frontotemporal, parietooccipital, región mastoidea y nuca. Cada padre de familia o tutor a cargo diligenció un consentimiento informado y respondió una encuesta estructurada.

Resultados. La prevalencia de *pediculosis capitis* en la población infantil estudiada fue del 11.5%. Las variables asociadas a la ectoparasitosis fueron sexo femenino, pelo largo (>3cm) y prurito del cuero cabelludo.

Conclusiones. La *pediculosis capitis* está presente y se perpetúa en niños de Popayán. Se recomienda realizar campañas de promoción, prevención y desparasitación.

Palabras clave: Pediculosis; Piojos; Niños; Prevalencia (DeCS).

López-Valencia D, Medina-Ortega A, Vásquez-Arteaga LR. [Prevalencia y variables asociadas a la pediculosis capitis en un hogar infantil de Popayán, Colombia]. Rev. Fac. Med. 2017;65(3):425-8. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.58812.

Introduction

Pediculosis capitis is the most prevalent ectoparasitosis worldwide. Most cases are found in children between 3 and 11 years of age, more frequently among women than in men (1,2). This infestation is caused by the hematophagous insect *Pediculus humanus capitis* (known as head louse), order *Phthiraptera*, suborder *Anoplura* and family *Pediculidae*. The life cycle of this insect depends entirely on humans, since it is adapted to humidity and temperature conditions found in the scalp, on which it feeds (3-5). Based on a phylogenetic analysis, lice are classified according to four mitochondrial genotypes:

clades A (subclades A1 and A2), B, C and D, each with a different geographic distribution (6,7).

Currently, *P. capitis* is considered as a vector of infectious agents such as *Rickettsia prowazekii* (typhus epidemic), *Bartonella quintana* (trench fever), *Borrelia recurrentis* (recurrent epidemic fever), *Yersinia pestis* (plague) and *Acinetobacter baumannii* (7,8). Likewise, complications such as allergies, severe anemia (9) and superinfections (10) have been reported in infested individuals, while resistance to pediculicides has been documented in several regions around the world (11,12). For these reasons, this ectoparasitosis prevails in the population, harming school performance in those affected, and generating anguish within the family and the community.

In Colombia, little is known about the clinical and epidemiological profiles of *pediculosis capitis* for each region. However, two studies conducted in the Cauca Department (13,14), which are more than ten years old, show the magnitude and characteristics of this phenomenon. In consequence, knowing the prevalence and the variables that are associated with lice infestation in the population from this region is highly convenient.

Materials and methods

This was a cross-sectional study including 200 students enrolled in the institution Los Hoyos, attached to the Colombian Family Welfare Institute (ICBF by its acronym in Spanish), in Popayán, Colombia. A specific sample of 148 students aged between 1 and 5 years was obtained (mean: 3.12 years, standard deviation: 1.056, male sex: 55.4%, female sex: 44.6%). Popayán is the capital of the Cauca department, located at 1 735 meters above sea level, with an average temperature of 19°C, temperate climate and average humidity of 77.75% (15).

Inclusion criteria comprised children aged 1-5 years enrolled in the institution. Individuals who were absent from the kindergarten during the observation and sample collection period were excluded. The bioethical endorsement for this project was granted by the ethics committee of the vice-rector's office of Universidad del Cauca.

Ectoparasitological diagnosis

Only the head was examined by combing the wet hair, covering the frontotemporal, parietooccipital, mastoid and nuchal regions. The examination was done on wet hair because this condition slows the movement of nymphs and adult lice, which facilitates visualization and collection (5). The criterion for a positive result was the visualization of nits, nymphs or adult lice, which were mechanically removed afterwards. The ectoparasites were collected and stored in alcohol for further studies. Each parent/guardian completed an informed consent and responded to a structured survey.

Statistical analysis

The collected information was stored in a database that was exported to the SPSS version 10 statistical package to determine the prevalence and most relevant characteristics of the positive and negative groups using the chi-square test.

The variables considered for the study were age, sex, socioeconomic stratum, hair length, hair type, daily hair hygiene, co-sleeping, lice information and lice inspection. Long (>3cm) and short (<3cm) hair were differentiated (16), as well as straight and wavy hair for each inspection. The parents or guardians were asked about their socioeconomic stratum by means of a survey. The variable "lice information" was defined as whether the parent or guardian had received or read any kind of information about ectoparasitosis in the last 6 months. The variable "lice inspection" was directed to know whether the respondent inspected the child or if, to their knowledge, someone else did it.

Data was incomplete in relation to the variables "hair type" and "co-sleeping." In the first case, information was not obtained because it was omitted; in the second, the guardians of the children could not provide the required information because they did not live together and had no knowledge. No clinical assessment was performed to identify scalp pruritus since this information was asked to the guardians.

Results

P. capitis is a ubiquitous ectoparasite, and the global prevalence of its infestation varies according to the geographical region, the climate and personal habits. Thus, in developing countries, prevalence rates have been determined at around 40% (17). In this study, the prevalence is 11.5%.

Statistical significance was found in the variables female sex, long hair and scalp pruritus. Table 1 synthesizes the variables that were associated with *pediculosis capitis* in the studied children.

Table 1. *Pediculosis capitis* and associated variables in children from Popayán, Colombia.

Variable		Total sample		Total positives		p
		n	%	n	%	
Age	1-2 years	39	26.4	1	2.6	0.253
	3-5 years	109	73.6	16	14.7	
Sex	Male	82	55.4	1	1.2	0.001 *
	Female	66	44.6	16	24.2	
Socioeconomic stratum	1-2	106	71.6	15	14.2	0.284
	3-4	42	28.4	2	4.8	
Length of hair	Long	56	37.8	15	26.8	0.001 *
	Short	92	62.2	2	2.2	
Type of hair †	Wavy	49	37.2	8	16.3	0.428
	Straight	81	62.8	9	11.1	
Daily hair hygiene	Yes	142	95.9	17	12	1
	No	6	4.1	0	0	
Co-sleeping †	No	87	61.7	4	4.6	0.327
	Yes	54	38.3	11	20.4	
Scalp pruritus	Yes	17	11.5	8	47.1	0.001 *
	No	131	88.5	9	6.9	
Information about lice	Yes	119	80.4	16	13.4	0.130
	No	29	19.6	1	3.4	
Lice Inspection	Yes	140	94.6	16	11.4	0.632
	No	8	5.4	1	12.5	

* Statistically significant.
† Missing data.
Source: Own elaboration based on the data obtained in the sudy.

Discussion

Latin America is not the exception to the global trend; prevalence rates and variables associated with *P. capitis* are disparate among regions and vary according to climatic conditions (18-20). In Yucatán, Mexico, Manrique-Saide *et al.* (21) found a prevalence of 13.6% in a population similar to this study (19/140 children aged 7-12 years).

In Venezuela, Cazorla-Perfettl *et al.* (16) also reported similar figures (10.1%), with a significant infestation rate in the variables girls/boys (90%/10%), long hair (>3cm) and straight type. The symptoms associated with *P. capitis* were pruritus and excoriation, which is consistent with this study in terms of a greater association in the female sex (94.1%/5.9%), long hair and scalp pruritus variables.

In Chile, Gazmuri *et al.* (22) found an infestation prevalence of 40.3%, mostly in girls (55.2%). In Brazil, Fragoso-Rocha *et al.* (23) studied 147 children from a primary school (4-11 years) and found prevalence rates of 44.9% and 32.8% in two different observations, which are higher than the ones presented in this study (11.5%.)

There is little research in Colombia about this type of ectoparasitosis. Ríos *et al.* (24) conducted a study in a kindergarten of Bogotá D.C. for 7 months, estimating a *P. capitis* prevalence between 2.9% and 33.3%. The variables associated with infestation were long hair, living with more than five people in the same house and poor hygienic habits. This study also found an association of pediculosis capitis with long hair.

In 2006, at the local level, Hurtado *et al.* (13) studied a sample of 177 children between 3 and 4 years of age, and found that 85.8% of the population were classified in a low socioeconomic stratum and that the prevalence of *P. capitis* was 54.2%, the highest rate nationwide. Associated clinical manifestations were scalp pruritus (62.5%) and neck pruritus (67.34%). The association of *P. capitis* with scalp pruritus was similar in this study (47.1%) (13).

Also in Popayán, Gonzales *et al.* (14) found a prevalence of 39% in a population of 326 students in 2001. In addition, *P. capitis* was more frequent in girls (72.4%) and, according to the socioeconomic stratum, infestation was more prevalent in stratum 1 (61.3%). Most of the children affected by *P capitis* in this study were also girls (94.1%) and children in low strata (88.2%). The prevalence found in this research was 11.5%, much lower than that reported by the other two local authors. Although the difference in the prevalence of *P. capitis* in the three studies is not similar, it proved that ectoparasitosis is prevalent in the school population and requires greater attention of public health.

The female sex and long hair variables could favor infestation by lice since, usually, girls have long hair and frequently share utensils such as combs or clothing for socialization purposes.

Unlike other studies, hair type was not statistically significant, which could be explained by the loss of data at the time of filling out the survey with the parents. Other authors reported protective factors such as daily hair wash (16,24), previous information on *P. capitis* and children inspection, which were not related to infestation prevalence in this study.

Conclusions

The results of this study suggest that *P. capitis* in Popayán children is present and tends to be perpetuated, which is evident the three local studies (2001, 2006 and the present).

According to Colombia's Decennial Plan for Public Health 2012-2021 (25), *P. capitis* and other ectoparasitosis are not considered as current public health problems. It is necessary that governmental entities incorporate and implement promotion, prevention and pediculicide programs, since this problem can affect the learning processes and the general welfare of children and families. Such policies should be implemented in schools, homes, health centers and the community in general to diagnose and treat affected children. Since no one is free from lice infestation, this is a public health challenge that should be categorized as a neglected ectoparasitosis with reemerging potential.

Conflict of interests

None stated by the authors.

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ORIGINAL RESEARCH

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Experience and results of laparoscopic inguinal herniorrhaphy

Experiencia y resultados de la herniorrafia inguinal por laparoscopia

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| Abstract |

Introduction: Due to the invention of minimally invasive surgery, inguinal hernia repair by laparoscopy has become a common procedure. This paper presents the results of 92 inguinal hernia repairs by laparoscopy performed using the transabdominal pre-peritoneal technique (TAPP) between August 2001 and January 2014.

Objective: To present our results regarding recurrence rate, postoperative pain and need for conversion.

Materials and methods: The results of the procedure using TAPP were retrospectively analyzed based on an average follow-up time of 8 years.

Results: Three (3.2%) cases required conversion, three (3.2%) were recurrent and six (6.4%) presented chronic pain.

Conclusion: Laparoscopic hernia repair by TAPP is a safe procedure. Effectiveness and complication rates have shown to be similar to open and TEP techniques.

Keywords: Hernia; Laparoscopy; Recurrence (MeSH).

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| Resumen |

Introducción. Con la invención de la cirugía poco invasiva, la herniorrafia inguinal por laparoscopia se ha convertido en un procedimiento de realización frecuente. En el presente artículo se publican los resultados de 92 herniorrafias inguinales por laparoscopia realizadas con técnica transabdominal preperitoneal (TAPP) entre agosto de 2001 y enero de 2014.

Objetivo. Presentar resultados en cuanto a tasa de recurrencia, dolor post-operatorio y necesidad de conversión en las herniorrafias inguinales por laparoscopia analizadas.

Materiales y métodos. Se analizaron de manera retrospectiva los resultados del procedimiento realizando técnica TAPP con seguimiento promedio de 8 años.

Resultados. Se presentaron tres (3.2%) casos que requirieron conversión, tres (3.2%) de recurrencia y seis (6.4%) de dolor crónico.

Conclusión. La herniorrafia por laparoscopia con técnica TAPP es un procedimiento seguro; esta tiene tasas similares de efectividad y complicaciones a la técnica abierta y totalmente extraperitoneal TEP.

Palabras clave: Hernia; Laparoscopia; Recurrencia (DeCS).

David Felipe López-Atehortua. [Experiencia y resultados de la herniorrafia inguinal por laparoscopia] Rev. Fac. Med. 2017;65(3):429-32. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.56429.

Introduction

Abdominal wall hernias have been historically reported in human beings. The first reference on this pathology was found in the Ebers papyrus, written in 1560 BC, which defined it as a tumor in the genital area where the intestines move. The history of studies and treatment attempts dates back to the fourth century BC with Hippocrates. In this period, anatomical descriptions were obtained through multiple studies in cadavers, as well as hundreds of fruitless procedures that included skin and herniary sac cuts —despite of not knowing its content—, which could lead to death. Eventually, inguinal sclerosing drugs were implemented (1-5).

The implementation of the laparoscopic procedure began in the 1990s as reported by Ger (6), Schultz (7), Corbitt (8) and Filipi (9). Later, other techniques were developed with excellent results, including the totally extraperitoneal repair (TEP), transabdominal preperitoneal repair (TAPP), internal ring closure, mesh plugs and onlay mesh techniques. The first two techniques use the principle described by Stoppa (10), which states that the mesh is placed in the preperitoneal space.

Endoscopy has been established in the last years as the most preferred technique for the management of inguinal wall defects. This procedure has shown benefits in terms of aesthetics, postoperative

pain and size of surgical wounds (11-13). In terms of costs, TEP approach is cheaper than TAPP. However, both are more expensive than open surgery in relation to direct costs, but have equivalent social costs, since social productivity is better in laparoscopic approaches because patients resume their activities faster (12). TAPP technique is performed by placing three laparoscopy trocars on the umbilical area (10mm) and on each flank (5mm). The pneumoperitoneum with carbon dioxide is achieved by inserting a Veress needle at the Palmer's point, and increasing intra-abdominal pressure up to 12 mmHg. After obtaining adequate pressure, the umbilical port is located to insert the optic, and a 5mm trocar is positioned under direct vision on each flank to avoid injuries in abdominal organs.

Then, once the reference points of the inguinal region have been identified, a horizontal cut in the anterior parietal peritoneum is made about 2cm above the anterior superior iliac spine until the medial umbilical ligament. Such cut is made underneath the ipsilateral side of the hernia. The next step is to dissect the preperitoneal space by sectioning the areolar tissue with a hyfrecator or scissors. Then, the dissection of the medial part is initiated until visualizing an adequate dissection of the Retzius space and the pubic symphysis, so that the pectineum or Cooper's ligament can be observed. This procedure is done laterally, visualizing the inferior gonadal and epigastric vessels. The preperitoneal is exposed until about 3cm lateral to the anterior superior iliac spine.

The hernia sac is then identified and released from the cord elements using traction-countertraction maneuvers until they are properly reduced. Afterwards, through the umbilical trocar, a 15x12cm low density polypropylene mesh is inserted into the preperitoneal space. The cover mesh is extended near the lateral half of the Retzius space, attached to a Cooper's ligament with a titanium fastener. The lateral extension is continued until adequately covering the inguinal region, and the mesh is fixed to the lateral side of the abdominal wall avoiding the vascular triangle and pain in the posterior face of the anterior and lateral rectus muscle of the transverse muscle fibers. Finally, after achieving adequate extension, the preperitoneal space is closed with continuous suture in the parietal peritoneum using a 2-0 gauge polyglactin (14-16).

This study reports the experience gained by the authors while managing 92 cases of inguinal herniorrhaphy by laparoscopy using the TAPP technique from August 2001 to January 2014. Data were obtained retrospectively based on a follow-up period between 8 and 120 months

Materials and methods

Inguinal hernia diagnosis was given by a physician specialist in general surgery based on clinical findings. No diagnostic images were taken. The laparoscopic technique used in all patients was inguinal herniorrhaphy via transabdominal preperitoneal pathway. The study was carried out on men and women of legal age who presented with both primary and recurrent inguinal hernia, as well as unilateral or bilateral hernias.

The clinical records of patients who underwent laparoscopic inguinal herniorrhaphy between August 2001 and January 2014 were retrospectively reviewed. The studied clinical outcomes included complications such as postoperative pain (defined as persistent pain for more than 2 months), need for conversion to open surgery and hernia recurrence. The follow-up was personally performed by a general surgeon during the first month, and then by telephone with an average of 2 956 days of follow-up.

Results

Laparoscopic inguinal herniorrhaphy was performed in 100 patients, out of which 92 were successfully monitored after the intervention (Table 1). In the unilateral group, the most common type of primary hernia was indirect (58.2%), while all the hernias in the bilateral group all were direct/direct (57.2%). In the reproduced unilateral group, the most frequent type was indirect (50%) (Table 2).

Table 1. Characteristics of patients.

Total sample	n=92 (100%)
Male	70 (76%)
Female	22 (24%)
Age in years at the time of the procedure (mean ± SD)	51.15±16.05
Primary	81 (88.04%)
Reproduced	11 (11.96%)
Unilateral	77 (83.7%)
Bilateral	15 (16.3%)
Comorbidities	29 (31.5%)
Hypertension	11 (11.9%)
Diabetes mellitus	2 (2.2%)
COPD	2 (2.2%)

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

Table 2. Classification of inguinal hernias.

Primary (%)	
Unilateral (%)	**Unilateral (%)**
• Indirect: 39 (58.2%) • Direct: 19 (28.3%) • Indirect and femoral: 6 (9%) • Pantaloon: 3 (4.5%)	• Direct/direct: 8 (57.2%) • Indirect/indirect: 5 (35.7%) • Direct/femoral: 1 (7.1%)
Reproduced (%)	
Unilateral (%)	**Bilateral (%)**
• Indirect: 5 (50%) • Direct: 2 (20%) • Combined: 2 (20%) • Femoral: 1 (10%)	• Indirect/indirect: 1 (100%)

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

The operating time of primary unilateral inguinal herniorrhaphy, excluding patients requiring conversion, was 39.9±19.5 minutes. For the primary bilateral group, time was estimated at 67.27±26.6 minutes, and in the unilateral reproductive group at 46.5±25.4 minutes (Figure 1). Regarding hospital stay, 87 (94.5%) procedures were outpatient, 4 (4.3%) patients required hospitalization for one day, and 1 (1.1%) patient required hospitalization for three days. The latter patient underwent prostatectomy during the same surgery, which required post-operative hospitalization. Furthermore, three conversion (3.2%) cases occurred due to large fibrosis around the hernial sac area.

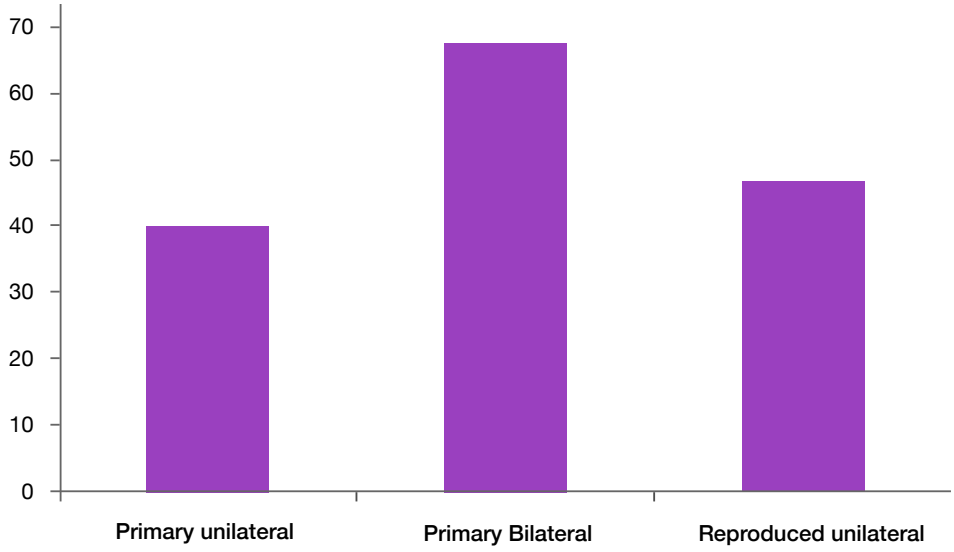

Figure 1. Average operating times among each group expressed in minutes.
Source: Own elaboration based on the data obtained in the study.

Regarding complications, no infection cases of the operative site were observed; 3 (3.2%) cases presented with seroma; 3 (3.2%) developed inguinal hematoma —2 handled with medication and 1 with surgical drainage—; 1 (1.1%) case had epigastric lesions that were controlled by laparoscopy; 3 (3.2%) cases documented hernia recurrence, and 6 (6.4%) cases had post-operative pain for more than 2 months (Table 3).

Table 3. Complications observed during inguinal herniorrhaphy.

Type of complication	n=92 (100%)
Infection	0 (0%)
Seroma	3 (3.2%)
Hematoma	3 (3.2%)
Epigastric vessel injury	1 (1.1%)
Recurrence	3 (3.2%)
Postoperative pain	6 (6.4%)
Conversion	3 (3.2%)

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

Discussion

The first inguinal herniorrhaphy by laparoscopy was described by Ger *et al.* (17) in 1990, which consisted in covering the defect with a mesh. In 1992, Arregui *et al.* (18) described the TAPP technique, and in 1993 McKernan *et al.* (19) presented the TEP technique. In 2010, during the European Association of Endoscopic Surgery Congress, attended by 100 surgeons, it was concluded that the most widely used laparoscopic herniorrhaphy technique is TAPP (20). Unfortunately, no literature was found in Colombia which could be used to compare our results. However, they are good when compared to international studies.

The mean surgical time in this series (39.9 minutes for primary unilateral and 67.27 minutes for primary bilateral) was within the ranges described in larger series (unilateral 25-102 minutes, and bilateral 38-123 minutes) (21,22).

As for early complications, no injuries in intra-abdominal organs were observed, nor conditions that would endanger the life of patients in the short-term. Additionally, no association was found between comorbidities and seroma and hematoma complications. Nevertheless, among the patients that required conversion to open technique, there was a case with a history of Fournier gangrene, which was probably associated with the great adhesion process found intraoperatively around the sac that could not be reduced by the endoscopy.

With regard to recurrence, the three cases presented here are among the first 50 studies performed, which may suggest that they are associated with the learning curve. When attempting associations with the chronic pain presented by the six patients who reported it, no data were found within the variables studied. Moreover, the range was within those described in the literature (11,12,23,24,25) (Table 4).

Table 4. Recurrence and postoperative pain.

Study	% of recurrence (number of cases/sample)	% of postoperative pain (number of cases/sample)
Liem *et al.* (14)	4.9% (24/487)	4.9% (24/487)
Neumayer *et al.* (12)	10.1% (100/989)	9.8% (97/989)
Schultz *et al.* (23)	1.04;26% (2500):	0.4% (10/2500)
Cawich *et al.* (24)	0.97% (1/103)	0.97% (1/103)
Soltés *et al.*(26)	0.96% (10/1058)	
Vărcus *et al.* (25)	2.17% (1/46)	2.17% (1/46)

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

Conclusion

Laparoscopic herniorrhaphy with TAPP technique is considered to be a safe procedure, with a low rate of complications, which can be performed by expert hands in short surgical times with low recurrence rates. In addition, due to the experience and the temporality of recurrence, it could be suggested that the learning curve for performing the procedure is 50 cases under the supervision of an expert.

Conflict of interest

None stated by the authors.

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ORIGINAL RESEARCH

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Results of total colonoscopy in the diagnosis of polyps. Case studies in Villavicencio, Colombia

Resultados de colonoscopia total en el diagnóstico de pólipos. Análisis de casos presentados en Villavicencio, Colombia

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| Abstract |

Introduction: Any elevation above the normal plane of the colonic mucosa is considered a polypoid projection. As age increases, polyps are more likely to be found; in addition, polyps larger than 1 cm of diameter may potentially lead to a malignant neoplasm.

Objective: To establish the frequency, size, location and age groups of colonic polyp lesions in patients who underwent colonoscopy at Hospital Departamental in Villavicencio during 2009-2014.

Materials and methods: The results of 411 diagnostic colonoscopies were analyzed. Data collection and statistical description was done using SPPSS 2011 software.

Results: 43 (11%) polyps were smaller than 1cm; 16 (4%) were between 1cm and 2cm long; no polyps larger than 2cm were found, and the remaining results did not show any abnormality. Polyps were found in all segments of the colon in the 41-50 age group, but the highest percentage (11%) was observed in the 71-80 age group. 68.7% of polyps larger than 1cm and 67% smaller than 1cm were found in the left colon.

Conclusion: In population groups under 40 years of age, the incidence of polyps is low in the left colon and very low in the right colon.

Keywords: Colonoscopy; Proctosigmoidoscopy, Colonic polyps; Cancer Screening (MeSH).

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| Resumen |

Introducción. Cualquier levantamiento por encima del plano normal de la mucosa colónica es considerada proyección polipoidea. A mayor edad es más probable encontrar pólipos; además, los >1 cm de diámetro tienen mayor potencial de desarrollar neoplasia maligna.

Objetivo. Establecer la frecuencia de lesiones polipósicas del colon, su tamaño, su localización y los grupos de edades donde están presentes en pacientes a quienes se les realizó colonoscopia en el Hospital Departamental de Villavicencio en el periodo 2009-2014.

Materiales y métodos. Se analizaron los resultados de 411 colonoscopias diagnósticas. La recolección de datos y descripción estadística se hizo con el software SPPSS 2011.

Resultados. Del total de la muestra, 43 (10.46%) pólipos fueron ≤1cm de diámetro, 16 (4% 3.89%) estuvieron entre 1cm y 2cm, no se encontraron pólipos >2cm y en el resto de resultados no se hallaron estas anomalías. En el grupo de edad de 41 a 50 años se presentaron pólipos en todos los segmentos del colon, pero el de mayor porcentaje (11%) fue el de 71 a 80 años. En el colon izquierdo se presentó el 69% de los pólipos >1cm y el 67% de los <1cm.

Conclusión. En grupos de poblaciones <40 años de edad, los hallazgos de pólipos son bajos en colon izquierdo y muy bajos en colon derecho.

Palabras clave: Colonoscopia; Proctosigmoidoscopia, Pólipos del colon (DeCS).

Melo-Peñaloza MA. [Resultados de colonoscopia total en el diagnóstico de pólipos. Análisis de casos presentados en Villavicencio, Colombia]. Rev. Fac. Med. 2017;65(3):433-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.49484.

Introducción

Any elevation above the normal plane of the colonic mucosa is considered a polypoid projection. Colon polyps may be non-neoplastic, such as inflammatory, hyperplastic, and cystic polyps. Neoplastic polyps (new mucosal growth) may be benign —including tubular, tubulovillous and hairy adenomas— or malignant, and are precursors of colon cancer. Therefore, removing them is important to prevent the development of malignant polyps. The malignant potential of polyps is variable (1).

The World Health Organization classifies neoplastic polyps into: 1) tubular adenomas (tubular epithelial glands) when 20% or less of their architecture is histologically villous, 2) tubulovillous adenomas when a mixed pattern is observed, and 3) hairy adenomas when papillary processes are predominant (2).

Hairy architecture is understood as digitiform or papillary processes made up of connective tissue covered by epithelial cells. They are usually bulkier than tubular and sessile adenomas in most cases. The villous adenoma, due to its histology and bigger volume, has the greatest potential for malignancy, which has been estimated at 5% (2).

The prevalence of adenomas leading to cancer ranges from 0.2% to 11% in endoscopic series of polyp resection; currently, these values are greater due to screening programs. In asymptomatic patients older than 50 years, a prevalence of 0.8% of adenocarcinoma has been estimated, of which 50% is *in situ* (intramucosal tumor without submucosal invasion) (3).

Adenomas have been found to be larger, more frequent and located on the left side of the colon. A study of 233 414 adenomas found in 142 686 patients showed that those on the right side were smaller (8.2mm vs. 12.4mm) and had a lower percentage of high dysplasia (OR=5.27 95%CI: 4.06-6.82) and adenocarcinomas (OR=4.89, 95% CI: 4.34-5.51) than those on the left side (4).

The size of the adenoma depends on many factors, including age, race, sex and the presence of multiple polyps. Regarding age, a linear relationship may be observed, since size seems to increase in older patients; also, bigger sizes have been found in black population in comparison with white population; regarding sex, they are larger in men than in women, and the probability of a larger size is greater in the presence of multiple polyps (5-7).

Potential malignancy is related to irregular morphology, in other words, if polyps are depressed at the center or ulcerated, if they are immotile (sessile) and if they have no stalk. Size is also influential, since polyps smaller than 1cm, known as advanced neoplasias, are more related with malignancy (8).

Most adenomas do not progress to cancer, but finding tumors larger than 1cm is an indicator of risk for the development of colorectal cancer. In these cases, endoscopic follow-up should be done at shorter intervals after diagnosis (9,10).

About 75% of colorectal cancers come from adenomatous polyps. There is an adenoma-carcinoma sequence that involves a mutation of the APC gene (inactivation) as an early event, followed by accumulation of genetic mutations that activate oncogenes and inhibit suppressor genes. Since there is a strong link between the presence of adenomas and the subsequent risk of developing colorectal cancer, the main objective of colonoscopy screening is to find and remove adenomas for further study, which may prevent the progression of premalignant lesions to malignant lesions (10).

Colonoscopy is an endoscopic study done with a flexible device that allows visualizing the surface of the colon, taking biopsies and resecting lesions found on its surface. It is indicated to study rectorrhagia/hematochezia, chronic diarrhea, changes in intestinal habits, anemia, ulcerative colitis, Crohn's disease, positive fecal occult blood test, radiological anomalies, and to detect cancer in risk groups (11,12).

From an endoscopic perspective, polyps can be classified as benign or malignant according to the findings. The Kudo classification for colonoscopies with magnification —in which the surface of the adenoma is observed— is divided into: type I, uniform round pits; type II, stellar or papillary pits; type III, large tubular or roundish pits, but smaller than type I pits; type IV, branch-like or gyrus-like pits, and type V, non-structural pits (13).

With this classification, types I and II represent, histologically, hyperplastic or inflammatory polyps, whereas type III, IV and V are neoplastic polyps. This method has a sensitivity of around 89% (95%CI: 85.2-91.9) and specificity of 85.7% (95%CI: 81.3-89.2) (14).

Colon cancer is the third leading cause of death in the USA; in 1999, the age-adjusted incidence was 40.56 per 100 000 inhabitants, and the number of deaths was estimated at 47 900 (15). In 2001, the age-adjusted incidence for Colombia was 11.8 and the age-adjusted mortality rate was 5.87 per 100 000 inhabitants (16).

Several professional associations recommend initiating with screening colonoscopies at age 50; this recommendation is based on the fact that the incidence of colorectal cancer increases around the sixth decade and that, therefore, premalignant lesions could be detected in this age group. Additionally, a greater number of polyp lesions larger than 1cm and advanced neoplasias have also been observed in this group (17).

In the USA screening for colon cancer increased from 38% in 2000 to 53% in 2008 in the population with access to health insurance. Despite this, 53 000 people die every year as a result of colorectal cancer. There is still no agreement as to which is the best screening system because, in the 50-59 age group, only 11% use occult blood test as a screening system; actually, 49.5% use rectosigmoidoscopy for the first time and then sigmoidoscopy in the following 10 years (17). A history of pelvic irradiation or cancer in first-degree relatives are risk factors; therefore, in these cases, a total colonoscopy examination is highly recommended in younger populations (<50 years).

Follow-up of (one or two) polyps of 1cm is recommended once every 5 years, since they are considered as low risk. If 3 to 4 polyps smaller than 1cm are found at colonoscopy, and at least one is larger than 1cm, they are considered as intermediate risk and follow-up should be done every 3 years. When more than five polyps smaller than 1cm and at least 3 larger than 1cm are found, they are considered as high-risk and annual follow-up is advised (18,19).

Colonoscopy in people older than 80 years with a diagnosis of polyps and without associated risk factors has a greater number of complications, so it should be done after carefully considering the pros and cons, even if there are more adenomas smaller than 1cm and advanced adenomas, since life expectancy is clearly lower than in younger age groups (20).

In countries with limited resources such as Colombia, patients can be on long waiting lists for their colon to be examined. It should also be borne in mind that total colonoscopy studies require trained personnel and, in most cases, endoscopy rooms with sufficient capacity to sedate the patient, which increases the cost of the procedure. Therefore, selecting the patients who should undergo a total colonoscopy procedure, both by age and symptomatology, is of great importance in order to optimize the use of this resource.

The objective of this research is to determine the frequency of polyp lesions in the colon, their size, location and the age groups of patients undergoing total colonoscopy in the endoscopy unit of Hospital Departamental in Villavicencio, Colombia.

Materials and methods

This is a descriptive, retrospective, transversal and analytical study in which the reports of diagnostic or screening colonoscopies done until the caecum and performed in the Endoscopy Unit of the Hospital Departmental in Villavicencio between 2009 and 2014 were included. All endoscopies that did not allow reaching and adequately visualizing the caecum due to technical reasons, such as poor preparation, loops or irreducible endoscopic angulations were excluded. Reports in which colon surgery had been proven or in which colon cancer had already been diagnosed by some other diagnostic means were also excluded. The patient information considered for the study were age,

endoscopic diagnosis and location of the colon segment, in which the alterations found were ≤1cm, >1cm and ≥2cm.

For this study, the endoscopic diagnosis of polyps in the different segments of the colon was taken into account and histopathological findings were ruled out because they could only be obtained in a few cases. Colonoscopies with diagnoses different from polyps were added to the total amount of performed colonoscopies.

The association between the patient's symptoms leading to the completion of colonoscopy and polyp findings was not evaluated, as most were not recorded in the examination report. The Kudo endoscopic classification was not evaluated either due to the lack of endoscopes with magnification and narrow-band imaging (NBI).

Statistical analysis

All data were entered into a spreadsheet and analyzed with the statistical package SPSS. Cases with polyps were divided by age groups at 10-year intervals: 20-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90 and 91-100. Elevated lesions that might suggest polyps were classified as ≤1cm, >1cm and ≥2cm to establish their frequency in each age group. The size of the polyp was determined by visual estimation and comparison with open colonoscopy biopsy forceps, yielding a size of 0.7cm. The findings in each group were tabulated according to the segment of the colon diagnosed, and the frequency was determined subsequently.

Ethical considerations

According to the Declaration of Helsinki (21) and the Resolution 8430 of the Ministry of Health of Colombia (22), this research does not represent any risk. During the study, respect for the dignity of the subjects and the protection of their data prevailed.

Results

A total of 411 colonoscopies that met the criteria described were analyzed. The mean age was 53 years (SD 14.88, mode 54, minimum 20 and maximum 93). The number of normal colonoscopies was 231 (56%), and 121 (29%) had abnormalities different to polyps. 43 (11%) polyp lesions <1cm, 16 (4%) polyps ≤2cm, and no polyps >2cm were found; the remaining reports did not yield relevant results.

In the 41-50 age group, the mean age was 45 years, the mode 42 years and the SD 2.87; lesions in all segments of the colon, as well as the highest number of polyps <1cm (n=4; 33%) were found in this group. The colon segment with the highest number of polyps found was the sigmoid with 14 cases (33%). In the 51-60, 61-70 and 71-80 age groups, polyps were also found, and the lowest percentage was found among 81-90 (Table 1 and Figure 1 and 2). 67% of all lesions <1cm were found in the left colon (rectum 14%%, sigmoid 32%% and descending colon 19%).

In the 20-30 and 31-40 age groups, only two lesions were found in the rectum, while a significant increase was observed in the 41-50, 51-60, 61-70 and 71-80 age groups. In the 81-90 age group, lesions decreased noticeably. In relation to elevated lesions >1cm, 16 cases were found, which represent 4% of the cases (Table 2).

Only one polyp lesion >1cm was found on the right side of the colon in the 20-30 age group, and one in the 41-50 age group. In all groups >50 years, polyps >1cm were found, with the highest percentage (11%) found in the 71-80 age group. Polyps >1cm in the left colon were found in 69% of the cases.

Table 1. Elevated lesions <1cm, location and age groups.

Age groups	20-30 n=27	31-40 n=52	41-50 n=95	51-60 n=104	61-70 n=73	71-80 n=47	81-90 n=13	Total n=411
Rectum	1	1	1	1	1	1	0	6
Sigmoid	0	0	4	3	5	1	0	13
Descending	0	0	1	1	3	1	0	6
Transverse	0	0	2	0	1	0	0	3
Ascending	0	0	3	1	1	3	1	9
Caecum	0	0	1	0	0	0	0	1
Sigmoid and descending (Simultaneous)	0	0	0	0	1	2	0	3
Ascending and transverse (Simultaneous)	0	0	1	0	0	0	0	1
Ascending and descending (Simultaneous)	0	0	1	0	0	0	0	1
Total	1	1	14	6	12	8	1	43
Percentage *	3.7%	2%	15%	6%	16%	17%	7.%	11%

* This percentage was estimated based on the number of patients in each age group.
Source: Own elaboration based on the data obtained in the study.

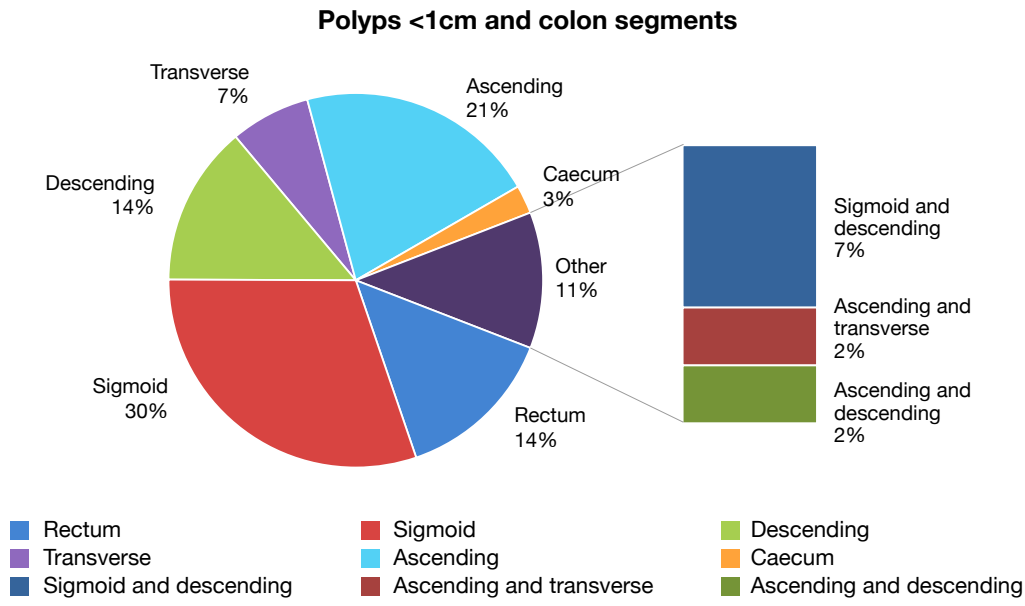

Figure 1. Percentage of polyps <1cm in colon segments.
Source: Own elaboration based on the data obtained in the study.

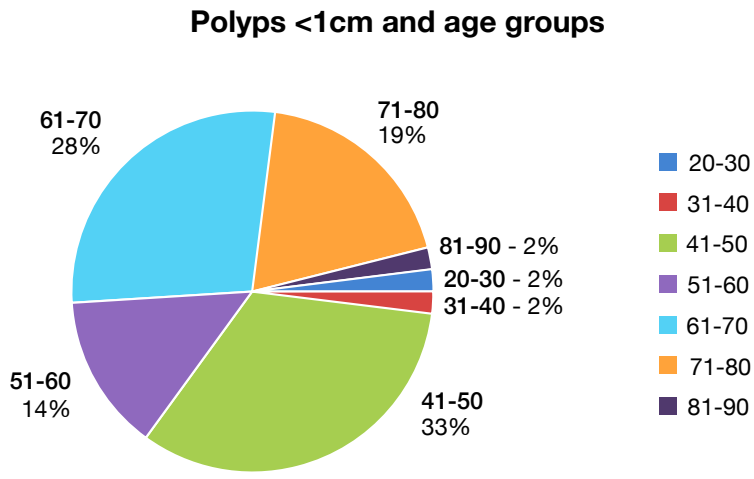

Figure 2. Percentage of polyps <1cm and age groups.
Source: Own elaboration based on the data obtained in the study.

Table 2. Elevated lesions >1cm, location and age groups.

Age groups	20-30 n=27	31-40 n=52	41-50 n=95	51-60 n=104	61-70 n=73	71-80 n=47	81-90 n=13	Total n=411
Rectum	0	0	0	1	0	0	1	2
Sigmoid	0	0	0	2	3	4	0	9
Descending	0	0	0	0	0	0	0	0
Transverse	0	0	0	0	0	0	0	0
Ascending	0	1	0	2	1	1	0	5
Caecum	0	0	0	0	0	0	0	0
Sigmoid and descending	0	0	0	0	0	0	0	0
Total	0	1	0	5	4	5	1	16
Percentage *	0	2%	0	5%	6%	11%	8%	4%

* This percentage was estimated based on the number of patients in each age group.
Source: Own elaboration based on the data obtained in the study.

Discussion

Polyps <1cm were found in 11% (n=43) of all cases, which is similar to Silva *et al.* (23) who obtained positive results in 207 (12.54%) cases from sample of 1 650 reports. In a Chilean follow-up program, in which fecal occult blood test was performed for asymptomatic persons >50 years to decide a colonoscopy, a frequency of 40.2% of polyps <1cm was found —476 cases in a sample of 1 184 (24)— indicating that if the test is performed with the intention of finding precursor lesions for cancer, the result is optimized. Such results contrast with this research because the reason for the examination was different in all cases, and the number was not determined in screening cases.

In this series, colonoscopy proved to be an efficient examination tool for the diagnosis of colon polyps; in addition, colonoscopy results showed a significant relationship with age groups, since the 41-50 group, with 14 cases (14.73%), had the highest number of polyps smaller than 1cm, as well as 32.55 % of total polyps regardless of size.

In Ko & Youn's study (25), with a sample of 3 114 colonoscopies, the frequency of polyps in the 40-49 age group was 42.7% (440 cases in a sample of 1 038 reports) —these authors make reference to any polyp size. The study by Bafandeh (26), done in a low prevalence area with 480 colonoscopies, reported that 12.2% of polyps were found in the 40-49 group; size was not specified either. An Iranian series of 240 reports, considered as low frequency, showed 21 cases (8.75%) of polyps <1cm in a group 4 050 samples (27).

On the other hand, the findings of this research are similar to those obtained by Rundle *et al.* (28), who found that 135 out of 905 colonoscopies showed elevated lesions, and that these lesions represented 14% in the 40-49 age group and in 16% the group of 50-59; in the latter group, a greater number and larger sizes were observed, as well as cancer.

Regarding localization, 67% of the polyps <1cm were on the left side of the colon (rectum, sigmoid and descending). A similar result was found in the series by Silva *et al.* (23) with 71.4% (n=148) and in an Iranian series with 80.4% (n=193); the latter did not establish if they were bigger or smaller than 1cm, but reported a greater proportion of high-grade dysplasia on the left side (29). An Italian series found 59 cases (53.15%) of polyps on the left side of the colon in a sample of 111 reports (30). Bafandeh *et al.* (26) also reported that 72% of the polyps were found on the left side of the colon (26% descending, 26% sigmoid and 20% rectal). Eshghi *et al.* (31) found in a retrospective study that the percentage of adenomatous polyps on the left side of the colon was 60.44%. These findings may indicate that the study of the left side of the colon remains important for follow-up of in populations at risk (32).

If OR (odds ratio) in the Ko & Youn series (25) is considered, the value for type of neoplasia in the colon, including adenoma and cancer, was 2.38 for the 40-50 age group (95%CI: 1.79-3.17), 4.73 in the 50-60 age group (95%CI: 3.55-6.30) and 5.42 in the 60-70 age group (95%CI: 3.89-7.56). The study by Giuliani *et al.* (30) showed that the OR in people >55 years is 5.1 (95%CI: 4.15-6.33) compared to all <55, regarding polyps. The research of Morimoto *et al.* (32) reported that the OR for adenomatous polyps in the 40-49 age group was 1.5 (95%CI: 0.9-2.6), whereas for the 50-59 group was 2.3 (95%CI: 1.4-3.9), and 3.8 (95%CI: 2.3-6.3) for the 60-69 group. The description in this study and the quoted series show an increased possibility of finding polyps in the age groups over 40; performing a total colonoscopy is crucial among population this age.

