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PEDIATRIC OPHTHALMIC TRAUMA

Intraorbital foreign body case report

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PEDIATRIC OPTIC NEURITIS

Editorial

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Optic neuritis in the pediatric population greatly differs from its presentation in the adult population. Firstly, it is usually bilateral in children and mostly unilateral in adults. (1,2,3) Second, it is generally associated with inflammation of the optic disc in pediatrics (1,2,3), whereas the inflammation is often retrobulbar in adults. (2) Finally, pediatric optic neuritis is often considered a post-infectious condition that is not usually associated with the subsequent development of multiple sclerosis (MS) (4,5,2), while in adults, the demyelinating event often precedes the clinical onset of MS. (6)

The neuroimmunological mechanisms involved in several of the demyelinating disorders that affect the optic nerve in children have been elucidated, including the role of B cells and antibody-mediated mechanisms. (7) The diagnosis and management of pediatric optic neuritis is currently based on the search for molecular biomarkers, such as antibodies against aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG), especially in children with recurrent optic neuritis. (7)

The presence of anti-AQP4 antibodies is synonymous with neuromyelitis optica (NMO) (8), while anti-MOG antibodies are mostly found in children with recurrent optic neuritis, acute disseminated encephalomyelitis (ADEM), and some NMO and MS phenotypes. (9,7) Patients with anti-MOG antibodies are usually younger (10) and more likely to develop optic disc inflammation than those without anti-MOG antibodies; these types of optic neuritis tend to be bilateral and more dependent on steroids than in patients with negative MOG antibodies. (9,11) Several recent studies have found that anti-MOG antibodies are generally associated with a course of disease without MS in children. (12,13)

In general terms, in the presence of a more severe initial involvement of the optic nerve, this condition can be associated with NMO, while alterations of the white matter in MRI can be associated with MS. (14) As more biomarkers are identified, it is possible to conclude that infections or immunizations are the triggering stimuli that most frequently activate the cascade of neuroinflammatory events that have historically been diagnosed as post-infectious optic neuritis. (15)

NMO, formerly known as Devic's disease, is an autoimmune demyelinating disorder that causes recurrent episodes of optic neuritis and transverse myelitis. (16) This disease should be considered as a diagnostic option in any child or adult who develops unilateral or bilateral optic neuritis and myelopathy within a short period of time. (17)

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PEDIATRIC OCULAR TRAUMA: INTRAORBITAL FOREIGN BODY. CASE REPORT

Keywords: Craniocerebral Trauma; Orbit; Penetrating Eye Injuries; Penetrating Head Injuries; Penetrating Brain Injuries; Eye Foreign Bodies.
Palabras clave: Traumatismos craneocerebrales; Órbita; Heridas penetrantes; Traumatismos penetrantes de la cabeza; Lesiones traumáticas del encéfalo; Cuerpos extraños en el ojo.

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ABSTRACT

Introduction: Penetrating traumas in the orbit and intraorbital foreign bodies during pediatric age are rare and could be associated with vascular and optic nerve injuries.

Clinical case: Five-year-old female patient with penetrating trauma in left orbit of 1 hour of evolution caused by a brush after accidentally tripping with a classmate while painting during art class. The patient was taken the pediatric emergency department of the Clinica Universitaria Colombia in Bogotá where she was admitted, assessed with scanographic studies and taken to surgery to remove the intraorbital foreign body.

Discussion: The case of this patient was characterized by indemnity of the eyeball, central artery and vein of the retina and optic nerve, in addition to timely and interdisciplinary management that reduced the risk of complications.

Conclusions: The analysis of the clinical evolution of the patient allowed identifying the key events to approach this type of cases, as well as the multiple management and prognosis alternatives according to the type and trajectory of the penetrating object.

RESUMEN

Introducción. Los traumas penetrantes en la órbita y los cuerpos extraños intraorbitarios durante la edad pediátrica son raros, pero pueden asociar compromiso vascular y del nervio óptico.

Presentación del caso. Paciente femenino de cinco años de edad con trauma penetrante en órbita izquierda de una hora de evolución causado con un pincel. La niña tropezó con un compañero mientras pintaba durante la clase de artes cuando se produjo el accidente. Fue llevada a urgencias pediátricas de la Clínica Universitaria Colombia en Bogotá, donde fue ingresada, valorada con estudios escanográficos y llevada a cirugía para extracción del cuerpo extraño intraorbitario.