In all the studies reviewed, polyps >1cm were found in the age groups >50; the group with the highest percentage of polyps was 71-80 with 10.6%, and the most frequent location was the left side of the colon with 11 cases (68.7%). Only one polyp lesion >1cm was found on the right side of the colon in the 20-30 and 41-50 groups. The Ko & Youn series (25) described polyps >1cm in 4 (0.8%) of the 483 reports on the 30-40 group, 44 (3.7%) out of 1 200 reports in the 40-50 group, and 77 (7.5 %) out of 1 038 reports on the 60-70 group.

In the specific follow-up program of Castells *et al.* (33), 493 cases (9.74%) were found in 5 059 reports, of which 244 were observed in the left colon; the 50-59 group had 132 cases and the 60-69 group, 175. In the study by Terhaar Sive Droste *et al.* (34), in which the usefulness of colonoscopy in the follow-up of individuals >50 years of age was evaluated, polyps >1cm were found in 496 cases (10.72%) in a sample of 4 623 reports, 67% of them in the left colon, 13% in the 50-60 group, 17% in the 60-70 group, and 20% in the 70-80 group. In a series with seniors with a mean age of 62 years, 228 (7.3%) cases of polyposis lesions >1cm were found in a sample of 3 121 reports. These reviews showed that if colonoscopy is done in the context of an established follow-up program, the probability of finding lesions >1cm increases.

In groups <40 years, the frequency of polyps is low; this research found only two polyps in the 21-30 and 31-40 groups, which were located in the rectum. Similarly, in a Korean series, 71 (14.7%) cases were found in the 30-39 group (25); Zare-Mirzaie *et al.* (27) described a frequency of 1.25% in <20 years, 0.8% in the 20-29 group, and 5.41% in the 30-39 group, 76.5% of which were located on the left side of the colon. Morimoto *et al.* (32) found 23 cases (5.26%) <40 years in a sample of 437 reports. Eshghi *et al.* (31) found 5.40% in the 18-30 group and 11.90% in the 31-40 group. These numbers suggest that rectosigmoidoscopy examination would be sufficient for patients <40 in the absence of risk factors and clinical or laboratory findings (35-37).

This description has several limitations, such as sex, height, weight, body mass index, alcohol or cigarette consumption, as well as the impossibility of finding and correlating pathological studies. Another limitation relates to the population studied since it is not at risk, therefore it is not a screening sample; however, even with these restrictions, the similarity with other series is striking, especially when addressing factors such as age and limitations (38).

Conclusions

The frequency of polyps in the colon, both smaller and greater than 1cm, is similar to the international series. The age group in which these lesions begin to be reported is 41-50 years; in younger groups, findings in the left colon are less common. Adequate use of resources indicates that the rectosigmoidoscopy study is sufficient for people <40 years old, who do not present risk factors or abnormal laboratory indicators, and that colonoscopy would be indicated for the early detection of polyps in the 40-50 group.

If finding colon cancer at earlier stages of development is the goal, screening programs should be directed to persons at risk >50 years of age, just like programs for controlling hypertension or diabetes. Likewise, other studies are necessary to establish an association between the presence of polyps, their location and histopathological alterations.

Conflict of interests

None stated by the author.

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Iván "Ivanquio" Benavides
"El niño vacío" – 003
Técnica: tinta, color digital

ORIGINAL RESEARCH

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Problems perceived and experienced by health professionals rendering social service in Ancash, Peru. 2015

Problemas percibidos y experimentados por profesionales de salud durante el servicio social en Ancash, Perú. 2015

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| Abstract |

Introduction: Social health services in Peru have certain problems such as unsafe work conditions, mortality associated with traffic accidents and poor insurance coverage.

Objective: To describe the problems perceived and experienced by health professionals who render Rural and Urban Marginal Health Service (SERUMS in Spanish) in Ancash (Peru), and to evaluate their association with the profession and the category of the facilities where SERUMS is rendered.

Materials and methods: In April 2015, an analytical cross-sectional study was carried out in professionals who were rendering SERUMS in facilities of the Ministry of Health in Ancash. Surveys were applied to collect general data, and characteristics and problems of SERUMS.

Results: 364 surveys were analyzed. 79.3% were females, and the average age was 27.4±5.0 years. During SERUMS, 80.0% of participants perceived lack of supplies, 54.4% perceived excessive workload, and 14.7% suffered some traffic accident. Being a physician and working in I-1 health facilities were factors associated with suffering traffic accidents and other kind of accidents.

Conclusions: Respondents reported excessive workload, lack of supplies, and accidents. Accidents were more frequent in physicians and in I-1 health facilities.

Keywords: Primary Health Care; Rural Health; Health Personnel; Job Satisfaction (MeSH).

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| Resumen |

Introducción. En Perú, durante el servicio social en salud se han reportado problemas como condiciones laborales riesgosas, mortalidad asociada a accidentes de tránsito y déficit de cobertura de aseguramiento.

Objetivo. Describir los problemas percibidos y experimentados por los profesionales de salud que realizan el Servicio Rural y Urbano Marginal de Salud (SERUMS) en Ancash, Perú, y evaluar su asociación con la práctica de los profesionales y la categoría del establecimiento donde se realiza el SERUMS.

Materiales y métodos. Durante abril del 2015, se realizó un estudio transversal analítico con profesionales de salud que realizaban el SERUMS en establecimientos del Ministerio de Salud de Ancash. Se aplicaron encuestas para recolectar datos generales, características y problemas del SERUMS.

Resultados. Se analizaron 364 encuestas. El 79.3% de los participantes fue de sexo femenino, la edad promedio fue de 27.4±5.0 años, 80.0% percibió carencia de insumos, 54.4% percibió carga laboral excesiva, y 14.7% sufrió algún accidente de tránsito durante el SERUMS. Ser médico y laborar en establecimientos I-1 fueron factores asociados a haber sufrido accidentes de tránsito y otros imprevistos.

Conclusiones. Los encuestados reportan carga laboral excesiva, carencia de insumos y accidentes. Los accidentes son más frecuentes en médicos y en establecimientos de categoría I-1.

Palabras clave: Atención primaria de salud; Salud rural; Personal de salud; Satisfacción en el trabajo (DeCS).

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Introduction

Given the inequities in the distribution of human resources in health, many countries establish social service policies, which encourage, condition or force health professionals to work in areas with poor access to health services to serve the most vulnerable populations (1-3). In Latin America, the obligatory nature of social service has been discussed in publications of Colombia (1), Mexico (2) and Peru (3).

In Peru, social service in health is known as *Rural and Urban Marginal Health Service* (SERUMS in Spanish) and the professionals who render their services are known as *serumists*. SERUMS regulates the practice of physicians, dentists, nurses, obstetricians, chemist-pharmacists, nutritionists, medical technologists, social workers, biologists, psychologists, veterinarians and sanitary engineers. Rendering SERUMS is mandatory to apply for positions in public entities, study professional specialization programs in Peru, and receive scholarships or other equivalent aids from the State (4).

SERUMS has managed to locate health professionals in many rural and remote areas of Peru. However, serious problems for professionals have been reported when rendering their services, such as the mandatory nature of the service, risky working conditions and real danger of death (3). In addition, studies carried out in physicians who render SERUMS have identified poor health insurance (5) and high mortality due, to a great extent, to traffic events (6,7).

In spite of the relevance of these problems, studies on serumists are scarce and have focused only on physicians. Due to the lack of information on the frequency of the problems and their risk groups, designing and prioritizing the corresponding interventions is difficult (8). Therefore, this study aims to describe the problems perceived and experienced by serumists in Ancash - Peru, and to evaluate their association with the professional practice of serumists and the category of the facilities where SERUMS is rendered.

Materials and methods

Study design and context

An analytical cross - sectional study was carried out applying surveys to healthcare professionals rendering SERUMS in Ancash, Peru.

In Peru, health facilities are divided into first, second and third level of care. First level prioritizes health prevention and promotion, and is divided into four categories: I-1, I-2, I-3 and I-4. Usually, category I-1 includes facilities with few equipment and are found in most rural areas away from reference health centers (9).

SERUMS is regulated by Law 23330 (4), which establishes that it must be rendered in public health facilities of the Ministry of Health (MINSA), Social Security (EsSalud) or the Health Departments of the Armed Forces and the National Police of Peru for a year. Each year two processes are opened to award contracts: one in May (with the highest number of open positions) and another in October (with fewer positions).

Participants

This study included health professionals who were rendering SERUMS at a MINSA facility in Ancash during April 2015. This region was chosen because of the logistical support provided by the Regional Health Directorate of Ancash (DIRESA-Ancash). Working with MINSA health facilities was agreed because more serumist specialists are found there, and contact between them and the SERUMS coordinators, who were in charge of applying the surveys, is more frequent.

DIRESA-Ancash is divided into six geographically distributed health networks: Pacífico Sur (South Pacific), Pacífico Norte (North Pacific), Huaylas Sur (South Huaylas), Huaylas Norte (North Huaylas), Conchucos Sur (South Conchucos) and Conchucos Norte (North Conchucos). Each health network has a SERUMS coordinator, who is in charge of directing the work of the serumist specialists in their network.

During April 2015, 644 health professionals were rendering SERUMS in DIRESA-Ancash: 573 (89.0%) were located in MINSA health facilities, 42 (6.5%) in EsSalud health facilities, and 29 (4.5%) in health facilities of the Health Departments of the Armed Forces and the National Police.

Out of 573 MINSA members, the coordinators managed to involve 364 (63.5%), all of whom agreed to participate in this study. The health network with the highest percentage of respondents was Conchucos Sur (92.3%), and the lowest percentage was observed in Pacífico Norte (23.6%) (Figure 1).

Procedures

DIRESA-Ancash permission was requested to carry out the study and, with their support, the SERUMS coordinators of each health network in Ancash were trained to apply the surveys and respond the questions raised by serumists. The telephone number of the principal investigator was provided in all the surveys so that serum specialists could contact him in case of doubt.

In order to apply the surveys in their respective network, the SERUMS coordinators used two methods: a) applying the survey to serumists in person during meetings and supervision sessions in the health facilities, and b) sending the surveys to the health facilities where the serumists worked. In both cases, the participants used an envelope to submit their answers anonymously. This data collection was conducted throughout April 2015.

Then, two authors typed the surveys twice in the Excel 2010 program (Microsoft Corporation, USA), while a third author verified if both versions coincided. Mismatches were typed again.

Variables

The survey was developed by the researchers and included the following sections: general data such as age, sex, marital status, place where the undergraduate program was studied, financing of the university where the undergraduate program was studied, profession, year of graduation, as well as characteristics of the SERUMS such as type of contract, category of the health facility, process of enrollment in SERUMS (2014-I or 2014-II), at least three months being the head of the health facility, SERUMS problems, among others.

Regarding problems with SERUMS, the survey inquired about experiencing the following during the past month or at some point of their SERUMS: perception of lack of supplies that has prevented the basic management of a patient, some traffic accidents while working or traveling to the health facility, some other accidents (blows, burns, falls, etc.) while working that has caused incapacity for at least a few hours, or some theft while working.

In addition, data on other variables that are not included in this article were collected and will be presented in a subsequent analysis.

These variables correspond to the following parts of the survey: difficulty of SERUMS, violence during SERUMS, depressive symptoms during the last two weeks, professional expectations and retention.

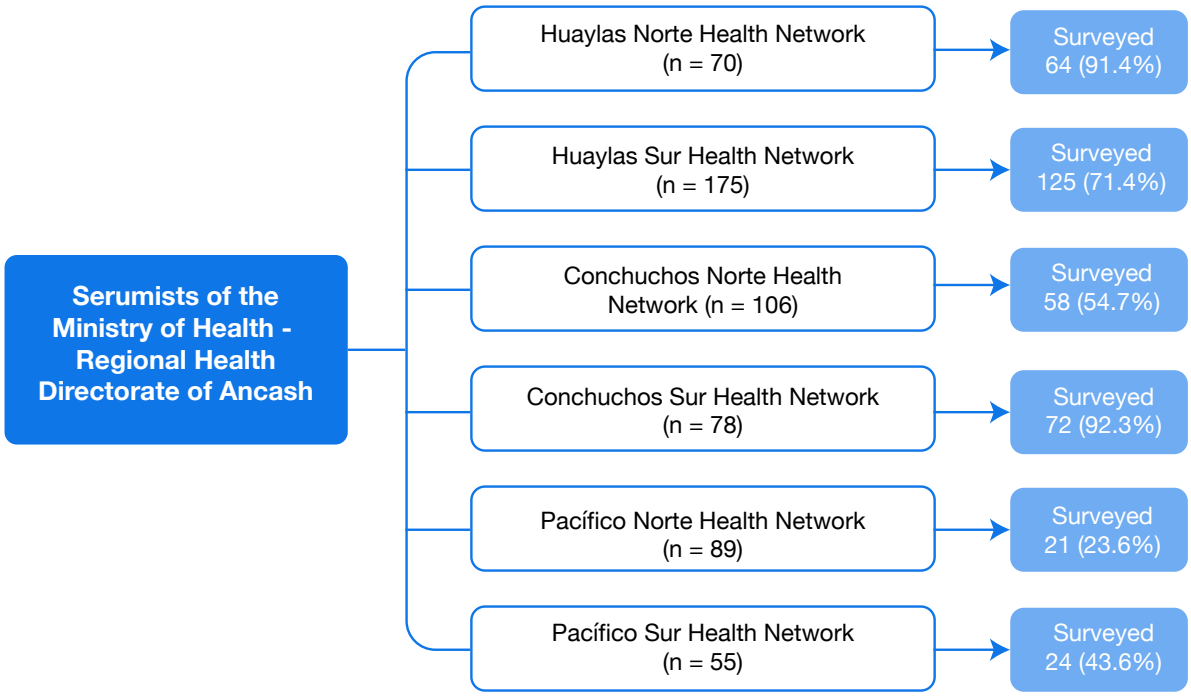

Figure 1. Serumists from the Ministry of Health surveyed in each of the six networks of the Ancash Regional Health Directorate.
Source: Own elaboration based on the data obtained in the study.

Analysis plan

Data analysis was performed using the statistical software Stata v14.0 (StataCorp LP, USA). Central tendency measures, dispersion measures, absolute frequencies and relative frequencies were used for a descriptive presentation of the results. Prevalence ratios (PR) and 95% confidence intervals (95%CI) were estimated using crude and adjusted Poisson regressions with robust variance. $p<0.05$ was considered statistically significant.

The regression models evaluated the association between five outcomes of interest (excessive workload in last month, lack of supplies in last month, traffic accident during SERUMS, another type of accident during SERUMS, robbery during SERUMS), and two variables of interest (being a physician and rendering SERUMS in a category I-1 health facility).

For multiple regression models, the associations were adjusted for sex, age, undergraduate studies in Ancash, years passed since graduation until starting SERUMS, having a remunerated SERUMS contract, having served as head of the health facility for at least three months during SERUMS, rending SERUMS at an I-1 health facility, and being a physician.

Ethical considerations

The project was approved by the Ethics Committee of Hospital Nacional Docente Madre-Niño San Bartolomé (RCEI-40). Surveys were voluntary and anonymous, so participants signed an informed consent. The confidentiality of the collected data was preserved.

Results

364 surveys were applied to professionals who rendered SERUMS at MINSA facilities in Ancash in April 2015. 79.3% were female, the mean age was 27.4±5.0, 75.0% were single, 70.1% studied an undergraduate program in a university of Ancash, 45.6% were nurses, 24.3% were physicians, 47.4% entered the SERUMS just after graduating, 79.5% were rendering SERUMS in an I-1 health facility, and 81.5% were rendering SERUMS and being remunerated (Table 1).

When evaluating the problems faced by serumists during their service, it was found that 80.0% perceived that they lacked the necessary supplies for the basic management of a patient, and 51.6% perceived it during the last month. 54.4% perceived that the workload was excessive at some point, while 28.8% perceived it in the last month. 14.7% suffered some traffic accident during SERUMS while working or when traveling to their workplace, and 4.0% suffered it in the last month. 26.2% suffered other accidents (bumps, burns, falls, etc.) during SERUMS, which made them unable to work for at least a few hours, and 9.3% suffered an accident during the last month. 12.4% were robbed during SERUMS activities, and 9.3% was robbed during the last month (Table 2).

When evaluating the association between variables in the adjusted model, it was observed that rendering SERUMS at an I-1 health facility was associated with traffic accidents (PR=2.64; 95%CI: 1.00-6.99) and to suffering another accident during SERUMS (PR=2.81; 95%CI: 1.26-6.26). Similarly, being a physician was a factor associated with suffering another accident during SERUMS (PR=1.66; 95%CI: 1.00-2.75) (Table 3).

Table 1. Characteristics of the surveyed population (n=364).

Characteristic		n (%)
Female		287 (79.3)
Age in years	22-25	130 (37.5)
	26-27	112 (32.3)
	28-60	105 (30.0)
Marital status Single		270 (75.0)
Place of undergraduate studies	Ancash	251 (70.1)
	Lima	65 (18.2)
	Other provinces	31 (8.7)
	Abroad	11 (3.0)
Undergraduate program in a public university		122 (34.1)
Profession	Nurse	165 (45.6)
	Physician	88 (24.3)
	Obstetrician	54 (14.9)
	Other	55 (15.2)
Period before joining SERUMS	Immediately after graduation	164 (47.4)
	One year after graduation	108 (31.2)
	Two or more years after graduation	74 (21.4)
Category of the health facility where SERUMS is rendered	I-1	283 (79.5)
	I-2	58 (16.3)
	I-3	15 (4.2)
Joined SERUMS during the 2014-I process (May) *		237 (66.0)
Paid service agreement for rendering the SERUMS †		290 (81.5)
Chief of the health facility for at least three months		118 (32.9)

* The others entered during the 2014-II process (October).
† The others had an equivalent contract *(ad honorem)*.
Source: Own elaboration based on data obtained in the study.

Table 2. Problems perceived and experienced sometime during SERUMS and sometime during the last month.

Problems		Total	Level of the health facility		Profession		
			I-1	I-2/I-3	Nurse	Physician	Other
Sometime during the SERUMS	Lack of supplies	280 (80.0) *	221 (79.8)	59 (80.8)	119 (73.9)	75 (85.2)	91 (85.1)
	Excessive workload	191 (54.4)	159 (56.6)	32 (45.7)	96 (60.0)	47 (53.4)	49 (44.9)
	Traffic accidents	50 (14.7)	45 (16.6)	5 (7.3)	19 (12.2)	19 (22.4)	12 (11.5)
	Other accidents	91 (26.2)	84 (30.3)	7 (10.0)	37 (23.0)	35 (41.2)	21 (19.6)
	Thefts	43 (12.4)	36 (12.9)	7 (10.3)	19 (11.8)	16 (18.2)	9 (8.7)
Sometime during the past month	Lack of supplies	129 (51.6)	98 (50.3)	31 (56.4)	52 (45.6)	33 (54.1)	47 (59.5)
	Excessive workload	84 (28.8)	70 (30.6)	14 (22.2)	44 (34.7)	18 (25.0)	22 (22.5)
	Traffic accidents	13 (4.0)	10 (3.9)	3 (4.4)	5 (3.3)	2 (2.6)	6 (5.8)
	Other accidents	29 (9.3)	29 (11.8)	0 (0.0)	16 (10.7)	6 (8.8)	8 (8.0)
	Thefts	13 (3.9)	12 (4.5)	1 (1.5)	9 (5.8)	3 (3.7)	1 (1.0)

* n (%).
Source: Own elaboration based on data obtained in the study.

Table 3. Variables observed and their association with working in a category I-1 health facility or being a physician.

Characteristic	Health facility of category I-1		Medical profession	
	Crude	Adjusted †	Crude	Adjusted ‡
Lack of supplies in the last month	0.99 (0.87-1.12) *	0.94 (0.82-1.08)	1.09 (0.98-1.21)	0.99 (0.86-1.15)
Excessive workload in the last month	1.24 (0.94-1.63)	1.07 (0.81-1.43)	0.99 (0.79-1.24)	0.95 (0.71-1.29)
Traffic accidents during SERUMS	2.29 (0.94-5.56)	2.64 (1.00-6.99)	1.87 (1.12-3.14)	1.49 (0.76-2.92)
Other accidents during SERUMS	3.03 (1.47-6.27)	2.81 (1.26-6.26)	1.90 (1.35-2.68)	1.66 (1.00-2.75)
Thefts during SERUMS	1.25 (0.58-2.70)	1.13 (0.49-2.62)	1.72 (0.98-3.03)	1.99 (0.80-4.92)

* PR (95%CI).
† Adjusted for sex, age, university region, year of graduation (delay), equivalent contract, head of health facility and profession.
‡ Adjusted for sex, age, university region, year of graduation (delay), equivalent contract, head of health facility and health facility category.
Source: Own elaboration based on data obtained in the study.

Discussion

Excessive workload

54.4% of respondents perceived that the workload during SERUMS was excessive at some point, while 28.8% perceived it in the last month. These high figures could reflect the lack of staff in the health facilities where SERUMS is rendered, as well as inadequate training of serumists or lack of support from senior staff of the health facility.

Serumists often have little work experience. In addition, they must perform administrative and institutional management tasks for which they may not have adequate preparation during undergraduate training. It is therefore necessary to explore this workload and to evaluate proposed solutions such as telemedicine —which has proven to be effective to reduce the burden on health professionals working in rural areas in other countries— (10) or different training methods to assist serumists in their clinical and administrative work.

Lack of supplies

51.6% of the respondents said that the lack of supplies hindered the fulfillment of their duties some time during the last month. These shortcomings are characteristic in rural health services worldwide, especially in low and middle-income countries. They usually occur because budgets prioritize urban areas, while the budg*et all*ocated to rural areas is misapplied under the belief that these areas are "small cities" and that their health facilities are supplied in the same way as urban areas (11,12).

In Peru, first level health facilities are designed to carry out mostly promotional and preventive activities and to manage a small group of pathologies, deriving the most complex conditions to higher-level health facilities (13). However, this is not always possible due to the patients' fear, their economic status, the need for immediate action, the distance from higher-level health facilities or their denial to receive patients. These situations force health professionals to treat pathologies for which they do not have enough supplies (14, 15), and to provide suboptimal care that ends up promoting health inequity in rural areas (12).

To intervene this inequity, it is necessary to study in depth the lack of supplies and the best ways to overcome the situation. A recent qualitative study indicates that the interviewed serumists require diagnostic tests for specific decisions such as making a differential diagnosis between malaria and pneumonia in the jungle (14). These studies would identify the particular needs of each region and guide an efficient investment in supplies that could be used in rural areas (16).

In addition, it is important for health personnel at all levels of care to know what kind of pathologies they can treat in the health facilities where they are working and how they should refer patients to the next level of care. These issues could be assessed during pre-SERUMS training (17,18).

Accidents

In Peru, the estimated incidence of traffic incidents in persons over 18 years of age was 223 per 100 000 people in 2008 (19). This study found that 14.7% of the respondents (14 700 per 100 000 people) reported being involved in a traffic accident during their SERUMS (that is, during the last 6 or 12 months). Despite the methodological differences between the cited study and this study, it is possible to assume that serumists have a high risk of suffering this type of accidents compared the rest of Peruvian inhabitants.

A report that only included serumist physicians in the 2006-2009 period identified traffic accidents as the leading cause of death, with a record of 7 deaths by traffic accidents out of 5 531 medical professionals (126.6 deaths per 100 000) (6). This incidence is much higher than that observed in reports of deaths among young physicians in other countries (20). Moreover, during that period, the estimated incidence of fatal traffic incidents among Peruvian citizens over the age of 18 was only 20 per 100 000 inhabitants (19).

The models evaluated in this study show that the prevalence of suffering traffic accidents during SERUMS is higher for physicians than for non-physicians, although, in the adjusted analysis, this association is not significant. This may occur because physicians make more trips, either referring patients or returning to their cities of origin, which may be quite distant, and because more than two thirds of the physicians surveyed have completed their studies in regions other than Ancash. Furthermore, an association between traffic accidents and SERUMS was found in relation to a category I-1 facility; this can be attributed to the remoteness and difficult access to these health facilities and their annexes.

Unfortunately, national data on mortality in non-medical serumists is not available. Data on other consequences of traffic accidents, such as temporary or permanent disability, are not available either. These data are necessary to develop and evaluate prevention policies (21).

The prevalence of other accidents (blows, burns, falls, etc.) while fulfilling serumist work was also higher in category I-1 health facilities. This may happen due to the fact that the communities served by these health facilities are more distant, which forces professionals to move for great distances to provide care, often using unsafe means of transportation in irregular terrains that may cause failures. In addition, these accidents were more prevalent in physicians, perhaps because they are more likely to move to remote locations, even to other villages, to treat their patients.

Unfortunately, many serumists do not have health insurance to protect them in case of accidents. Reports show that within three months after starting the contract, only 6.6% of the serumist physicians are provided with a social health insurance coverage for accidents and death (5), which causes multiple expenses and inconveniences to serumists who are involved in these accidents.

Now that the risks to which serumists are exposed are known, it is imperative that the relevant authorities take action. It is necessary to monitor the minimum security and access conditions to health facilities, to give serumists the possibility of accumulating days off to reduce the number of trips, and to provide vehicles or fuel for mobilization to remote communities. Interventions and monitoring should be prioritized for the groups at risk, in other words, physicians and those who work at I-1 health facilities.

It should be noted that this problem affects staff satisfaction and negatively influences the retention of health personnel (22), since it discourages serumist workers from working at the first level of care, as suggested by a previous cohort (23).

Limitations

This study has some limitations, such as the fact that our outcomes of interest were evaluated in a subjective way, according to the perception of the surveyor. In addition, the SERUMS coordinators could not find 36.5% of the serumists. It is possible that the missing population corresponds to those who render SERUMS in the most remote health facilities and, therefore, those who have more problems; hence, the results may underestimate the true magnitude of this issue.

Likewise, the extrapolation of the results is limited only to serumists of MINSA health facilities in Ancash. Serumists working for other health care providers or in other regions are likely to provide very different figures, which should be the subject of future studies.

The size of the sample included in this study has a power greater than 80% to determine PR values greater than 2.1 using multiple Poisson regressions, calculated with the PASS program v13.0 (NCSS, LLC, USA.). This implies that some associations could not be statistically confirmed due to the small size of the sample. However, no more subjects could be obtained since this was a census evaluation.

Strengths

To the knowledge of the authors, this is the first study to carry out a quantitative evaluation of the problems reported by the professionals who render SERUMS in Peru. The results reveal the magnitude of certain problems and identify two risk groups, which will help to develop and implement interventions to improve the working conditions of the serumist specialists.

Conclusions

The professionals who render SERUMS in Ancash suffer from excessive workload, lack of supplies, accidents and thefts. Being a physician and working in category I-1 health facilities are factors associated with suffering traffic accidents and other accidents that endanger integrity and even life. The relevant health authorities must supervise access and security conditions in such health facilities, prioritizing the identified risk groups.

Authors' contributions

This article was planned by ATP and PMT. ATR and MIVT were in charge of data collection. ATP, KCD, JMQ and PMT analized and interpreted the data. Finally, all authors participated in the drafting and approval of the final version of this document.

Conflict of interest

During the study, María Isabel Vidal-Torres was in charge of the Regional Coordination of SERUMS in the Regional Health Directorate of Ancash. The remaining authors do not state any conflicts of interest regarding the publication of this article.

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ORIGINAL RESEARCH

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Nutritional status, cardiovascular health, VO_2 max and habits in university students: a comparison between two health promotion careers

Estado nutricional, salud cardiovascular, VO_2 máx y hábitos de vida en estudiantes universitarios: comparación entre dos carreras promotoras de salud

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| Abstract |

Introduction: University students are at a moment of their life cycle that is key for the adoption of different lifestyles.

Objective: The purpose of this study was to determine and compare VO_2 max, fat mass percentage, biochemical profile, and alcohol and tobacco consumption in university students of two undergraduate programs.

Materials and methods: 53 first year students with an average age of 19.25 years were included in this study. 30 were enrolled in the in Physical Education Pedagogy program, and 23 in the Nutrition and Dietetics program offered by Universidad La Frontera, class of 2014. Assessment included weight, size, BMI, waist circumference, fat mass percentage, blood pressure, biochemical profile and VO_2 max.

Results: 32% of the students were overweight, 50.9% reported altered blood pressure, 28.3% had prehypertension, and 22.6% had high blood pressure. Furthermore, 50.9% had a fat mass level above normal, 18.8% were regular smokers, and 41.5% reported frequent alcohol use. Regarding VO_2 max, 48.9% were in the poor to fair range. The comparison by program showed significant differences in the variables height, VO_2 max (maximum aerobic capacity) and fat mass percentage ($p<0.05$).

Conclusions: Students are prone to develop chronic noncommunicable diseases, which is a worrying situation since they will become promoters of healthy lifestyles according to their career path.

Keywords: Obesity; Oxygen Consumption; Lifestyle; Hypertension (MeSH).

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| Resumen |

Introducción. Los estudiantes universitarios se encuentran en una etapa del ciclo vital clave para la adopción de estilos de vida.

Objetivo. El propósito de este estudio fue determinar y comparar el VO_2máx, el porcentaje de masa grasa, el perfil bioquímico y el consumo de alcohol y tabaco en estudiantes universitarios de dos carreras.

Materiales y métodos. Participaron en la investigación 53 estudiantes universitarios de primer año con un promedio de 19.25 años de edad. 30 eran de la carrera de Pedagogía en Educación Física y 23 de Nutrición y Dietética de la Universidad de La Frontera en el año 2014. Se evaluó peso, talla, índice de masa corporal, contorno cintura, porcentaje de masa grasa, presión arterial, perfil bioquímico y VO_2máx.

Resultados. El 32% de los estudiantes presentó exceso de peso, 50.9% reportó alteración de la presión arterial, 28.3% tuvo prehipertensión y 22.6%, hipertensión arterial. A su vez, el 50.9% presentó un nivel sobre lo normal de masa grasa, el 18.8% manifestó hábito tabáquico y el 41.5% reconoció consumir alcohol con frecuencia. En relación al VO_2máx, se observó que un 48.9% estaba ubicado en el rango de malo a regular. Respecto a la comparación por carreras, se encontraron diferencias significativas en las variables talla, VO_2máx (capacidad aeróbica máxima) y porcentaje de masa grasa ($p<0.05$).

Conclusiones. Los estudiantes son propensos al desarrollo de enfermedades crónicas no transmisibles, lo que supone una situación preocupante, pues en el área profesional se transformarán en promotores de estilos de vida saludable.

Palabras clave: Obesidad; Consumo de oxígeno; Estilo de vida; Hipertensión (DeCS).

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Introduction

Overweight and obesity affect a large percentage of adults worldwide, reducing life expectancy and posing a great economic burden for society. Between 2009 and 2010, the National Health Survey (ENS in Spanish) reported a high prevalence of overweight (64.5%), sedentary lifestyle (88.6%) and metabolic syndrome (35%) in the adult Chilean population (1). These high figures have also been obtained in young university students (2,3).

There is a clear relationship between lifestyles and risk factors (4), which are also associated with cardiovascular diseases (CVD). Currently, obesity is the leading cause of death in adults (5,6), thus generating a serious public health problem around the world (7). In Chile, the situation is similar due to the demographic and epidemiological transition of the last decades (8,9).

Physical inactivity is a risk factor (10) that can be observed in the alteration of muscles when metabolizing fats and glucose, resulting in modern chronic, metabolic and cardiovascular pathologies (11). In this sense, VO_2 max measuring is recommended as an indicator of aerobic capacity, as it shows the real health status and allows to detect risk groups prone to suffer morbidity conditions, since a healthy person should have an acceptable aerobic capacity (12).

University students are at a point in their lives that is key for adopting different lifestyles, which they will share with their relatives, and in social and work environments (13). For this reason, in order to achieve successful prevention programs, several studies have suggested the importance of identifying risk factors in young adults (14-16).

The purpose of this study was to determine VO_2 max, fat mass percentage, biochemical profile, and alcohol and tobacco consumption in first year university students enrolled in the Nutrition and Dietetics and Physical Education Pedagogy programs at a Chilean university.

Materials and methods

53 students voluntarily participated in this research during their first year in two health promotion careers at Universidad de La Frontera in 2014. 30 were enrolled in the Physical Education Pedagogy program (62.5%), and 23 in the Nutrition and Dietetics program (52.3%).

This study followed the agreements of the Declaration of Helsinki 2013 (17) and was approved by the Ethics Committee of Universidad de La Frontera. Each student signed an informed consent to participate in the research.

Data collection

The students were summoned to a lecture where the objectives of the research were exposed. Personal history (age, date of birth, contact data), and smoking and alcohol consumption were determined after interviewing each participant. Smoking one or more cigarettes per day, as well as drinking alcohol one or more times per week were considered relevant for the study, since these two factors generate alterations at the endothelium level.

Blood pressure (BP) measurement complied with the procedure established by the Clinical Guide for Primary or Essential Hypertension in persons aged 15 years and over (18). An arm digital blood pressure monitor CITIZEN CH-452 was used. Prior to the evaluation, the subjects were asked to have a 10-minute rest period sitting down. Values of ≥130/85 mmHg were considered as prehypertension and values of ≥140/90 mmHg as hypertension, according to the classification of the European Society of Hypertension (19).

Weight and fat mass percentage (FM%) were determined through bioimpedanciometry using Tanita TBF-300A. During this stage, participants were barefoot and in underwear. Ranges from 8% to 15% (men), and from 13% to 20% (women) were considered as normal for fat mass percentage (20). In order to calculate height, a portable ADE set in millimeters was used. Size was classified as normal from 18.5 kg/m^2 to 24.9 kg/m^2, overweight from 25 kg/m^2 to 29.9 kg/m^2, and obesity ≥30 kg/m^2. The waist circumference (WC) was established with a Lufkin W606PM anthropometric tape set in centimeters, yielding normal values of <90 for men and <80 for women (21).

The assessment of the biochemical parameters was done taking blood samples after fasting for eight hours or more. Samples were centrifuged at 2500 rpm for 10 minutes. Basal glycemia was determined through the GOD-PAP method, with normal values of <100mg/dl. Basal insulin was measured by chemiluminescence, with normal values of <12mg/dl. The lipid profile was obtained using CHOD-PAP for total cholesterol, with normal total cholesterol values of <200, LDL <100 and HDL >45. Finally, triglycerides were measured through immunological GPO-PAP-HDL, with normal triglycerides values of <150 (22). In addition, insulin resistance was observed through HOMA based on the formula fasting insulin values x fasting glycemia/405, obtaining <2.5 as a normal value (23).

In turn, aerobic capacity was assessed using a cycle ergometer (Corival-Lode, Groningen) and a gas analyzer (Ultima™ CPX Medgraphics, Minesotta), previously calibrated for volume and reference gases. VO_2 max was evaluated through continuous heart rate monitoring (Polar FT4, Finland) using the modified Astrand Test (24). The parameters considered for men were: poor <24.8 ml/kg/min; fair from 25 ml/kg/min to 33.9 ml/kg/min; average from 34 ml/kg/min to 42 ml/kg/min; good from 43 ml/kg/min to 52.9 ml/kg/min, and excellent >53 ml/kg/min. On the other hand, the parameters considered for women were: poor <23.9 ml/kg/min; fair from 24 ml/kg/min to 30.9 ml/kg/min; average from 31 ml/kg/min to 38.9 ml/kg/min; good from 39 ml/kg/min to 49 ml/kg/min, and excellent >49 ml/kg/min (24).

Statistical analysis

Data were presented as mean ±SD, frequencies and percentage (%). The normality of the variables was measured through the Kolmogorov-Smirnov test. The Student's T test was used for comparing quantitative parametric variables between two groups, and the Mann-Whitney U-Test for the non-parametric variables. All analyzes were done using the SPSS program, version 22.0. The confidence level was 95% ($p<0.05$).

Results

When comparing by academic programs, significant differences were found in the variables VO_2 max and body fat mass ($p<0.05$). The other study variables did not report any statistical differences (Table 1).

Table 1. Comparison of variables per academic program.

Characteristics	Total (n=53)	Nutrition and dietetics (n=23)	Physical Education Pedagogy (n=30)	p value
Age	19.25±1.59	18.61±1.08	19.73±1.76	-
BMI (kg/m²)	24.38±4.74	25.27±6.37	23.69±2.87	0.851
WC (cm)	78.51±10.93	79.659±13.80	77.67±8.40	0.897
Fat mass (%)	24.34±10.33	28.47±11.05	21.18±8.65	<0.001
Systolic pressure (mmHg)	126.10±13.13	123.36±12.34	128.10±13.52	0.379
Diastolic pressure (mmHg)	72. 29±11.78	73.73±9.70	71.23±13.17	0.162
Basal glucose (mg/dl)	89.94±6.77	89±7.03	90.67±6.59	0.380
Basal insulin	10.01±6.08	11.46±7.44	8.90±4.63	0.311
IR index	2.24±1.47	2.53±1.83	2.01±1.12	0.467
Total cholesterol (mg/dl)	157.22±33.71	157.04±39.91	157.37±28.78	0.547
cHDL (mg/dl)	68.94±11.95	68.04±12.90	69.63±11.34	0.973
cLDL (mg/dl)	69.62±23.39	68.45±25.25	70.47±22.33	0.636
Triglycerides (mg/dl)	89.45±61.42	90.70±83.11	88.50±39.10	0.154
VO_2 max	34.67±11. 39	30.27±10.50	38.55±10.90	0.005

Data presented as mean ±SD; p values <0.05 are significant; BMI: body mass index; WC: waist circumference. cHDL: HDL cholesterol; Total Col: total cholesterol; cLDL: LDL cholesterol; IR index: insulin resistance index.
Source: Own elaboration based on the data obtained in the study.

32% of the students had excess weight, of which 18.8% were overweight and 13.2% were obese. 50.9% had pressure alteration; 28.3% prehypertension, and 22.6% hypertension. Regarding fat mass percentage, 50.9% of students reported a level above normal, being higher in Nutrition and Dietetics students with 69.5% versus 36.6% in Physical Education Pedagogy (Table 2).

Table 2. Frequency of students.

	Nutrition and Dietetics (n=23)		Physical Education Pedagogy (n=30)		Total (n=53)	
	n	%	n	%	n	%
Thin	0	0	0	0	0	0
Normal	14	60.8	22	73.3	36	67.9
Overweight	4	17.3	6	20	10	18.8
Obese	5	21.7	2	6.6	7	13.2
Prehypertensive	8	34.7	7	23.3	15	26.4
Hypertensive	3	13	9	30	12	22.6
High FM%	16	69.5	11	36.6	27	50.9

Data presented as number of students by category and percentages according to the study sample. FM%: fat mass percentage.
Source: Own elaboration based on the data obtained in the study.

Moreover, Table 3 shows that 18.8% of the students had a smoking habit, and 41.5% reported frequent alcohol use.

Table 3. Frequency of students who smoke and consume alcohol.

	Nutrition and Dietetics		Physical Education Pedagogy		Total	
	n	%	n	%	n	%
Alcoholc onsumption	9	17	13	24.5	22	41.5
No alcohol consumption	14	26.4	17	32.1	31	58.5
Smoker	4	7.5	6	11.3	10	18.9
Non-smoker	19	35.8	24	45.3	43	81.1

Data presented as number of students by category and percentage according to the study sample.
Source: Own elaboration based on the data obtained in the study.

Regarding VO_2 max, the students, in general, were in the range between poor and fair (48.8%). Similarly, 27.6% were included in the parameters good and excellent; most of them were students of the Physical Education Pedagogy program (36%), and 18.1% of the Nutrition and Dietetics program (Table 4).

Table 4. VO_2 max per academic program.

VO_2 max level	Nutrition and Dietetics		Physical Education Pedagogy		Total	
	n	%	n	%	n	%
Poor	7	31.8	0	0	7	14.8
Fair	7	31.8	9	36	16	34
Average	4	18.1	7	28	11	23.4
Good	3	13.6	6	24	9	19.1
Excellent	1	4.5	3	12	4	8.5
Not rated	1	4.5	5	20	6	12.8

Data presented as number of students by category and percentage according to the study sample.
Source: Own elaboration based on the data obtained in the study.

Discussion

The results of this study show low levels of physical fitness, since 48.8% of the evaluated students presented a VO_2 max between fair and poor, which are negative values compared to the results of a study conducted at other Chilean universities (27).

The mean BMI was 24.38 kg/m², which is lower than that reported in a sample of Mexican students (27). 32% of the students evaluated had excess weight, of which 18.8% were overweight and 13.2% were obese. These values are similar to those of university students in the same city —in which 35.6% were overweight or obese (28)— and to the findings obtained in students from Saudi Arabia, which reached 31.2% (29). However, differences can be found with other research works that assessed Chilean students as well, obtaining a figure of 78.6% students with normal ranges and only 12% overweight (26).

Regarding fat mass percentage, 50.9% of the evaluated students had excess body fat, which is lower than the results in São Paulo, where the same measurement characteristics were used, finding that 60% of the students reached these levels (30). Furthermore, Cossio *et al.* (31) found 55%, and Zea *et al.* (32), 56.3% of body fat excess in university students.

It should be noted that excess body fat and sedentary lifestyle determine the true risk for health-related obesity. Therefore, including their assessment in health and lifestyle studies is highly relevant (33).

The students had a mean blood pressure of 126.10 mmHg, similar to that reported in university students from northern Turkey (34), but higher than that reported in university students from southern Chile (35.36) and from Somaliland (37). It is alarming that 34.7% of Nutrition and Dietetics students were prehypertensive, and that 30% of students of Physical Education Pedagogy had high blood pressure, which are results similar to those in students from the same country, where 35.1% were prehypertensive (38), although the classification criteria were different. The latter condition is associated with alcohol and nicotine consumption, as well as with poor diet schedules and quality, and physical inactivity.

This work showed alcohol consumption in 41.5% of the students, which coincides with the results of a research conducted in Colombian medical students (39). Regarding tobacco consumption, 18.9% claimed they were smokers, which is lower than numbers of sedentary university students from Temuco, who reached 45.1% (40). These results are alarming, since, in most cases, these habits have been proven to increase as university studies advance (41). For this reason, reducing tobacco use would reduce plasma disorders caused by smoking (42). In relation to this, total cholesterol, HDL-C, LDL-C and triglycerides showed lower values in these students than in other investigations, in which smoking was higher (36,40), as in basal glucose (35).

The university population is considered essential for the promotion and prevention of health for future generations (43). Studies have shown that risk factors in students tend to increase, even during the first semester in the university (44). In consequence, identifying their nutritional status and the frequency of physical activity is crucial to actually understand the resources necessary to promote a healthy lifestyle (45).

Conclusions

The results obtained in this research show a poor physical condition in students, who have high fat mass percentages and high levels of overweight or obesity and blood pressure. This proves that they are in a critical period, during which they are prone to develop noncommunicable diseases. This is a highly concerning situation, since they will turn into professional role models of healthy lifestyles. Thus, it is necessary to create greater and better instances of education in order to generate an impact, that is to say, to improve the quality of life and to create concrete habits in relation to food consumption and physical activity.

Conflict of interests

None stated by the authors.

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ORIGINAL RESEARCH

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Phase analysis for the assessment of left ventricular dyssynchrony by Gated Myocardial Perfusion SPECT. Importance of clinical and technical parameters

Análisis de fase para la valoración del sincronismo mecánico del ventrículo izquierdo mediante Gated-SPECT de perfusión miocárdica. Importancia de los parámetros clínicos y técnicos

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| Abstract |

Introduction: Phase analysis (PA) of the left ventricle is a new tool in nuclear cardiology studies used to assess left ventricular mechanical timing based on different clinical applications. However, the use of this tool is relatively unknown.

Objective: To expose the feasibility of the new PA tool in myocardial perfusion (Gated-SPECT) to assess left ventricle mechanical timing, and to verify the differences between values depending on clinical and technical conditions.

Materials and methods: The study included consecutive patients evaluated by Gated-SPECT. The main variables were different depending on clinical and technical conditions. PA was assessed using the PHASE tool of the QPS-QGS program (Cedars-Sinai Medical Center, Los Angeles, USA). The following parameters were obtained: histogram bandwith (HB), standard deviation (SD) and entropy (E). A descriptive and analytical analysis of means and/or medians was performed using parametric or non-parametric tests. Statistical significance was $p < 0.05$. IBM-SPSS V21® was used.

Results: 300 patients were included in this study with a mean age of 65±12.7. No differences were found in relation to the study phase (stress-rest) [HB (p=0.4), SD (p=0.6), E (p=0.8)], stress type [HB (p=0.38), SD (p=0.8), E (p=0.06), E (p=0.06)], dose used [HB (p=0.19), SD (p=0.05), E (p=0.06)], gamma camera [HB (p=0.02), SD (p=0.06), E (p=0.08)], or history of coronary heart disease [HB (p=0.44), SD (p=0.18), E (p=0.17)].

Furthermore, differences in conduction disorders were observed [HB (p=0.001), SD (p=0.02), E (p=0.001)], ejection fraction < or >35% (p=0.001), E (p=0.001)] normal or necrosis study [HB (p=0.001), SD (p=0.001), E (p=0.001)], and gender [HB (p=0.002), SD (p=0.006), E (p=0.005)].

Conclusions: The new PA tool of nuclear medicine is feasible in our context. The type of stress, the administered dose, the study phase or the gamma camera used did not affect the parameters. However, gender, interventricular conduction disorders, necrosis and systolic dysfunction did have an impact on them.

Keywords: Myocardial Perfusion Imaging; Radionuclide Imaging; Cardiac Resynchronization Therapy (MeSH).

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| Resumen |

Introducción. El análisis de fase (AF) del ventrículo izquierdo es una herramienta de reciente introducción en los estudios de cardiología nuclear, que permite valorar el sincronismo mecánico de la contracción del ventrículo izquierdo con diferentes aplicaciones clínicas, si bien es poco conocida.

Objetivo. Mostrar la factibilidad de la nueva herramienta AF por perfusión miocárdica (Gated-SPECT) para valorar el sincronismo mecánico del ventrículo izquierdo y verificar diferencias entre sus valores, según situaciones clínicas y condiciones técnicas.

Materiales y métodos. En el estudio participaron pacientes consecutivos con Gated-SPECT. Las variables principales fueron diferentes condiciones clínicas y técnicas. La valoración del AF se realizó mediante la herramienta FASE del programa cardiodedicado (QPS-QGS, Cedars-Sinai Medical Center, Los Angeles, USA). Se obtuvieron los siguientes parámetros: ancho del histograma (AH), desviación estandar de la fase (DE) y entropía (E). Se realizó análisis descriptivo y analítico de medias o medianas a través de test paramétricos o no paramétircos. El límite de significancia estadísitca fue $p<0.05$. Se utilizó IBM-SPSS V21®.

Resultados. Con un total de 300 pacientes y una media de edad de 65±12.7, en el análisis del AF no existieron diferencias según la fase del estudio (estrés-reposo) [AH (p=0.4), DE (p=0.6), E (p=0.7)], tipo de estrés [AH (p=0.38), DE (p=0.8), E (p=0.84)], dosis utilizada [AH(p=0.19), DE (p=0.05), E (p=0.06)], gammacámara [AH (p=0.02), DE (p=0.06), E (p=0.08)] ni entre antecedente de enfermedad coronaria [AH (p=0.44), DE (p=0.18), E (p=0.17)].

Hubo diferencias según trastornos de conducción [AH (p=0.001), DE (p=0.02), E (p=0.001)], fracción de eyección < o >35% [AH (p=0.001), DE (p=0.001), E (p=0.001)], estudio normal o con necrosis [AH (p=0.001), DE (p=0.001), E (p=0.001)] y género [AH (p=0.002), DE (p=0.006), E (p=0.005)].

Conclusiones. El uso de la nueva herramienta del AF de medicina nuclear es factible. Sus parámetros no se afectaron por el tipo de estrés producido, dosis administrada o fase del estudio por la gammacámara empleada. Por su parte, sí fueron afectados por género, trastornos de conducción interventricular, necrosis y disfunción sistólica.

Palabras clave: Imagen de perfusión miocárdica; Cintigrafía; Terapia de resincronización cardíaca (DeCS).

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Introduction

The prevalence of heart failure is rapidly increasing with major repercussions for patients and the health system. Cardiac resynchronization therapy (CRT) is a new treatment for symptoms associated with heart failure caused by cardiomyopathy and dyssynchrony during the ventricular contraction. Cardiac dyssynchrony is the uncoordinated distribution of electrical activation in the heart pathways, which can be observed in the disordered activation of contractile structures. When the electrical waves are altered or the contractile segments susceptible to stimulation fail, the time of onset of contraction varies with respect to the normal segments (1).

Some patients with cardiomyopathy and heart failure have abnormalities in the electrical system of the heart, such as complete left bundle branch block (LBBB), resulting in an uncoordinated (asynchronous) contraction of the heart muscle. Basically, the goal of CRT is to restore the coordinated action of ventricular pumping back to normal.

However, between 20% and 40% of patients with associated morbidity undergoing this expensive treatment do not show an adequate response (2). The best possible explanation for this phenomenon is that CRT selection criteria —the most relevant include the QRS complex width >120 milliseconds, and the ejection fraction <35% (3,4)— may be insufficient, since electrical synchrony may differ from the mechanical synchrony of the left ventricle. Therefore, it is highly important to carefully select candidates for this type of treatment, and to have the appropriate tools to establish the degree of left ventricular synchronism.

Gated myocardial perfusion by single-photon emission computerized tomography synchronized with electrocardiogram (Gated-SPECT) is widely used in nuclear medicine around the world to diagnose and provide prognosis for ischemic heart disease. It supplies information on global and regional ventricular function, coronary insufficiency and myocardial viability, since many patients with heart failure will undergo a Gated-SPECT as part of their study, and they could benefit from the addition of a new automated technique that allows assessing the left ventricle mechanical synchronism.

Some versions of this tool are already available in the processing programs used by nuclear cardiology studies. The technique is known as phase analysis (PA) by Gated-SPECT and was developed in 2005 by Chen *et al.* (5,6). It is intended to obtain basic information on myocardial perfusion, function parameters, left ventricle mechanical synchronism, and myocardial viability during the same study —which is useful for detecting non-viable territories which are not suitable for implantation of stimulation devices (7)—. Thus, phase analysis is an automatic, reproducible, simply to implement tool that is already included in the latest versions of the main processing programs available in nuclear cardiology (5,8-10). Gated-SPECT myocardial perfusion does not require extra time for its interpretation and is not a dependent operator (1,11).

To obtain the parameters for phase analysis with Gated-SPECT, complex mathematical calculations are performed on the synchronized study with the electrocardiogram to determine systolic thickening (12-14). The values are usually given in degrees (0º-360º), since this range comprises a period of time between the beginning and the end of each cardiac cycle. These values are obtained for each segment of the left ventricle analyzed and indicate at what point of the cycle the contraction begins (15). In this way, it is possible to measure the degree of synchronism of the ventricular contraction, considering that less synchrony implies greater temporal dispersion of contraction.

The main indication for the use of this technique is the prognostic evaluation of the patients who will undergo CRT, which determines if dyssynchrony detectable by usual methods translates into mechanical synchrony and, consequently, if these patients will receive some real benefit from the treatment. In addition, the role of Gated-SPECT becomes relevant when establishing the feasibility of the optimum placement site for the electrodes (16-20).

Furthermore, this technique has been used in patients with heart failure to predict cardiac events, differentiate ischemic heart disease from non-ischemic heart disease, and to predict cardiac events in patients with chronic diseases (21-25).

Different North American and European groups have carried out extensive studies to determine the normal values of the phase analysis parameters (5,11,26,27). Also, an attempt has been made to assess the factors that may or may not influence the parameters that result from the use of the tool, depending on methods, protocols, radiotracers or clinical conditions, among others (28-31). In spite of this, it is possible to see that there is still evidence that supports the definitive inclusion of the technique in clinical guidelines, management protocols and selection criteria of patients who will undergo a CRT.

It should be noted that despite the rapid knowledge and implementation of the technique in international clinical and research fields, there is a certain lack of knowledge about the technique and its availability in clinical practice and research among the medical specialists involved (nuclear physicians, clinical cardiologists and electrophysiologists) in almost the entire region in this context.

In consequence, the objectives of this study are to continue demonstrating the feasibility of the technique, to increase the knowledge of this tool within the local and regional scientific community, and to identify the influences and differences between the obtained values of the phase analysis with Gated-SPECT according to different clinical and technical conditions, usually in the daily practice of nuclear cardiology.

Materials and methods

A retrospective, analytical, observational and non-experimental study was designed in the nuclear medicine service of the institution where this service is provided. All consecutive patients who underwent a Gated-SPECT study of myocardial perfusion between February and March 2016, who had "raw" purchased studies available, were included in order to carry out the required analysis. Patients with a history of rhythm disorders similar to atrial fibrillation were excluded, since they do not allow achieving a good quality GS-PMI study.

The studies were done using two different gamma cameras. Ambulatory studies were usually performed on a Symbia T6 equipment (SIEMENS®), while an INFINIA HAWKEYE (GENERAL ELECTRIC®) equipment was used for hospitalized patients or emergency patients.

The radiopharmaceutical used was ^{99m}Tc-Sestamibi, and the doses administered ranged from 12 mCi (444 MBq) to 30 mCi (1110 MBq) per dose, with a total of 444 MBq (12 mCi) for patients requiring only the post-stress phase. The dose was 888 MBq (24 mCi) for those who required both phases on different days, and 1554 MBq (42 mCi) for those who required two phases on the same day. Patients with outpatient treatment followed a protocol of one or two days (post-stress and post-rest phases on the same day or on a different day) in the post-stress phase (pharmaceutical substance with intravenous dipyridamole or dobutamine or physical exercise) and in the post-rest phase. Inpatients or emergency patients followed a one-day protocol. When the post-stress study was normal, the post-rest phase was not performed due to radiation protection and quality measures.

Both gamma cameras have two heads located in 90° orientation with low energy and high-resolution collimators. Window pulse analyzers at 20% located in 140 KeV photopic were used. The matrix used was 64x64 with maximum zoom of 1.23. Thirty-two images of 20 seconds each were taken per head, for a total of 64 images in step and shot modality. In addition, contour orbit was made in a counterclockwise direction to verify the free execution of the rotation, without touching the patient or the stretcher, with 180° orbits and initial acquisition angle of -45°, with subsequent acquisitions up to 135°.

Tomographic reconstruction was performed using filtered back-projection (Butterworth filter of order 5, and cutoff frequency of 0.5), reorienting the axes of the heart to generate the coronal (short axis), sagittal (long vertical axis) and axial (horizontal long axis) sections. At least one physician with experience in nuclear cardiology carried out the normality assessment of a Gated-SPECT test, presence of ischemia or necrosis, and severity and extent.

To assess the phase analysis of the studies, the PHASE tool of the QPS-QGS program (Cedars-Sinai Medical Center, Los Angeles, USA) was used. The following parameters were obtained from the phase analysis, as well as the corresponding histogram curves: histogram bandwidth (HB), which includes 95% of the values obtained during the measurement phase; standard deviation of the phase (SD), in reference to the distribution phase; entropy (E), a variability measure expressed as a percentage from 0% to 100%, where 0% corresponds to perfect synchrony, and 100% to the maximum possible dyssynchrony in the ventricular contraction, and average regarding the obtained angles. To date, SD and HB are the parameters considered for clinical assessment (14). The least useful recognized parameter is average, so it was excluded from this study. The final display of the tool showing PA parameters considered as normal and abnormal is shown in Figures 1 and 2.

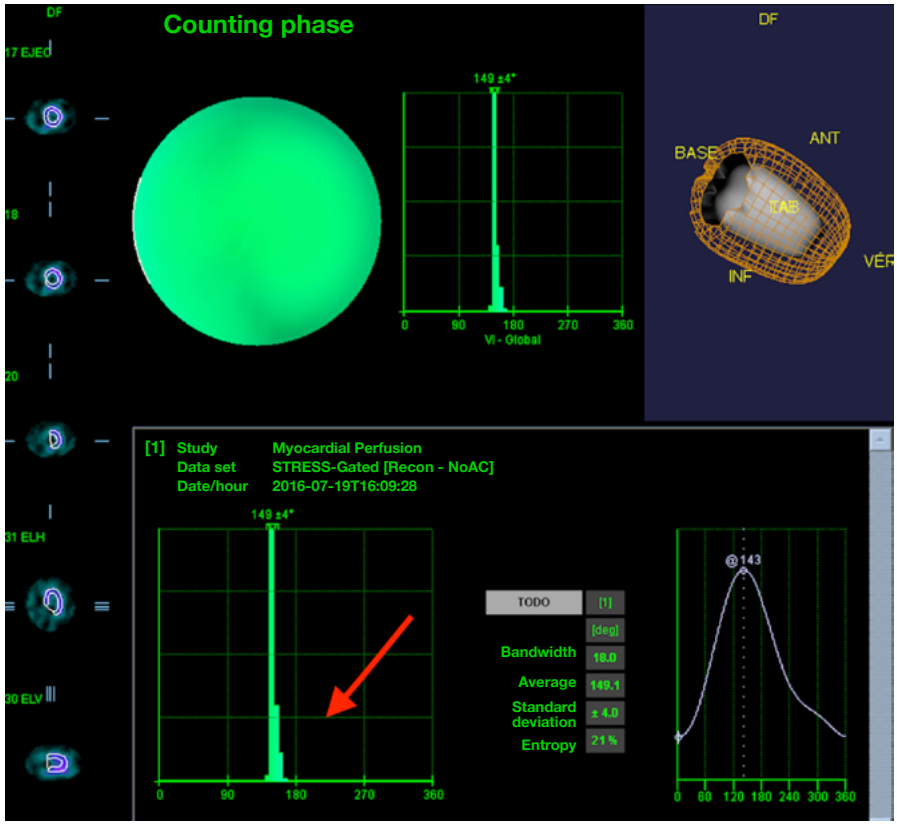

Figure 1. Female patient who underwent a Gated myocardial perfusion SPECT. Histogram representation of phase analysis with narrow bandwidth (arrow) and evidence of left ventricle mechanical synchronism. Source: Own elaboration based on the data obtained in the study.

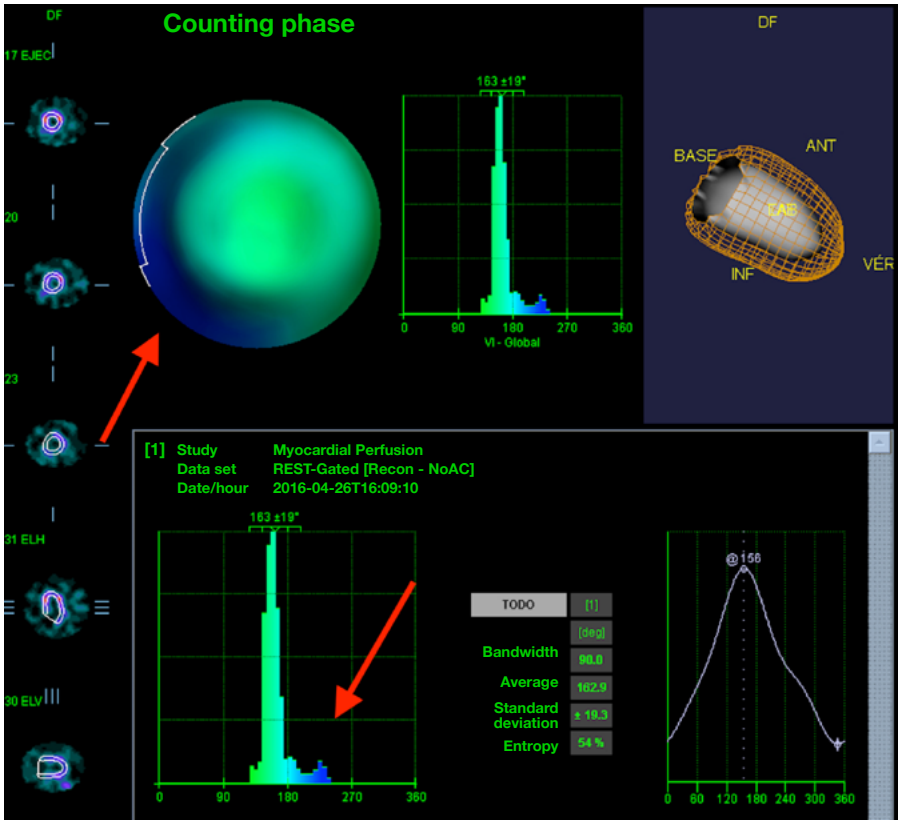

Figure 2. Phase analysis for left ventricular mechanical synchronism assessment by myocardial perfusion SPECT. Phase analysis in which wide bandwidth can be observed over the histogram with evidence of mechanical dyssynchrony of the left ventricle with septal predominance (arrows).
Source: Own elaboration based on the data obtained in the study.

The tool automatically yielded the quantitative parameters for the post-stress and post-rest phases. Based on these data, the corresponding analyzes and comparisons were made.

A descriptive analysis was performed using frequencies in the case of qualitative variables. On the other hand, quantitative variables, whether or not they followed a normal distribution (after applying the Kolmogorov-Smirnov normality test), were expressed by means and standard deviation or medians and interquartile range (IR). For the comparison of means or medians of the quantitative variables, parametric or non-parametric tests were used for independent or related samples, depending on the case. The value $p < 0.05$ was taken as the limit to establish statistical significance. The IBM-SPSS V21® package was used for statistical analysis.

The protocol followed all relevant ethical recommendations and was formally reviewed and approved by the Ethics and Research Committees of Fundación Cardioinfantil - Instituto de Cardiología

Results

300 patients (117 women and 183 men), with a mean age of 65±12.7, were included. The most common indication for the study was chronic or acute chest pain (37.7%), followed by a history of coronary disease at follow-up (22.7%) and thoracic pain in patients with a history of known coronary disease (17%). The remaining 22.5% had other indications such as syncope study, recent arrhythmias, control of patients at cardiovascular risk, dyspnea, cardiac failure, myocardial viability assessment, and preoperative assessment. The technique was applied to all patients, since their study was properly synchronized with the electrocardiogram.

Of all patients, 31 (10.3%) had LBBB interventricular conduction disorders or a history of pacemaker implantation. Depending on the type of stress, 194 patients (64.7%) achieved vasodilator stress with intravenous dipyridamole; 94 (31.3%) with physical exercise test; 6 (2%) with dobutamine, and 6 (2%) with rest study, since they were requested to assess myocardial viability.

Of all the studies performed, 169 (56.9%) were interpreted as totally normal; 39 (13%) presented some degree of ischemia; 62 (20.7%) presented necrosis; 8 (3.7%) ischemia and necrosis, and 22 (7.3%) some type of finding other than ischemia or necrosis, but not considered as completely normal.

114 (38%) patients had their exam taken with a General-Electric® gamma camera and 186 (62%) with a Siemens® gamma camera.

An average dose of 1 GBq (27 mCi) per patient was given in one-day (23.3%) and two-day (62.3%) protocols. The stress-only protocol (12.3%) that was performed in hospitalized or emergency patients had normal results, therefore the rest study was not necessary. 8.7% of the patients presented an ejection fraction <35%, while the remaining 91.3% presented an ejection fraction >35%. The results shown and recorded in the tables are those obtained in the resting phase, except for patients who did not have a resting phase, which correspond to the aforementioned 12.3%.

When analyzing entirely technical factors, only normal perfusion studies were considered to avoid bias as much as possible, taking into account secondary parameter alterations in perfusion defects or synchronism of the patients. Thus, when analyzing normal perfusion studies, no differences were found in any of the parameters regardless of the type of stress exerted [HB (p=0.38), SD (p=0.8), E (p=0.84)], and used dose [HB (p=0.19), SD (p=0.05), E (p=0.06)]. Also, no

differences between patients with or without a history of known coronary disease were observed [HB (p=0.44), SD (p=0.18), E (p=0.17)]. As for the gamma camera used, a difference in one of the parameters was found, while the other two did not show any [HB (p=0.02), SD (p=0.06), E (p=0.08)].

The analysis of PA parameters in patients undergoing both phases of the study (post-stress and post-rest) showed that there were no significant differences (analysis for related samples) when examining HB (p=0.4), SD (p=0.6) and E (p=0.7) in normal perfusion studies. On the other hand, when all the studies were analyzed, only differences in E values (p=0.01) could be observed, with no differences in HB (p=0.09) or SD (p=0.2).

Significant differences were found between the parameters of patients who had conduction disorders and those who did not: HB (p=0.001), SD (p=0.02), E (p=0.001). In turn, there were differences when comparing patients with ejection fraction greater or lower than 35% in all parameters, regardless of the phase: HB (p=0.001), SD (p=0.001), E (p=0.001).

There were significant differences in all parameters when comparing normal perfusion studies with necrosis studies: HB (p=0.001), SD (p=0.001), E (p=0.001). The observation of the parameters in both normal perfusion studies and all studies showed significant differences between men and women in all parameters: HB (p=0.002), SD (p=0.006), E (p=0.005). The numerical values are shown in Table 1.

Table 1. Relevant results of phase analysis parameters.

Parameter	Subgroup (n)	HB	p	SD	p	E	p
Dose *	24 mCi (98)	18 IR: 12	0.19	4.1 IR: 6	0.05	24 IR: 11.3	0.06
	42 mCi (34)	24 IR: 18		5.7 IR: 3.9		29.5 IR: 12	
Study phase	Post-stress (257)	24 IR:24	0.095	6 IR:6	0.2	32 IR: 18	0.01 0.7 *
	Post-rest (257)	24 IR: 24		5.7 IR: 7.2		30 IR: 20	
Gamma Camera *	Siemens (110)	18 IR: 12	0.02	4.1 IR: 2.5	0.06	24 IR: 12	0.08
	General-Electric (59)	24 IR:12		5.9 IR: 4.6		29 IR: 17	
Type of stress *	Physical (60)	18 IR:12	0.38	4.2 IR: 2.4	0.8	24 IR: 11.3	0.84
	Pharmacological (153)	18 IR: 18		4.3 IR: 3.5		25 IR: 16.5	
Conduction disorder	Yes (31)	42 IR: 48	0.001	10 IR: 5.3	0.02	38 IR: 33	0.001
	No (269)	24 IR: 18		5.3 IR: 5.3		29 IR: 19	
Result	Normal (169)	18 IR: 6	0.001	4.2 IR: 2.7	0.001	24 IR: 13.6	0.001
	Necrosis (62)	42 IR: 54		11.9 IR: 19.6		44 IR: 22.5	
Gender	Male (183)	30 IR: 30	0.002	7 IR:8.6	0.006	35 IR:21	0.005
	Female (117)	18 IR: 12		4.1 IR: 2.6		24 IR:12	
Ejection fraction	>35% (273)	24 IR: 12	0.001	5.2 IR:4.5	0.001	28 IR: 16	0.001
	<35% (27)	104 IR: 103		28.8 IR: 26.3		58 IR: 9.8	

* Patients with normal Gated-SPECT.
IR: inrequartile range; HB: histogram bandwidth; SD: Standard deviation of the phase; E: entropy.
Source: Own elaboration based on data obtained in the study.

Discussion

This research demonstrates the feasibility of the technique known as phase analysis of gated SPECT myocardial perfusion in nuclear medicine services and, therefore, in the current context of the profession. This is an automatic tool that is easy to apply to all Gated-SPECT studies and has gradually increased its usefulness worldwide.

The study did not show differences between parameters in both phases when examining only the normal studies. Only differences in entropy were found in all studies. These results are similar to those found by Zhou *et al.* (32), who studied 60 patients without finding differences between PA parameters in post-stress and post-rest studies. This is one of the most relevant findings of this study and is of great importance, since many nuclear medicine services conduct Gated-SPECT studies only in the post-rest phase, while other studies (as this one) do not include the post-rest phase if the post-stress phase is normal. The results show that the tool can be used in any of the phases without differences in the results. Furthermore, no dose-dependent differences were found, which is important since not all services, phases and patients use the same doses of radiotracer.

No relevant differences were found in relation to stress type (physical or pharmacological). This is of great importance because the type of stress can be provided in the aforementioned manners without affecting PA parameters based on the type of patient or clinical indication. Additionally, whether or not a patient has a known coronary disease does not seem to be influential, as long as the perfusion study is normal. That one of the analyzed parameters showed differences while the other two did not show any depending on the gamma camera used, which implies that it could be completely confirmed in other studies, although there is a trend towards non-difference.

As expected, significant differences were found between patients with and without conduction disorders when comparing all studies. In consequence, it is possible to effectively differentiate patients without conduction disorders from those with electrical synchronism alterations

and left ventricle mechanical synchronism alterations. This finding is similar to other studies, and confirms the usefulness of the technique in this regard (11,14,26). However, the real usefulness of the tool, rather than discriminating between patients with or without conduction disorders, is to determine the cut-off points of the parameters of the phase analysis, which will help to establish if patients would respond or not to the CRT, although, this is not an objective of this study.

Moreover, differences were found among PA parameters regarding gender. When observing all studies or only normal studies, the parameters were higher in men than in women. The most relevant studies published that sought to obtain normal values and cut-off points of normality were carried out by Chen *et al.* (5) and Romero-Farina *et al*. (11), which also showed these differences. Thus, normality parameters should be considered for each gender.

Similarly, significant differences were observed between patients with normal myocardial perfusion studies and necrosis, as well as between patients with or without major systolic dysfunction (ejection fraction < or >35%, respectively). These results are consistent with other studies that included patients with necrosis or systolic dysfunction, and showed that the degree of left ventricular mechanical dyssynchrony is directly related to systolic dysfunction and to the extent of perfusion defects (33,34).

Continuing this type of studies is important to familiarize the branches of medicine involved (nuclear medicine and cardiology) with the tool and its clinical utility, to gradually resolve any concerns that may arise from it.

A possible limitation of the study, and a possible source of error, is its retrospective character. With this in mind, the methodology and results obtained make it difficult to perform an adequate multivariate analysis to assess the influence of some variables on others.

Another factor that should be considered is that, when referring normal perfusion studies, patients are not necessarily completely normal from a clinical cardiovascular point of view, but are patients with normal perfusion studies. This occurs because few clinically normal patients who require myocardial perfusion studies are referred to these services. Likewise, as the clinical implementation of the tool increases, the number of clinically normal patients who would benefit from the study decreases.

In addition, this article approaches clinical reality without having normal patients as a direct objective, but considering the patients who, in general, are studied in myocardial perfusion investigations and those who would receive potential benefits from the technique.

Conclusions

The use of the phase analysis tool included in the main programs for the processing of myocardial perfusion studies is feasible in the current professional context and can be used in the corresponding clinical scenario.

The parameters of the phase analysis are not affected and can, therefore, be used without depending on the type of stress (physical or pharmacological), the dose administered, the phase of the study in which the test is performed (post-stress or post-rest), or the gamma camera used.

Nevertheless, these parameters are affected by the variables of the patients themselves, such as gender (which must have normal values), the presence of intracardiac conduction disorders or fixed perfusion defects considered as necrosis, and systolic dysfunction.

Conflict of interest

None stated by the authors.

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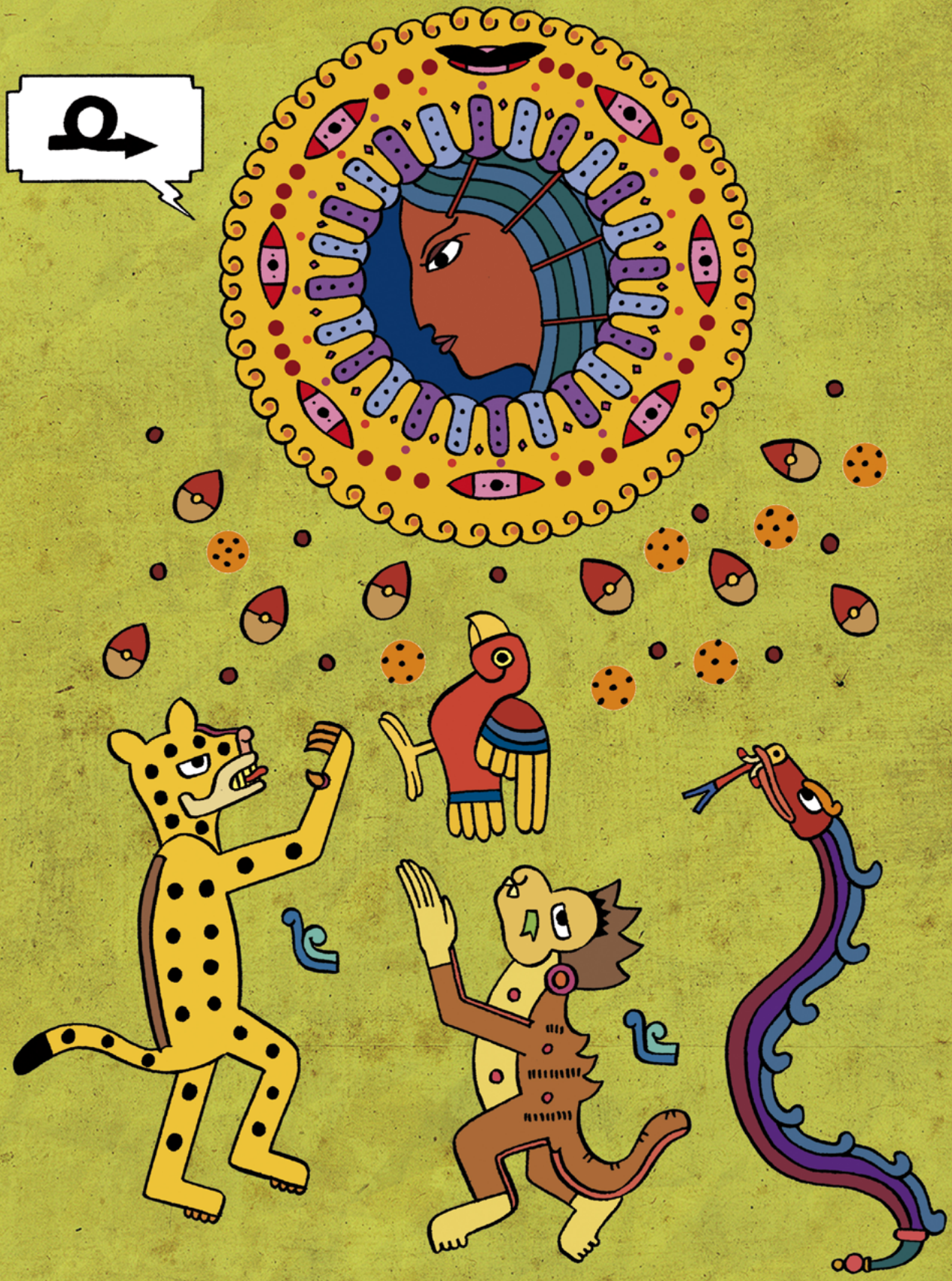

Iván "Ivanquio" Benavides
"El niño vacío" – 005
Técnica: tinta, color digital

ORIGINAL RESEARCH

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Health, mental health, music and music therapy in a Colombian indigenous community from Cota, 2012-2014

Salud, salud mental, música y musicoterapia en una comunidad indígena colombiana. Cota, 2012-2014

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| Abstract |

Introduction: The intercultural approach to indigenous peoples in the American continent requires knowledge of the concepts and cultural practices that favor or impair health, considering their own perspective.

Objective: To understand the meaning of health and mental health in the context of a Muisca community from Cota, Colombia, as well as the potential of music therapy to promote health.

Materials and methods: Case study with a qualitative approach —social research of second order. Data collection included social cartography, in-depth interviews, focus groups, participant observation, and music therapy sessions.

Results: This community has a different conception of health in relation to the beliefs of the dominant society, since health and mental health are not separate ideas. Music is integrated to community activities and health practice.

Conclusions: The re-indigenization process is a political decision with cultural, health and organizational consequences. This type of communities cannot be equated with the dominant society or other indigenous groups in terms of health decisions. Public health requires an intercultural dialogue to work adequately with these communities.

Keywords: Indigenous Population; Health; Mental Health; Music Therapy; Public Health; Colonialism (MeSH).

Morales-Hernández LA, Urrego-Mendoza ZC. Health, mental health, music and music therapy in a Colombian indigenous community from Cota, 2012-2014. Rev. Fac. Med. 2017;65(3):461-5. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.56413.

| Resumen |

Introducción. El enfoque intercultural hacia las comunidades nativas americanas requiere el conocimiento de los conceptos y las prácticas que favorecen o perjudican la salud de estas poblaciones desde su propia perspectiva.

Objetivo. Comprender el significado de salud y salud mental que circula en las narrativas de la comunidad reetnizada indígena muisca de Cota y el potencial de la musicoterapia comunitaria para promoverlas.

Materiales y métodos. Estudio de caso con enfoque cualitativo tipo investigación social de segundo orden. Para la recolección de datos se utilizó cartografía social, entrevistas a profundidad, grupos focales, observación participante y proceso musicoterapéutico.

Resultados. La comunidad maneja un concepto de salud diferente al de la sociedad mayoritaria. No hay división entre los conceptos de salud y salud mental. La música está integrada a las actividades comunitarias y de sanación.

Conclusiones. La reetnización es una decisión política con implicaciones culturales, organizativas y de salud. Las comunidades reetnizadas no pueden ser equiparadas con la sociedad dominante ni con otros grupos indígenas en cuanto a decisiones en salud. La salud pública requiere un diálogo intercultural que permita el trabajo adecuado con estas comunidades.

Palabras clave: Población indígena; Salud; Salud mental; Musicoterapia; Salud Pública; Colonialismo (DeCS).

Morales-Hernández LA, Urrego-Mendoza ZC. [Salud, salud mental, música y musicoterapia en una comunidad indígena colombiana.

Cota, 2012-2014]. Rev. Fac. Med. 2017;65(3):461-5. Ennglish. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.56413.

Introduction

The cultural capital of a community (ancestral knowledge, music, community practices, stories and accounts) is part of its legacy, defines its identity and supports its functioning. The concepts of a community, the related aspects, and the cultural practices that have an influence on health define the approach, in general and from a public health perspective.

The Muisca community that participated in this study lives in Cota, Cundinamarca, near Bogotá. It is an indigenous community, currently undergoing a re-indigenization process, for which the reconstruction of its cultural elements has been fundamental. Music, in a broad sense (body-sound-musical narrative), was used as the main means of contact with this community and as a therapeutic tool (music therapy) (1,2).

Culture and health

The colonialism imposed by Europe 500 years ago, and perpetuated by hegemonic science, is an epistemic obstacle to learn about the concepts of the indigenous communities and to define approaches suitable for each context. An intercultural understanding is necessary (3) to make proposals closer to local cultures, especially indigenous cultures. Interculturality facilitates describing and understanding ontologies, epistemologies and practices from different perspectives of reality, and appreciating their uniqueness.

The dominant concepts of health and mental health are based on models alien to indigenous cultures, which must be re-dimensioned to understand their knowledge, customs and strategies, and to avoid authoritarian and colonialist perspectives. Only in this way, a closer approach to the contexts and interests of these communities can be achieved.

Health, mental health and interculturality

The concept of health for indigenous peoples is different from the hegemonic concept of European medicine, even in its paradigmatic foundations. Usually, some native peoples have an idea of unity between body, mind, actions, community, health (4,5) and the onset of a disease. Others conceive disease as the product of an alteration of the mind, which occurs when such unity, or balance, is lost (6). This is not an individual phenomenon, but the manifestation of a disorder within the community itself.

In this context, the concept of mental health is meaningless for the indigenous peoples, because there is no fragmentation of the individual-community unit. The recipients of healing include the individual, the territory and the community, who are healed by sacred plants (7), music (in a ritualistic performance), words, *pagamentos*[1], among others, in a period and territory established by the law of each community.

Intercultural understanding requires a dialogue between different strands of knowledge, that is, a participatory process between the authors and the addressed peoples. Interculturality can be observed at interpersonal, group and structural levels, and it will be achieved when we become equal while being different (8). Furthermore, interculturality represents the relationship and the attitude of the members of one culture towards the elements of another. In the case of the indigenous peoples, interculturality regarding health implies equally incorporating their perspective on rights, understandings and epistemologies (9).

Decolonization, hybridization and re-indigenization processes

European colonization brought along a model for the valuation of people, knowledge and cultures that became hegemonic. According to this model, white men are the center of history, and their patterns and values are ethnically focused on Europe; likewise, in their epistemological model, the observer transcends the object (10). This object, in turn, is fragmented in different pieces —reality is reduced to a mechanical level—, which are analyzed (11) based on a numerical rationality (12). Results, knowledge and production are more valued, if they stick to this model.

Since the end of the XX century, a hybridization process begun to take place. Hybridization is an epistemological operation in which different structures, objects and practices (with different origins) are combined to generate new structures, new objects and new practices (13). In this way, culture and identity are no longer a set of fixed traits in a fluid and interconnected world, and different definitions emerge in each of their expressions. The understanding of indigenous and Latin American cultures requires open and plural readings to construct coexistence projects.

The need to decolonize the Latin American society in all its structures, forms and purposes is perceived in the academy and in other cultures. It is sought that the "subalterns" tell their own story, to decolonize beings and knowledge, in the framework of a transformational project through critical praxis. Thus, a Latin American model based on ancestral knowledge is proposed, in which the epistemological dialogue allows positioning a different idea of interculturality and the emergence of frontier thinking (14).

The re-indigenization processes help turning cultural diversity into heritage to consolidate a pluralist image of the nation. In accordance with the political environment, rights are claimed. In the case of the indigenous community of Cota, a generic identity (being indigenous) and a particular way of identifying themselves (member of the Muisca community) have been sought (15).

Faced with such situations, communities take cultural elements with which they identify, and build a pattern that is later staged (performative development). Thus, they validate cultural singularities —for example, cultural reconstruction— and neutralize racial traces, thereby strengthening language, clothing, customs and continuity in time and space.

In indigenous cultures, performance is clearer in music or healing rituals, since they follow steps and methods that are visible to the spectator, who also takes part. During community practices, the youngest perform rituals accompanied by music and clothing, create spaces for social communication and inclusion, and become camouflaged. In consequence, the community rebuilds its political spaces in a counter-hegemonic way, establishing itself as the center and source of its own transformation. Mimesis involves taking the cultural traces, making them visible, and experiencing them, so that they can be used to establish and lead the way (16). With this in mind, all the elements of the Muisca re-indigenization (revitalization) are valid.

The indigenous Muisca community of Cota has undergone a re-indigenization process and has reconstructed its memory based on

1 Translator's note: *Pagamento* refers to actions done based on a principle of reciprocity, giving always something in return, whether it is material or in species.

the *muysqubum* language, their ancestral community practices, and the knowledge of other Colombian and American indigenous peoples. All these peoples have created a relationship network and have incorporated musical, bromatological, medicinal and organizational elements, among others.

Indigenous cultural practices and music

According to the principles of each indigenous community, cultural practices obey the legacy of their ancestors, that is to say, their origins. These practices, in a ritual context, give meaning and sense to the existence of the community and to each of its members. Rituals keep the contact with the origin law alive, articulate the culture of the community with the cosmos, and give coherence to daily life. Cultural practices (music, dance) are mechanisms for communication between the communities and, in a broader sense, are ways to commemorate, contact and provide unity with the cosmos, based on the concept that each indigenous group has. The spoken word should be full of meaning and sense. In community life, words are used in different practices, and are given different categories: *word of life, word of advice, word of work, word of abundance* and *word of community* or *government*. Each one has an organizational power.

The expression of the shamanic song (amensural chants) is full of meaning, because the shaman is the holder of the worldview and the mythology of the group, which are transmitted through his songs. The songs are learned from communications with the beyond using entheogenic weeds, and are transmitted from generation to generation, often in a secret language. Chants and music have the power to invoke powerful spirits (17).

Music and music therapy in public health

The knowledge of cultural referents is a particular universe of languages with its own meaning —in the same fabric or narrative— that unifies words, stories, movement, mimics and music, among other elements.

Music is a cultural expression that is part of the knowledge of a community and, therefore, is transmitted in their educational systems. Music creates imaginary spaces, offers social cohesion, opens up possibilities for subjectivation and is involved in communicative strategies —at the market level. It also fulfills other social functions such as aesthetic enjoyment, entertainment, communication, symbolic representation, physical response and reinforcement, in accordance with norms, social institutions and religious rites. It also contributes to the continuity and establishment of culture and the integration of society (18). A narrative space of great symbolic content is created through music, which offers identity from and for the group that constructs and uses it.

An important concept to understand the role of music in health is "musicing", which refers to any activity related to the musical act. In general, it refers to the relation of humans with music during a performance, and to the power that this mutual relation has on the experiences, feelings, thoughts, images and interactions, in other words, the influence music has on the lives of the people around it (19).

The spectrum of "musicing" involves the entire network of relationships involved in a performance. Stige (20) states that "musicing" refers to both music and a particular activity that involves multiple people and social relationships when it is staged. The meaning of "musicing" (an action that has an effect) is difficult to express in simple words. It is easier to experience it in a sensory way; it resembles the grooving (atmosphere) that a musical rhythm generates or the description of a flavor for who has not tried it yet. This is a key concept in the development of music therapy as a performance, to understand how the music therapist and the consultant correlate —whether it is a person, a family or a community—, and how they experience its effect in practice.

In music therapy, a qualified therapist uses music or its elements (sound, rhythm, melody and harmony) on a person or group to facilitate and promote communication, relationships, learning, mobilization, expression and organization, in order to solve physical, emotional, mental, social and cognitive needs.

The objective of music therapy is to develop potential skills or to restore the individual's functions through prevention, rehabilitation or treatment, with the intention of achieving a better intra or interpersonal integration (21). Its focus is to strengthen social representations (22), consolidate cultural capital (23), and promote social welfare in, through and with the community.

Regarding music therapy and its effect on mental health in indigenous communities, specific works that directly answered the question raised in this research were not found. In consequence, this work intends to understand the meaning of health and mental health in the narratives of the inhabitants of the Muisca community from Cota, and the potential of community music therapy to promote them.

Materials and methods

A case study (community being the case) was conducted with a qualitative approach based on a second order social research for a period of 32 months (Figure 1). In addition to music therapy, social cartography, in-depth interviews, focus groups and participant observation were used as data collection techniques. A snowball sampling (25) was used to select the subjects. The systemic constructivist-constructionist approach was used as a theoretical and epistemological resource.

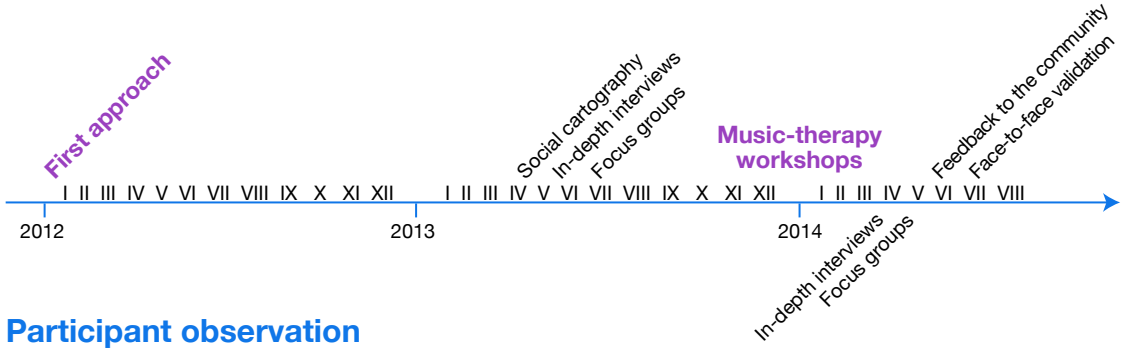

Figure 1. Study timeline.
Source: Own elaboration based on the data obtained in the study.