Discusión. El caso de esta paciente se caracterizó por la indemnidad del globo ocular, la arteria y vena centrales de la retina y el nervio óptico, además de un manejo oportuno e interdisciplinario que disminuyó el riesgo de complicaciones.

Conclusiones. El análisis del curso clínico de la paciente permitió identificar los eventos clave para el abordaje de estos casos, sus variaciones de manejo y el pronóstico según el tipo y la trayectoria del objeto penetrante.

INTRODUCTION

Trauma to the orbital region involving an intraorbital foreign body injury in children under five years of age is usually generated by casual play, being more frequent in males. (1) The symptoms associated with this disorder are varied and depend on the extent of the injury, the composition of the foreign body, its trajectory, the speed of the impact against the orbit, among other factors. (2)

The first step to take is the stabilization of the patient to be able to perform a complete ophthalmological examination. It is worth noting that not all periorbital foreign bodies should be removed; therefore, the procedure will depend on the characteristics of the material and its location. (3) Computed tomography (CT) of the orbit and skull is an important tool for identifying the severity of the injuries and making therapeutic decisions.

Foreign bodies usually penetrate the orbit and slide between the orbital wall and the eyeball, without affecting the latter; they rarely cross the orbit to penetrate the paranasal sinuses or the intracranial space, possibly involving neurovascular elements. (2,4,5) This paper presents the case of a foreign body that passed through the orbit and penetrated the skull, reaching the temporal lobe without affecting the eyeball.

CASE PRESENTATION

This is the case of a five-year-old girl, mestizo, student, from Bogotá D.C., of a middle-income household.

The patient was admitted to the pediatric emergency department of the Clínica Universitaria Colombia in Bogotá D.C. due to a clinical picture of an hour of evolution of left penetrating intraorbital injury caused by a lodged foreign body. This occurred after an accident during arts class, where a paint brush penetrated the orbit causing a visible injury without eye pain or loss of visual acuity associated with two emetic episodes; the patient's mother denied bleeding and other associated symptoms. Healthy patient with no relevant history. The student did not receive any treatment at school or from her relatives; prehospital staff monitored her and transferred her to the hospital for assessment.

On physical examination, the patient was conscious, with stable vital signs and left eye with foreign body (brush) in ocular orbit, with eyelid hematoma that did not allow her to open the eye, and without apparent eye involvement or hemorrhage. The paint brush was partially visible inside the eyeball and an approximate surface of 14cm protruded to the outside; the initial ophthalmic exam revealed lateral deviation of the upper rectus muscle. Considering the findings, she was transferred to the pediatric resuscitation room and coagulation times, complete blood count and renal function tests were requested, which yielded normal results. A simple CT scan of the skull study was indicated.

The tomography showed an intraorbital route of the foreign body towards the right side, and above the left eyeball towards the temporal lobe; no intraconal or intraocular lesions were evident, and no intracranial, subdural or epidural hematomas or retroconal bleeding were observed (Figures 1 and 2).

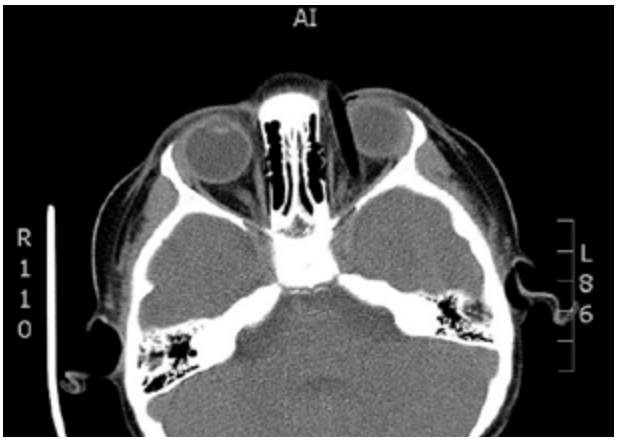

Figure 1. Intraorbital foreign body.
Source: Document obtained during the study.

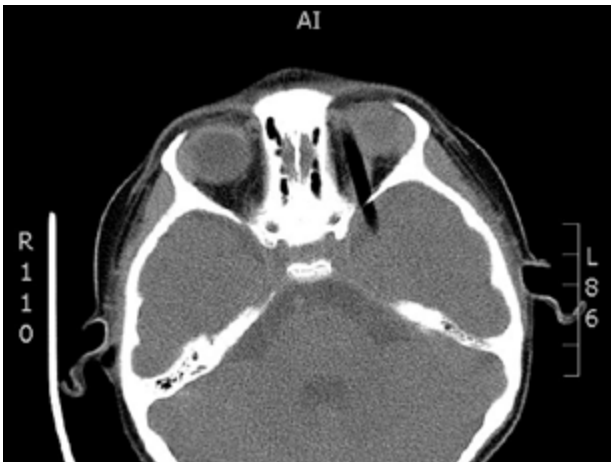

Figure 2. Intracranial trajectory of the foreign body.
Source: Document obtained during the study.