A narrative and a paradigmatic analysis were performed on the narratives obtained from participant observation, interviews and focus groups (26). The programs NVivo (QSR International, Australia) and CmapTools (Florida Institute for Human and Machine Cognition, USA) were used to assist the organization and analysis of information.

Results

Description of the Community

Culture and traditional medicine are of great importance to the community. Medical practice is built together with other town councils and indigenous reservations, and involves health, music, culture, territory and networks. Consciousness of territory as a spiritual and wisdom source was a constant variable for the analysis, since, for the inhabitants, "the body is our territory" and there is continuity between the mother earth and the individual body. Some problems regarding internal communication within the community (inadequate, confusing or incoherent messages) were found. Likewise, discrimination, especially sexism, was observed, as well as conflicts of power among leaders, and resolution mechanisms for such problems in community spaces.

Health and mental health

There is not a clear differentiation between health and mental health. Health is understood as "integrity", "community" and "it emerges from us." It is related to balance and here, just like in other vitalist medicine models, symptoms are manifestations of real diseases such as predominance of individualism, loss of connection with the mother earth and the spiritual father, lack of awareness of the law of origin, corruption and lack of integrity, coherence and communication. This contrasts with the conception that the traditional medicine has on the same topic, that is, that symptoms are the disease.

Mother earth and music are equally considered as intrinsic elements of health. Music is expressed as a factor that promotes health and a component of healing activities. The narrative analysis mentions the vibrational and energetic links that it generates.

Some constitutive elements of healing are plants and music (or chants). The relationship between healing and the awareness of the "gardener" role —being responsible for the mother earth and members of a community— is evident. Healing also relates to the coherence between heart, thought, word and action.

Health and mental health appear as a continuum in both analysis; the understanding of this concept includes the individual, and transforms into completeness connecting the collective, the spiritual and the relationship with other living beings.

Cultural components associated with music

In general, music (dance, sound, singing, cooing, etc.) makes up more than half of the cultural activities and expressions of the community. The construction of musical instruments occurs in a smaller proportion.

Dances have a repetitive circular and spiral movement, which closes and opens the spaces and has a direct relation with territory awareness. The Andean music, used with symbolic meaning, is linked to the experience of traditional medicine, and its meaning seeks to be cosmic.

Music is connected with community healing practices, territory-body relationship, recovery of ancestral memory, balance and energy, and holistically approaches the concept of health. Music has different uses: recreational and educational, integration of the community, and ceremonial and ancestral aspects associated with spirituality and health.

Connections between music and health

There is evidence of a direct connection between dance and health, which integrates vibration and culture. Dance has a special effect on the sense of community (the conjugation of the subject *we*), as it links its members to each other and to mother earth.

Conscience music integrates the system and provides health to people and the community; it is a community practice related to ancestral heritage, territory, medicine and healing. This healing occurs between the members of the community (people) and nature. More than being a ludic musical activity, it establishes contact with consciousness at the different levels of the system: vibrations, memory, molecules, medicine, people, community and culture.

Music and dance connect with health and have the ability to transform the state of things, people and relationships. For this community, music and health have several connections, some at the molecular level, and others in the internal structures of a person or the community.

Thus, music can be a healing or distorting element, depending on how it is used. It can be used, for example, to share and socialize, to accompany the rite, to heal directly as a part of the dance, with a meaning different to the healing ritual that emphasizes on the cosmic, communitarian and territorial dimensions. In other words, "you are what you listen to", how aware you are, how you perform, and your intention during the act as a whole.

Contribution of music therapy to health processes

Music therapy, as a tool, has the power to give order to the body, the territory and the environment. It contributes to the expansion of awareness of the harmony between the body and the environment, as well as of internal-external communication, the ancestral memory, the harmonization of community relations, and the connection with cosmic principles (law of origin) ruling this community.

Discussion

Decolonized and re-indigenized knowledge is different from traditional knowledge in Western cultures (15). For example, while white peoples see only a plant, indigenous peoples perceive the cosmos, the people and the powers. In this scenario, there is a difference between the myth of nature and the reality of the myth. In order to approach the meaning of this knowledge, it is necessary to "demythologize history and re-enchant it in a reified representation (7, p39)."

Today, re-indigenization (revitalization of the indigenous) identifies the Muisca community of Cota as a private, independent community with its own (rebuilt) cultural elements, knowledge and alliances with other ethnic groups that recognize them as indigenous in their cultural, organizational and political structure. This community reached a symbolic status with a transforming effect of the reality that characterized its Muisca identity.

It is worth mentioning that the community prefers the expression "resignification of the indigenous" over the term " re-indigenization." Its members shared the conclusions, participated in the discussion and were motivated to continue with music and music therapy activities for community strengthening. The relationships that this community establishes with music generate bonds between its members and with the self in its entirety, from a molecule to Mother Nature, passing through the community in its cosmic sense.

Future research on mental health and public health with indigenous peoples should be directed towards a truly transformative intercultural dialogue between public health and the communities, in order to contribute in a relevant way to the good life of the ethnic group, respecting their ancestry and their methodologies to build knowledge.

Conclusions

The concept of health found in the community narrative encompasses individuals, mind, body, territory, and mother earth. In this concept, both the spiritual and the ecological elements are involved. There is no difference between health and mental health, because the latter only emphasizes the first. Disease is related to the supremacy of individual interests over community interests.

For the re-indigenized Muiscas from Cota, health and healing are holistic phenomena that surpass an individualist approach, and are connected to the universe —it is better to say multiverse— of relationships (27,28), in which performance includes consciousness, plants, sound, music, thought, spirit, territory and their connections in a syncretic web woven with ancestral and contemporary elements.

Music is a cultural element evident in most of the community's activities; it is a tool that helps strengthen and heal the community. In such context, music therapy is a transformative act when conditions are given to experience the performance. The "musicing" act allowed the emergence of special states of consciousness and the contact with the ancestral memory. In addition, it allowed the Muiscas to verify the manifestation of knowledge related to health and mental health. This knowledge could be incorporated into their new law of origin (neomuisca), which is memory and code for these people.

Conflict of interests

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ORIGINAL RESEARCH

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Effects of yoga *(pranayama)* on lung function and lactate kinetics in sedentary adults at intermediate altitude

Efectos de la práctica de yoga (pranayamas) sobre la función pulmonar y cinética del lactato en adultos sedentarios de altitud intermedia

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| Abstract |

Introduction: Clinical evidence-based medicine has found increasing benefits of yoga.

Objective: To describe the effects on lung function assessed by rest spirometry —vital forced capacity (VFC), forced expiratory volume in one second (FEV1), and FEV1/VFC ratio— in a group of apparently healthy adults, as well as to explore the effects of *pranayama* techniques in lactate kinetics.

Materials and methods: Quasi-experimental study performed in sedentary adults with no prior experience in yoga practice, who received a stimulus during 12 weeks with a minimum frequency of two sessions per week. They were divided into a yoga group (YG) and a control group (CG). Body composition, blood pressure, heart rate, double product (DP), peripheral oxygen saturation (SpO_2), blood lactate ($Lact_s$), hematocrit (Htc) by micromethod, and spirometry were determined before and after a training plan with *Pranayama*. The variables analyzed were forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and FEV1/FVC ratio.

Results: Significant differences were found in FVC, FEV1 and lactate among YG and CG ($p<0.05$), and before and after the stimulus in the YG ($p<0.05$). The double product improved in both groups.

Conclusions: Targeted practice of *pranayama* for 12 weeks improved FVC, FEV1, double product ($p <0.05$) and lactate production capacity (anaerobic capacity).

Keywords: Yoga; Lactic Acid; Spirometry; Altitude; Sedentary Lifestyle (MeSH).

| Resumen |

Introducción. La medicina basada en evidencia clínica encuentra cada vez más beneficios del yoga en sus practicantes.

Objetivo. Describir los efectos en la función pulmonar y la cinética del lactato ocasionados por la práctica de *pranayamas* en adultos con apariencia saludable.

Materiales y métodos. Se realizó un estudio cuasiexperimental en adultos sedentarios sin experiencia en la práctica de yoga, quienes realizaron un estímulo durante 12 semanas con un frecuencia mínima de dos sesiones por semana. Se dividieron en un grupo de yoga (GY) y un grupo de control (GC). Se determinó composición corporal, presión arterial, frecuencia cardíaca, doble producto (DP), saturación periférica de oxígeno (SpO_2), lactato en sangre ($Lact_s$), hematocrito (Htc) por micrométodo, y espirometría previa y posterior a un plan de entrenamiento con *pranayamas*. Las variables analizadas fueron: capacidad vital forzada (CVF), volumen espiratorio forzado del primer segundo (VEF1) y relación VEF1/CVF.

Resultados. Los resultados de la CVF, VEF1 y lactato presentaron diferencias significativas entre el GY y el GC ($p<0.05$), antes y después del estímulo en el GY ($p<0.05$). El doble producto mejoró en ambos grupos.

Conclusiones. La práctica dirigida de *pranayamas* durante 12 semanas mejoró la CVF, el VEF1, el doble producto ($p<0.05$) y la capacidad de producción de lactato (capacidad anaeróbica).

Palabras clave: Yoga; Ácido láctico; Espirometría; Altitud; Estilo de vida sedentario (DeCS).

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Introduction

Yoga is an ancestral philosophy that developed more than 5000 years ago and is based on metaphysical dualism (*Sankhya*) (1). It promotes the harmony of the body, mind and soul with the rhythms of the universe for an integral growth (2). In Western countries, yoga is practiced by a large number of people and its popularity continues to grow. It favors diffusion and oxygenation processes in tissues, and has shown benefits in the control and management of autonomic nervous system alterations (3), high blood pressure, angina pectoris (4), bronchial asthma (5), depression (6) and oxidative stress management (7).

Yoga is represented by a tree with eight limbs (Figure 1), each symbolizing a precept: universal morality (*yama*), personal observances (*niyama*), body postures (*asana*), breathing techniques (*pranayama*), sense withdrawal (*prathyahara*), focused concentration (*dharana*), devotion or meditation (*dhyana*) and complete meditation or trance (*samadhi*) (2,3). The most popular yoga practices emphasize on postures, breathing exercises, concentration and meditation (8,9).

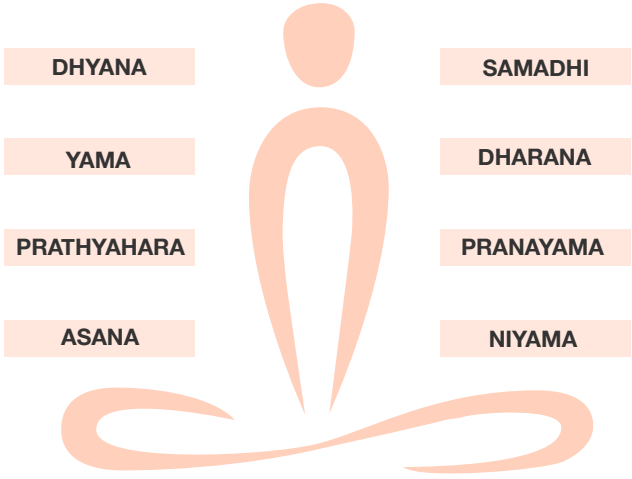

Figure 1. Eight limbs or precepts of yoga.
Source: Own elaboration based on the data obtained in the study.

The purpose of this study is to describe the effect of yoga on respiratory function at intermediate altitudes, and to assess the changes in the lactate kinetics of people who have never practiced this discipline. Each type of yoga stimulates specific physiological processes; however, the study focuses on the effect of *pranayama* on respiratory function and anaerobic capacity.

Ventilatory mechanics is a mixed process in terms of energy expenditure. While meditation decreases the metabolic rate, *pranayama* increases it (10); this phenomenon has been associated with the diversity in the composition of the fibers and the energetic pathways used by the muscles involved in ventilation (11-16). Mechanical action correlates to the energy system used as well as to the production-clearance of intermediary metabolites.

The isometric contraction of the laryngeal muscles (17) that have a high anaerobic component (19-21) and the rapid contractions of the genioglossus, genihyoid and sternohyoid muscles with type II fibers distribution pattern require a higher production of lactate (22,23). The lactate production capacity of the diaphragm varies according to:

a) The presence of different isoforms of troponin in the three portions of the diaphragm (sternal, costal and lumbar), which confers different strength capacity depending on the number of sites where Ca^{++} can be bound (fast: TnC-f with 2 binding sities; slow: TnC with 1 binding site).
b) The presence of different myosin isoforms, which allows different degrees of resistance to fatigue (resistant: IIa-$MyHC_{2A}$, intermediate: IIx$MyHC_{2x}$, and highly susceptible to fatigue with high glycolytic capacity and low oxidative activity: IIb$MyHC_{2B}$ + $MyHC_{2X}$) (12).
c) The presence of structural ($MyLC_{20}$) and regulatory ($MyLC_{17}$) myosin.

Due to immunohistochemistry, the transition from embryonic and fetal myosin isoforms to adult isoforms has been documented, but further studies are still required.

Therefore, it is possible to think that respiratory muscles can be trained (24,25) and that this training can be assessed by means of spirometry, ultrasound (26), and the determination of intermediary metabolites in the blood (such as lactate). Another determinant of respiratory muscle work is blood flow, since a limitation in respiratory muscle perfusion can affect performance and contribute to fatigue (27). The blood flow can be modified with postures and breathing techniques.

It has been estimated that energy expenditure during pranayama practice ranges from 1.91 kcal/min[1] to 3.79 kcal/min[1], with a metabolic rate between 1-2 units of metabolic equivalent of task (MET), (26,27). This fact, together with the diversity of fibers and the energetic pathways used, leads to an increase of lactate concentrations in the blood after practicing *pranayama* (29). The level of lactate depends on the type of load, the level of oxygen consumption (VO_2), and the training level of the individual (30). Although yoga practice remains below the lactic threshold (26), physical performance may improve due to increased ventilatory efficiency and increased cardiovascular reserve.

The metabolic effects observed in yoga practitioners have allowed to understand the modification mechanisms of risk factors for cardiovascular disease (31,32), as well as the metabolic pathways used during practices that require greater energy expenditure and increased accumulation of blood lactate.

The purpose of this study is to evaluate the respiratory and metabolic effects of a *pranayama* practice performed for 12 weeks by a population of adults with no prior experience in this discipline. Respiratory effects were assessed through respiratory function tests (FVC, FEV1 and FEV1/FVC). The metabolic effect was assessed by lactate variation after *pranayama* practice, and was compared to blood lactate variation after exercise on a cycle ergometer.

Materials and methods

A quasi-experimental study was conducted with 103 people, 14 men (M) and 89 women (W), living in Bogotá (altitude: 2600 m, barometric pressure: 564.9±1.05 mmHg, temperature 12.5±0.9°C). The individuals were divided into two groups: the yoga group (YG), including 72 people (M: 11, W: 61) who practiced *pranayama* for 12 weeks, and the control group (CG) with 31 people (M:3, W:28) who performed programmed physical exercise according to the physical activity plan of the neighborhood of residence. This plan included strength work through bodyweight exercises, mobility of large muscle groups for aerobic work, stimulation for cardiovascular and respiratory system maintenance, and coordination exercises.

The sample was selected for convenience, and participants enrolled voluntarily in two programs supported by the Physical Activity and Culture Training Center of SENA and offered by the Local Mayor's

Office of Kennedy. The study variables were resting spirometry (FEV 1, FVC and FEV 1/FVC ratio) for lung function, and blood lactate for blood chemistry. Control variables were age, sex, weight, height, BMI, BF% and hematocrit. Attendance to training sessions was the third variable. The analysis of data only included the information of individuals who attended 90% of the sessions in the YG and the CG.

A medical examination was performed to participants; vital signs at rest (blood pressure, heart rate, peripheral oxygen saturation) were recorded and body composition was determined by bioimpedanciometry (Fit-Scan BC-585F of Tanita®, Japan; and Harpenden anthropometer of Holtain®, United Kingdom). These measurements were taken between 7:00 a.m. and 9:00 a.m., based on a protocol of no intense physical activity 24 hours before the practice, ingestion of liquids on demand, and no intake of energy drinks, tea or caffeine. Informed consent was signed after the presentation and explanation of the study.

The next day, at 7:00 a.m., three resting spirometry measurements were taken, and the data of the best tests were retained. FVC, FEV1 and FEV1/FVC ratio were recorded using the Metamax-3B gas analyzer (Cortex®, Germany). Blood lactate from the left ear lobe (Lactate Scout+®, EKF, Germany) and hematocrit by micromethod of a blood sample obtained from the same site (Microcentrifuge CT- 1, Indulab®, Colombia) were examined at rest, 5 minutes before starting the exercise. A submaximal effort test (Cycle 4000 Ergometer, Ergo-fit®, Germany) was performed using a physical work capacity protocol (PWC-150) with a heart rate limit of 150 beats/min.

The study was approved and funded by the Technical Committee of the Physical Activity and Culture Training Center of SENA-Bogotá, and complied with the requirements of the Declaration of Helsinki (33). Exclusion criteria included previous experience in yoga practice, smoking, diabetes mellitus or uncontrolled hypertension, history of respiratory disease (tuberculosis, chronic obstructive pulmonary disease, and pulmonary thromboembolism), disabling spinal deformities, major surgery, and previous sports training. The study respected the dignity and well-being of subjects, and was in line with the ethical and scientific principles of human research. According to Resolution 8430 of 1993 of the Ministry of Health (34), the level of risk for the participants was classified as research with minimal risk. The measurements were taken by specialized medical personnel of the Physiology Research Laboratory of the Physical Activity and Culture Training Center, SENA-Bogota.

The stimulus consisted of two yoga sessions per week, 75 minutes per session, for 12 weeks, between at 6:15 a.m. and 7:30 a.m. Each session began with joint mobility exercises (*pawanmuktasanas*), accompanied by acupressure and warm-up breathing exercises followed by postures (*asanas*). All sessions began with *nadi shodhana pranayama (anuloma viloma* or alternate nostril breathing) for two minutes. During the first two weeks, *nadi shodhana pranayama* and *sheetali pranayama* were practiced (refreshing breathing in the central phase of the session). *Sheetali pranayama* and *sheetkari pranayama* (wheezing) were practiced in weeks three and four. During the fifth and sixth week, individuals practiced *sheetkari* and *bhramari pranayama* (bumblebee breath). During the eighth and ninth week, *bhramari* and *ujjayi pranayama* were performed. During weeks 10 and 11, *bhastrika* and *kapalbhati pranayama* were practiced. Finally, in the last week, individuals learned *agni pranayama* or breath of fire. On the other hand, the control group performed physical activity with a functional training plan simultaneously.

The post-stimulus control sample was performed 12 weeks later. Again, the level of lactate, hematocrit and resting spirometry were determined during the same time periods as the initial sample. After a *pranayama* session, a blood lactate control sample was taken from the left ear lobe. The blood sample was obtained 5 minutes after the end of the session.

The submaximal test was performed at 24 hours, and the blood lactate of the ear lobe was taken 5 minutes after the test was completed, at which time blood pressure was measured. Heart rate was monitored during the test, which was terminated when the patient reached a rate of 150 beats/min. The recovery heart rate was measured at minutes 1, 3 and 5 post-exercise. For the calculation of double product, the data of the resting heart rate was considered. For the statistical analysis, data normality was verified, and the ANOVA and t-Student tests were applied using the SPSS Statistics 21 program (IBM, USA).

Results

On average, the mean age of the total population was 46±14.3 years, weight was 60.7±9.6kg, height 1.6±0.06m, BMI 24.9±3.9kg/m^2 and body fat percentage 29.8±7.7%. Table 1 shows the comparative results between the yoga group (YG) and the control group (CG).

Table 1. Comparative results Yoga Group and Control Group.

Variable	CONTROL GROUP			YOGA GROUP		
	Initial measure	Final measure	Final-initial difference	Initial measure	Final measure	Final-initial difference
FCV (L)	4.1±1.19	4.2±1.13	0.1±0.23	4.2±1.13	4.3±0.88	0.3±0.38 *
FEV1 (L/s)	2.8±0.55	2.9±0.7	0.1±0.25	3.0±0.72	3.3±0.64	0.3±0.3 *
FEV1/ FCV (%)	70.8±14.5	71.8±12.5	1±7.42 *	75.5±11.2	80±8.6	2.6±8.1
SPO_2 (%)	944±2.71	94.6±1.21	0.2±2	94.7±1.3	95.4±1.2	0.2±1.2
Double product (%)	84.8±8.21	81.2±6.92	-3.6±9.08 *	86.9±18.8	80.7±12.6	-6.2±11.9 *
Lactate delta (mMol/L)	0.8±0.77	1.3±0.94	0.4±1 *	1.9±0.84	3.2±0.89	1.4±1.18 *
Hematocrit (%)	50.7±3.42	50±1.84		50.4±4.63	48.9±2.51 *	
Sub-maximal lactate (mMol/L)	1.6±0.3			2.1±0.88 †		

* Statistically significant differences were observed between the final and initial values with p<0.05.
† Statistically significant differences were observed during a submaximal cycle ergometer test with p<0.05.
Source: Own elaboration based on the data obtained in the study.

Respiratory function tests

FVC: an increase was observed after 12 weeks of practice in both YG and CG. In YG, the increase was 6.9% of the predicted value ($p<0.05$). In the CG, an increase of 2.3% was observed, which is not statistically significant (Table 1).
FEV1: an increase of 9.4% of the predicted value was observed after 12 weeks in YG ($p<0.05$). In the CG, the increase was not significant (3.4%).
FEV1/FVC: an increase in both groups was observed, but none was statistically significant (YG: 2.7%, CG: 1.4%).

Hematocrit

This variable reduced by 2.6% ($p<0.05$) in the YG. A decrease of 1.4% was observed in the CG, with no statistical significance.

Peripheral oxygen saturation

A non-significant increase of 0.2% was observed in both groups.

Lactate

Comparison between both groups: after a *pranayama* session, between weeks 1 and 12, lactate delta (ΔLac) showed an increase of 1.1mMol/L (12%, $p<0.05$) in the YG. After training at 75% of maximum heart rate (MHR), the CG showed an increase in ΔLac of 3.2% with no statistical significance.
Comparison of lactate level in the YG during two activities: At week 12, a comparison was performed between the lactate level that this group reached after a 75-minute *pranayama* session and after a 45-minute cycle ergometer session at 75% of their MHR. Greater production was observed after the *pranayama* session (3.2mMol/L vs. 2.1 mMol/L), but no statistical difference was found after the cycle ergometer session.

Double product

There was a decrease in both groups, but it was greater in the YG ($p<0.05$).

Discussion

The results of this study allow to raise a discussion about three aspects: what characteristics qualify a stimulus as adequate to improve pulmonary function? Does altitude have any effect on yoga practice? Does training of respiratory muscles increase anaerobic capacity?

Most studies agree that, by increasing intrathoracic and intraabdominal negative pressure due to a greater diaphragmatic excursion (35), yoga practice —especially *pranayama*— leads to higher FVC, FEV1 and FEV1/FVC ratio (36-38), although, some studies have not found changes in the FEV1/FVC ratio (39). Likewise, studies have not found evidence proving that the observed effects on saturation are caused by better diffusion (37), a longer length of time of erythrocytes in the recruited capillaries, or changes in the recruitment patterns of accessory muscles (36). These effects can be achieved through apnea maneuvers and increased positive pressure during exhalation, which may cause changes in volume, capacity and airflow.

Some pranayama techniques include glottal muscle contraction exercises, which have been correlated with improvement of saturation without significant changes in heart and respiratory rates (39). A better percentage of saturation, higher O_2 pressure in the alveolar gas, greater arterial content of O_2, and better delivery in the tissues allow to explain the decrease of Htc (40-42) in people trained with this technique, which was evidenced in the YG of this study (Table 1).

The stimulus observed in several series consists of periods of practice longer than 6 weeks, although changes become more evident after 10 weeks and are more relevant in people without previous experience in yoga (43). In the course of the initial phase, the stimulus used in this study included joint mobility and low impact and low energy expenditure *asana* (postures) techniques. During the central phase, *pranayama* was used in a sitting or standing position, so that the ventilation/perfusion ratio was not affected by position changes or were prone to stimuli. The CG also performed physical work in a standing position, suggesting that the observed changes may be the result of alveolar recruitment maneuvers and respiratory musculature exercise.

In relation to altitude, the results of this study coincide with findings from other series performed at intermediate altitudes (1500 to 3000masl), especially regarding FEV1 and FVC (40). At higher altitudes, people trained in yoga have a better performance in lung function tests; for example, Buddhist monks do much better than Sherpas (42,44,45). The volume of studies at intermediate altitudes is small, so there are still some gaps to explain the ventilatory response to hypoxia in this context. This could be the basis for the design of new studies.

As for anaerobic capacity and lactate production, meditation decreases the metabolic rate while *pranayama* increases it (8), which is likely to happen due to the stimulation of the fibers that use glycolytic pathways. The result is different for expert practitioners (athletes), since they accumulate less lactate with equivalent workloads (30). Although yoga practice is considered as a low intensity activity, it can increase lactate levels, even up to the lactic threshold, especially with *pranayama*, as observed in some subjects of this study.

Concerning probable biases and confounding variables, it should be mentioned that the reduced number of male participants does not allow a sex comparison. The intensity of the load in the CG was not established according to a training plan but in response to the evolution of the participants' capacities (strength, endurance, coordination). Also, it should be taken into account that the measurement of post-exercise lactate levels were performed five minutes after the end of the activity; if a clearance behavior analysis is intended, studies should be designed to include measurements of this metabolite during a longer post-exercise period.

Conclusions

Pranayama targeted practice for 12 weeks, at least twice a week, in untrained, sedentary and inexperienced subjects in yoga practice, improves FVC and FEV1. In addition, blood oxygenation and glycolytic capacity in healthy adults are stimulated, which has a favorable impact on variables that can measure cardiovascular risk, such as double product and anaerobic capacity.

This practice can produce an accumulation of lactate, equivalent to the results of work on a cycle ergometer for 45 minutes with an intensity at 75% of the MHR. Thus, yoga practice with an emphasis on *pranayama* may be considered as useful for improving lung and cardiovascular function.

Conflict of interests

None stated by the authors.

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REFLECTION PAPER

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A historical approach to the ventricular system of the brain

Una aproximación histórica del sistema ventricular en el sistema nervioso central

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| Abstract |

Introduction: The ventricular system of the brain was first described, partially, in the third century BC. Since then, several researchers have contributed to better understand this system, unraveling its position in the central nervous system, and relating it with certain functional aspects following philosophical concepts that have allowed a clearer approach to cavitations regarding the formation of the cerebrospinal fluid.

Objective: To describe the most relevant concepts of the history of the ventricular encephalic system of the brain.

Materials and methods: Various literature sources related to the ventricular system were consulted, and then chronologically organized, so that a more concrete approximation of the functional morphology of the ventricular system could be provided.

Conclusion: Aristotle was the first to approach the ventricular system of the brain. Over time, his knowledge on the organization, function and number of cavities was debugged to the point of proposing the existence of eight ventricles. Today, five ventricles are recognized, four of which are encephalic components: two in the brain, one in the diencephalon, other in the brainstem, and a fifth in the terminal part of the spinal cord.

Keywords: Cerebrum; History; Cerebrospinal Fluid; Neuroanatomy (MeSH).

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| Resumen |

Introducción. El sistema ventricular encefálico se conoció, con parcialidad, en el siglo III a.C., fecha desde la que diversos investigadores contribuyeron a una mejor comprensión de dicho sistema, desentrañando sus ubicaciones en el sistema nervioso central y relacionándolos con ciertos aspectos funcionales que surgieron de conceptos filosóficos. Esto permitió un acercamiento más objetivo hacia las cavitaciones relacionadas con la formación de líquido cerebroespinal.

Objetivo. Referenciar, de forma cronológica, los conceptos más trascendentes de la historia del sistema ventricular encefálico.

Materiales y métodos. Se consultaron diversas fuentes bibliográficas relacionadas con el sistema ventricular, para después ordenarlas según su cronología, de modo que se concluyera con una aproximación más concreta de la morfología funcional del sistema ventricular.

Conclusión. Aristóteles fue el primero en abordar el sistema ventricular encefálico, de modo que, conforme el paso de los años, su conocimiento se fue depurando en cuanto a organización, función y número de cavidades, hasta llegar a proponer la existencia de ocho ventrículos. En la actualidad se reconocen cinco ventrículos, de los cuales cuatro son componentes encefálicos: dos en cerebro, uno en diencéfalo, otro en tronco encefálico y un quinto en la parte terminal de la médula espinal.

Palabras clave: Encéfalo; Historia; Líquido cefalorraquídeo; Ventrículos encefálicos (DeCS).

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Introduction

The history of the ventricular system

Aristotle (384-322 BC) was perhaps the first person to report the existence of brain cavities, particularly those located in each cerebral hemisphere. He pointed the presence of a small hole in the center of the brain in most of the animals he studied (1). However, Herophilos of Chalcedon (335-280 BC), a Greek physician and precursor of teaching and learning of human anatomy, was the real discoverer through the first dissections in human cadavers following the scientific rigor of his time (2), which allowed him to identify and describe such ventricles (3,4). He also described the choroid plexuses (5,6) as constituent elements of these chambers, and thought that the pineal organ was some sort of valve capable of closing the cerebral aqueduct to prevent the passage of *pneuma psykhikon (spiritus animalis)* to

the posterior ventricle, where memory was believed to exist, acting as a guardian of psychic activity (7).

Around that time, Erasistratus of Ceos (304-250 BC), a disciple of Herophilus, proposed the ventricular theory to explain the function of the pneuma. He stated that the *pneuma zoticon (spiritus vitalis)*, found in the blood, extended from the heart to the brain, and turned into *pneuma psykhikon* in the lateral ventricles (5,8,9), controlling structure-function relationships until traveling through the motor nerves to the muscles (3,10).

Although Herophilus and Erasistratus are credited with the identification of the cerebral ventricles, Rufus of Ephesus (110-180), teacher of Galen of Pergamum, detailed the lateral ventricles —the third and fourth ventricles— and the mesencephalic aqueduct (11). Similarly, Galen (130-200) described this ventricular system with detail and believed in the presence of pneuma, conceived as a breath emanated from the cosmos that circulated through these cavities, serving as a mediator between body and soul. In addition, he considered that the superior vermis of the cerebellum acted as a valve to prevent the passage of *pneuma psychicon* to the posterior ventricle (12), and that seizures were originated by the obstruction of the exit of the cerebral ventricles.

Galen not only provided a correct view of the morphology of the four ventricles by dissecting oxen encephala, but also found that the anterior ventricle was even (9) and that the mental faculties were located in the solid portions of the brain. In 390, Nemesius of Emesa refuted this idea, and claimed that all mental faculties were located inside the ventricles and that, following the antero-posterior pattern proposed by Posidonius of Byzantium, they could be observed through lesions in different cerebral regions (14). For example, injuries to the anterior ventricle of the brain impaired fantasy and imagination, whereas lesions in the posterior region affected memory and, if damage occurred in the middle portion, reasoning was altered (1,15). This tricameral functional pattern was preserved for several centuries (1) until the Renaissance, when Leonardo da Vinci and Andreas Vesalius challenged this idea.

In *Anathomia*, written in 1316, Mondino de Luzzi (1270-1326) maintained the tricameral theory (16) for cerebral ventricles (Figure 1) and, although he contributed his own ideas to anatomy based on his observations of human dissections, he followed the Galenic tradition in his work. On the other hand, Mondino proposed, as a new element, that the choroid plexus was the valve that regulated the flow of *spiritus animalis* (12). Accustomed to iterate the dogmas of Greek and Latin academic authorities generated by the school of Hippocrates and the teachings of Galen, the classical academic tradition prevailed without any relevant demonstrations or conceptual advances about the ventricular system.

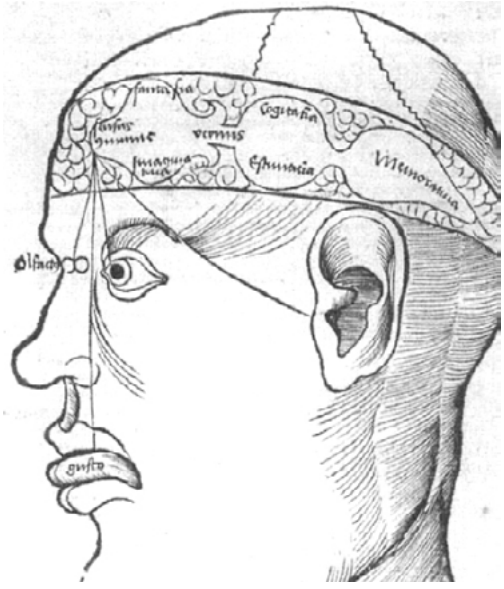

Figure 1. Gregord Reisch's scheme (1503), which shows the typical medieval conception of the human brain and its tricameral composition. Source: Own elaboration based on Martensen (27).

Then, this tradition was subverted by Leonardo da Vinci (1452-1519) and his first anatomical drawings, which date back to around 1487 (17). Da Vinci's drawings are of admirable clarity, despite having some errors, and reflect his wish to delve into the mechanisms of the most intimate functions and relations of the deepest organs, such as the brain ventricles. He stated in his notes that the anatomy of the brain had two vents in the large ventricles, in which molten wax was injected to fill the cavities of the brain. Once the wax hardened, it was removed from the brain to see the exact shape of the three ventricles (12,15,18,19). Thus, da Vinci extracted a mold that showed the three-dimensional shape of the ventricular labyrinth in the brain of an ox (15), and made the first realistic drawing of the cerebral ventricles (15,20,21). This greatly coincided with what is now known about the ventricular system, since his drawings showed at least the occipital horns of the lateral ventricles.

Nevertheless, da Vinci could not identify the temporal horns of these ventricles due to the absence of openings to access them and the use of unpreserved brains. Also, in his notes on the ventricular system, he thought that the spinal cord ended in the fourth ventricle, and concluded that the sense of touch went through there (15), opposing the ideas about the flow of pneuma.

Afterwards, such wax mold was extrapolated to humans, which can be observed when comparing W19127r and Schlossmuseum paints (Figure 2). The wax technique was not used again until the seventeenth century by Ruysch (15).

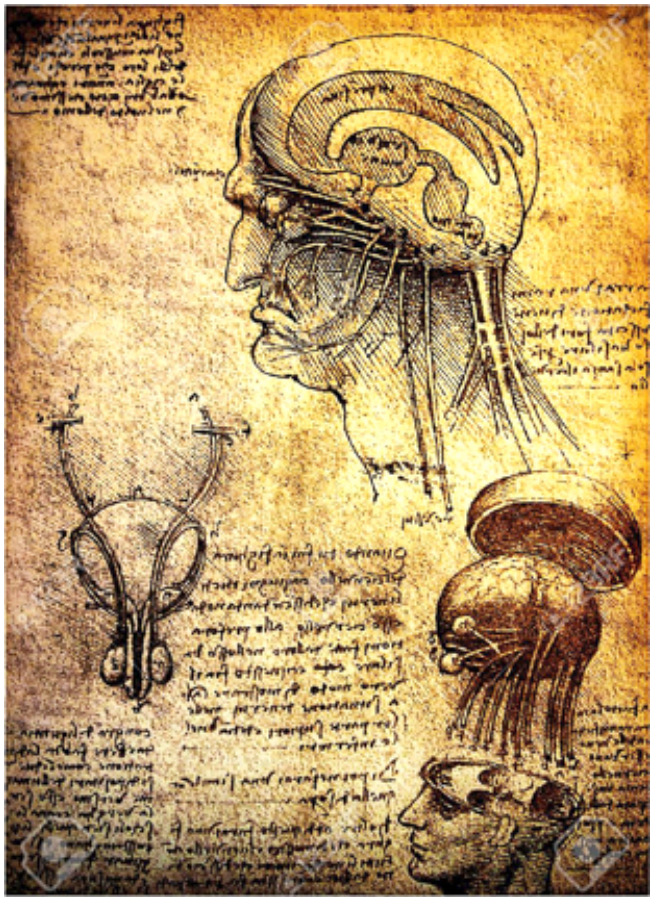

Figure 2. The four encephalic ventricles at the top. Leonardo da Vinci's drawing. Source: (22).

Furthermore, the great anatomist Andreas Vesalius (1514-1564), contemporary of Leonardo, came to conclusions that contradicted established galenic dogmas by means of dissections made in executed criminals. For example, he noted that the structure of the brain was different from that of Galen, and that the brain ventricles did not contain any *spiritu*, but were filled with a clear fluid, later called *cerebrospinal fluid* (CSF). References of this clear fluid inside the skull had already been made in the past; in a papyrus dating from the seventeenth century BC, a skull fracture is described in the occipital region with a fluid leak (23).

Vesalius also rejected the idea of Herophilus, in which the pineal organ was a kind of valve capable of closing the cerebral aqueduct (9). Around that date, Juan Valverde de Amusco (1525-1588), Spanish physician and anatomist, indicated in his in History of the composition of the human body (seventh book) that the brain tissue has four ventricles, known as ventrezillos, interconnected by the mesencephalic aqueduct, which is described as a small brook (24).

Similarly, Giulio Cesare Casserius (1552-1616), an anatomist from Padua, discovered the arachnoid granulations (25) where CSF passes into the venous circulation. These granulations were described in 1705 by Antonio Pacchioni (1665-1726) in his work *Dissertatio epistolaris de glandulis conglobatis dura e meningis humanae, indequeortis lymphaticis ad piammeningem*, through which CSF flows into the venous sinuses (26).

Thomas Willis (1621-1675), a century after Vesalius, proposed that CSF originated in the choroid plexus, inside the ventricles, and that it circulated through these cavities and preserved body heat through blood (1). In that same century, René Descartes (1596-1650) hypothesized that the fluid in the brain ventricles was under pressure and that the pineal organ turned in a particular direction when the mind decided to perform a certain action, causing the flow to move from the brain to the nerves. In consequence, such flow was the cause of the movement (27-28) in different directions to facilitate the distribution of the spirits (29). Thus, Descartes supported the concept of *spiritus animalis* of Galen (20). On the other hand, his contemporary Niels Stensen (1638-1686) refuted this hypothesis and, through careful dissection, revealed the correct position of the pineal organ, proving that it was a fragile structure fixed directly to the brain, which tended to break easily if it was moved; therefore, it could not produce movement as Descartes stated (29).

In 1851, Andrea Verga (Italy, 1811-1895) described a posterior prolongation that he called *cavum septum pellucidum* (30), a triangular space whose base is attached superiorly to the corpus callosum, and runs as a sheet down to the fornix (31). Over time, this region was known as *cavum vergae* or sixth ventricle. It is located in the midline of the brain, and its name does not indicate anything about its nature (32). In recent years, it has been established that the *cavum* does not have the characteristics of a true ventricle, since it does not have an ependymal lining (33) and lacks CFS, although it is hypothesized that the liquid found there derives from neurons and glial cells (34).

In 1859, Stilling (1810-1879), German anatomist and surgeon, was the first to describe the terminal ventricle as a cystic cavity lined by ependymal cells, located in the conus medullaris (35), which was, at that moment, the seventh ventricle. Then, in 1875, Krause identified it as a true ventricle, delimited by ciliated ependymal cells, and called it the fifth ventricle (36). In his honor, the eponym Krause's ventricle was used. In 1924, Kernohan performed complete anatomical studies and determined that it usually appears during the embryonic development of the marrow, but that it tends to disappear after birth or may persist as a residual ependymal tissue (37). Even so, Anatomic Terminology includes this ventricle as one more element of the ventricular encephalic system, with the reference A14.1.02.006 (38).

Another element that was associated with the CFA is the interposed veil cistern. It is a retreat of the pia mater found between the roof of the third ventricle and the fornices, a location that usually presents as a small triangular subarachnoid space. However, when this cistern is enlarged, as a result of the abnormal separation of the fornix pillars, it is called cavum of the interposed veil (39).

So far, throughout history, up to eight saccular dilations have been associated with the ventricular system; three of them correspond to subarachnoid dilatations, while the remaining five are ventricles that derive from the normal development of the neural tube.

In the end, the mechanical hypothesis that the pineal organ was a regulating element in the flow of animal spirits was rejected and modified by Magendie (1783-1855), who proposed that a flow of CFS occurred there (40). On the other hand, diagnosis by lumbar puncture to obtain CFS was not introduced until 1891 by the neurologist Quinke (1842-1922) (41), who expanded the field of medical understanding about the conditions associated with CFS through its application to clinical events.

The ventricular system: current concept

Today, Anatomical Terminology accepts that the ventricular system is made up of a series of dilatations, orifices and ducts and that the central nervous system is a part of it (38). The neuroanatomical description of the latter, complemented by neuro-navigation techniques (42), confirms that four ventricles are located in the brain region: two lateral ventricles located in the brain, a third ventricle in the diencephalon, and the fourth ventricle located behind the encephalic trunk. In

addition, there is a fifth ventricle in the terminal part of the spinal cord, known as terminal ventricle (38). The four brain ventricles are interconnected by the interventricular foramina and the cerebral aqueduct, so the fourth ventricle also establishes direct communication with the subarachnoid space through two lateral foramina and one medial foramen (42,43). Finally, the medullary region is traversed longitudinally, discontinuously or closed to the stretches (44) through the central conduit or epindemal cell, which ends in the fifth ventricle (35) or caudal apex in smaller vertebrates (45).

Also, the ventricular system has elements associated with the formation and circulation of CFS, which is produced continuously and is subjected to circadian rhythms through mechanisms operated by sympathetic cholinergic innervation, receptors in the choroid plexus for dopamine, serotonin, melatonin and neuropeptides, such as vasopressin, atrial natriuretic polypeptide and angiotensin II (45). This allows the permanent production of CFS, which oscillates between 100 mL and 150 mL in young adults; approximately 30 mL are found inside this ventricular system (40,46,47).

The production of CFS is estimated at about 500mL per day (40,46-48), of which about 70-80% —in other words, 350-400 mL equivalent to 350 microliters per minute— is produced in the choroid plexus (49) thanks to mechanisms involving passive transports such as osmosis and diffusion, and active transports such as transcytosis, including endocytosis and exocytosis. In addition, due to the lack of an ependymal barrier between the extracellular fluid and CFS, some substances in the cerebral parenchyma may be the main source of non-choroidal fluid, representing the remaining 10%-30% of the total CFS. Most of this fluid is removed permanently into the blood through the arachnoid villi, while a small portion is lymphatically removed via the nerve roots (49).

This cerebrospinal fluid plays an important role in the maintenance of homeostasis in the central nervous system, because it provides buoyancy of the brain and nerve roots, transports nutrients, peptides and proteins, regulates the brain volume through osmoregulation mechanisms, transports transducing signals to cells, and eliminates unnecessary substances and metabolites (50). Thus, it is known that several signaling molecules are directed from the blood to the cerebrospinal fluid, as is the case of spondine, transthyretin and fibroblast-derived growth factor. In addition, these molecules participate in the neurogenesis of stem cells, both in intrauterine and postnatal life (51).

Conclusions

Knowledge on the existence of ventricles in the central nervous system dates back to Aristotle. Three ventricles were initially proposed (anterior, middle and posterior), but the ideas, concepts and hypotheses about the ventricular system underwent modifications over time, in terms of chambers number, their organization and their function. At some point, even eight brain ventricles were proposed. Today, the existence of five ventricles in the human ventricular system is recognized: one is located in the terminal part of the spinal cord and the remaining four are located in the encephalon. With the exception of the terminal ventricle, the others are interconnected by foramen and ducts, through which cerebrospinal fluid circulates but not *spiritus animalis*, as ancient scholars thought.

Conflict of interest

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Medical students and their relation with the pharmaceutical and medical device industry

Los estudiantes de medicina y su relación con las industrias farmacéuticas y de dispositivos médicos

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| Abstract |

Introduction: The relation between physicians and the medical industry is a common subject of research in public health. According to Austad *et al.*, 61% - 100% of medical students in the United States reported some kind of interaction with the pharmaceutical industry. Although physicians take a position regarding the medical industry early in their careers, little is known about this key stage of their medical training.

Objective: To identify the perception of medical students about the relation between physicians and pharmaceutical or medical device industries.

Materials and methods: Articles were identified through a non-systematic search in the Cochrane, EMBASE, LILACS and MEDLINE databases. The search was limited by year of publication (2006-2016) and not by language or abstract.

Results: Although no articles discussing this relation were found in Colombia, eight cross-sectional articles and a systematic review in other populations were consulted.

Conclusion: There is insufficient understanding of the relation between the industry and medical students in Colombia and its role in medical practice.

Keywords: Medical Students; Pharmaceutical Industry; Medical Device (MeSH).

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| Resumen |

Introducción. La relación entre los médicos y la industria ha devenido un punto de investigación importante en salud pública, evidencia de esto es el estudio de Austad *et al.*, donde cerca del 61% y 100% de estudiantes de Medicina en EE. UU. ya habían interactuado con la industria farmacéutica. Aunque las actitudes de los médicos hacia la industria se forman en su carrera desde temprano, poco se conoce sobre este aspecto clave en la formación médica.

Objetivo. Identificar cuáles son las percepciones de los estudiantes de medicina sobre la relación entre los médicos y la industria farmacéutica y de dispositivos médicos.

Materiales y métodos. Se identificaron artículos mediante una búsqueda no sistemática en las bases de datos Cochrane, EMBASE, LILACS y MEDLINE. Esta se limitó por años de publicación (2006-2016) y no por idioma o resúmenes.

Resultados. Aunque no se encontraron artículos sobre dicha relación en Colombia, sí se leyeron ocho artículos de corte transversal y una revisión sistemática en otras poblaciones.

Conclusiones. No existe suficiente comprensión de la relación entre la industria y los estudiantes de Medicina en Colombia y su implicación en la práctica médica.

Palabras clave: Industria farmacéutica; Dispositivo médico; Estudiantes de medicina (DeCS).

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Introduction

Medicine is a dynamic and changing science that poses a challenge for physicians, who must acquire a greater number of skills to practice their profession. Although medical training programs are designed to provide physicians with the necessary tools for the development of their profession —knowledge, skills and perspectives—, some gaps may still be observed at the end of their training. One of these gaps is how to interact with the pharmaceutical or medical device industries (1).

In Colombia, however, no research has been done on how medical students come into contact with pharmaceutical or medical device companies, even though international studies report that between 74% and 100% of the students had some interaction with them at some point of their career training (2,3). The different types of contact are similar to the treatment between physicians and pharmaceutical or medical device companies (2,4).

Pharmaceutical and medical device industries have a major role in health care and improvement of the quality of life of patients because of their commitment to research and development of new products. As this relation between physicians and industry is maintained on a daily basis, each professional has the responsibility to look for benefits for patients as a result of this interaction.

In addition, it is more common for members of medical schools to participate directly in the development of drugs, medical devices or diagnostic tests (5). Therefore, these students must have the necessary skills to interact adequately with the industry, in order to seek the benefit of patients. With this in mind, this topic is an area of public health research (6), due to its impact on clinical decision-making.

This work intended to conduct a literature review of ten years of research on this topic from a student perspective, to analyze if the relation between undergraduate education and the pharmaceutical or medical devices industries has an effect on their training and future professional practice.

Materials and methods

In order to identify articles, a non-systematic search was carried out in the Cochrane, EMBASE, LILACS and MEDLINE databases, using as search descriptors the terms "medical students" AND "pharmaceutical industry", "medical students" AND "medical device industry", "medical students" AND "industry", "medical students."

Since few articles were retrieved, no limits or filters were specified to debug the search, including language or abstract, except for years of publication (2006-2016).

Results

Six of the articles found addressed the clinical question, but did not consider the Colombian or Latin American population. The results of the assessment, which was applied to the literature used to prepare this proposal, are listed in Table 1.

Table 1. Articles obtained during this review.

Author	Year of publication	Country
Austad *et al.* (7)	2011	United States
Lea *et al.* (2)	2010	Norway
Larrañaga *et al.* (8)	2014	Spain
Siddiqui *et al.* (9)	2014	Pakistan
Hyman *et al.* (10)	2007	United States
Soyk *et al.* (11)	2010	United States

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

The following are the associated aspects in the treatment of the relation between medical students and pharmaceutical or medical device companies.

Frequency of interaction with the industry

These students report a frequent interaction with the marketing areas of pharmaceutical or medical device industries. Austad *et al.* (7) found that between 61% and 100% of students were exposed to the industry, which increased as they progressed in their careers. Furthermore, Lea *et al.* (2) reported that 73.9% of Norwegian students have had some contact with the pharmaceutical industry, with a higher frequency (89.9%) during the last year of their training.

Level of acceptance of gifts from the industry

Larrañaga *et al.* (8) stated that 78.6% of medical students of Universidad de Zaragoza reported receiving a gift unrelated to academic training, while 68% received a medical journal or a brochure containing information on a drug. In the study by Siddiqui *et al.* (9), 303 medical students were surveyed about their perception regarding the pharmaceutical industry, reporting that 30% did not feel comfortable receiving gifts from the pharmaceutical industry, while another 30% felt comfortable.

Likewise, 26% of 107 students at the Harvard Medical School concluded that accepting gifts from the pharmaceutical industry is inappropriate (10). According to Larrañaga *et al.* (8), this occurs because 30.4% of the students think that receiving gifts from the industry increases the likelihood of prescribing products associated with the company in the future.

Should medical students have contact with the pharmaceutical or medical device industry?

42.7% of medical students of two universities in Pakistan (public and private) think that there should not be interactions with the pharmaceutical industry during the medical career (9). Likewise, 23% of students at Harvard Medical School are against events sponsored by the pharmaceutical industry during their careers, while 36% strongly disapprove them (10). Moreover, 22.6% of medical students at Universidad de Zaragoza believes that the Faculty should prohibit pharmaceutical representatives or visitors from interacting with students (8).

How influential is the contact with the industry on students?

At the University of Wisconsin, Soyk *et al.* surveyed 348 students from the Faculty of Medicine and Public Health, who believed that pharmaceutical marketing affects, to a certain extent, their decision-making. They also suggested that gifts do increase the likelihood of prescribing company drugs (11). In addition, 3 out of 4 students in Norway believe that the industry can influence their prescribing habits in the future (2). Moreover, 43.4% of medical students at Universidad de Zaragoza do not approve accepting gifts from the industry due to the influence it can exert, so only 24.7% agreed to receive those products (8). Similarly, Austad *et al.* (7) report in their systematic review that the pharmaceutical industry can affect 24% of students when prescribing drugs in their clinical practice.

Discussion

This literature review shows that students are often exposed to the pharmaceutical or medical device industries and have different opinions in this regard. However, it is unclear whether students should have contact with the industry during their undergraduate training,

since 1 in 3 students think it is inappropriate, while the remaining students have a neutral position (9).

In general, they say that more education is needed on how to relate appropriately to the industry. A study of the Harvard Medical School concluded that those students who were better educated to interact with the industry were less skeptical about its involvement in their medical training (10).

The literature suggests that the interaction of physicians with the industry begins early in their medical career (2), which is confirmed by the percentage of students exposed to industry marketing in countries such as the United States, Norway, and Pakistan (2,9,10). This exposure is greater for last year students, as it increases as the medical career progresses, which proves that they are an important target of the pharmaceutical (2) and medical device industry.

One important aspect derived from this review is that there are no works that study this phenomenon in Colombia and Latin America, nor tangible data on how this relation is developed while physicians are being trained, which creates a gap in knowledge that must be addressed. These relationships should be oriented towards the benefit of patients to develop new technologies through new research that works in an integral way with the industry and medical schools.

Conclusions

In Colombia, there is no scientific evidence on how the relation between medical students and the pharmaceutical and medical device industry is developed. Worldwide, different opinions about this interaction can be found, and the influence that it may have on the future of clinical practice, as well as on how physicians relate to the industry, is not clear.

In addition, medicine faculties lack training on how to interact with the industry, which generates skepticism and distrust. In consequence, any possible relation between them is affected.

Hence, a perception survey in Colombia is necessary to measure the interaction between students and the industry. This will be developed in a following work proposed by the authors, in order to establish guidelines for in the country.

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REVIEW PAPER

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Electrocardiographic alterations associated with heart transplantation. Triggers, mechanisms and meaning

Alteraciones electrocardiográficas en el paciente con trasplante cardíaco. Desencadenantes, mecanismos y su significado

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| Abstract |

Introduction: Heart rhythm disorders are associated with increased morbidity and mortality. However, triggers and implications in patients with heart transplantation are not clear.

Objectives: The purpose of this research paper is to identify and explain the determinants for the onset of electrical conductivity alterations in patients with a heart transplant, as well as to describe the most common arrhythmias and their pathological implications.

Materials and methods: A literature review was made in the PubMed online database for a total of 411 results. In addition, clinical practice guidelines on cardiac transplantation, cardiovascular electrophysiology and infective endocarditis were searched. Sixty articles related to the objectives of this study were chosen.

Results: Surgical technique, heart denervation, sinus node trauma, graft rejection, endomyocardial biopsies and infections are the main factors that compromise organ viability and the life of transplanted patients. These factors can be observed as sinus rhythm disturbances.

Conclusions: When a cardiac arrhythmia is detected, the medical team must provide a treatment that is not limited to symptomatic and sinus rhythm control. An active search of the etiology must be initiated since it may indicate an underlying pathological process.

Keywords: Heart transplantation; Arrhythmias; Cardiac; Bradycardia; Tachycardia (MeSH).

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| Resumen |

Introducción. Las alteraciones del ritmo cardíaco están asociadas con un aumento en la morbimortalidad; sin embargo, en pacientes con trasplante cardíaco no son claros sus desencadenantes ni implicaciones.

Objetivos. Realizar una búsqueda en la literatura para identificar y explicar los determinantes en la generación de alteraciones de la conducción eléctrica en pacientes con trasplante cardíaco, así como describir las principales arritmias que pueden presentarse, explicando sus implicaciones patológicas.

Materiales y métodos. Se realizó una búsqueda en la base de datos PubMed que arrojó un total de 411 resultados. Además, se buscaron las guías de práctica clínica sobre trasplante cardíaco, electrofisiología cardiovascular y endocarditis infecciosa. Se eligieron 60 artículos que lograban responder a los objetivos de este estudio.

Resultados. La técnica quirúrgica, la denervación cardíaca, las lesiones del nodo sinusal, el rechazo del injerto, las biopsias endomiocárdicas y las infecciones son los principales factores que comprometen la viabilidad del órgano y la vida del paciente trasplantado, manifestándose como alteraciones del ritmo sinusal.

Conclusiones. Ante la detección de alguna arritmia cardíaca, el equipo médico debe proporcionar un manejo que no se limite al control sintomático y del ritmo sinusal, sino que se debe iniciar una búsqueda activa de su etiología, ya que esta puede ser la manifestación de un proceso patológico subyacente.

Palabras clave: Trasplante de corazón; Arritmia cardíaca; Bradicardia; Taquicardia (MeSH).

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Desencadenantes, mecanismos y su significado]. Rev. Fac. Med. 2017;65(3):483-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.57498.

Introduction

Despite the progress in pharmacological treatment, organ transplantation can lead to multiple chronic pathologies that cannot be properly addressed with medical management (1). Cardiac transplantation is reserved for patients with heart disease who evolve to advanced and symptomatic heart failure despite optimal medical management, in other words, functional status D and functional class IV according to the New York Heart Association classification (NYHA) (2).

With the development and improvement of surgical techniques, as well as the improvement of post-transplant management, the patient is expected to restore hemodynamic stability, improve functional class and have a better quality of life, reaching survivor rates at 1 year and 10 years close to 90% and 50%, respectively (2-5).

Often, survival and quality of life are compromised by the onset of arrhythmias at any time after transplantation, and triggers and implications are not clear to date. The purpose of this article is to conduct a literature review to identify and explain the variables associated with cardiac transplantation that influence alterations in sinus rhythm and electrical conduction, during or after surgery. Similarly, a description of the main arrhythmias that patients may suffer after orthotopic cardiac transplantation and its consequences is presented.

Materials and methods

A systematic review was made in the PubMed database based on multiple combinations of MESH terms: "heart transplantation", "Arrhythmias, Cardiac", "Tachycardia, Ventricular", "Tachycardia, Supraventricular", "Bradycardia", "Pacemaker, Artificial" and "Catheter Ablation". The search was limited to studies in human. Articles that addressed heterotopic heart transplantation or that were written in a language other than English or Spanish were excluded. 411 articles were obtained.

The abstracts obtained after the search were analyzed, and those that coincided with the objectives of this study were selected. In addition, the national guidelines for cardiac transplantation and cardiovascular electrophysiology were consulted in the official website of the Colombian Society of Cardiology, while information on clinical practice guidelines for infective endocarditis were obtained from the European Society of Cardiology website. In total, 60 articles were chosen and used as reference for this review.

Factors associated with the development of cardiac arrhythmias

Surgical technique

The biauricular transplantation technique was first described by Lower and Shumway in the 1960s, and is characterized by myocardium anastomosis between both donor atria and a remnant of these structures in the recipient. Later, in the 1990s, the literature described the bicaval technique, in which anastomosis occurs in the large vessels in both portions of the vena cava and around the pulmonary veins, resulting in less manipulation and alteration of the atria (6).

Currently, a strong discussion has taken place around which techniques should be preferred, since long-term results do not show significant differences, although multiple publications demonstrate the benefits of the bicaval technique with respect to the standard technique (3,7-11).

The biauricular technique has demonstrated that suture lines form scars that act as low voltage areas, and that they isolate electrically the donor tissue from the receptor tissue, which is the reason for a higher incidence of flutter-type arrhythmias in patients who undergo this surgical technique.

Furthermore, randomized controlled studies have reported that the use of the bicaval technique needs less pacemakers implantation; however, no association was established between the permanent use of this device and long-term survival (12- 14). Czer *et al.* (12) developed a study comparing the functional class of transplanted patients with both surgical techniques during physical activity, considering variables such as heart rate, oxygen consumption, carbon dioxide production and duration of exercise, without finding differences between both groups.

Denervation and reinnervation

All surgical techniques involve cardiac denervation, which causes the heart to lose its autonomic regulation and, in consequence, the variability of the heart rate as a way of physiological adaptation to different stimuli of the environment. For this reason, the transplanted organ is guided by the sinus node rhythm and only responds to chronotropic, inotropic and dromotropic stimuli of the circulating catecholamines (15), and to the changes in blood volume caused by the venous return that stimulates a determined contraction force according to Frank-Starling's law (16).

Similarly, sympathetic reinnervation is considered unpredictable, disordered, often incomplete and variable among patients, leading to aberrant reinnervation, which may cause multiple sinus rhythm disorders (17-20). A study led by Uberfuhr (20) in Germany found that about 60% of patients with orthotopic heart transplantation had some degree of sympathetic reinnervation.

Sinus node dysfunction

Sinus node dysfunction —defined as the absence of sinus rhythm, sinus node recovery time greater than 1.4 ms or secondary electrical pauses during electrophysiological examinations— is the most common cause of early implantation of pacemakers in transplant patients, that is, before 3 months after surgery (21-23). Depending on the series, a prevalence between 10% and 45% of early sinus dysfunction is reported, reaching implantation rates of up to 30% in this group of patients (12,24). Early sinus dysfunction is largely attributed to the surgical procedure, whether caused by trauma, node ischemia due to nodal artery injury, or prolonged ischemia times. Over the years, a decrease in the incidence of sinus node alterations has been reported, which has been attributed to the improvement of the surgical technique (25).

Deleuze *et al.* (13) compared the results of both surgical techniques in the postoperative period of 81 heart transplants, finding that the biauricular technique showed a higher prevalence of sinus node dysfunction, while patients treated with the bicaval technique did not require implantation of a pacemaker within the first 30 days, although 12.5% of them did (25). AV blocks and sinus dysfunction three months after the procedure are, to the same extent, the main indication of the implantation of a permanent pacemaker.

Recovery of sinus node function is common, particularly, when these changes occur rapidly after transplantation (21,26,27). Late sinus node dysfunction occurs three months after transplantation, and about 5% of patients require implantation of pacemakers for this

reason according to a study published by Luebbert *et al.* (6), who did not find a higher prevalence related to any surgical technique, age, sex or pre-transplant diagnosis.

Rejection of the graft

About 20-30% of patients have experienced graft rejection during the first year after transplantation. This process is defined as the presence of inflammatory infiltrate in the transplanted tissue. Hence, taking endomyocardial biopsies is necessary for diagnosis and classification. Based on the results of the histological examination of the sample, it can be established whether there is any degree of cellular or humoral rejection according to the International Society for Heart and Lung Transplantation in 2004 (28,29). Despite the efforts and good results that relate findings by magnetic resonance to graft rejection cases, the gold standard is still histological study (30). Some series claim that the presence of acute graft rejection is closely related to the onset of cardiac arrhythmias, especially with flutter and atrial fibrillation, but this remains a controversial issue. Ahmari *et al.* (31) from the Mayo Clinic state that the recurrence of moderate to severe acute rejections results in cardiac fibrosis that compromises diastolic function and predisposes the development of atrial flutter, and that these markers imply poor prognosis in the long term. Thus, the next step should be to rule out acute rejection of the graft to detect de novo alterations (17,32).

Chronic graft rejection in heart transplantation refers to cardiac graft vasculopathy (CGV). Although this process was initially understood as an immune-mediated process, today it is now known as a multifactorial process that includes alloimmune, autoimmune and non-immune mediated responses (24).

The progression of intraluminal changes, which ends in the occlusion of the coronary macrovasculature and microvasculature flow, begins as a lesion and apoptosis process in the endothelial parenchyma that leads to the concentric proliferation of the smooth muscle and to the failure of the cardiac graft, creating a terrain for the onset of both atrial and ventricular arrhythmias (24).

The development of CGV is the most predisposing factor to myocardial tissue ischemia and fibrous tissue formation, and the one that affects survival the most; thus, it is the main cause of death at 3 years after transplantation, together with malignant processes (30). At 5 years, 30% of transplant patients suffer CGV (24,33), and multiple episodes of acute rejection are considered as a risk factor for its development. The gold standard for this pathology is coronary angiography, which is why it is performed routinely in these patients.

Biopsies

Biopsies are routinely performed, and in cases when the medical team deems them necessary to rule out acute rejection of the graft. This procedure is usually performed under local anesthesia, has a mortality rate of 0.4% (29), and is considered the gold standard for detecting rejection (34).

Despite being relatively safe, the main complications of biopsy are ventricular perforation and cardiac tamponade, atrial or ventricular arrhythmias, pneumothorax, tricuspid insufficiency, ventricular coronary fistula, transient cardiac arrest, carotid artery puncture, infection and venous hematoma (29,35).

For this type of procedure, the transjugular route is the first option for access, whereas the femoral vein route is used in case of difficulty with jugular access or if coronary angiography is performed during the procedure.

There is no consensus as to how often routine biopsies should be taken. The Colombian cardiac transplant guidelines of 2009 suggest that 11 biopsies should be taken during the first year (29), while the international guidelines for cardiac transplantation and lung cancer of 2010 propose 18 biopsies during the same period of time (36). Nguyen *et al.* (37) recommend a maximum of 31 endomyocardial biopsies, since they demonstrated that exceeding this number of repetitions increases the risk of severe tricuspid insufficiency.

Over time, progress in immunosuppressive treatment has decreased rejection rates, which would explain the decrease in the frequency of this diagnostic procedure. However, further studies are needed to establish a global consensus in this regard, since acute rejection is usually a subclinical process with severe long-term repercussions.

During the procedure, ventricular arrhythmias are common, but they are usually temporary and transient. In the long term, third degree atrioventricular (AV) blocks have been associated (27) because of the frequency of this procedure, although this is not widely described in the literature and is considered an uncommon event.

Magnetic resonance imaging is suggested to replace endomyocardial biopsies, obtaining promising results in preliminary studies (38,39).

Infections

Immunosuppressive therapy opens the door to a large number of microorganisms that the immune system could control if it functions properly. According to the type of therapy and the postoperative time, the etiological agents of greater incidence vary (29). About 12% of deaths after transplantation within the first month are associated with infections by nosocomial bacterial microorganisms in different sites. Between the second and sixth month, infectious pathologies are usually caused by opportunistic infections and the reactivation of latent infections. Finally, microorganisms acquired in the community are the most frequent after the sixth month (29,40).

Estimations indicate that about 1.5% of cardiac transplant patients are infected with infectious endocarditis (IE), mostly by *Staphylococcus aureus* and *Aspergillus fumigatus*. Risk factors include the use of central catheters in the perioperative period and frequent endomyocardial biopsies (41).

Electrical conduction disorders are observed in 1% to 15% of IE patients, mostly manifested as AV blocks, branch blocks and atrial fibrillation. The presence of these alterations is associated with poor prognosis and higher mortality (42). Infections caused by agents such as cytomegalovirus and *Chlamydia pneumoniae* favor the development of CGV and, consequently, graft failure and cardiac arrhythmias caused by the mechanisms described above. *C. pneumoniae* infection is associated with greater severity of CGV (24).

Drugs

The average effect of amiodarone is prolonged, so it is possible to continue to observe its effects for several days in patients who took it before the transplantation. In patients who develop early sinus dysfunction, the effect of amiodarone may further compromise the electrical conduction of the transplanted organ (17).

Arrhythmia in the transplanted patient

Tachyarrhythmias

Supraventricular tachyarrhythmias

Supraventricular tachyarrhythmias have a high incidence in transplanted patients, greatly compromising their quality of life and survival. Dahu *et al.* (43) proposed five mechanisms involved in

the development of atrial arrhythmias: 1) reentrant in the donor's atrium associated with the scar or the valve; 2) focal tachycardia in the donor's atrium; 3) atrial fibrillation in the donor's atrium; 4) re-entry arrhythmias that compromise two or more reconnections between donor and recipient atrium, and 5) arrhythmias originating in the recipient atrium that pass to the donor through one or more focal reconnections.

In turn, Vaseghi *et al.* (32) reviewed supraventricular tachycardia, and proposed another mechanism related to pre-existing alterations in the electrical conduction of the donor, which are manifested as AV nodal reentrant tachycardia and re-entry tachycardia associated with abnormal beam (32,44).

Supraventricular tachyarrhythmias can be classified as:

Atrial fibrillation, which is common in the early postoperative period and is almost always associated with graft manipulation, inflammatory period and autonomic changes. The incidence of atrial fibrillation decreases progressively, becoming exceptional during the late postoperative period in the absence of vasculopathy, rejection or infection (17,32,43,45). These low numbers are associated with the isolation of pulmonary veins, cava veins and the posterior wall of the atrium, which are the main foci of generation. This occurs because the surgical scar acts as an electrical insulator between recipient and donor atria remnants (46).

When atrial fibrillation is identified, the first step to take should be discarding the clinical cases previously mentioned as possible triggers. The control of these pathologies may be sufficient in most cases to stop their development. Antiarrhythmic drugs of choice are amiodarone and procainamide, which are not usually formulated for a long time because of the high resolution rate of this type of cardiac arrhythmia, which is associated with the management of its triggers. Controlling immunosuppression levels is necessary due to the interaction of amiodarone and warfarin with ciclosporin and tacrolimus (17). In case of persistence, catheter ablation is the treatment of choice for this disorder (17).

Atrial Flutter is the most common type of arrhythmia in patients after a heart transplant. In non-transplanted patients, the isthmus-dependent atrial flutter is formed by a counterclockwise circuit, which compromises the tricuspid valve, the Thebesian valve, the opening of the superior and inferior vena cava, and the crista terminalis. In transplanted patients, a similar circuit is formed, with the difference that the posterior line of the latter conforms the atrial suture line (47). This type of arrhythmia is more common in the biauricular technique (48).

Mitral annular flutter is less common and has no major incidence on a particular type of surgical technique. Just like atrial fibrillation, the development of flutter is also associated with periods of acute rejection, infection or vasculopathy, and their identification should stimulate the active search of these entities in the transplanted patient. When these causes are discarded and treated, as well as ventricular dysfunction and valvular pathology, catheter ablation is recommended to form an electrical block line between the tricuspid ring and the atrial suture for the right atrial-dependent flutter (48), whereas ablation of the anterior line of the circuit is recommended for the left atrium (49).

Focal atrial tachycardia is caused by the formation of depolarization foci near the atrial scar that take control of the heart rhythm. Scars, together with fibrosis, predispose to the formation of areas of slow electrical conduction, and provide the substrate for the production of macroreentrants and the development of focal atrial tachycardia. Elsik *et al.* (45) reported patients in whom the focus is found in the donor's atrium, while Vaseghi *et al.* (32) describe cases in which depolarization begins in the atrial remnant of the recipient and passes into the donor tissue through bridges formed by fibroblasts, which create gap-like junctions that allow electrical transmission. Definitive treatment is focal catheter ablation.

Atrial reentrant and nodal reentrant tachycardia require a preexisting route in the donor that allows a macroreentrant. Although they have been described in the literature, they are uncommon in transplanted patients. Radiofrequency ablation is curative (32).

Ventricular tachyarrhythmias

Ventricular extrasystoles and non-sustained ventricular tachycardia may be common in the early post-transplant period. The subsequent development of sustained and non-sustained ventricular tachycardia suggests an episode of acute rejection or graft vasculopathy (18), while taking into account other rare etiologies that may have similar clinical features and may be reversible, such as idiopathic fascicular ventricular tachycardia (50).

The most common arrest rhythm in cardiac denervation in sudden death events is asystole, followed by pulseless electrical activity; both are non-defibrillating rhythms, so the use of automatic implantable defibrillators remains controversial (17,51).

Bradyarrhythmias

Bradyarrhythmias may appear during the early or late period after a heart transplant, and can be caused by sinus node dysfunction or errors in the electrical conduction, with functional or dysfunctional sinus node.

In the early postoperative period, the transplanted heart usually requires positive chronotropic agents or temporary pacemaker implantation. It has been demonstrated that the donor's sinus node is hypersensitive to these pharmacological agents, so its use must be cautious (52).

Early sinus node dysfunction puts the patient's life at risk in the early postoperative days, and its multifactorial etiology is almost always associated with circumstances that depend on the surgical procedure (12,21,53,54). As for late sinus dysfunction, the role of graft rejection in its development is controversial.

Sinus dysfunction may be paroxysmal or persistent, and may be manifested as sinus bradycardia or as a total stop of the sinoatrial node (53,54). To control these entities, a therapeutic test can be performed with isoprenaline, dopamine, dobutamine or theophylline in search of increased heart rate and recovery of sinus rhythm. If this therapy fails, the use of pacemakers should be considered (21,55).

The 2011 Colombian guide to cardiovascular electrophysiology (56) provides the following recommendations for the implantation of a permanent pacemaker:

Class I: it is indicated in symptomatic, inappropriate, persistent or not-expected-to-improve bradycardia.
Class IIA: it is considered in symptomatic, recurrent and prolonged bradycardia that limits rehabilitation or discharge during the post-surgical recovery phase of the transplant (level of evidence C).
Class IIB: it is considered in patients with syncope after cardiac transplantation although bradyarrhythmia has not been documented (level of evidence C).

Early implantation of a permanent pacemaker occurs when the heart rate has not been normalized with other interventions after three weeks (57). Early sinus dysfunction in the early postoperative period is usually not associated with damage to the electrical conduction system, so bicameral pacemakers with AAIR/DDDR function that seek physiological stimulation and preserve AV synchrony have been

widely used in the last years. However, after one year of implantation, the frequency of activity of these devices decreases, in most cases due to the recovery of the sinus function (55,57,58).

In the late postoperative period, errors in the conduction of the nerve impulse are predominant, with AV blocks being the leading cause of implantation of cardiac pacemakers in this period. This phenomenon has been attributed to the development of graft rejection, since electrical conduction tissue has been proven as a typical target of humoral response during this process (52,56,59).

Conclusions

The development of arrhythmias is a frequent issue and, in some cases, puts the life of the patient at risk. This complication is related to multiple triggers. There are factors associated with the surgical procedure itself, such as ischemia times, sinus node injury, and excessive manipulation of the atria due to the surgical technique and cardiac denervation, as well as other mechanisms related to the preoperative and post-surgical periods, such as acute rejection episodes, reinnervation, ventricular biopsies, graft vasculopathy, systemic infections, and drug effects.

The most common arrhythmias are bradycardia, which, in a significant percentage, will require implantation of permanent pacemakers. The most frequent tachyarrhythmia is the isthmus-dependent flutter, which can be treated with catheter ablation. The most common rhythm of cardiac arrest in these patients is asystole, unlike the general population, where more defibrillatory rhythms such as tachycardia and ventricular fibrillation occur.

The detection of any cardiac arrhythmia should lead to think of the possibility that this is the manifestation of an underlying pathological process that puts at risk the viability of the organ and the life of the patient. The medical team is obliged manage this condition in a way that is not limited to symptomatic control and sinus rhythm, but to initiate an active search for its etiology to give optimal therapeutic management to each patient.

Conflict of interest

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REVIEW PAPER

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Hand Transplantation: Current concepts and management algorithm

Trasplante de mano: conceptos actuales y algoritmo de manejo

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| Abstract |

Introduction: Hand transplantation was first reported in 1964, and is currently one of the challenges that the 21st century poses to Medicine. Several related studies and advances have been achieved, thus allowing to explore new alternatives for patient management. Many reference centers have performed their own analyzes based on their experience, which has led to increase the viability of this type of transplant.

Objective: This review seeks to provide an overview of hand transplantation and to propose a management algorithm.

Materials and methods: Several criteria must be met to select candidates, including clinical, paraclinical and psychosocial assessment performed by a multidisciplinary team. Immunosuppression seeks to avoid rejection, while immunosuppressants must have appropriate serum levels to reduce adverse effects. Classical and atypical acute rejection cases have been reported, where the skin is the main target tissue. Chronic rejection cases are related to the blood vessels that become affected. Monitoring is performed using several tests, considering skin biopsy as the gold standard.

Results: Drug therapy complications derive from drug toxicity, which are manifested as metabolic disorders, development of opportunistic infections and neoplasms. Rehabilitation and social aspects, such as patient satisfaction, should be evaluated during recovery to ensure adherence to immunosuppressive therapy. In 2011, the international registry of hand and composite tissue transplantation reported 39 cases of upper limb transplantation with multiple results. All this proves that to achieve optimal and viable results, a multidisciplinary team must conduct proper follow-up, and that the patient should have a support and motivation network, and comply with pharmacological management.

Conclusion: Further research is expected to create strategies to develop tolerance and, thus, reduce management by immunosuppression.

Keywords: Hand Transplantation; Immunosuppression; Composite Tissue Allografts; Graft Rejection; Infection.

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| Resumen |

Introducción. El trasplante de mano ha sido uno de los retos del siglo XXI, cuyo primer caso reportado ocurrió en 1964. En este campo se han hecho estudios y avances que permitieron explorar nuevas alternativas para el manejo del paciente con trasplante de mano, por lo que diversos centros de referencia han realizado análisis basados en sus experiencias, las cuales permitieron lograr la viabilidad de este tipo de trasplante.

Objetivo. Esta revisión busca dar una visión general sobre el trasplante de mano y proponer un algoritmo de manejo.

Materiales y métodos. La selección de candidatos requiere una serie de criterios, tales como evaluación clínica, paraclínica y psicosocial, desarrollados por un equipo multidisciplinario. La inmunosupresión busca evitar el rechazo y los inmunosupresores deben tener los niveles séricos apropiados para reducir sus efectos adversos. Se han reportado casos de rechazo agudo clásico y atípico, donde la piel es el principal tejido blanco, y rechazo crónico, en el cual se afectan los vasos sanguíneos. El seguimiento se realiza con varias pruebas, de modo que la de oro es la biopsia de piel.

Resultados. Las complicaciones del tratamiento farmacológico derivan de la toxicidad de los medicamentos y se manifiestan como alteraciones metabólicas, infecciones oportunistas y neoplasias. La rehabilitación y los aspectos sociales, como el grado de satisfacción del paciente, deben ser evaluados durante la recuperación para asegurar adherencia al tratamiento. En 2011 el registro internacional de alotransplante compuesto de mano reportó 39 casos de trasplante de extremidades superiores con resultados variables; todo esto evidencia que para lograr un resultado óptimo y viable del trasplante debe realizarse seguimiento por un equipo multidisciplinario, red de apoyo del paciente y motivación del mismo, junto con el cumplimiento del manejo farmacológico.

Conclusión. Se espera que nuevas investigaciones puedan crear estrategias para desarrollar tolerancia y, de esta forma, reducir el manejo mediante inmunosupresión.

Palabras clave: Trasplante de mano; Inmunosupresión; Alotrasplante compuesto vascularizado; Rechazo de injerto; Infección (DeCS).

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Introduction

Hand transplantation is categorized as vascularized composite allotransplantation (VCA) (1), and is different from solid organ transplantation (SOT), whose histological composition homogeneity is greater, and functionality occurs since the moment the transplantation takes place. In the case of VCA, transplantation consists of tissues such as skin, bone, muscle, tendons, nerves and blood vessels (2) that generate greater antigenic heterogeneity.

Although the survival of the recipient does not depend on VCA, as in most SOT cases, both improve the quality of life of patients (3). Despite these differences, VCA was equated to SOT in France as per Act 800 of August 6, 2004 (4). Furthermore, the U.S. Department of Health and Human Services published its decision to recognize VCA as organs (5). This decision was based on the following criteria: a) vca is vascularized and requires surgical anastomosis after transplantation; b) it is composed of multiple tissues; c) it must be recovered from a donor as an anatomical unit; d) it is transplanted into a recipient as an anatomical unit; e) it requires minimal manipulation; f) its use is homologous; g) it is not combined with devices or other elements; h) it is susceptible to ischemia, and i) it is susceptible to rejection (5). Additionally, the changes proposed to the National Organ Transplant Act in the United States would facilitate the hand donation and transplantation process (6).

Several reports on limb and face transplantation showed that VAC is more akin to SOT than to tissue transplantation (7-9). By the same token, the organ and tissue transplantation line of Universidad Nacional de Colombia considers that VAC should be treated as a solid organ. This procedure requires health personnel trained in transplantation to standardize management, and to open new scenarios for the application of organ transplantation (10).

History of hand transplantation

In 1964, Gilbert (11), ten years after the first successful kidney transplantation (12), performed the first hand transplantation in Ecuador. The procedure consisted of a unilateral graft transplant, and immunosuppressive management with azathioprine and prednisone to achieve graft survival for three weeks only (13). Due to these unsuccessful results, research on this field was halted for about three decades. Then, in 1998, a second attempt was made in Lyon (14); this time, the graft was removed 29 months after transplantation due to rejection caused by lack of adherence to treatment. In any case, these results allowed a new period for hand transplantation in the 21st century.

Today, several groups work on hand transplantation with good results. The most relevant are found in Poland (15), France (16), Innsbruck (17) and Louisville (18).

Materials and methods

Patient selection and contraindications

The Baltimore group proposes the following inclusion criteria for the selection of candidates: age between 18 and 69 years, no coexisting medical conditions that may affect the outcome of the transplant (immunomodulatory, surgical or functional conditions), no psychiatric pathologies, no history of neoplasms in the last 10 years or HIV infection, and amputation for at least six months prior to the transplantation, with a good faith attempt to use prostheses and rehabilitation.

Moreover, for solid organ transplantation (SOT), additional criteria must be met (19,20). Inherited peripheral and inflammatory neuropathies, as well as neuropathies associated with systemic (diabetes, amyloidosis) and toxic diseases (metals and drugs) should be considered as relative contraindications for VAC, since transplantation requires post-transplant nerve regeneration, which could negatively affect the recovery of sensitivity or motor function in the hand (3,21).

In general, exclusion criteria to be considered include patients under 18 or over 69 years of age, and conditions that affect: a) the immunomodulatory protocol, such as chronic infections (HIV, hepatitis C), and preexisting immunological malignancies or deficiencies; b) surgical success and healing of coagulopathies, hematological diseases, vascular collagen disorders or connective tissue disorders; and c) functional results (healing of nerves or bones) in the presence of lipopolysaccharidosis, amyloidosis, metabolic diseases or bone genetic diseases. Other exclusion criteria are autoimmune inflammatory arthritis and extensive and severe osteoarthritis. In addition, patients may be excluded due to any other problem developed during the selection process (19,20). Similarly, the loss of the hand should be unilateral or bilateral and the level of amputation limited to the forearm.

Thereafter, a panel of screening tests is performed, including hematologic tests such as complete and differential blood count, reticulocyte count, platelet count, PT (prothrombin time), PTT (partial thromboplastin time), INR (international normalized ratio), ABO (for blood type compatibility; blood type A, B or O), Rh factor, major histocompatibility complex (MHC) and panel reactive antibodies (PRA).

Metabolic tests include serum electrolytes, renal function panel, creatinine, uroanalysis and liver function. Infectious tests involve cytomegalovirus detection, Epstein-Barr, herpes simplex, toxoplasmosis, varicella-zoster (IgG and IgM when indicated), HIV 1 and 2, hepatitis C, syphilis, hepatitis B and Mantoux skin test (TST). Cardiopulmonary tests involve electrocardiogram and echocardiogram or pulmonary function test with DL02.

Finally, radiology tests include abdomen ultrasound (to discard a tumor), hand and stump ultrasound, computerized axial tomography (CT), conventional angiography, functional magnetic resonance, paranasal sinus x-ray (to discard an infection or tumor), thoracic and simple bilateral hand x-ray, and wrist and forearm x-ray as indicated (19,20).

Diagnostic images (radiography, CT, NMR, among others) are important because they characterize the structural integrity of soft tissues and the bone of the receptor, which indicate how healthy a tissue is, and prevents anastomosis in a diseased or injured tissue. In addition, they describe structural damage (maceration of distal residual tissues, bone fragmentation, intra-articular fracture extension), either caused by amputation or by subsequent surgical procedures. This guides the surgical process, in the best possible way, where muscle mass and bone integrity need to be preserved. They also exclude any underlying disease that may compromise the function of the transplant or contraindicate life-long immunosuppression.

Angiography or angioresonance is used to identify the appropriate anastomotic vascular pedicle (radial or ulnar) for grafting. It is worth noting that ultrasound is useful for identifying signs of endothelial proliferation during postoperative surveillance, which would indicate graft rejection (22).

However, the assessment of coincident MHC is recommended, since the number of acute rejections seems to correlate with the

number of mismatched MHC, whose compatibility, according to one hypothesis, correlates with the development of antibodies in the donor. Therefore, this also influences the risk of developing graft vasculopathy in VAC (23,24).

Lastly, a multidisciplinary team should perform a complete clinical assessment of the candidates, including specialists (gastroenterologist, ophthalmologist, dentist, etc.) and psychological and social work support (19,20).

Immunology of the hand

Unlike solid organs (kidney, heart, liver, etc.), the hand is coated with skin, which has a very high antigenic load (25). In 2005, Tung *et al.* demonstrated that skin rejection is the first event in studies of limbs transplantation in mice (26), which coincides with findings in humans. The cellular components of the skin, associated with immune response, are keratinocytes, langerhans cells and dendritic cells. Keratinocytes produce proinflammatory cytokines that activate these cells in the dermis and epidermis, and chemokines that attract circulating lymphocytes into inflammatory foci and regulate the function of langerhans cells in the immune response (27).

On the other hand, Sugita *et al.*, when performing epidermal cell cultures, found that the expression of the major histocompatibility complex (MHC) class II in keratinocytes was promoted in this type of cells, while CD86 was expressed in langerhans cells. This finding allows identifying the role of keratinocytes in the appearance of antigens, through toll-like receptors, as well as their role in the regulation of the immune response (28). These results confirm that skin has the ability to trigger a large-scale immune response that can lead to skin rejection in hand allografts.

Immunosuppressive protocols

Induction therapy with both monoclonal (alemtuzumab/basiliximab) and polyclonal antibodies (ATG, that is, antithymocyte globulin) has been used since the Lyon transplant in 1998 based on the patient's immunological risk, and is followed by maintenance management, combined with mycophenolate mofetil (MMF), tacrolimus and steroids (25). In many studies, skin cell components have been characterized while searching alternatives to induce tolerance such as chimerism by transplantation of hematopoietic cells, together with cytokines of peripheral blood mononuclear cells in animal models, or reduction of pharmacological immunosuppression. This has yielded varying results, either transitory chimerism or risk of generating graft-versus-host disease (29-31).

Similarly, the experience of the Polish group, with six patients transplanted until 2011, reported the following scheme as a management protocol:

a) Induction: basiliximab, tacrolimus 5mg oral, MMF 2g oral, and methylprednisolone 1g intravenously.
b) Day 1: tacrolimus 5mg oral twice a day, MMF 1g oral twice a day, and methylprednisolone 500 mg intravenously.
c) Day 2: basiliximab intravenously, tacrolimus 5mg oral twice a day, and MMF 1g oral twice a day.
d) Days 3-7: tacrolimus (seru level 20 ng/mL), MMF 2g oral (daily), and methylprednisolone 500mg intravenously.
e) Maintenance: tacrolimus (peak level 10-15 ng/ml), 56 months after transplantation. Management was done with tacrolimus (peak level 10 ng/mL), steroids (5 mg / d), and MMF (2g/d) (15).

Until the report disclosed in 2011, the French group had performed five hand transplantations with ATG or alemtuzumab for the management of induction therapy, and tacrolimus, prednisone and MMF for maintenance (16). Despite the low number of patients, both protocols have shown favorable outcomes. Therefore, it is suggested that each center, according to its experience and the individual characteristics of each patient, creates its own protocols for immunosuppression (15-18,32-40).

Surgical procedure

As for the surgical procedure to implant the hand, bones, tendons, nerves and blood vessels of both the stump and the hand graft are identified. The order of the union is: fixation of the bones by means of plates and screws usually used in cases of arm fracture, anastomosis of arteries and veins, muscle and tendon repair, nerve repair, and skin closure. Cold ischemia time varies between 50 minutes and 12 hours (mean: 6 hours, 12 minutes) and depends, to a great extent, on the geographic distance between donor and recipient hospitals. (32,41,42).

Complications

Acute rejection

Globally, 85% of all hand transplant recipients have experienced at least one episode of rejection unrelated to induction or maintenance therapy (25) within the first year of transplantation. This is why it is considered as one of the main complications.

Rejection is identified by visual inspection and confirmed by skin biopsy, as it is a highly immunogenic tissue (43-46). Classical acute rejection is observed as an erythematous (diffuse or focal) maculopapular eruption, accompanied or not by edema and vesicles. Other clinical signs are desquamation, ulceration or necrosis (47,48). In addition, manifestations of atypical acute rejection affect the palmar skin and nails, so the lesion appears as a desquamative rash associated with dry skin, red papules and palmar thickening or lichenification, nail dystrophy, deformation or nail loss (47).

Treatment for acute rejection includes topical tacrolimus or clobetasol ointments, as well as systemic steroids and monoclonal antibodies as needed (49,50). The histopathological characterization of skin rejection is performed using the Banff classification (51,52). In the skin samples, an increase in the expression of adhesion molecules (Intercellular Adhesion Molecule 1 o ICAM-1, E-Selectin and P-Selectin) is evidenced in the vascular endothelium of the graft, which is associated with the severity of the rejection (25, 53). In addition, lymphocyte infiltrate is observed with predominance of T CD4+, CD8+, CD3+, and CD68+ lymphocytes, and Foxp3 transcription factor expression, which is also correlated with the severity of rejection (53-57).

Chronic rejection

Little is known about the risk of chronic rejection in humans, whereas hindlimb animal models with rats have shown thickening of the intima and light occlusion of the graft arteries at a histological level (47,58). In this model, repetitive episodes of acute rejection were induced and histological changes of chronic rejection were achieved, including loss of hair follicles and epithelium, and adnexial muscle atrophy, with macrophage infiltration and fibrosis.