The diagnostic images were evaluated by neurosurgery, which considered removing bone splinters. The operative report of this procedure described the presence of a foreign body above the left eyeball; the foreign body was completely removed by traction.

After the removal, a control CT of the skull and orbits was performed, reporting left eyelid hematoma and in the left upper rectus and lateral rectus muscles. A frontal subdural and temporal left laminar hematoma was observed in the cranial cavity, without compressive effects.

The patient was treated along with the ophthalmology service in the pediatric critical care unit (CCU) without initial evidence of neurological or ophthalmic injury. On physical examination, ophthalmology found mild proptosis, hematoma of the upper eyelid limiting ocular opening, clear cornea, formed anterior chamber, healthy iris, 3mm pupil, photopupillary reflexes and preserved ocular movements.

In the CCU, the child received antibiotic synergy with vancomycin 220mg every 6 hours intravenously, later increased to 250mg every 6 hours, and ceftriaxone 1g every 12 hours intravenously; anti-inflammatory management with intravenous dexamethasone and mechanical ventilation was indicated. The control CT scan of the orbit taken the first post-operative day showed a decrease in the upper subperiosteal hematoma and hematoma adjacent to the lateral rectus muscle; this retroconal hematoma had orbital extension and persisted on site in the three thirds of the orbit, greater in the anterior third and without signs of optic nerve compression or other alterations of intraorbital structures. In addition, control CT scan of the skull showed subarachnoid hemorrhage over the tentorium of the left cerebellum and falx cerebri, as well as acute frontal basal left and temporal left subdural hemorrhage with an extension of 5mm.

On the second day of stay in the CCU, the patient was extubated and an ophthalmology assessment was performed again, reporting a reduction of eyelid edema, clear cornea with a healthy anterior chamber, normal near and distant visual acuity in both eyes, left subconjunctival hemorrhages resolution and left intraocular pressure of 14/15 mmHg. Moreover, dilated fundus examination was made using drops of benoxinate hydrochloride and 0.5% tropicamide with 5% phenylephrine hydrochloride; after pharmacological dilation, disc with excavation of 0.3/0.3, normal retinal vessels and healthy macula were reported for both eyes.

Taking into account the satisfactory evolution the following day, the patient was sent to the pediatric floor, where she evolved satisfactorily without neurological or visual impairment, nor need for new surgical interventions. The last control CT scan of the orbit revealed slight reduction of retroconal hematoma, persistence of left frontal and temporal subdural collection and slight subfalcine hernia of 3mm, without evidence of transtentorial hernia, expansive lesions, cysts or calcifications.

The girl completed a five-day antibiotic and anti-inflammatory scheme, with favorable evolution and no adverse events or reactions to the established treatment; in consequence, she was discharged with control by external consultation with pediatrics, ophthalmology and neuropediatrics. No topical ophthalmic management was indicated during hospitalization. During the control consultations, the patient remained asymptomatic and had an adequate recovery.

It should be noted that considering the trajectory of the penetrating object and its intraorbital accommodation prior to splinterectomy was highly relevant; this case was characterized by the integrity of the central artery and vein of the retina and the optic

nerve as the foreign body was at the extraconal space without intraocular involvement. The neurological evolution was satisfactory with a retroconal hemorrhage that was adequately reabsorbed and small laminar subdural hematomas, which demonstrates the importance of timely and interdisciplinary management to reduce the risk of complications in the eyes (cellulite, restrictive or paralytic strabismus, etc.) and the brain (skull base osteomyelitis, brain abscess, etc.)

The differential diagnosis depends on the kinetics of the trauma, the accommodation of the foreign body and, mainly, the findings by orbit and skull imaging. Diagnostic difficulty increases when the foreign body is metallic or has irregular contours, generating artifacts and difficult radiological reading.

For the analysis of the reported case, a non-systematic search of the literature was performed in the databases PubMed, Embase, ClinicalKey and Scopus and in Google Scholar using the keywords "trauma orbitario penetrante" and "cuerpo extraño intraorbitario" and their English equivalents "penetrating eye injuries" and "eye foreign bodies". The information retrieved was filtered by title match and date of publication over the last 10 years (2008-2018). The report and case analysis were presented to the Research Ethics Committee of Fundación Universitaria Sanitas for approval.