Vascular alterations are late findings of rejection, suggesting that multiple episodes of acute rejection may lead to vasculopathy in the graft (47,59,60). Therefore, TH1 and TH2 have been proposed as immune activation pathways mediated by Helper TCD4+ T cells. The former is associated with acute rejection and is mediated by IFN-, TNF-α and IL-2 proinflammatory cytokines that increase immunogenicity in allografts. On the other hand, the TH2 pathway induces tolerance by means of IL-4,5,6 and IL-10 , which inhibit the production of IFN , and Th1 cells to suppress the production of IL-6 and TNF-α from monocytes. Nowadays, it is suggested that the TH2 pathway favors the production of alloantibodies, cytokines, and growth factors that induce the proliferation of TCD8+, cells, natural killer (NK) cells, B cells, macrophages, smooth muscle and endothelial cells that favor chronic rejection (61-63).

Pharmacological immunosuppression

Complications secondary to the immunosuppressive protocol, which prevent hand allograft rejection, may appear including infection, post-transplant diabetes, hypertension, nephrotoxicity, hyperlipidemia, leukopenia, cardiovascular disease, bilateral hip osteonecrosis, and increased risk of developing certain cancers (3).

Opportunistic infections

One of the most common is cytomegalovirus (CMV) infection, perhaps due to the high risk of latent virus transmission forms in leukocytes, epithelial cells and hematopoietic bone marrow stem cells found in the hand allograft (64). This may increase morbimortality in the recipient, as well as decreased graft survival and increased risk of acute rejection episodes (14,65-68). Negative CMV receptors may get infected through blood transfusions, community transmission and false CMV negatives in the donor. In addition, treatment with drugs such as Ganciclovir (GCV), Valganciclovir (ValGCV), Foscarnet and Cidofovir, alone or in combination, should be initiated, while monitoring is performed with polymerase chain reaction (PCR) for CMV (55).

Bonatti *et al.* (56), of the Innsbruck group, reported that their three hand receptors received antiviral prophylaxis with Ganciclovir (GCV) or Valganciclovir (valGCV) and still developed an infection by CMV. Two of them developed a complicated infection that required anti-CMV, hyperimmunoglobulin, cidofovir and foscarnet. In contrast, the third patient suffered from one type of non-invasive viremia by CMV. Furthermore, Ravindra *et al.* (69), of the Louisville group, reported that two of their three patients developed CMV infection; one of them went into remission with oral GCV, and the other was administered the same medication but intravenously, with complete remission.

Other infections reported in these patients were caused by human papilloma virus, herpes simplex, *Staphylococcus aureus, Clostridium difficile*, contagious molluscum, Pseudomonas sp., candida mycosis and *Alternaria alternata* (32,70,71). In general, it is necessary to contemplate the same considerations of solid organ transplantation, although there is no evidence regarding prophylaxis.

Neoplasms

Since hand transplantation patients have been monitored for less than 10 years, many of the side effects of long-term immunosuppression are still unknown, considering that, in general, they are healthy patients.

So, people undergoing solid organ transplantation are known to be at least three to five times more likely to develop neoplasms compared to the general population. The most frequent types of cancer are associated with virus and skin cancer (72,73), which is why it is essential to consider the risk of developing different types of neoplasms in patients with vascularized composite allograft (VCA), in particular hand transplantation. The risk of developing different types of neoplasms must also be considered. Landin *et al.* (74) reported basal cell carcinoma in a bilateral hand transplant recipient in 2006; the patient had received alemtuzumab and then combination therapy using tacrolimus, MMF and prednisone. 360 days after the transplantation, a nodular, rounded, pigmented and smooth lesion of 3 mm of diameter was found in the right nasal wing, which was removed without recurrence.

Kaufman *et al.* (18) reported the detection of mantle cell lymphoma in the third patient, who underwent hand transplantation by the Louisville group, and received alemtuzumab as an inducer, while tacrolimus and MMF were administered for maintenance.

Psychological aspects

The psychosocial factors in hand transplantation patients affect graft function and survival (75,76). This can be identified in the second hand transplantation in the world, which was performed in Lyon in 1998. This surgical procedure was successful although the patient did not adhere to the immunosuppressive management, nor to physical therapy; therefore, the patient required amputation of the graft in 2001 (14). This was related to the motivation and ability to incorporate transplantation experience in patients, which may lead to non-compliance with the pharmacological or rehabilitation regimen (77,78).

Some of the risk factors identified in psychological assessments in candidates for hand transplantation include social isolation, shame, decreased self-esteem, depressive coping style and poor quality of life (79). For this reason, it is important to conduct a detailed psychiatric interview in which transplantation is addressed, and to supplement it with psychological tests to assess body image adaptation and integrity, before and after the transplant (80-84). This is useful to perform the necessary therapeutic interventions, detect difficulties in the psychological integration process of the graft and, thus, obtain the best possible results in the long term.

Rehabilitation

Although part of the success of hand transplantation is attributed to surgical planning, it is not the only aspect to be taken into account to achieve a successful outcome (85). Rehabilitation programs are fundamental for the recovery of functionality in the transplanted hand, since a successful process requires patient commitment. It is also necessary to ensure that the patient will count on a team of experts that can provide guidance in terms of long-term recovery goals and expectations (86-91).

Before transplantation, therapists collect data on motion range, strength, stump sensitivity, and history of prosthesis use. They also find out if the patient feels pain, which is recorded by analogous verbal scale (48). As for the team of hand therapists, they should be responsible for the planning of therapy sessions, patient education and familiarization with information from transplant centers (32), which allows them to know the main complications and possible management. In addition, it is recommended to initiate therapy one week after surgery.

However, this therapy should be performed five days a week for an average of four hours a day for the first three months after transplantation (48), which requires commitment from the patient and the caregiver. Likewise, since the intensity in days and hours

varies among patients, they should be adjusted based on recovery in each case (90,91).

Research on the emotional aspects of these patients has focused on depression, anxiety, personality disorders and substance abuse, since they are the most frequent alterations, and are associated with functionality recovery expectations after the transplantation (92,93). With this is mind, the need to assess the degree of satisfaction and improvement of the quality of life of transplanted patients arises. These aspects are assessed through evaluation questionnaires that have not been standardized yet in all hand-transplantation programs (94-97). Such questionnaires include a) DASH (Disabilities of the Arm, Shoulder and Hand), which allows obtaining subjective and objective data from the patient, if a decrease of 15 points or more is found, a significant recovery in functionality is considered (98); b) Sollerman Hand Function Test, which incorporates tasks based on the patient's work and takes into account the quality of the grip patterns and strength to perform them (99,100); and c) The Carroll Upper Extremity Function Test, which evaluates the functional recovery of the graft (101).

Finally, the role of the caregiver is fundamental during the first post-transplantation phase, since patients, especially those receiving bilateral hand transplants, depend on someone else for daily living activities for weeks or months after the surgery. This is exacerbated by the physical fatigue caused by rehabilitation, immunosuppressive drugs and the emotional challenges of the demanding general program (48). Therefore, throughout the process, the family must be included to be provided with the necessary tools to meet this challenge in the best possible way.

State of the art

Information on the experience of each transplant center in the world is compiled by the International Registry of Hand and Composite Tissue Transplantation (IRHCTT), where reports are delivered voluntarily (non-mandatory). In total, 89 hand transplantations were performed between 1998 and 2010 (102). The last report was published in 2010 and provides data on the follow-up of 49 hand transplantations in 33 patients (18 bilateral and 17 unilateral). Follow-up was performed on 31 patients for minimum one year; the age range was 19 to 54 years, with a mean age of 32 years. Regarding sex, 31 patients were males. Finally, in relation to the transplantation itself, wrist (46%), distal forearm (19%), middle forearm (17%), proximal forearm (14%) and elbow (4%) were the most common.

As a result, 30 patients regained tactile and discriminative sensitivity. Motor recovery was initiated in the extrinsic muscles (gross motor), and then in the intrinsic muscles of the hand, for 9 to 15 months, in most transplanted patients (32). This motor return depends on the anatomical level of the transplant (distal is better than proximal), and on the postoperative rehabilitation regimen; sensory feedback is conditioned to the regeneration of the nerve (47). Quality of life improved in 75% of patients, which enabled them to resume their work activities. Moreover, the systematic review by Landin *et al.* found that the score decreased by an average of 27.6±19.04 points, through a disability comparison with the DASH survey, before and after the transplantation. Significant functional gains of the transplanted limb were also evidenced (103).

The main complications associated with transplantation are (32): a) opportunistic infections by CMV and herpes (29 cases); b) limited cutaneous necrosis (6 cases); c) permanent hyperglycemia (3 cases); d) arterial thrombosis (1 case); f) arteriovenous fistulae (1 case); g) end-stage kidney disease (1 case) that required hemodialysis 8 years after hand transplantation; h) transplant loss (1 case) due to poor adherence to treatment (29 months post-transplant), with conscious patient decision to suspend immunosuppression; i) intimal hyperplasia at day 245 post-transplant (1 case); j) bilateral transplantation involving bacterial infection (day 45 post-transplant), and k) bilateral hand and face transplantation, which resulted in death by cerebral anoxia (day 65 post-transplant).

However, IRHCTT does not take into account the cases reported by the Chinese groups, including Pei *et al.* (104), who reported 15 hand transplantations performed in 12 patients between 1999 and 2008, with a mean age of 34 years (19-52 years). Seven of these patients lost the grafts due to lack of adherence to the treatment. Overall, the results were poor, compared to transplantations performed in other centers around the world.

When comparing unilateral and bilateral transplantation with DASH scores, better functional results were observed in bilateral transplants. Even so, the results were positive for both groups from an overall perspective, which implies independence and return to the patients' work activities (105,106).

Future of hand transplantation

Despite advances in immunosuppressive management and rehabilitation programs, there are still limitations, such as nerve regeneration of the transplanted hand, which occurs both at the distal and proximal levels. The case of proximal segment amputations is more relevant due to the difficulty of adapting to the prosthesis, which is why the transplant is required. Nevertheless, new research is expected to develop strategies to improve this aspect (3,107).

Immunosuppressive protocols are another important factor in hand transplantation, since there would be no graft survival without them. Currently, no protocols develop immunocompetence in the transplanted patient to avoid immunosuppression. Thus, these strategies are expected to be established in the future, to prevent the side effects of pharmacological immunosuppression.

It should be noted that protocols that include transient or sustained chimerism have already been developed; however, in this case a living donor is needed, which is not possible in hand transplantation (108).

Today, research on autotransfusion protocols and mesenchymal stem cells that regulate the possible decline of the immune response can be found, even if its use is limited to experimental studies. Although the use of mesenchymal bone marrow cells has shown to generate stable chimerism and prolong transplant survival in animal models, it has not yet been tested in humans (109,110).

Another modality under study is based on the use of bioreactors to prolong ex vivo, that is, outside the donor and the recipient, in an alternate environment, to extend the survival of the graft and to modulate its immunogenicity so as to improve the function of the graft (111).

It has also been mentioned that patients undergoing hand transplantation have a history of difficulty to adapt to prostheses, despite their interest and the interventions made by specialists to achieve this goal. This entailed high rejection rates of these devices (112,113). The options offered to patients with amputations of upper limbs have changed and expanded in order to cover the physical demands of potential candidates.

At present, advances have been made in prostheses adaptation and management, such as the case of selective muscular reinnervation in proximal amputation cases, which has allowed to develop the perception and position of the amputated segment. This technique consists of using non-functional muscles as amplifiers of the non-functional nerves and, thus, extending the nerve cover as distal as possible, approaching the distal end of the prosthesis (115,116).

However, the main causes of prostheses abandonment include adaptation difficulties, lack of participation in the selection of the prosthesis, functionality, patient expectations and education on the proper use of the prosthesis. Thus, people who participate in the selection of devices are more successful in adherence to their everyday use. (117).

In addition, there are six options in the market for the patients with upper limb amputation: not using a prosthesis, using passive prosthesis, body propulsion, electric propulsion, hybrid propulsion or specific activity propulsion. Choices must be made with the patient, so that proper assessment and advice can be provided for a correct selection (118). Because the devices do not fulfill all the activities of daily life, and to be able to respond to the demands of the users and their profession, it is necessary to use more than one device. To be successful and to meet patient expectations, their opinion on the process is essential (119,120).

Finally, hand transplantation and prosthesis adaptation should not be seen as mutually exclusive, but as treatment options that differ from the risk and benefit profile for the patient, and from their ethical, clinical, aesthetic and functional implications (121).

Conclusions

Hand transplantation, rather than a composite tissue transplant, should be considered as an organ transplant that depends on the comprehensive management by a multidisciplinary team, which requires a support network and motivation from the patient, along with compliance with pharmacological management.

When rejection occurs, it should be classified in order to determine the treatment. In consequence, a skin biopsy is considered as the gold standard for diagnosing acute rejection, although its role in chronic rejection should be questioned, since it can generate false negatives according to the depth of the sample.

Also, rehabilitation is a vital process to recover the functionality of the hand, as well as psychological accompaniment to prevent graft loss due to lack of adherence to the treatment.

Finally, new research is expected to create strategies to develop tolerance and thereby reduce management through immunosuppression. In addition, the pros and cons of hand transplantation, the experience of the transplant group, the side effects of short- and long-term drugs, and the possible complications associated with immunosuppression in each of the hand VAC cases should always be evaluated.

To see the management algorithm, please refer to Annex 1.

Conflict of interest

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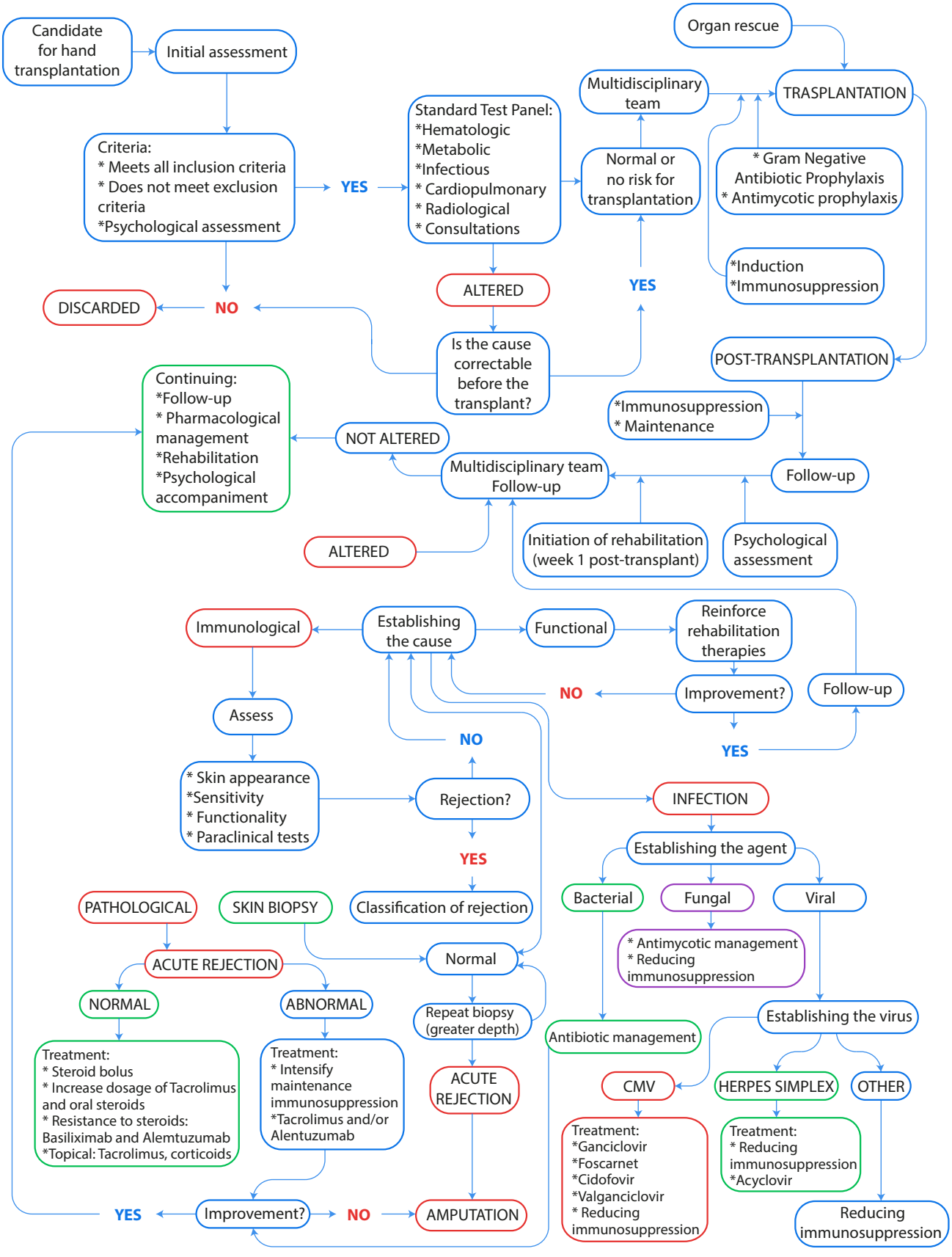
Annex 1. Hand transplantation flow chart.



REVIEW PAPER

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Potential pharmacological use of salivary compounds from hematophagous organisms

Uso potencial farmacológico de los compuestos salivares de organismos hematófagos

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| Abstract |

Introduction: The saliva of hematophagous or blood-sucking insects contains different substances that allow obtaining and ingesting the blood of their vertebrate hosts without being detected.

Objective: To explore the salivary compounds of hematophagous insects which have vasodilator, anticoagulant, anti-inflammatory, immunomodulatory and anesthetic properties, and that can be exploited due to their high pharmacological potential.

Materials and methods: A non-systematic literature review was done in PubMed, EMBASE, and ScienceDirect OvidSP; data was not limited by date, language nor item type. Articles on salivary compounds of blood-sucking insects, whose main topic was the effects on hemostasis, immunomodulation and drug use, were sought. 59 articles met the criteria for inclusion in the review.

Conclusions: The saliva of hematophagous insects has a wide variety of molecules that constitute a source of research and have an incalculable potential for the discovery of compounds that could be pharmacologically useful.

Keywords: Saliva; Pharmacology; Anticoagulants; Vasodilators; Anti-inflammatory; Anesthetics (MeSH).

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| Resumen |

Introducción. La saliva de los artrópodos hematófagos contiene un arsenal de compuestos que les permite acceder a la sangre de sus hospederos vertebrados sin ser detectados.

Objetivo. Explorar los compuestos salivares de insectos hematófagos que tienen propiedades vasodilatadoras, anticoagulantes, antiinflamatorias, inmunomoduladoras y anestésicas, las cuales se pueden aprovechar por su alto potencial farmacológico.

Materiales y métodos. Se realizó una revisión no sistemática de la literatura mediante búsqueda electrónica en las bases de datos PubMed, EMBASE, OvidSP y ScienceDirect; la búsqueda no se limitó por fecha, idioma ni tipo de artículo. Se buscaron artículos sobre los compuestos salivares de los insectos hematófagos, cuyo tema central fuese los efectos en la hemostasia, inmunomodulación y uso farmacológico. Se encontraron 59 artículos que cumplían con los criterios para ser incluidos en la revisión.

Conclusión. La saliva de los insectos hematófagos posee gran variedad de moléculas, lo que ofrece una fuente de investigación y un potencial incalculable para el descubrimiento de compuestos que podrían llegar a tener utilidad farmacológica.

Palabras clave: Saliva; Farmacología; Anticoagulantes; Vasodilatadores; Antiinflamatorios; Anestésicos (DeCS).

Velásquez JJ, Navarro-Vargas JR, Moncada L. [Uso potencial farmacológico de los compuestos salivares de organismos hematófagos]. Rev. Fac. Med. 2017;65(3):501-5. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.52835.

Introduction

Hematophagy or feeding on blood has been seen in various taxa along the evolutionary tree. This is especially relevant in arthropods because they are vectors of different pathogens. Arthropods within the class Insecta or Hexapoda are among the most numerous and diverse of the animal kingdom, with almost 1 200 000 species described, which corresponds to 80% of all animals (1).

In general, the saliva of insects has several functions: digestion, water balance, antagonism of host defense systems, maintenance of the mouthparts, and secretion of pheromones; also, it is believed to have antimicrobial substances (2). Hematophagy is one of the many feeding habits that these species have, that is, they ingest vertebrate blood, including human blood.

Hematophagy is not unique to arthropods and occurs throughout the evolutionary scale; parasites such as *Entamoeba histolytica* and different species of *Plasmodium* consume blood or parts of its components. Leeches, *Annelida* phylum invertebrates and higher animals such as some species of bats of the *Desmodontinae* subfamily, better known by the name of vampires, also feed on blood.

Apparently, the ability to feed on vertebrate blood was developed during the Cretaceous period (3) in parallel to the early division of mammals and birds that replaced dinosaurs. One hypothesis of the evolution of hematophagy is that insects that lived very close to birds or mammals went from being detritivores to hematophagous, with a subsequent modification of the mouthparts, which means that the association between vertebrates and hematophagous insects induced coevolution.

Hematophagy appeared independently during the evolution of arthropods and was only developed by 14 000 species, distributed among 400 different genera from more than one million species of insects (4). These numbers suggest that hematophagy presented mechanical and physiological difficulties during its evolution (5), since it involved the modification of the mouthparts to penetrate, cut and suck, in addition to the challenges for digesting and using blood for different processes related to growth and development or for the maturation of eggs. The detoxification of the *heme* group was also very important, for which they had to chelate it and thus produce hemozoin (5).

Insects ingest the blood in two different ways: some take the blood directly from channel blood vessels —solenophagy— and others break the tissues and produce multiple wounds forming a pool of blood —telmophagy (6). In both cases, insects had to develop an arsenal of molecules with different effects, such as vasodilators, anticoagulants, antiplatelets, anti-inflammatories, immunomodulators, analgesics and, apparently, local anesthetics in order to counteract defenses and other responses of the hosts against the damage inflicted by the hematophagous animal (7).

However, not all haematophagous insects use blood for the same purposes. For example, insects such as Triatomines need blood to cover all physiological requirements, whereas some species of the *Culicidae, Ceratopogonidae* and *Simuliidae* families need blood only to mature the eggs —in this case the composition and morphology of the salivary glands are different in both sexes (8).

Vertebrates have three efficient defense systems that make hematophagy potentially difficult, which are hemostasis, inflammation mechanisms and immunity. With all of these factors in mind, insects may be potentially beneficial for the discovery of new molecules and, perhaps, new drugs.

Below, different molecules that have been found in the salivary glands of hematophagous insects are described, and some research developed on their applicability in medicine are summarized.

Vasodilators

Vasoconstriction is one of the first reflex mechanisms against bleeding and capillary damage; for this reason, hematophagous insects have developed various vasodilator molecules to ensure blood intake. Some examples of this type of substances include nitroporins, which are molecules with a *heme* group that reversibly bind to nitric oxide and are then released into the host to exert a vasodilator and antiplatelet effect. Nitroporins have been identified in *Rhodnius prolixus* (9) —the main vector of *Trypanosoma cruzi* in Colombia—, are known as np1 and np4 and belong to the lipocalines group (10,11). They have also been identified in *Cimex lectularius*, or bed bug (12), but these nitroporines belong to the inositol phosphatases group (13).

In addition, ticks produce prostaglandins in large quantities; so far, PGE2 and PGF2 alpha have been identified (14,15). Diptera of the genus *Phlebotomus* produce adenosine, which is secreted by 75-80% after initiating blood ingestion, and its vasodilatory and antiplatelet activity has been demonstrated (16,17). Insects of the genus *Lutzomyia* have a potent vasodilator, maxadilan, which binds to the PACAP receptor and has 500-fold more vasodilatory activity than the peptide related to the calcitonin gene, the most potent vasodilator compound known to date (18,19). Other examples of isolated and characterized vasodilator molecules are type I and II sialokinins found in *Aedes aegypti* (20,21).

The species *Simulium vittatum* belongs to the *Simuliidae* family —known in Colombia as *jején, mosquito*, among others— and has a 15-kDa protein called *Simulium vittatum* erythema protein or SVEP in its saliva, which increases the perfusion of blood in the cutaneous capillaries and triggers the erythema associated with the insect bite. Apparently, its vasodilation mechanism relaxes smooth muscles, since it stimulates the opening of K+ channels that dependend on ATP (22,23).

Finally, a peroxidase has been identified in the female *Anopheles albimanus*, one of the three main vectors of malaria in Colombia, which exerts its vasodilatory effect by destroying norepinephrine and serotonin (24).

Anticoagulants

Hemostasis, a mechanism used by animals as a response to tissue damage, involves three processes: platelet aggregation, coagulation and vessel constriction. This mechanism represents a major challenge for hematophagous animals, since thrombin inhibitors have multivalent reactions in common, which results in high specificity and affinity, besides of blocking interactions with possible substrates and cofactors. One of the best inhibitors of hematophagous animals is hirudin, extracted from the *Hirudo medicinalis* leech, although other serine proteases with the same function have also been found in other leeches (25).

Anti-hemostatic molecules show the great diversity of compounds derived from the saliva of hematophagous animals. For example, apyrase belongs to a family of enzymes that hydrolyze ATP and ADP to yield AMP, and that may have an anti-inflammatory and antihemostatic effect (26-27). These molecules can be found in various insects such as *Aedes aegypti* (28), vector of some flaviviruses including dengue, zika and chikungunya in Colombia; *Lutzomyia longipalpis*, vector of *Leishmania infantum* in many Latin American regions (29); *Phlebotomus papatasi*, vector of *Leshmania donovani* in the Old World and of bedbugs (30), and *Cimex lectularius* (31) and *Ayadualina* extracted from the salivary glands of *Lutzomyia ayacuyensis*, whose function is to inhibit collagen-induced platelet aggregation and ADP (32). Higher concentrations of heparin have been found in the midgut of *Aedes togoi*, which is related to the salivary glands of females who have ingested blood (33). An isolated Factor Xa inhibitor, characterized and known as anticoagulant Factor Xa (AFXa), belongs to the superfamily of serpins and can be found in *Aedes aegypti* (34,35).

Several thrombin inhibitor compounds such as Mandanin-1 and Mandanin-2 —competitive inhibitors of thrombin and extracted from the saliva of the tick *Longicornis haemaphysalis*— (36) have been recently discovered. Other examples of thrombin inhibitors include the Americanin molecule, obtained from the salivary glands of the tick *Amblyomma americanum* (37); the Anopheline molecule from the *Anopheles albimanus* mosquito (38,39), and the CE5 protein found in *Anopheles gambiae* (40), and AaTI or *Aedes aegypti* thrombin inhibitor (41,42).

Anti-inflammatories and immunomodulators

Studies and isolations of these types of compounds have been carried out, for the most part, with the saliva of ticks, since these arthropods remain close to the host for several days and have developed potent anti-inflammatory and immunomodulatory compounds. By means of these compounds, ticks manage to delay the immune response of the host vertebrate and, thus, prolong their feeding.

The most studied compounds are anti-complement compounds such as the saliva of *Ixodes scapularis* or Isac (43), the IRAC I and IRAC II proteins found in *Ixodes ricinus*, which inhibit the alternative complement pathway (44), and the salivary protein 20 found in *Ixodes scapularis* or SaIp20, which acts by dissociating C3 convertase (45).

Another site of action is the effect on cells of the immune system. For example, the saliva of *Ixodes dammini* inhibits the functionality of neutrophils (46), whereas *Dermacentor reticulatus* and *Ixodes ricinus* suppress the functions of NK cells, the production of interferon and interleukins (47,48), and the proliferation of lymphocytes (49,50). Salivary extracts of *Amblyomma americanum* and *Dermacentor variabilis* ticks are also capable of affecting the proliferation, migration and phagocytosis of macrophages (51,52). In addition, the maturation of dendritic cells is inhibited by the saliva of *Rhipicephalus sanguineus* (53).

On the other hand, the saliva of some ticks has shown an important effect on chemotaxis, the production of various cytokines and the modification of the Th1 and Th2 response (54,55). It also has the ability to interfere in healing since it hinders fibroblast migration, decreases the production of growth factors and the formation of the cellular cytoskeleton (56,57), and alters angiogenesis —which is product of the effect of the calreticulin protein (54) found in the saliva of *Ixodes Scapularis* and *Amblyomma americanum* (58).

The *Trypansoma brucei* vector —producer of American trypanosomiasis and found in the saliva of *Glossina morsitans*— has a peptide named Gloss 2 which inhibits the secretion of TNF-α factor, IFN-γ and IL-6, apart from affecting the humoral immune response by inhibiting the production of IL-10 (59).

Anesthetics

Little has been studied about the anesthetic effect of the saliva of hematophagous insects. However, the presence of mechanisms through which pain is blocked have been proposed, since many of such insects are big, produce a non-painful sting and can suck blood for long periods of time without being perceived.

Regarding this hypothesis, there is a study that shows that the saliva of *Triatoma infestans*, the main vector of *Trypanosoma cruzi* in the southern cone of South America, has an inhibitory effect on nerve transmission, as it achieves a progressive reduction of the action potential amplitude on a rat sciatic nerve model. In the same study, an inhibition of sodium-dependent voltage channels in cultures of neuronal GH3 cells was demonstrated, leading to hypothesize that the saliva of these insects may decrease the generation and conduction of nerve action potential, similar to local anesthetics currently used (60).

Pharmacological usefulness

One of the best examples of pharmacological use of compounds derived from the saliva of hematophagous insects is the development of direct thrombin inhibitors: bivalirudin, argatroban and desirudin, derivatives of the Hirudin anticoagulant peptide obtained from the saliva of the leech Hirudo medicinalis (61).

The Maxadilan peptide, found in the saliva of *Lutzomyia longipalpis*, is a potent agonist vasodilator specific for the PACAP type I receptor, which is widely distributed in the brain. In a study with rabbits, this compound was useful for the management of cerebral spasms secondary to subarachnoid hemorrhage (62). In addition to its vasodilatory effect, its influence on the metabolic level has also been observed, since prolonged administration in murine models increases insulin sensitivity and lowers basal plasma glucose (63). Likewise, Maxadilan has been shown to prevent apoptosis of human pluripotent cells by regulating caspases 3 and 6, without affecting the karyotype or pluripotent state of insect cells (64).

Two molecules are involved in clot formation. One of them is simplagrin, found in *Simulium nigrimanum*, which inhibits the interaction of the von Willebrand factor with type III collagen by specifically and completely blocking platelet adhesion under high flux conditions —it has been proven useful in inhibiting the formation of carotid thrombi in mice (65). The other is aegeptin, which binds to collagen and inhibits platelet aggregation to soluble or fibrillar collagen and the interaction of the Von Willebrand factor (66).

Considering the properties of tick saliva to inhibit cell migration and healing, a study on osteosarcoma tumor cells and breast cancer was performed, finding that saliva had an inhibitory effect on the migration and metastatic invasion of these cells (67).

Conclusions

This review has explored how hematophagous insects have an important variety of molecules capable of acting on hemostasis, immunity and response to vertebrate pain, thus ensuring their engorging. Similarly, different compounds are being investigated for pharmacological use in circulatory, metabolic and even oncological pathologies.

All this leads to conclude that the saliva of hematophagous insects offers a great source of research and incalculable potential for the discovery of new compounds that could become pharmacologically useful and even provide valuable medical alternatives for humanity.

Conflict of interests

None stated by the authors.

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REVIEW PAPER

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Interdisciplinary management of infantile colic

Manejo interdisciplinario del cólico del lactante

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| Abstract |

Infantile colic is one of the main reasons for consultation in pediatric gastroenterology and pediatric nutrition services. This pathology has multiple etiologies such as family dysfunction, gastrointestinal alterations, food allergies or intolerances, food imbalance and improper eating habits. It is acute, of sudden onset, and tends to disappear between 3 and 6 months of age. To date there is no consensus on the management protocols of this condition or indicators of therapeutic efficacy. Medications, dietary regimens and dietary supplements specific to this pathology (anti-colic) have been developed for some years to help address this issue.

This article presents a structural review of evidence on the fundamentals and progress in the treatment of infantile colic, and compiles the characteristics of this pathology, the medical and nutritional therapeutic measures, the clinical approach and the techniques to help the patient and his family. This study seeks to provide technical tools to health professionals whose target population is children younger than 2 years of age.

Keywords: Infantile Colic; Gastroenterology; Infant Nutrition Disorders; Infant Formula; Diet Therapy (MeSH).

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| Resumen |

El cólico del lactante es uno de los principales motivos de consulta en los servicios de pediatría, gastroenterología y nutrición pediátrica. Esta patología posee múltiples características etiológicas como disfunción de la mecánica familiar, alteraciones gastrointestinales, alergias o intolerancias alimentarias, desbalance alimentario e inadecuados hábitos alimenticios. Es de carácter agudo, con inicio súbito que tiende a desaparecer entre los 3 y 6 meses de edad. Hasta el momento no existe un consenso sobre los protocolos de manejo de esta condición o sobre sus indicadores de eficacia terapéutica. Desde hace algunos años se han desarrollado fármacos, regímenes dietarios y complementos alimentarios específicos para esta patología (*anticólico*). Este trabajo es una revisión de la evidencia sobre los fundamentos y avances en el tratamiento del cólico del lactante en el que se recopilan las características de esta patología, las medidas terapéuticas médicas y nutricionales, el abordaje clínico y las técnicas para ayudar al paciente y su entorno familiar. El presente estudio busca brindar herramientas técnicas al profesional de la salud cuya población objeto de atención es menor de 2 años.

Palabras clave: Cólico; Gastroenterología; Nutrición del lactante; Fórmulas Infantiles; Dietoterapia (DeCS).

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Introduction

Infantile colic (IC) is a clinical entity characterized by a sudden episode —almost always in the evening— of unexpected and uncontrollable crying. It usually occurs in the third week of life and decreases by the time the child is between 3 and 6 months of age (1). These pathological features, along with the lack of international consensus on the definition, diagnostic methods and management algorithms, make the proper management of this entity difficult to achieve (2).

Several criteria for the diagnosis of IC diverge widely from each other. One of them is the duration and definitive characteristics, which are more associated to the consumption of infantile formulas. Wessel defines IC as "episodes of intense and vigorous crying at least 3 hours a day, 3 days a week for at least 3 weeks in a healthy and well-fed infant" (3, p4). This concept is the most common in the scientific literature and its incidence oscillates between 20% and 40% in infants younger than 4 months. According to the Rome III criteria, IC is defined as "paroxysms of irritability, fussiness or crying that start and stop without obvious cause, episodes lasting 3 hours or more per day and occurring at least three days per week for at least one week; and no failure to thrive" (4, p5). Furthermore, Rome IV criteria describe

it as a behavioral syndrome in infants aged 1 to 4 months of age that inexplicably cry for extended periods, and are difficult to soothe (5).

Carey (6) concludes that these manifestations are variable and are associated with intrafamilial problems. Also, Barr proposes a reduction of the crying time required to establish a diagnosis by stating that IC appears in "a healthy child whose crying is perceived as excessive by the parents" (7, p1). This definition is inconvenient because of the subjectivity it implies, and because of the difference between the parenting patterns of first-time parents and experienced parents. Based on these clinical conditions, health professionals should be aware of the regular length of crying in infants (8). According to some studies, it ranges from 1 to 2 hours with a high intensity variability that affects the percentage of adequate diagnosis (1,2).

For this review, literature databases of the last two decades were consulted on aspects such as classification, diagnostic method and integral management of IC using the following MeSH terms: infantile colic, integral management, infant, nutrition, infant formula, pharmacotherapy and probiotics. 246 articles were obtained, of which 69 were selected according to the AGREE (Appraisal of Guidelines for Research and Evaluation) criteria, including review articles, cohort studies, systematic reviews and meta-analyzes.

Pathophysiology of infantile colic

Several causes seem to increase the incidence and prevalence rates of IC in infants younger than 4 months. Prevalence is estimated between 8% and 40% according to studies by Ortega & Barroso of the Spanish Society of Pediatrics (9). Although the specific etiology of IC has not been conclusively confirmed, at least three causes have been identified: dietary, gastrointestinal and psychosocial factors (9).

Dietary etiology

In the presence of IC, the initial etiological suspicion is usually an alteration in the pattern of food intake or in the nutritional composition of the diet. Two possible causes of this pathology include inadequate breastfeeding patterns and food intolerance or allergy.

It has been proven that there is no difference in the incidence of IC in the population fed through breastfeeding or infant formula (IF) (10). However, considering the imbalance that occurs in the physiological process of breastfeeding according to the breastfeeding pattern, a direct relationship between the alteration in this pattern and the increase in the probability of the onset IC can be inferred (11). For example, frequent and short intakes result in an imbalance of the macronutrient characteristics of breast milk, since they favor the consumption of carbohydrates and cause an imbalance in the distribution of the total caloric value in relation to other macronutrients. These should be consumed proportionally when the breast is empty, since the composition of breast milk during each intake is rich in water and sugar at the beginning, and rich in fat at the end.

In this sense, the type of milk consumed by infants increases the available amount of fermentable carbohydrates in the intestines, which causes an increase in gas and, consequently, the onset of dyspepsia and colic (12). These patterns usually derive from poor nutritional knowledge in the family and from the lack of training of health personnel committed to breastfeeding counseling, which usually include specialists in pediatric nutrition and general pediatrics.

Gas (flatus) is generated by the metabolic pathway of fermentable carbohydrates degradation, especially glucose (Embden-Meyerhof pathway), which produces organic acids as final product. This degradation is carried out by means of methanogenic bacteria —such as *Clostridium difficile*— that produce substrates by converting glucose and some amino acids into butyric and acetic acid, CO2 and H2 depending on the organism involved (13).

Such symptoms can lead to progressive infant weight loss and crying associated with food intake. These consequences are directly related to the deficiencies in initial/final lactation, and are two of the differential complications of inadequate breastfeeding patterns. Occasionally, its occurrence is considered a complication related to IC (14).

On the other hand, cow's milk protein allergy (CMPA) as a probable cause of IC is a theory that has become stronger based on the studies of Shannon (cited by 2), who postulated that allergy to the protein derived from the milk is a very probable cause of inconsolable crying in infants (15).

Breast milk and infant formula consumption in Colombia

In Colombia, bottle and IF use in infants and toddlers is high and could be related to IC. It has been found that at the end of the first three months of life, 57% of the children are fed with formula, although the proportion decreases rapidly with age (less than 40% among children of almost one year of age). These data are similar to those reported in the 2005 National Nutrition Situation Survey (ENSIN in Spanish), in which several mothers were asked about different aspects of breastfeeding, reporting that the main reasons for not breastfeeding are: "the milk does not come out, the child refuses to suckle, the death of the baby, maternal and child illness, nipple problems and drawbacks with suction" (16, p5).

The results of the 2010 National Demographic and Health Survey (ENDS in Spanish) show that 31% of the children who receive a drink other than breast milk within the first three days after delivery were mainly given formula milk (68%), followed by tea or tisanes (8%); only water (5%); milk or water (2%); and liquid milk (2%) (17). The percentage of children who are exclusively breastfed rapidly declines during the first 6 months of life, from 63% in the first two months to 24% at five months. According to the 2010 results, the median duration of breastfeeding remained the same as the reports of the 2005 ENSIN (14.9 months), while the duration of exclusive breastfeeding decreased from 2.2 to 1.8 months (16). These data are of great concern to country authorities and urge further promotion of breastfeeding.

The results show that IF consumption is also the same, which could increase health problems caused by artificial feeding. Without data on the Colombian population, the question is whether the incidence and probability of occurrence of IC can be determined by the use of bottle and IF consumption.

Gastrointestinal etiology

Some gastrointestinal factors can cause IC, and they are the most studied by physiology since they are related to metabolic disorders. First, it is necessary to understand that, physiologically speaking, infants go through a gastrointestinal tract maturation process, which can generate a fluctuating hormonal transit. At this stage, the low level of cholecystokinin —hormone responsible for satiety and postprandial contraction of the vesicle— and the high level of motilin —in charge of peristalsis— explain the presence of crying in patients diagnosed with IC (18).

On the other hand, the immaturity of the gastrointestinal tract of infants generates hypertonia in the internal anal sphincter. This causes a contractile wave in the evacuation process, which increases the likelihood of colic and constipation (18). These symptoms could be caused by poor breastfeeding practices, the consumption of IF or by mixed consumption (19).

Other studies report a direct correlation between IC and colitis caused by an alteration in the intestinal microbiota given the increased presence of *Escherichia coli* and *Lactobacillus lactis* (18-20). This condition is exacerbated by gas located in the gastrointestinal tract, which is increased by fermentative bacteria in the lumen, and by infant crying that generates air ingestion (15-22). Elevated levels of fecal calprotectin are physiological markers that may help infer the presence of IC, according to Rhoads *et al.* (11).

Psychosocial etiology

It is worth mentioning that most of the current studies on IC consider some psychosocial or behavioral factors as probable causes, such as the alteration of the paternal or maternal relationship (23-26). According to Carey (26), parental rejection is defined as the absence of warmth, affection or love of parents to their children, or their significant deprivation. This attitude can take three forms: a) hostility and aggressiveness, b) indifference and negligence, and c) undifferentiated rejection.

Although inadequate upbringing patterns and difficulty in acquiring adequate food are not the main causes of colic, they are factors that contribute to the onset and continuity of the disease (26). For example, the feeding pattern of the mother is directly related to their degree of nutritional culture and income capacity, which is why socioeconomic risk (measured in poverty indicators) and educational level could be related to the risk of IC onset (27-29). For this reason, social history is relevant to make diagnosis easier and to determine the clinical behavior for treatment.

Interdisciplinary management

The crying of infants caused by IC can produce high irritability in the parents; this, along with the scarce or null food intake in the infant and the likelihood of associated complications such as weight loss due to hyporexia, gastroesophageal reflux without esophagitis or persistent constipation (chronic constipation), requires comprehensive therapeutic measures to respond to this pathology.

In the Colombian health system, the professionals who make the initial contact with pediatric patients are general practitioners. Occasionally, the patient is referred to the growth and development group, where a direct consultation with the pediatrician is highly possible. This is the right time to identify the possible causes of IC, request concepts from several professionals that complement the clinical findings, and decide the steps to follow. Undoubtedly, the management of this entity should begin with food and nutrition education accompanied by counseling in breastfeeding and medical-dietary treatment (Figure 1 and 2). Then, if necessary, the psychotherapeutic support of a social worker can be included and, as a last resort, if the health professional considers it after analyzing the evolution, pharmacological treatment can be initiated.

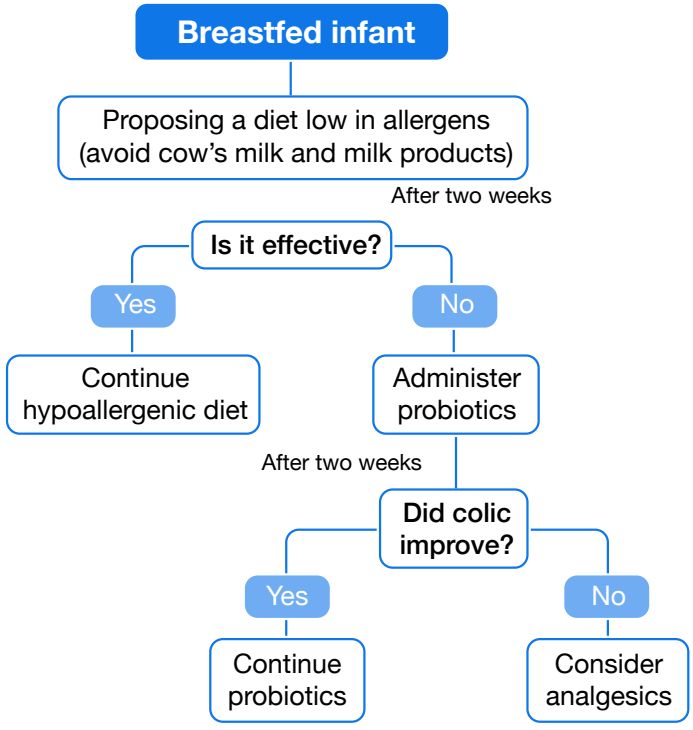

Figure 1. Treatment of colic of the breastfed infant.
Source: Own elaboration based on Lindberg (30).

Food education and breastfeeding counseling

Studies by Taubman (31) showed that feeding education for the mother, as well as adequate breastfeeding techniques, could be more effective than using hydrolyzed formulas and pharmacological treatment. Soothers and relaxing and distracting massages seem to be the best way to approach IC from a family point of view. Taubman (31) provided training to parents on behaviors to respond to crying and feeding patterns for nursing mothers; this proved to be more effective for handling IC than hydrolyzed formulas.

Breastfeeding counseling should promote the consumption of human milk before 6 months of age, which is the period when IC symptoms appear. From this age onwards, appropriate supplementary feeding should be started. In addition, it is necessary to provide

sanitary education on practices such as washing and disinfecting the elements in which breast milk or formula are preseved or administered. Likewise, breastfeeding should be encouraged in working mothers by creating nursing areas at work.

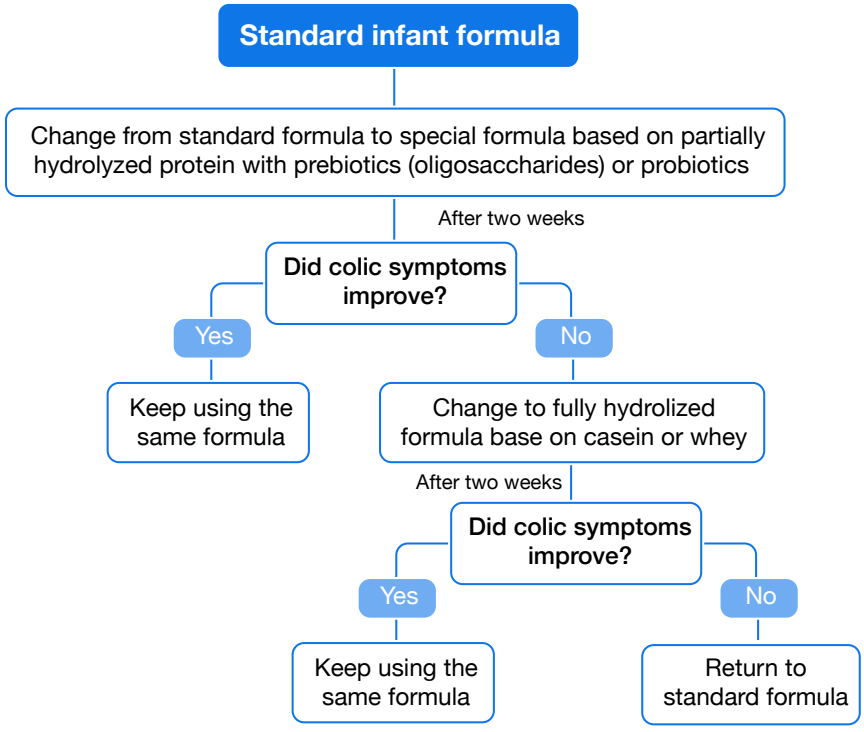

Figure 2. Treatment of colic in infants fed with formula.
Source: Own elaboration based on Lindberg (30).

Dietotherapeutic management

Since the highest incidence of IC is observed between 21 and 90 days after birth, mothers should implement dietary management as a therapeutic measure. Supplementary feeding protocols from the World Health Organization (WHO) recommend the introduction of dairy products after 12 months of age, when the infant exceeds the age range in which IC is usually self-limiting. However, these therapeutic measures may also be used in older infants, always under the strict supervision of a pediatric clinical dietitian or general pediatrician (32-45).

One of the most accepted recommendations is suppressing or reducing in a ponderous way the consumption of proteins derived from cow's milk, as they produce a significant improvement of IC (46). If human milk cannot be supplied, it is recommended to replace it with casein hydrolysates, since, according to a large number of studies, the symptoms of moderate to severe IC are improved (47-50). Studies such as Zeiger *et al.* (50) show that regimens free of food allergens (dairy products, eggs, shellfish and nuts) reduce the incidence and severity of IC. This treatment is recommended for older infants (51).

Breastfeeding counseling is essential in the dietary management of IC. Breastfeeding provided on demand and completely emptying the mammary gland adequately balances the milk content and the percentage distribution of the macronutrients, thus avoiding overeating carbohydrates and their fermentation in the intestines with the complications already exposed (52-54). No conclusive studies on the use of lactose-free formulas or disaccharides in this pathology are known. However, the use of formulas with partially hydrolyzed proteins, a mixture of galactosaccharides and fructooligosaccharides, low lactose and modification of palmitic acid in vegetable oil has shown good results in the reduction of IC (48).

The use of soy-based formulas is widely rejected, because of its low rate of acceptance due to its taste, and because the allergy to proteins derived from this legume has the same incidence as allergy to cow's milk proteins.

Given the wide offer of IF, health professionals should remember that IF should be prescribed and administered following medical indications. In addition, they should know the ingredients that benefit the management of IC, such as proteins with partial hydrolysis and increased serum proteins that facilitate digestion. By decreasing the lactose content, both digestion and lactase function improve. However, removing lactose of IF can alter bone mineralization and decrease calcium deposition. IC may be associated with constipation, so the contribution of beta-palmitic acid in these products avoids the formation of calcium soaps and, therefore, the probability of presenting minor digestive disorders (55-59).

The low presence of melatonin in soy protein isolates is another factor against its consumption. Some studies have identified a direct correlation between melatonin and decreased IC episodes, especially at night, when melatonin production in breast milk is increased by serotonin, producing a relaxing and pseudo-sedating effect in infants (60).

Phytotherapy as an alternative or complementary dietary treatment

The use of infusions and phytotherapeutic recipes is one of the first measures of parents to deal with crying caused by IC. However, this type of practice following the popularity of "home remedies" is based

on ambiguous concepts that can sometimes exacerbate symptoms. Perry *et al.* (36) showed that fennel, chamomile, mint and verbena infusions significantly decreased IC compared to placebo.

Although these therapeutic methods are widely used, there is no consensus among studies to support their safety and determine the dose to be administered to the infant. Similarly, overdosage of phytotherapeutic agents such as anethole —an active ingredient found in aniseed— has been linked to convulsive syndrome, generalized hypotonia, and irritability due to excessive anisette in animal experiments (39-43), therefore professional management is always required.

The continuous use of herbal infusions or phytotherapies in young infants, whose gastric capacity is low, can further decrease gastric capacity and, therefore, the nutritional contribution of breast milk. For this reason, infants under this treatment are more susceptible to abnormal weight loss by hypoingestion.

Pharmacotherapy

To treat IC, the first pharmacological line to be implemented is probiotics, especially *Lactobacillus reuteri*, because of their adequate safety spectrum and therapeutic properties. This bacterium was first isolated from the feces of a healthy human being in 1965, and has interesting therapeutic effects (59). Its role in intestinal microbiota has been documented for the treatment of IC (60), and seems to have an immunomodulatory effect on the intestines regulating the fermentation of carbohydrates, positively impacting the symptomatology (61).

On the other hand, pharmacological surfactants such as simethicone —whose function is to reduce the surface tension of gases— have not shown greater therapeutic effect than other drugs. There is insufficient evidence to opt for surfactants to treat IC (62).

Evidence indicates that dicyclomine hydrochloride is the only drug that improves the frequency and severity of IC compared to placebos in more than 53% of cases due to its anticholinergic activity. However, it has side effects such as apnea, syncope and dissociative seizures, reason why it has been excluded from the pharmacological arsenal for the treatment of this pathology (62).

Conclusions

It is necessary to have strong diagnostic figures and clear possible causes of IC to adopt preventive measures in prenatal control programs and breastfeeding counseling. In this way, it is possible to avoid the unnecessary use of the emergency department and external consultation, thus optimizing health resources.

The management of this pathology should be interdisciplinary. IC can be addressed through holistic therapy to achieve adequate, agile and practical goals that contribute to the recovery of infants. To this effect, it is necessary to develop a clinical practice guide with contributions from different specialties. In very specific IC cases that are managed individually, a comprehensive assessment of the conditions of children and their families is required to identify whether IC is secondary to other pathologies.

Conflict of interest

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REVIEW PAPER

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Acute corneal edema without epithelium compromise. A case report and literature review

Edema de córnea agudo sin compromiso epitelial. Reporte de caso y revisión de literatura

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| Abstract |

Acute corneal edema is caused by various factors, with different levels of severity, and various forms of presentation. This paper reports the case of a male patient presenting with acute corneal edema without epithelium compromise, whose clinical picture, ophthalmological examination and additional tests did not reveal its etiology. Also, a review of available literature was conducted looking for all known causes of acute corneal edema, which are classified according to the etiology of the corneal edema into injury or inflammation of the corneal epithelium or stroma, endothelial dysfunction or increase in intraocular pressure.

Keywords: Cornea; Anterior Chamber; Endothelium; Corneal Edema; Etiology; Causality (MeSH).

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| Resumen |

El edema de córnea es una entidad que se produce por un gran número de causas y tiene diversas formas de presentación y diferentes grados de afección. En este artículo se reporta el caso de un hombre con edema de córnea agudo sin compromiso epitelial, en el que el cuadro clínico, el examen oftalmológico y los estudios de extensión no lograron establecer su etiología. Además, se hace una revisión de la literatura disponible respecto a todas las posibles causas de edema de córnea agudo, agrupándolas en aquellas que ocasionan el edema por lesión o inflamación epitelial o estromal, por disfunción endotelial o por un aumento en la presión intraocular.

Palabras clave: Córnea; Cámara anterior; Epitelio posterior; Edema; Etiología; Causalidad (DeCS).

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Introduction

The cornea is a transparent avascular tissue exposed to the external environment and responsible for about two thirds of the refractive power of the human eye (1). Its transparency depends on a dehydration state regulated by the inner (endothelium) and external (corneal epithelium) layers (2) that maintain a careful hydroelectrolytic balance to guarantee low levels of water. Corneal endothelial cells play a major role in this equilibrium as they carry sodium and bicarbonate ions from the corneal stroma to the anterior chamber, so that water flows passively out of the cornea preventing edematization, which would damage its transparency (3,4).

Acute corneal edema may present with different levels of endothelial, stromal or epithelial involvement (5). Two pathophysiological mechanisms that are prominent in the production of acute corneal edema without epithelial compromise include alterations in endothelial function and elevation of intraocular pressure (6). This paper reports the case of a patient with unilateral sudden corneal edema without epithelial compromise, in whom a clear cause was not established, thus motivating this investigation.

It is worth noting that, according to the objectives of this paper, some known causes of corneal edema, such as posterior corneal dystrophies or iridocorneal syndrome (7-9), are not included because of their chronic nature.

Case presentation

This paper reports the case of a 38-year-old male patient with motor and speech disability, who was taken by relatives to the emergency room reporting symptoms of eight days of evolution consisting of decreased visual acuity in the left eye, white coloration in the cornea

and red eye. The last symptom resolved after management with topical self-medicated vasoconstrictors, but the relatives went to the ophthalmology service after noticing that the bad vision persisted.

The patient had an ischemic stroke in the distal third of the left carotid artery two months before the onset of the symptoms, which required three surgical interventions: mechanical thrombectomy of the anterior cerebral artery and left middle cerebral artery with complete and partial recanalization respectively, decompressive craniectomy, and autologous cranioplasty. In consequence, the patient presented with a predominantly mixed motor aphasia and right hemibody paresis. Also, after being discharged, the patient was prescribed with 40mg of atorvastatin per day, 100mg of acetyl salicylic acid per day, and naproxen or acetaminophen on an occasional basis. In addition, they reported a family history of cardiovascular disease and cataracts.

On visual ophthalmologic examination, visual acuity was close to hand movement, but it could not be accurately determined due to the patient's neurological condition. Additionally, mild chronic hyperemia and an atrophic left temporal pterygium were observed in the conjunctiva of the left eye. A grade 3 diffuse corneal edema was evidenced with folds in the Descemet's membrane but without epithelial alterations (Figure 1 and 2). The cornea of the right eye did not present any alterations, and no fluorescein uptake was observed. The pupil was central and had adequate light reactivity. Finally, no opacities were evident in the lens (Figure 3).

Intraocular pressure detected by Goldman's tonometer was 16 mmHg. The bottom of both eyes was completely normal, as well as the excavation of the optic disc. Treatment with topical prednisolone (1 drop every 3 hours for 3 weeks) was initiated with no improvement of the edema. Given the persistence of the opacity in the cornea and the associated visual deficit reported by his relatives, a corneal transplant was recommended to the patient as a definitive alternative.

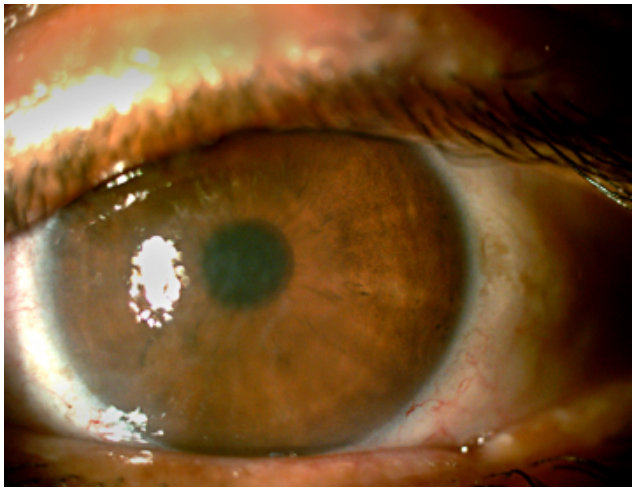

Figure 1. Slit lamp under diffuse light in the left eye with generalized edematized cornea.
Source: Own elaboration based on the data obtained in the study.

Causes of acute corneal edema

The causes of acute corneal edema can be divided into three large categories (10): triggered by epithelial or stromal noxas, such as trauma or viral infection (11-13); triggered by endothelial dysfunction, as will be discussed throughout this article; and triggered by elevation of intraocular pressure (IOP) (2).

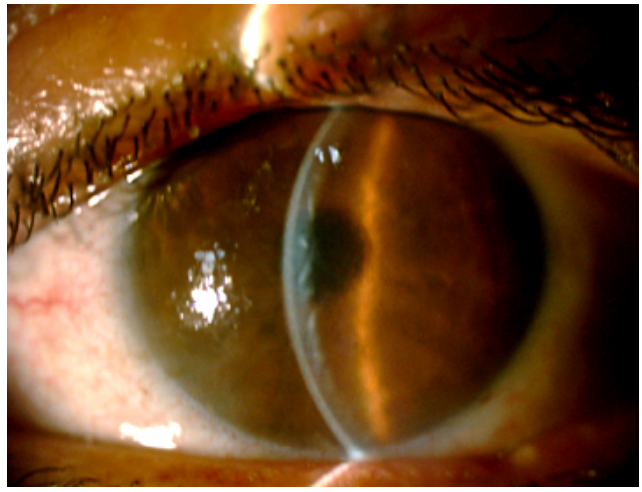

Figure 2. Slit cut under double illumination that allows to observe thickening, opacity and folds of Descemet's membrane.
Source: Own elaboration based on the data obtained in the study.

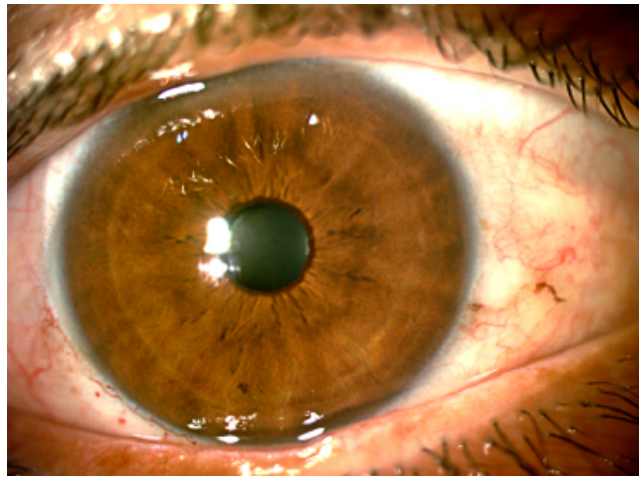

Figure 3. Cornea of the right eye without alterations.
Source: Own elaboration based on the data obtained in the study.

Since the objective of this article is to make an exhaustive review of the causes of corneal edema without epithelial damage and with normal IOP numbers, only the causes that result in edema will be thoroughly reviewed since they affect, one way or another, the dehydrating function of the corneal endothelium.

Regarding other causes, on the one hand, direct trauma, inflammation of the epithelium or corneal stroma may induce endothelial damage, leukocyte migration or rupture of the epithelial barrier (11,16), whereas IOP elevation can be caused when the ability of the endothelium to keep the cornea dehydrated is exceeded. This mechanism may be observed in scenarios such as acute angle-closure glaucoma, endotracheal intubation, and positive pressure ventilation (2).

In other scenarios, this entity is secondary to some alterations in the function of the corneal endothelium, produced by one of the following causes:

Drugs

The use of topical carbonic anhydrase inhibitors (CAI), especially in combination with other topical medications for chronic glaucoma such as latanoprost and timolol, has been reported as one of the causes of acute

corneal edema with a degree of severity as in the case reported in this study (17,18). Inhibiting carbonic anhydrase, which is involved in the expulsion of bicarbonate on the corneal endothelium, may lead to water retention (17). The inability of the epithelial barrier caused by the use of benzalkonium chloride —preservative found in several formulations of ophthalmic eye drops— favors this effect (19,20). Similarly, some association between the use of topical prostaglandin analogues, such as latanoprost and travoprost, and the development of anterior uveitis accompanied by corneal edema has been suggested (21,22).

The development of acute corneal edema secondary to the use of topical mitomycin C in the management of postoperative corneal opacities has been reported as well (23). This drug acts against cancer cells and normal cells during reproduction phases (24), therefore, it may limit subepithelial fibrosis that manifests as corneal opacity (25,26). In the case reported here, the development of the edema was attributed to the toxic effect of mitomycin C over the corneal endothelium, which was facilitated by continuous exposure to this drug in a cornea with denuded epithelium (23).

Aside from topical medications, oral medications are also reported to cause acute corneal edema. This is the case of two NMDA receptor agonists (N-methyl-D-aspartate): amantadine and ketamine (27-30).

Regarding amantadine, there is a relative risk (RR) of 1.7 (95%CI: 1.1-2.8) of developing corneal edema (31), whereas the use of ketamine alone has been clearly associated with only one case (27). This seems to be influenced by the binding of these drugs to NMDA receptors in the corneal endothelium under normal conditions (32), which can lead to the loss of corneal endothelial cells and the subsequent development of edema. In these cases, edema is usually bilateral and decreases after stopping the medication (27,30).

Other non-topical drugs have been considered as possible causes of acute corneal edema, including bacitracin, neomycin, polymyxin B, tetracaine, and phenothiazine (2,33).

Toxins

Some substances, when applied topically on the eye, can trigger endothelial dysfunction with consequent acute corneal edema. Such is the case of cardiac glycosides contained in species such as *Digitalis purpurea* or *Asclepias curassavica*, which may induce acute corneal edema as they inhibit Na+-K+-ATPase, which in turn participates in endothelial cell functions (34,35).

Foreign bodies in the anterior chamber

In some cases, the development of corneal edema has been attributed to the presence of foreign bodies in the anterior chamber, this edema being the first manifestation of their presence. With this in mind, it is possible to say that, on the one hand, these bodies can produce corneal edema by inducing a local inflammatory response, which damages some endothelial cells. This was reported in the case related to nuclear fragments found in the anterior chamber, even years after phacoemulsification (36,37). On the other, the object itself and its products can directly damage the corneal endothelium, favoring edema as in the case of worms trapped in the anterior chamber (filariasis) (38). Other examples include the presence of cotton waste or other products in the anterior chamber following intraocular surgical interventions (39).

Corneal endothelioma

Corneal endothelitis is an acute inflammatory process limited to the corneal endothelium that can be associated with acute corneal edema. There are three viruses in the *Herpesviridae* family that can trigger this ophthalmic entity: varicella-zoster virus, HSV (herpes simplex virus) and cytomegalovirus (40-42). In addition, cases of endothelitis caused by *Mixovirus parotiditis* have been reported (43).

This entity manifests as one or multiple acute red eye crisis, with ciliary and pain predominance, and often accompanied by acute corneal edema and keratotic precipitates, with or without manifest uveitis (40,42,44).

Uveitis

Acute corneal edema is a process that can be triggered by local inflammation in uveitis cases, which can damage the corneal endothelium affecting its function (45).

Postoperative period

Post-operative corneal edema is one of the most frequent causes of acute corneal edema (46). This category groups all the cases in which various ocular surgical procedures generate damages that lead to endothelial decompensation (47,48). Some of these procedures include cataract surgery with or without intraocular lens implantation, posterior vitrectomy, retinopexy, trabeculectomy, and other intraocular procedures. Minimally invasive procedures with different lasers such as iridotomy, trabeculoplasty and capsulotomy have also been reported (46,47,49,50).

Corneal edema can appear immediately after phacoemulsification because of the direct effect of this procedure on the surrounding structures, with damage to the endothelial cells and even detachment of the Descemet's membrane (51-54). This edema is mild and transient in most cases, and severe with associated endothelial cell damage in few cases.

Nine cases of corneal edema secondary to laser trabeculoplasty used to treat primary open-angle glaucoma have been reported (49,55-57). In all cases, the edema appeared within the first days after the surgery and resolved in the following weeks or months. In most cases, patients experienced different degrees of corneal opacities as sequelae; thinning of the cornea posterior to the edema with hypermetropic changes was evidenced in 6 of them.

Although the cause is not clear, two possible mechanisms have been proposed: first, changes in endothelial cells documented after laser trabeculoplasty can lead to corneal edema in extreme cases (58,59), and second, although highly unlikely, it may be secondary to the reactivation of HSV (57) since these patients were using topical prostaglandin analogs, which have been associated with this effect (60,61). This mechanism, added to inflammation induced by the surgical procedure, could cause an edema process.

The possibility of acute corneal edema due to the direct effect of the intraocular solutions used in surgery to maintain the anterior segment should be considered. Depending on their physico-chemical characteristics, these solutions can overcome the physiological resistance of the corneal endothelium, which tolerates changes in pH between 6.8 and 8.2, and osmolality variations of 200 to 450 mOsm (48,62). Thus, substances that test these resistance limits, as reported with the accidental instillation of CAI dissolved in distilled water with 0 mOsm (63), may cause acute corneal edema.

Similarly, depending on its components, some of these solutions may directly damage the endothelial barrier, as reported in components such as sodium bisulfate, thimerosal, chlorhexidine and even carbachol. These effects are favored by longer surgical interventions or by endothelium with preexisting damages (64,65).

Systemic diseases

The development of corneal edema has been reported in some mitochondrial diseases such as Pearson's syndrome, Kearns-Sayre syndrome or chronic progressive external ophthalmoplegia (66-69). These types of edemas are frequently chronic; however, some acute and even self-corrective cases have been reported, which can be attributed to acute decompensations of the patient's general condition, thus intensifying the failure of mitochondrial function (66,70).

Some rheumatologic diseases have been recognized as a cause of acute corneal edema, for example polyarteritis nodosa or Reiter's syndrome (9). On rare occasions, other systemic diseases such as Werner's syndrome, Zellweger's syndrome, facomatosis, Refsum's disease and serum sickness (usually bilateral) may lead to acute corneal edema (9).

Hypoxia

Corneal hypoxia can lead to edematization by causing endothelial dysfunction and alterations in corneal metabolism (71). Some examples include mild edema after using contact lenses or an oppressive occlusion (71,72); for the latter case, edema is proposed as the product of a mixture between corneal hypoxia and IOP elevation (73). Furthermore, chronic endothelial diseases such as Fuchs endothelial dystrophy or iridocorneal endothelial syndrome usually begin with predominantly morning edemas secondary to nocturnal palpebral closure, which generates some degree of corneal hypoxia.

Moreover, acute corneal edema can be triggered by endothelial ischemia in a rather unusual scenario, as reported by Nielsen *et al.* (74), who described the case of a patient with temporal arteritis and acute ischemia of the anterior segment of the eye who developed associated acute corneal edema and a decrease of 72% in the count of endothelial cells.

Environment

Based on case reports and biological plausibility, it has been proposed that cold may predispose to the development of acute corneal edema or trigger its onset in predisposed persons, particularly in high wind conditions. These conditions favor the evaporation of the tear film and inhibit the endothelial pump, which promotes the accumulation of water in the cornea (75).

Corneal ectasia

An acute corneal edema, known as acute corneal hydrops, has been reported on several occasions. It occurs in different corneal ectasias such as keratoconus, pellucid marginal degeneration, Terrien marginal degeneration, keratectasia after laser in situ keratomileusis (LASIK) and keratectasia after radial keratotomy (76-79). This entity occurs due to the rupture of a decemet membrane weakened and deformed by corneal ectasia, usually after mechanical stress, which often corresponds to scraping of the eye (80). This rupture leaves a space that allows the passage of fluids from the anterior chamber to the cornea, thus producing acute corneal edema (81).

Idiopathic

To date, nine cases of unknown causes have been reported, which are characterized by sudden unilateral corneal edemas with multiple parallel lines in the endothelium, associated with visual loss without pain. These are known as self-limited corneal edemas with multiple parallel lines on the endothelium (SCEMPLE) (82-84). Nevertheless, all these cases show a typical characteristic that was not found in the case reported here: the presence of parallel horizontal dotted lines along the corneal endothelium, visible by slit lamp, that correspond to detached endothelial cells grouped in aligned clusters (82). In addition, these symptoms resolved after a week without any kind of sequel.

A specific idiopathic entity was reported on a single occasion, which the authors called brush cell endotheliopathy (14). Such report presented the case of a woman with an acute crisis of corneal edema of 14 years accompanied by red eye and pain, with evidence of focal bullous keratopathy by slit lamp examination, and interdigitations in the margins of the endothelial cells, similar to a zipper, observed using confocal microscopy *in vivo*. The picture progressed over the years in terms of endothelial damage and the degree of corneal opacity, until a penetrating keratoplasty was necessary.

Discussion

Since the mid-twentieth century, the need for a constant state of corneal dehydration was recognized to ensure transparency, and the physiological mechanisms for the fulfillment of this task were clarified (85). To maintain this state, intact epithelium and endothelium are required.

The epithelium is a semipermeable membrane that allows the passage of water, but not of salts, and is located next to the precorneal fluid, the innermost portion of the tear film (86). Fluids are taken to a hypertonic state by the constant evaporation of water, which is compensated by the water leaving the cornea through the epithelium (86,87). However, this mechanism is of little importance compared to the pump function of the corneal endothelium, which passively entrains the water from the cornea by actively expelling sodium and bicarbonate towards the anterior chamber (3). The alteration of these processes, mostly by mechanisms that somehow alter endothelial function, can trigger corneal edema.

Since there was no epithelial compromise in the case reported here, the causes related to such compromise (traumas and infections) were ruled out. In addition, during the first consultation and subsequent check-ups, the patient presented normal IOP, so acute cornea edema caused by IOP elevation was discarded.

Regarding the causes mentioned in this article, medication did not appear to be the cause of the acute corneal edema presented by the patient, since he only used atorvastatin and non-steroidal anti-inflammatory drugs (NSAIDs), which have never been associated with this pathology. Also, it is very unlikely that he was exposed to toxins, especially considering his disability status.

The manifestations and signs of the patient did not suggest at all the presence of a foreign body in the anterior chamber or corneal ectasias, uveitis, corneal endothelitis, any event associated with corneal hypoxia or any of the systemic diseases associated with acute corneal edema mentioned in this article.

On the other hand, the environment, rather than being a cause, seems to be a trigger in predisposed people or a factor of what could be understood as acute multifactorial cornea edema. Actually, only one case in which cold and windy conditions are related to acute corneal edema has been reported; it occurred in an athlete clearly exposed to these conditions, in whom predisposing causes were not ruled out (75).

All of this leads to think that the most viable possibility in this case is acute corneal edema similar to those reported in the idiopathic category. The clinical picture of the patient did not meet the criteria of any of the two idiopathic entities mentioned, and slit lamp examination

did not show any of their characteristics. However, other cases of idiopathic acute corneal edema that are unknown or that have not been considered by the scientific literature may exist, although this is a thorough review. In any case, this is an unusual picture that could be the first or, at most, one of the first of its kind, for which the current scientific knowledge does not seem to be sufficient to elucidate its etiology, pathophysiology and optimal management.

Finally, it should be reiterated that, as described in several articles, the differential diagnosis of corneal edema of unclear cause can be established based on the endothelial characteristics observed by specular microscopy or confocal microscopy *in vivo* (7,10,88). In this case, none of these methods was available, which could have expanded the studies.

Conclusions

This review shows that the causes of corneal edema are multiple, both in relation to the underlying pathophysiological mechanism and the clinical presentation of the patient. These causes can be classified, based on the mechanism, into those that damage the corneal epithelium, an elevation of intraocular pressure and corneal endothelial dysfunction.

In most cases, the etiology can be suspected or confirmed by a good medical history and a comprehensive ophthalmological examination. In a few cases, like this patient, this does not seems to be enough. The case reported here may relate to a poor description in the scientific literature of idiopathic corneal edema, which, like others categorized as idiopathic, has not been adequately understood by the scientific community.

We expect that this report, along with other articles that will contribute to this topic in the future, may shed some light on this unusual presentation.

Author contribution statement

JAUD summarized the case and conducted the search of the scientific literature. JAUD and JSFO reviewed the content of the articles found and created a preliminary version of this article. GFE and GDS reviewed, completed and corrected this version.

Conflict of interest

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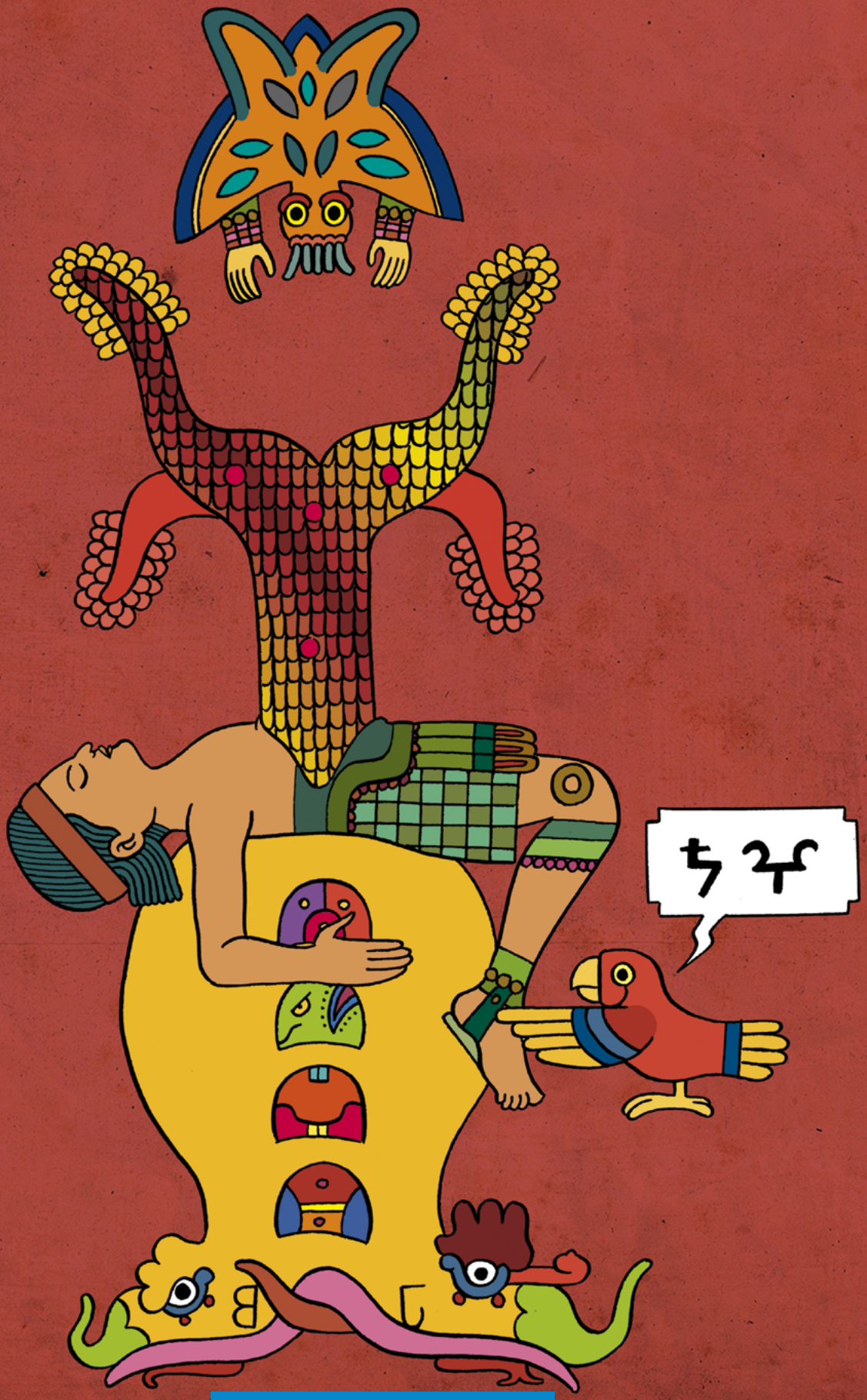

Iván "Ivanquio" Benavides
"El niño vacío" – 010
Técnica: tinta, color digital

CASE REPORT

DOI: http://dx.doi.org/10.15446/revfacmed.v65n3.55522

Hepatic metastasis of a parathyroid carcinoma treated with intra-arterial embolization

Metástasis hepática de un carcinoma de paratiroides tratada con embolización intraarterial

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| Abstract |

This paper reports the case of a patient with parathyroid carcinoma and metastatic parathyroid carcinoma in the liver, as well as persistent hypercalcemia resistant to the management with zoledronic acid and cinacalcet.

The patient was treated with intra-arterial embolization using polyvinyl alcohol microspheres in the right hepatic artery, achieving an excellent biochemical control after the intervention.

Keywords: Parathyroid Cancer; Hypercalcemia; Therapeutic Embolization (MeSH).

González-Clavijo AM, Fierro-Maya LF, Neira F, Guevara O. Hepatic metastasis of a parathyroid carcinoma treated with intra-arterial embolization. Rev. Fac. Med. 2017;65(3):521-4. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.55522.

| Resumen |

Se reporta el caso de una paciente con carcinoma de paratiroides metastásico al hígado con hipercalcemia de muy difícil control pese a manejo con ácido Zoledrónico y Cinacalcet. La paciente fue llevada a embolización intraarterial con microesferas de alcohol polivinílico de la arteria hepática derecha, con lo que se obtuvo un excelente control bioquímico después de la intervención.

Palabras clave: Hipercalcemia; Cáncer paratiroideo; Embolización terapéutica (DeCS).

González-Clavijo AM, Fierro-Maya LF, Neira F, Guevara O. [Metástasis hepática de un carcinoma de paratiroides tratada con embolización intraarterial]. Rev. Fac. Med. 2017;65(3):521-4. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.55522.

Introduction

Parathyroid carcinoma is a disease with a prevalence lower than 0.005% in the general population. In a meta-analysis of 20 255 cases of primary hyperparathyroidism reported in the USA, parathyroid carcinoma was found in only 0.74% of the observed patients (1). Metastases are rare, but are found especially in lymph nodes and lungs when they occur. In turn, liver metastases are even rarer with very few cases reported in the literature. The only curative treatment is complete resection when the disease is localized, but in the case of metastatic disease, only palliative management can be provided for biochemical control. This paper reports a case of parathyroid carcinoma with hepatic metastasis as the only dissemination site, which was treated with hepatic intra-arterial embolization achieving an acceptable transient biochemical control.

Case report

74-year-old patient with a history of hypertension, mixed anxiety-depressive disorder, stage B heart failure and NYHA (New York Heart Association) functional class II/IV, who was diagnosed with primary hyperparathyroidism three months before admission to the clinic. She presented with moderate hypercalcemia (13.4 mg/dl) and very high levels of parathyroid hormone (PTH) (942 pg/mL —the normal upper limit is 65 pg/mL). Physical examination revealed a mass of 2 cm in the territory of the right lower parathyroid gland without palpable adenomegaly. A parathyroid scan with Tecnecio Tc-99m sestamibi revealed only a capture of the above-mentioned mass, while computed tomography (CT) of the neck and thorax with intravenous contrast did not show other alterations.

Initially, the patient was given intravenous fluids and a dose of 4 mg of zoledronic acid intravenously, which reduced calcaemia to 12 mg/dl by the tenth day of administration, and then underwent oncologic surgery (total parathyroidectomy + thyroidectomy + central emptying). However, hypercalcemia was persistent and increased later, yielding serum calcium values up to 14.6 mg/dl, which required a second dose of intravenous zoledronic acid 15

days after surgery, and low doses of oral cinacalcet (120 mg daily) due to poor tolerance.

The lowest serum calcium value achieved with these interventions was 12.04 mg/dl. Multiple extension studies were performed, including neck ultrasound, cervicothoracic scan with Tecnecio Tc-99m sestamibi, and chest and abdomen contrast CT, which were all negative. A positron emission tomography (PET scan) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) was requested, and two hepatic metastases in segments V and VII were observed as the only site of disease persistence (Figure 1).

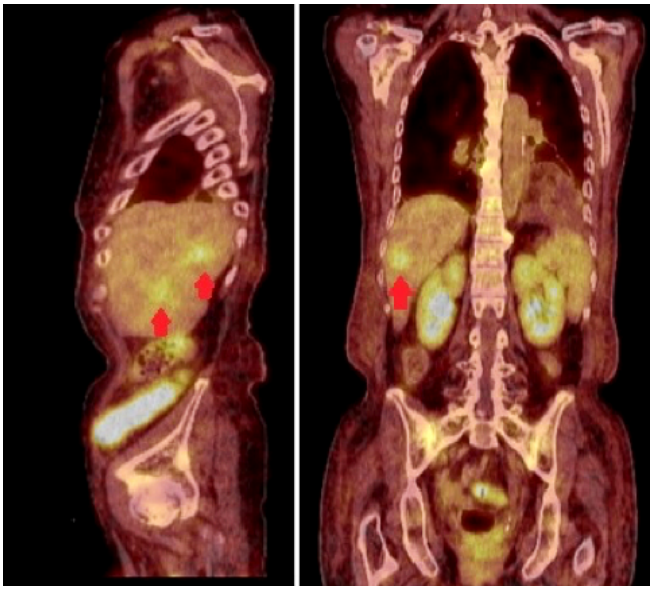

Figure 1. Positron emission tomography with 18fluor-fluor-deoxy-glucose. In the sagittal section (left), the arrows point to two hypermetabolic lesions in segments V and VII of the liver. The coronal section (right) shows the largest lesion in segment VII of the liver.
Source: Own elaboration based on the data obtained in the study.

A medical committee, in which a gastrointestinal surgeon and an endocrinologist also participated, discussed the management options for liver disease through surgical resection versus intra-arterial embolization. Considering the patient's opinion and the exposure to the lowest possible risk, intra-arterial embolization with polyvinyl alcohol microspheres in the right hepatic artery was chosen, and carried out without complications and excellent biochemical control after the intervention (Table 1). This allowed removing cinacalcet and zoledronic acid.

Authorization for the publication of this case report was provided by the relatives of the patient.

Table 1. PTH and serum calcium levels in the patient before and after hepatic arterial embolization of metastatic lesions (HAE).

	Before HAE	One day after HAE	Two days after HAE	Fifteen days after HAE
Intact PTH				
(pg/mL)	1632.0	235.0		110.0
Corrected calcium levels (mg/dL)	12.04	11.02	8.24	8.31

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

Discussion

Parathyroid carcinoma was described for the first time in 1904 by De Quervain (2). This is a rare endocrine neoplasm, which accounts for less than 0.5% of all malignant endocrine tumors (3,4), and represents only 0.4% of all primary hyperparathyroidism cases in Western countries (5).

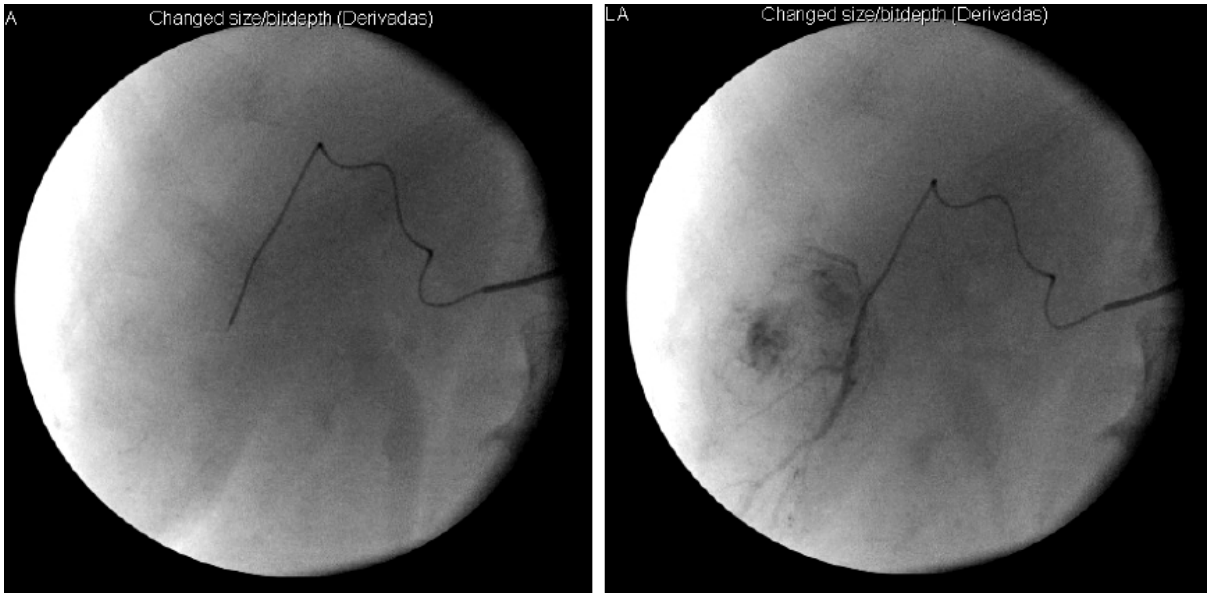

Figure 2. Hepatic arteriogram showing the vascularization of the two lesions before embolization (left) and the dye after embolization (right).
Source: Own elaboration based on the data obtained in the study.

About 25% of patients develop distant metastases at some point, especially in lymph nodes (30%) and lungs (40%) due to lymphatic and hematogenous propagation. Less common sites include liver (10%), bone, pleura, and brain (6).

Morbidity and mortality are usually the result of hypercalcemia leading to neurological, cardiovascular, and kidney disease. An overall five-year survival rate has been estimated at 81% (4).

Preoperative diagnosis requires high suspicion based on biochemical and clinical parameters (7-10) such as severe hypercalcemia —generally higher than 14 mg/dl, which is considerably high for the parathyroid hormone (PTH)—, high preoperative levels of alkaline phosphatase, palpable cervical mass, tumor size greater than 3cm, bone involvement due to the disease (brown tumors), and development of nephrolithiasis.

To date, en bloc resection is the only potentially curative treatment in localized disease (3,11-13), but therapeutic options are reduced (8,13-15) in cases of recurrent or non-operative metastatic diseases, which are usually limited to controlling hypercalcemia, since antitumor therapy with chemotherapy or radiotherapy is not effective.

Likewise, percutaneous or laparoscopic radiofrequency ablation and selective arterial embolization of metastases are useful palliative alternatives that have been previously used in isolated cases (16).

Hepatic intra-arterial embolization interrupts the delivery of oxygen and nutrients to tumor cells by destroying them without compromising healthy liver tissue. This is a palliative option reserved for patients who are not candidates for surgical management or do not respond to medical management and have preserved liver function. This technique has been successfully used in other neuroendocrine tumors (17,18).

The main expected benefit in a patient with metastatic non-surgical parathyroid carcinoma is the reduction of the functional tumor mass to decrease parathyroid hormone secretion, obtain the consequent reduction of serum calcium levels, and improve secondary symptoms. However, such benefit is usually transient, and reports an average duration between 6 and 42 months in other types of tumors, mostly due to the formation of new blood vessels and the development of collateral circulation (19,20).

The effectiveness of intra-arterial embolization in hepatic metastases of a parathyroid carcinoma for tumor and biochemical control cannot be evaluated on a large scale, although success has been reported in similar cases (16), including cases of hypercalcemia in neuroendocrine tumors producing PTH-related peptide (PTH-rP) (21).

Conclusions

To date, this is the first case known and reported in Colombia in which a parathyroid carcinoma with hepatic metastases as the only dissemination site has been documented through PET-CT 18F-FDG and treated with hepatic intra-arterial embolization. Biochemical control of the disease was achieved, highlighting the potential role of this non-invasive therapy in special situations such the one exposed in this article.

This case was presented as a poster at the 13th Colombian Congress of Endocrinology, Diabetes and Metabolism in April 2015 (22).

Conflict of interests

None stated by the authors.

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CASE REPORT

DOI: http://dx.doi.org/10.15446/revfacmed.v65n3.57414

Cri-du-chat syndrome diagnosed in a 21-year-old woman by means of comparative genomic hybridization

Síndrome de cri du chat diagnosticado en mujer de 21 años por hibridación genómica comparativa

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| Abstract |

The cri-du-chat syndrome is caused by a deletion on the short arm of chromosome number 5. The size of genetic material loss varies from the 5p15.2 region only to the whole arm. Prevalence rates range between 1:15000 and 1:50000 live births. Diagnosis is suspected on infants with a high-pitched (cat-like) cry, facial dysmorfism, hypotonia and delayed psychomotor development. In adults, phenotypic findings are less specific. It is confirmed through high-resolution G-banding karyotype, fluorescent *in situ* hybridization or microarray-based comparative genomic hybridization (a-CGH).

The following is the case report of a 21-year-old female patient with severe mental retardation and trichotillomania, who does not control sphincters and does not bathe or eat by herself. Her communication is based only on sounds and dysmorphic facies. The G-band karyotype reported is 46, XX. a-CGH shows 18.583Mb interstitial microdeletion in 5p15.33p14.3, including the cri-du-chat critical region. In children or adults with unexplained mental retardation and normal karyotype results (like this case), an a-CGH should be performed to make an etiological diagnosis, establish the prognosis, order additional medical tests and specific treatments, and offer appropriate genetic counseling.

Keywords: Cri-du-chat Syndrome; 5p Deletion Syndrome; Comparative Genomic Hybridization; Mental Retardation (MeSH).

Saldarriaga W, Collazos-Saa L, Ramírez-Cheyne J. Cri-du-chat syndrome diagnosed in a 21-year-old woman by means of comparative genomic hybridization. Rev. Fac. Med. 2017;65(3):525-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.57414.

| Resumen |

El síndrome de cri du chat o del maullido de gato es causado por una deleción en el brazo corto del cromosoma 5; el tamaño de la pérdida de material genético varía desde solo la región 5p15.2 hasta el brazo entero. La prevalencia va desde 1 por 15 000 habitantes hasta 1 por 50 000 habitantes. Su diagnóstico se puede confirmar con cariotipo con bandas G de alta resolución, hibridación fluorescente *in situ* o hibridación genómica comparativa por microarreglos (HGCm); este se sospecha en infantes con un llanto similar al maullido de un gato, fascies dismórficas, hipotonía y retardo del desarrollo psicomotor; sin embargo, en los adultos afectados los hallazgos fenotípicos son menos específicos.

Se presenta el caso de una mujer de 21 años con retardo mental severo y tricotilomanía, que no controla esfínteres y no se baña ni come sola; solo emite ruidos y tiene facies dismórficas. El cariotipo de bandas G es reportado 46, XX y la HGCm muestra microdeleción de 18.583Mb en 5p15.33p14.3, incluyendo región crítica de cri du chat. En pacientes de este tipo se debe realizar HGCm para hacer un diagnóstico etiológico, establecer un pronóstico, ordenar pruebas médicas adicionales y tratamientos específicos y realizar la adecuada asesoría genética.

Palabras clave: Síndrome del maullido del gato; Síndrome de deleción del brazo corto del cromosoma 5; hibridación genómica comparativa; Discapacidad intelectual (DeCS).

Saldarriaga W, Collazos-Saa L, Ramírez-Cheyne J. [Síndrome de cri du chat diagnosticado en mujer de 21 años por hibridación genómica comparativa]. Rev. Fac. Med. 2017;65(3):525-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.57414.

Introduction

The cri-du-chat syndrome (CdCS) or cat meowing is a disease caused by a deletion in the short arm of chromosome 5. The size of the genetic material loss varies and ranges between the whole arm and the 5p15.2 region only. This syndrome affects from 1 in 15 000 to 1 in 50 000 inhabitants (1,2).

A CdCS diagnosis is suspected in infants with acute crying, similar to a cat's meow; size and weight less than two standard deviations;

hypotonia; psychomotor development delay, and particular facies characterized by rounded face, hypertelorism, broad nasal bridge, epicantic folds, micrognathia and ears with low implantation (3). The disease is confirmed through cytogenetic techniques such as karyotype by light microscopy with high-resolution G-bands. Hybridization fluorescence in situ (HFIS) should be performed as the first molecular cytogenetic test, with a specific probe that includes the 5p15.2 (4,5) region, for those who have a suggestive phenotype and unaltered karyotype.

In order to find the etiology in patients with unexplained mental retardation and nonspecific phenotypic findings —for instance, adult patients with CdCS characteristics—, comparative genomic hybridization by microarrays (a-CGH) has been suggested, which is a different molecular cytogenetic test. This test examines the entire genome and can find numerical and structural chromosomal alterations similar to those diagnosed by the karyotype, while detecting losses or excesses of genetic material with a higher resolution level than that diagnosed by conventional cytogenetic techniques (6).

The objective of this report is to present the case of a 21-year-old patient with severe mental retardation of unexplained origin and a karyotype that did not show any cytogenetic alteration. The a-CGH for this patient reported a microdeletion in 5p15.33 p14.3, which served as the basis for a CdCS diagnosis.

Case report

21-year-old female patient born to non-consanguineous parents. The patient's mother got pregnant at age 23, and had adequate prenatal care with two obstetrical ultrasounds that did not detect any abnormality. The patient was delivered via cesarean section due to post-term pregnancy and acute fetal distress. The newborn was hospitalized for 10 days due to poor suction.

The patient has poor psychomotor development, and has not received any type of education due to learning and aggression problems. In addition, by the time of the assessment, she was unable to speak —she only produces noises—. Sphincters are not controlled, she does not bathe or eat by herself and presents with trichotillomania. Auditory potentials show mild bilateral hypoacusis and no abnormalities on the echocardiogram. A karyotype with G-bands with a resolution level of 550 bands (as reported by the laboratory) was performed at age 1, showing the chromosomal formula 46, XX.

Physical examination showed the following special findings: dysmorphic fasciitis due to bitemporal depression, right epicanthic fold, large nose with broad nasal bridge, microretrognathia, persistently large open mouth, macroglossia, short subnasal philtrum, and single transverse palmar crease (Figure 1). a-CGH and nuclear magnetic resonance were requested, but were not performed because the patient offered resistance during the procedure.

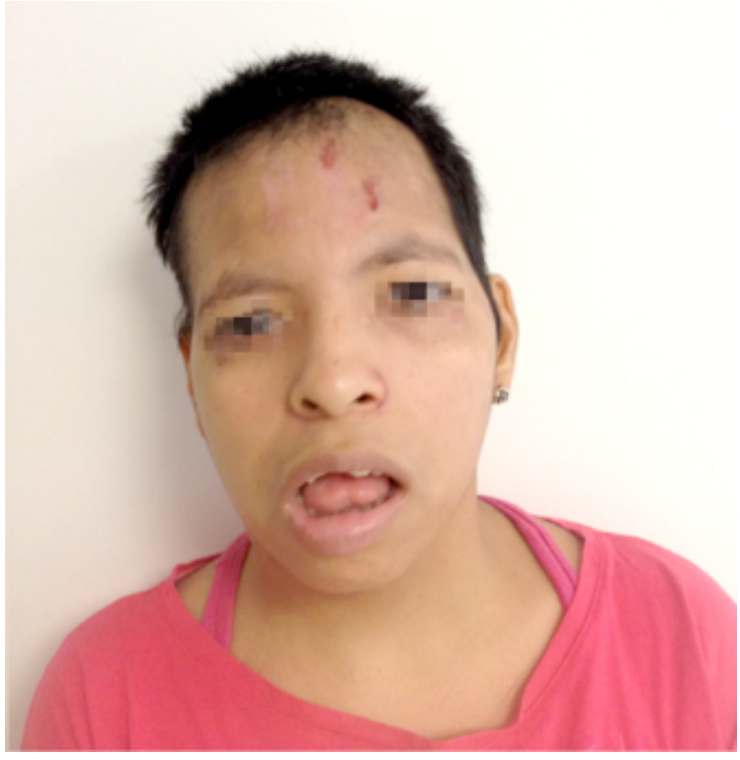

Figure 1. Patient with cri-du-chat syndrome.
Source: Own elaboration based on the data obtained in the study.

The genetic test was performed by extracting 10mL of peripheral blood in two tubes, one with sodium-heparin and another with ethylenediaminetetraacetic acid, which were subsequently sent to the Medical Genetics Laboratory of the Baylor College of Medicine. DNA was extracted using an automated nucleic acid extraction instrument (PerkinElmer Chemagen Technologie GmbH), which allows obtaining genetic material. A high-resolution chromosomal microarray analysis (HR-CMA) was performed using 180 000 oligos covering the whole genome at an average resolution of 30Kb.

Sample and control DNA were differentially labeled with fluorescence and were hybridized with the oligos. The a-CGH matrices used to analyze chromosome 5p were built by Agilent Technologies, which are based on the platform designed by the laboratory (BMGL V8.1.1). During the DNA study, the "Vysis Cri-du-Chat-Region Probe-

LSI D5S23" probe was labeled with green fluorochrome, and the "Vysis LSI EGR1" was used for control and labeled with orange fluorochrome. Results were analyzed using quantitative imaging methods and analytical software to identify the DNA sequences studied, as well as the loss (deletion), gain (duplication) or normality in the copies based on the presence or absence of signals for the D5S23 and EGR1 probes.

The patient's a-CGH result showed abnormal interstitial microdeletion of 18 583MB in the short arm of chromosome 5, 5p15.33p14.3, which includes the cri-du-chat critical region. Figure 2 shows a red area that identifies DNA in deletion and includes the CdCS critical region. The black spots represent chromosomes without an excess or deficit of genetic material.

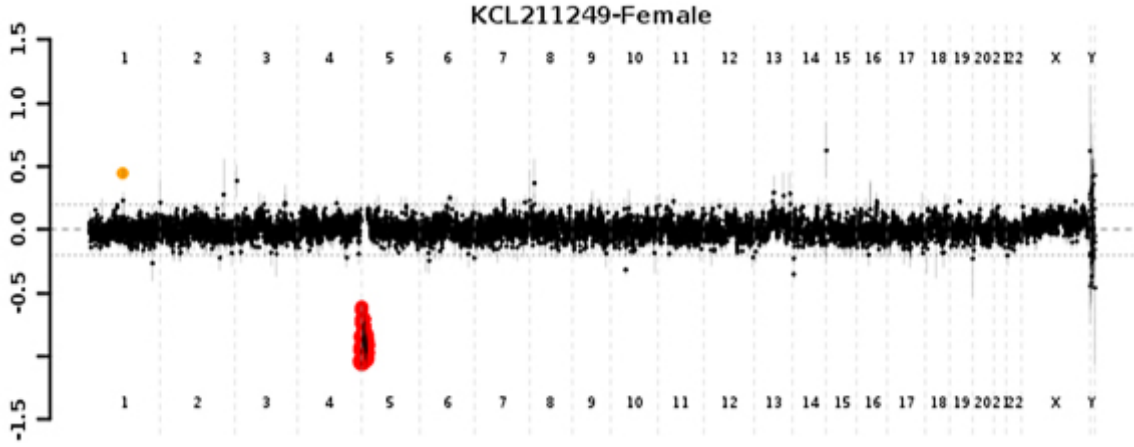

Figure 2. Graphical representation of the result for comparative genomic hybridization by microarray.
Source: Own elaboration based on the data obtained in the study.

A diagnosis of cri-du-chat syndrome by microdeletion, OMIM # 123450, was established. Since the patient's mother had a tubal ligation and the father had no reproductive expectation, no tests were performed to establish if any of them were carriers of a balanced translocation involving the chromosomal region under study. Both parents signed an informed consent to take photographs and use the medical history data.

Discussion

Lejeune *et al.* (7) first described CdCS in 1963. They gave the syndrome this name due to the characteristic cry of affected infants, which resembles a meowing kitten. The prevalence is very low, although it is estimated at 1 for every 350 individuals with mental retardation (1,2,8). This syndrome is caused by a deletion of the short arm of chromosome 5, which can involve total loss of the material on the short arm, or affect only the 5p15.2 region (9).

In CdCS, the loss of genetic material in a specific locus of the short arm of chromosome 5 has been related to particular phenotypic traits in affected patients. Likewise, a critical region located at 5p15.2, 1.7MB in size and strongly related to mental retardation, language delay, typical crying, microcephaly and dysmorphic fascicles has been described (8,10). Deletion in that region implies the loss of the CTNND2 genes, which encode the δ-catenin protein, and of MARCH6, which encodes the protein of the same name (membrane-associated RING-CH6 finger protein). The first is involved in cell motility, expressed in the early stages of neuronal development, especially in cellular migration processes, which is related to the characteristic mental retardation. The second is an E3 ubiquitin-ligase located in the membranes of the endoplasmic reticulum, which has been associated with typical acute crying, language problems and facial features in CdCS (11).

In addition, other genes with 5p loci and clinical significance in CdCS have been reported. SEMA5A (locus 5p15.31) encodes the semaphorin 5A protein associated with mental retardation caused by the reduction in the number of neurons to be differentiated, and to the migration from neurogenesis zones, which generates changes in the organization of the periventricular cortex layers and base ganglia (9). SLC6A3 (locus 5p15.33) encodes a dopamine transporter and is linked to attention deficit hyperactivity disorder and autistic features. CDH18, CDH12, CDH10 and CDH9 (locus 5p14.1 to 5p14.3) encode critical cadherins in cell adhesion during synapse formation and axonal growth. Finally, TERT (locus 5p15.33) produces reverse transcriptase associated with accelerated shortening of telomeres and premature aging (11,12).

In 2005, Zhang *et al.* (13) published a phenotype/genotype correlation study using microarray-based comparative genomic hybridization. They described three contiguous regions on the short arm of chromosome 5 called MR (referring to mental retardation): region I with locus 5p15. 31, size 1.2MB, related to moderate to severe mental retardation; region II, proximal to region I, size 8.9MB, associated to less severe mental retardation, and region III, proximal to region II, 13.8MB and without a consistent phenotype. Mental retardation increases progressively with the joint loss of the described regions, and the critical region would include MRI. In addition, the same authors specifically associated crying to the 5p15.31 region, language delay to the 5p15.32-15.33 region, and dysmorphic features to the 5p15.2-15.31 region (8,11,13). The loss of genetic material in this patient was located in the 5p15.33 p14.3 region, which includes all fragments of genetic material related to the pathological phenotype in CdCS. This loss accounts for severe mental retardation, microcephaly, and marked language deficit.

Between 80% and 90% of the deletions that cause CdCS are de novo, about 10% to 15% are the result of unbalanced translocations of parental, and some particular cases are attributed to rare cytogenetic alterations (1). The risk of recurrence is minimal in cases in which the deletion is de novo; however, the possibility of gonadal mosaicism in one of the parents cannot be disregarded. The probability is higher and becomes more important in familial balanced translocation cases that include the 5p fragment. Cerruti *et al.* (14) show that the risk of progeny with unbalanced chromosome alteration ranges between 8.7% and 18.8%, and that it is similar in carriers of both sexes. In cases

such as the one reported here, a balanced translocation in parents that included the missing 5p fragment in the patient (5p15.33p14.3) should be ruled out through a metaphase HFIS using the specific probe.

CdCS patients may present with typical crying, short stature and weight, severe psychomotor development delay, hypotonia, particular facies (4,8), recurrent vomiting, respiratory difficulties, severe heart disease and jaundice, which can lead to death within the first year of life (15), although none of them was found in the treated patient. As patients grow, the face becomes long, thin and asymmetrical, the nose becomes more prominent, and hypertelorism, epicanto and micrognathia are attenuated. Mental retardation becomes evident in preadolescents and adolescents, who usually do not speak and present periods of aggressive behavior and self-mutilation (9,15); all these characteristics were observed in the treated patient. Over time, the phenotypic traits in these patients become less specific and clinical diagnosis is more difficult (16). A differential diagnosis in adult patients without changes in karyotype can be performed based on the Mowat-Wilson and Wolf-Hirschhorn syndromes, 1p36 monosomy, 17q21 microdeletion, among others.

Usually, the diagnosis is suspected when the classic phenotypic characteristics appear in children younger than one year. To confirm it, a karyotype with G-bands must be performed, which, depending on the resolution level, can detect the total or partial absence of genetic material in the short arm of chromosome 5 (17). However, the diagnostic capacity of the karyotype in structural chromosomal alterations, such as CdCS, varies depending on whether the chromosomes are observed in prometaphase or metaphase, the type of staining and the level of resolution obtained according to the observed bands. In metaphase karyotypes with Giemsa staining (G-bands) and resolution levels between 400 and 500 bands, alterations greater than 10MB can be detected. The diagnostic capacity improves when the chromosomes are observed in prometaphase, which lead to diagnose losses or excesses of genetic material greater than 3MB (18).

The karyotype of the treated patient was performed with metaphase chromosomes, had a resolution of 550 bands and did not report any numerical or structural alterations despite having a deletion of 18MB in 5p that should have been found in that study. This may have happened because chromosome analysis by cytogenetics is a dependent operator, which does not occur with a-CGH, and has limitations in the resolution level due to difficulties in the visualization of specific areas considering the characteristics of the staining (18). Hence, the level of bands reached on chromosome 5 may not be optimal for the diagnosis.

In cases where the karyotype does not show any alteration and the phenotypic characteristics are suggestive, HFIS must be performed using probes that detect losses of fragments of different sizes in the short arm of chromosome 5, including the 5p13 to p15 regions; the most used is the one that hybridizes with the CdCS 5p15.2 critical region (5). In the case reported here, the karyotype was not repeated and the HFIS was not used, since this was an adult patient with no specific phenotype.

A-CGH has been suggested to find the specific etiology in patients with mental retardation, autism and multiple congenital anomalies (6); this is a molecular test that detects losses or excess of genetic material smaller than those diagnosed with cytogenetic techniques by light microscopy. However, it is not sensitive to detect chromosomal rearrangements such as balanced translocations or specify insertion location (19). Diagnosis rates in patients with delayed psychomotor development and mental retardation increased from 3% with karyotype to 12.2% with a-CGH (6).

Comparative genomic hybridization is available in Colombia and is performed in two laboratories of Bogotá D.C. or in reference laboratories from Europe and the USA, as was the case with this patient. The importance of the test lies in obtaining a diagnosis and thus establishing prognosis and ordering additional medical tests and treatments specific to the syndrome, besides offering genetic and reproductive advice (4,14,19).

Conclusions

The case of a 21-year-old female patient was reported in this paper. The patient presented with severe mental retardation of unexplained origin, with unchanged karyotype, and a-CGH with microdeletion in 5p15.33 p14.3, which led to the CdCS diagnosis.

A-CGH should be performed in adult patients with unexplained mental retardation with karyotype and without alteration, in order to obtain an etiological diagnosis, establish prognosis and perform differentiated interventions and genetic counseling.

Authors' contributions

WS and JRC performed the clinical diagnosis and the analysis of the a-CGH result. All the authors participated in the literature review and document writing.

Conflict of interest

None stated by the authors.

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CASE REPORT

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Rare chronic stridor: Case report and literature review

Estridor de extraña duración: reporte de caso y revisión

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| Abstract |

This paper reports the case of a toddler with chronic stridor of four months of evolution, treated several times by micro-nebulization (MNB) with beta 2, adrenergics, O_2 and corticosteroids with partial improvement. The patient did not have complementary studies nor a clear history of foreign body aspiration (FB). During the last visit to the ER, a neck X-ray revealed a stippling sign in the upper airway. A bronchoscopy was performed, and a sharp foreign body (fishbone) was found in the upper airway, which was subsequently removed. This case is reported due to the unusual evolution of the foreign body in the upper airway, which manifested as a chronic stridor that resolved without further complications.

Keywords: Stridor; Foreign-Body Reaction; Respiratory Aspiration; Laryngoscopy; Child, Toddler (MeSH).

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| Resumen |

Se presenta el caso de una paciente prescolar con estridor crónico de 4 meses de evolución, tratada varias veces mediante micronebulizaciones (MNB) con beta 2, adrenérgicos, O2 y corticoides con mejoría parcial, sin estudios complementarios ni antecedentes claros de atoramiento con cuerpo extraño (CE). Además, se realizó una radiografía de cuello (Rx) que reveló la presencia de imagen en punta de lápiz traqueal y una broncoscopia que comprobó la existencia de un cuerpo extraño puntiagudo (espina de pescado) en la vía aérea superior.

Este caso se reportó por su inusual presentación, pues es un CE en la vía aérea superior que se manifestó con estridor crónico, sin mayores complicaciones.

Palabras clave: Estridor; Reacción a cuerpo extraño; Aspiración respiratoria; Tráquea; Broncoscopía; Infante (DeCS).

Uribe-Parra JD, Lozano-Triana CJ, López-Cadena AF, Landínez-Millán G. [Estridor de extraña duración: reporte de caso y revisión]. Rev. Fac. Med. 2017;65(3):531-5. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.56010.

Introduction

Stridor is a respiratory symptom frequently observed in pediatric emergency services (1,2). It is defined as a high-pitched respiratory sound, usually associated with a mechanical obstruction of the air flow in the upper airway (3), located at the supraglottic, glottic or infraglottic level (4,5). The character of stridor itself is inherent to the obstruction level, therefore, when it is inspiratory, it is related to supraglottic obstruction, whereas it is associated with obstruction of the lower airway when it is expiratory, and with fixed lesions in the airway or with laryngomalacia and tracheomalacia, if it is biphasic (6,7).

However, stridor should be studied as a severe respiratory symptom that requires immediate medical attention. It can be caused by different factors, so a thorough analysis and deep studies must be done for timely diagnosis and treatment to avoid potentially life-threatening situations (8,9). The two most useful tools in the study of stridor are the preparation of a proper medical history and a thorough physical examination. It is worth noting that only specific cases require diagnostic aids (4,9,10), for example, when acute complications such as pneumothorax, pneumomediastinum, subcutaneous emphysema and esophageal perforation are suspected, or in the presence of chronic complications such as obstructive pneumonias, atelectasis and pulmonary abscesses (9,11-14).

The following is the case report of a patient with a FB located in the upper respiratory tract and chronic stridor, which was confused with croup.

Case presentation

A two-year-old patient attended the emergency room with a three-day history of upper respiratory symptoms caused by stridor, hyaline rhinorrhea, sneezing, and a sudden episode of perioral cyanosis that lasted for 10 seconds. On admission, the child was conscious, hydrated, afebrile, with significant inspiratory stridor, and signs of

moderate respiratory distress. The mother denied possible aspiration or recent intake of a foreign body. She also presented a positive respiratory contagion noxa, and reported that she had attended several emergency services due to similar symptoms in the past four months, which were interpreted as laryngotracheobronchitis and treated by corticoid and, in some cases, nebulized epinephrine. Furthermore, the stridor was nocturnal, had no triggering events nor feverish spikes, and was sometimes associated with cough or respiratory distress.

Chest and neck radiographs were requested for an initial approach (Figure 1 and 2). The radiology service found a steeple sign that suggested laryngeal croup in the anteroposterior (AP) projection of the second image. Likewise, the lateral projection shows an object that could be a foreign body. Chest X-ray was normal.

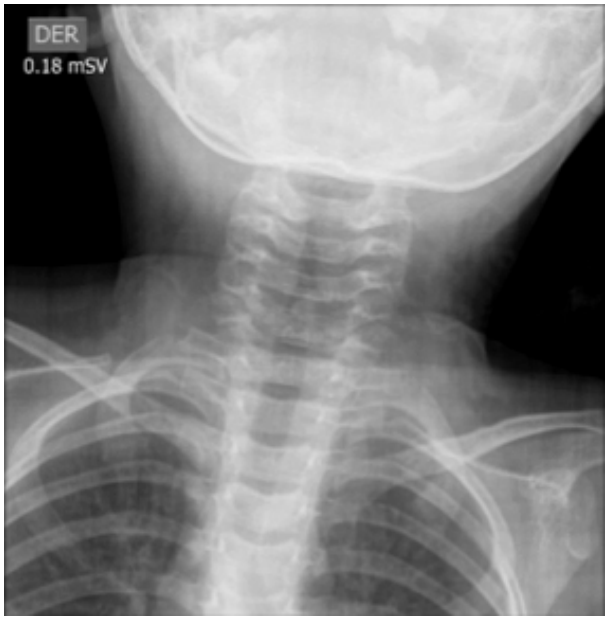

Figure 1. Anteroposterior radiograph of the neck. Steeple sign.
Source: Own elaboration based on the data obtained in the study.

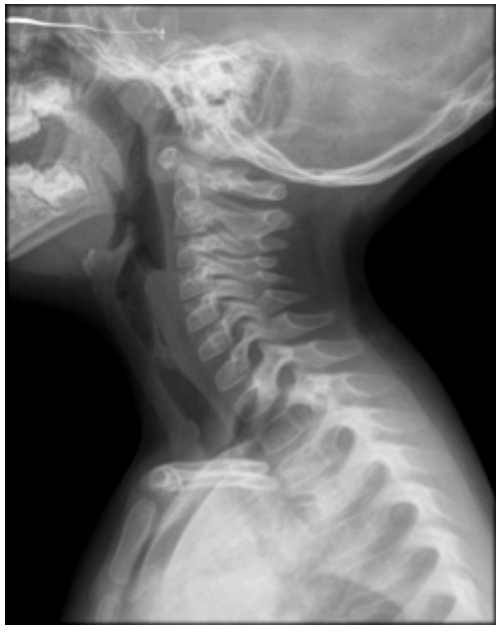

Figure 2. Lateral x-ray projection of the neck.
Source: Own elaboration based on the data obtained in the study.

Since the clinical picture did not coincide with the time of evolution, the patient was referred to otorhinolaryngological assessment. Thus, during the observation period, the patient presented respiratory pattern deterioration, with a new cyanotizing episode and persistent desaturation. In consequence, she was transferred to resuscitation, and oxygen therapy treatment was initiated along with intravenous corticoids, b-adrenergics and antihistamines to achieve a progressive improvement. However, the otorhinolaryngology service did not provide a clear diagnosis, so a nasofibrolaryngoscopy was scheduled.

After this procedure, adequate mobility of the vocal cords, complete glottic closure, and evidence of a subglottic foreign body with associated granuloma were reported. The foreign body was removed and biopsies and cultures were taken from the site. Considering the characteristics of the foreign body, it was concluded that it was a fishbone. Afterwards, the study was complemented with endoscopy of upper digestive tract, which ruled out the presence of other foreign bodies.

The patient continued with in-hospital treatment, where proper care and surveillance of the airway were provided. Inhaled corticosteroids and antibiotic coverage with ampicillin/sulbactam were also administered due to the presence of inflammatory signs found at the site of impact of the foreign body. After three days of hospitalization, the patient was discharged without further complications or symptoms and with a good general condition.

Discussion

The anatomy of the airway differs between children and adults (15,16). Basic physical principles have been described to explain predisposition to obstruction and difficult management of the airway in pediatrics (10). Resistance to air passage is inversely proportional to the airway radius, raised to the fourth power, therefore reducing airway diameter by half will increase resistance 16 times. According to this principle, Table 1 shows the reasons why obstruction in the upper airway is more frequent in pediatrics.

Table 1. Particularities of the airway in pediatrics.

Particularities	The larynx of children is placed in a higher position than in adults.
	The cricoid cartilage lies at C3-C4 level in newborns, while it is at C6-C7 level in adults.
	The cricoid cartilage is the narrowest area of the child's airway.
	Shorter trachea.
	The consistency of the cartilages and soft structures of the larynx, as well as a loose cartilaginous skeleton, which is collapsible depending on the variations of the respiratory cycle.
	Prominent and retroposed tongue in children.
	Superposition of uvula and epiglottis.
	Airway mucosa: more vascularized (greater risk of bleeding), more fragile (greater risk of injury) and laxer (greater risk of edema).
	Congenital craniofacial malformations.
	Newborns and infants are obligate nasal breathers.

Source: Own elaboration based on Santillanes & Gausche-Hill (10), Wilton *et al.* (15), Tahir *et al.* (16) and Srivastava (17).

Evidence shows that the pediatric population aged between six months and three years (1,16,18) has special characteristics, not only anatomical but behavioral, that makes it susceptible to these accidents.

Their learning process, desire for exploration, lack of teeth and cognitive inexperience (in terms of distinguishing safe food) are important associated factors, which is easily observed in 80% of accidental ingestion occurring in the pediatric population (6,18). However, some studies reveal a slight but higher incidence in men, with a ratio of 1.7:1 (9,19).

In the emergency department, the approach to upper airway obstruction syndromes must cover a broad spectrum of pathologies (Table 2).

Table 2. Frequent causes of stridor in pediatrics.

Anatomical	Laryngomalacia Paralysis of vocal cords Subglottic stenosis Tracheomalacia Vascular rings Hemangiomas Subglottic cysts Craniofacial malformations
External or internal compression	Laryngeal papillomatosis Vascular processes (hemangiomas, vascular rings) Neoplasms
Infectious	Croup Epiglottitis Bacterial tracheitis Retropharyngeal abscess
Other	Post-extubation obstruction Angioedema Foreign body aspiration Trauma Gastroesophageal reflux

Source: Own elaboration based on Pfleger & Eber (3) and Venkatesan *et al.* (20).

Regarding the case presented in this paper, intake and aspiration of foreign bodies is a common problem in the pediatric population (8,21) and is believed to be the second cause of urgent endoscopy (1,22). The average mortality rate associated with aspiration of foreign bodies in the airway is approximately 0.7-1.8%, but it varies according to the anatomical location of the object (4,9,21). Thus, complete larynx occlusion can lead to mortality rates of up to 45% according to the urgency of the diagnosis and treatment.

Moreover, children can ingest any kind of objects. However, in most cases, they pass into the gastrointestinal tract without further complication, and up to 50% of the cases may be asymptomatic (22-24), which may lead to significant complications and even death.

Besides the particular symptomatology associated with the location of the foreign body in this case, between 80-90% of the foreign bodies in the airway are found in the bronchial tree, since the objects are usually small enough to get past the trachea. In this case, the body impacted the tracheal wall due to the sharpness of the object. It can be said that only 4% of aspirated foreign bodies are extracted from the trachea and larynx (9,18,24).

In the natural history of foreign body aspiration, three phases have been described: the first occurs as an acute choking episode, and presents the largest amount of symptomatic manifestation, and the highest rates of patient consultation. The second phase is asymptomatic, since the initial symptoms resolve on their own. Finally, the third involves complications and chronic symptoms similar to asthma (25), recurrent pneumonia, pulmonary abscesses, bronchiectasis, subcutaneous emphysema or even pneumothorax (9,18,26); it is less frequent, so the diagnosis is more difficult. In the case reported here, the patient's symptoms were similar to asthma concomitant with chronic cough, episodic dyspnea, and episodes similar to bronchospasm, which was actually suspected during phase 3. In addition, the location of the foreign body in the main airway (subglottic region) may have had a fatal outcome.

Delay in diagnosis is one of the most significant and common factors (18) that increases the risk of complications (12). The most dangerous and frequent objects that can be ingested include flat batteries, magnets, short-piercing objects, bones (1) and fishbone (2,13,27,28). Considering patients of populations with higher risk factors such as basic psychiatric conditions, cognitive disabilities, delayed psychomotor development, autistic spectrum or swallowing disorders, is highly relevant, as well as being alert to inappropriate behaviors like child maltreatment, depression or behaviors suggestive of other systemic diseases such as pica (geophagia) in the context of iron deficiency anemia (11,29).

Foreign bodies in the airway are less common than in the digestive tract (2,12,13) and usually occur unexpectedly (in clinical terms), with a florid picture of respiratory symptoms. The clinical presentation of this patient was particular and recurrent, with occasional paroxysmal episodes that became severe, making it unusual. The absence of a clear episode of choking obscured the diagnosis, so she received treatment for croup on repeated occasions.

The presence of asymptomatic tracheal foreign bodies or with mild symptoms is rare (24), although some similar cases have been reported (5,24,26,30). With this in mind, the importance of having a complete medical history and a judicious physical examination to focus the diagnosis and treatment in an appropriate way is emphasized (31-33). Up to 40% of foreign body intake cases are not witnessed by an adult and, many times, children may remain asymptomatic. In this sense, this diagnosis is difficult, so up to 30% of patients are diagnosed only 6 months after the onset of the symptoms (18).

This case contrasts with literature reports, since patients with a history of cramping and subsequent FB diagnosis presented symptoms of paroxysmal cough (34), decreased respiratory sounds to unilateral or bilateral auscultation, wheezing and rales in up to 83.8% of cases. Only 4% presented cough as the only sign (18,29,35,36). Thus, knowing the value of clinical findings in relation to the suspicion of this pathology is important.

According to the evidence, the four most important specific criteria are (33,37-39): clinical history (S:90.5%, E:24.1%), symptoms (S:97.8%, E:7.4%), findings on physical examination (S:96.4%, E:46.3%), and radiological findings. The latter are important since they are low-cost diagnostic aids with acceptable performance (S: 71.7%, E: 74.1%) (29,40,41), and are also useful for early diagnosis of foreign body intake and high risk cases with acute complications such as flat batteries (42). In case of doubt, fiberoptic bronchoscopy is the diagnostic and therapeutic gold standard for suspected foreign body aspiration, and should be performed when available (21,35,43,44). Moreover, some studies have shown that axial tomography matches the level of performance of bronchoscopy, although it is not therapeutic (39,45).

In addition to early diagnosis, the physician should contribute to and promote the development of primary and secondary prevention programs in relation to FB intake in children, given its relatively high incidence and morbidity and mortality. Also, prevention strategies need to include education for parents, caregivers and the general population.

Finally, some strategic guidelines should include preventing children from eating, playing or crying with objects in their mouths; avoiding toys and small objects that are easily dismantled and can be sucked in; not administering food that contains seeds or nuts to children under 4-5 years; and teaching children to chew slowly, properly and not to talk or laugh during food intake (27).

Conclusions

A FB should be suspected in the presence of a chronic stridor accompanied by episodes of exacerbation that are difficult to manage, even if there is no evidence of a choking event in the medical history. A differential diagnosis in a child with stridor is highly suggested regardless of its time of evolution, for which an in-depth study including endoscopy is necessary, if the suspicion of a foreign body persists.

Clinical history and physical examination are the most important tools for the study of FB intake in pediatric patients, and should be complemented with diagnostic imaging aids.

The delay of diagnosis and treatment is directly proportional to the presence of serious complications that can compromise the patient's life, therefore, early diagnosis is very important. Likewise, physicians should implement childcare education strategies to reduce the incidence of aspiration and foreign body intake events.

Conflict of interests

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LETTER TO THE EDITOR

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Should male children be vaccinated against human papillomavirus?

¿Se debe vacunar contra el virus del papiloma humano a niños varones?

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Dear Editor:

Human papillomavirus (HPV) is the main risk factor for the development of cervical cancer in women and other types of malignancies in men, including penile, oropharyngeal and perianal cancer. These neoplasms take longer to be detected because the infection is asymptomatic and silent in men (1,2).

The serotypes with the highest infection frequency and greater virulence in both males and females are 16 and 18 (3). It is estimated that HPV infection has a prevalence of 7.5% in Peruvian women with normal cytological studies. Subtypes 16 and 18 have a prevalence of 3.8% in this population, and 68.3% in women with cervical cancer (4).

Between 2006 and 2011, the incidence of cervical neoplasms was 16 374 cases, with a mortality rate of 1 603 cases by 2011. In 2008, 35 489 healthy life years and 20 691 years of life lost due to premature mortality were observed (5). Furthermore, in 2014, there was an incidence of 310 oral cavity cancer cases, 72 anal cancer cases, and 42 penile cancer cases according to the National Institute of Neoplastic Diseases (INEN by its acronym in Spanish) in Peru (6). The US Food and Drug Administration (FDA) estimates that by 2020 this virus will be responsible for the incidence of penile, oropharyngeal and perianal cancers, which will be similar to or greater than the current incidence of cervical cancer, and would increase health costs for the treatment of this type of pathologies (7).

Currently, there is a tetravalent HPV vaccine that provides protection against serotypes 6, 11, 16 and 18. It is not only accessible, safe and effective, but also has few adverse effects on the male population, decreases the recurrence of anogenital cancer, reduces the incidence of intraepithelial neoplasm and persistent anal infection, and is effective in preventing external genital lesions (7).

A non-temporary vaccine is used in the United States, which, besides covering the aforementioned serotypes, protects against 31, 33, 45, 52 and 58, considered to be high risk factors for anogenital cancer. The FDA recommends its use in men —who are offered protection against genital warts and cancerous and precancerous anal lesions (1,8)— and women aged between 9 and 26.

To stop a virus from spreading, we must act on the vector, which in the case of HPV is men. Therefore, including vaccination against HPV for both men and women aged between 9 and 13 years in public health policies and immunization strategies is strongly advised.

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LETTER TO THE EDITOR

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Vaccination against HPV in Brazil: What is New in the Year 2017?

Vacinação contra o Papilomavírus Humano no Brasil: o que há de novo em 2017?

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Dear editor,

We would like to discuss briefly new information regarding the article "Evolução do sistema público de saúde no Brasil frente ao estágio atual da prevenção do câncer de colo uterino em mulheres jovens e adolescentes" (1).

In 2017, the Ministry of Health of Brazil started to implement the quadrivalent vaccination against human papillomavirus (HPV) for boys aged 12 to 13 years, thus making Brazil the first South American country that offers this vaccine for boys in the National Immunization Calendar through mass vaccination (2,3). In addition, the age group for vaccination of children and adolescent girls against HPV was extended from 9 to 14 years (2).

It is worth mentioning that in 2020, the vaccination of boys will be done beginning at age 9 (2,3). Today, vaccination against HPV is still provided to girls aged 9 to 26 years infected with human immunodeficiency virus (HIV), and vaccination to boys with the same condition was initiated in 2017 (2).

All these changes intend to decrease the number of HPV infection cases, as well as related deaths (3). However, according to Sanches *et al.* (2017), several barriers have been found that hinder the effective implementation of the vaccination against HPV in children and adolescents (1).

In consequence, we believe that improvements are necessary, especially regarding health education in schools and specific professional training to attend to the needs of this age group. Only when these requirements are met, it can be possible to provide adequate assistance to these individuals, with a significant increase in vaccination rates.

Conflicts of interest

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LETTER TO THE EDITOR

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Implications of technical-instrumental rationality in health education: pending challenges

Implicaciones de la racionalidad técnica-instrumental en la enseñanza en áreas de la salud: desafíos pendientes

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Dear Editor,

The current era, characterized by postmodernism, puts a strain on the true meaning of higher education, specifically in relation to health, which has been guided by logics binding the technical, reflective and critical rationality of those who train professionals. One of the core concepts of this contemporary debate is the imposition of technical-instrumental rationality as the only paradigm of knowledge. This imposition eclipses the epistemological foundation of educational work and the teleological problems of every teaching act (1). Actually, in the words of Heidegger, insofar as man technically constructs the world as an object, the path to the open is voluntarily and completely obstructed. (2, p218). In this context, it is possible to observe the technical-instrumental rationality of knowledge, which constitutes one of the cognitive interests that underlies all human practices and, specifically, the teaching methods in health.

In this field, the problem is generated when the traditional model of education is legitimized as unique, because here non-participatory teaching methodologies with marked teacher-centered emphases are used. As a matter of fact, a study revealed that teachers have what could be considered more as a behavioral view, since students must memorize information and teaching takes place through repetition and constant review (3). Thus, we find ourselves in the presence of a teaching crisis that hinders the foundations of thought. In this regard, a research conducted in health programs (Nutrition, Medicine, Dentistry and Nursing) showed that teachers require pedagogical knowledge to improve the quality of teaching (4).

The technical-instrumental rationality limits the actions of teachers and students due to the lack of critical and reflective thinking. This happens, in part, because technology has expanded to such an extent that provides physicians with more means to rely on, while reflection has been left aside (5). It is evident that health programs, in relation to pedagogical practices, have been automated and instrumented (6), causing a crisis in higher education, specifically in the quality of the training provided to students.

It is pertinent, therefore, to transform the teaching processes to generate a true scientific revolution based on a crisis that challenges the dominant paradigm and fosters the emergence of a new paradigm with a theoretical nucleus that supports a reflective practice. In this way, teachers should develop their practice not only in a mechanized way, but in a reflective way. According to Cassís (7), Schön stated that reflective professional practice allows the teacher to build knowledge by solving the problems found in practice, which implies building knowledge from actions to take decisions through the use of strategies and methodologies and to innovate focused on critical reflection. In this sense, pedagogical strategies such as collaborative work, problem-based learning, debates, Socratic dialogue, case studies, reflection, feedback, discussion groups and structured controversy are proposed as valid tools.

Reflective practice would allow teachers to analyze, debate and question their own practices to improve and, thereby, optimize the teaching-learning processes of students. Additionally, it would favor the development of reflexive and critical thinking in students regarding diverse pedagogical issues and problems that emerge in the health area. In conclusion, without excluding technique and practice, teachers should articulate their practices with reflective rationality aiming at professionalizing the pedagogical processes of the health disciplines, all this with the purpose of improving the quality of student training.

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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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El niño vacío

001: Había una vez un niño vacío, sin nada por dentro.
002: Molestaba a los animales y cortaba las plantas del bosque.
003: Molestos con el niño, los animales acudieron a Mamá Haya Waska.
004: Hace cientos de años, Mamá Haya Waska le había dado la inteligencia al ser humano a través del yagé.
005: Mamá Haya Waska pidió a los animales que trajeran al niño a su morada.
006: Entre los animales, el único valiente que decidió buscar al niño fue el mono.
007: El mono dijo: -Sé que eres muy malo, pero estoy seguro de que no podrás molestar al animal más grande de la selva.
008: Engañado, el niño vacío caminó hasta la casa de Mamá Haya Waska.
009: De inmediato, Mamá Haya Waska hizo que el niño cayera en un profundo sueño y pidió ayuda a los animales.
010: Mamá Haya Waska hizo un cesto con bejucos y así construyó su estómago. Lo llenó de mariposas para que revolotearan cuando el niño intentara hacer algo malo.
011: Mamá Haya Waska hizo su corazón de una arazá, dentro de ella puso a una ranita que saltaría cada vez que el niño intentara hacer algo malo.
012: Para hacer su cerebro, Mamá Haya Waska pidió ayuda a Papá Sol, hicieron una vasija y pusieron dentro de ella a uno de sus hijitos, los hombrecillos de sol. Así, el niño tuvo cerebro.
013: Ahora el niño tenía un estómago para desear cosas buenas, un corazón de puros sentimientos y un cerebro que resplandecía. El niño despertó con un brillo diferente en sus ojos.
014: El niño pidió disculpas a los animales y a las plantas. Desde entonces, cuidó de la selva con amor, ¡tanto tanto que llegó a ser tan verde como las hojas de los árboles y tan azul como las aguas del río!

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