DISCUSSION

Eye trauma during childhood is usually caused by bruising or penetrating mechanisms, resulting from games or sports (59%) and accidental bumps or falls (37%). These traumas can cause damage to varying degrees and can involve the patient's vision. This is the main cause of monocular blindness in the pediatric population, and requires immediate care. (6,7)

Although ocular trauma by intraorbital foreign body is rare in the pediatric population, it is an emergency when it occurs. From a physiopathological perspective, there is an increase in orbital pressure and, therefore, in its structures. The clinic includes diplopia, strabismus, pain upon eye movement, nausea and vomiting, which were not observed in the reported case. (1) Action in the emergency department must be precise and accurate, involving pediatrics, ophthalmology and neurosurgery. The diagnostic support of the CT scan is relevant to establish the location of the intraorbital lesion (intraconal, extraconal or intraocular) and the therapeutic plan to follow. (2,3,5)

In general, small or sharp objects traveling at high speeds can cause serious injury to different components of the orbit. Flying elements from a pruner, emery or any tool, lances, pencils and missiles can strike the eyes and pierce the eyeball (2,3), causing corneal lesions, hyphema (bleeding between the iris and the cornea), damage to the iris (causing a change in pupil size and shape), uveitis, cataracts, hemovitreous, retinal detachment, endophthalmitis, among others. (2) Their trajectories may also involve intraorbital structures outside the eyeball, such as the optic nerve, the vascular bundle of the retina, and the external muscles of the eye.

The main treatment in patients with intraorbital foreign body trauma is removal of the foreign body, given the risk of involvement of the eyeball and possible complications such as secondary infections, severe orbital inflammation, osteomyelitis and even brain abscess. (8) However, taking into account whether the foreign body is organic or inorganic, it is necessary to assess if it generates clinical manifestations or not, since its extraction can cause complications during surgical exploration because organic objects are associated mostly

with inflammatory responses and subsequent abscesses. (8,9)

When inorganic foreign bodies are present, the possibility of expectant management should not be ruled out, as long as it does not generate functional involvement in the patient. (9) The type of diagnostic imaging to be used is established depending on its composition, being CT scan of the orbit the one of choice. Magnetic resonance imaging (MRI) of the orbit may be considered as an imaging modality as long the foreign body does not have any metallic component. (10-12) Alternatively, and according to availability, ocular ultrasound can be used, which is especially useful to identify possible associated intraocular damage. (11-14)

The treatment plan for intraocular injury varies depending on whether the optic nerve or the neurovascular bundle of the retina are involved and the severity. Thus, repair surgery and medications that generate immediate action at the site of the condition can be provided; in these cases, the use of systemic steroids and decompressive surgery should be considered. (15) The evolution of vision will depend on the response to the treatment and may lead to monocular blindness, in addition to being associated with an increased risk of intracranial injury. (15,16)

Different factors (16,17) such as the material and trajectory of the foreign body and, especially, the location and extent of the involvement of the intraorbital lesion must be taken into account when starting the treatment: intraocular, intraconal or extraconal. (12,13)

CONCLUSIONS

Foreign body trauma to the eye is relatively rare, with varying incidence rates of approximately 13.2 cases per 100 000 inhabitants of all ages and described in 27.3 cases per 100 000 inhabitants in the United States. (18) When it occurs in children under five years of age, games and sports are precipitating factors, with a slight preponderance in the male sex and an increased risk of monocular blindness (19), of which no exact incidence has been reported.

Associated clinical manifestations, such as diplopia, strabismus, pain upon eye movement, nausea and vomiting, are related to the extent of the injury, the involvement of the transparent tissue and retina, composition, trajectory and velocity of the impact of the foreign body within the orbit. (20) Therefore, diagnostic and therapeutic interventions from the ophthalmology service are essential to ensure the preservation of vision.

CT scan of the skull and orbit is useful to focus management, which in turn requires a multidisciplinary team of professionals properly coordinated. (21) This case was characterized by an intraorbital trajectory of the penetrating object and interdisciplinary management (pediatrics, pediatric neurology, ophthalmology, neurosurgery and neuroradiology) that allowed preserving the patient's vision and extraocular movements, thus avoiding severe ophthalmic and neurological sequelae and evidencing that the adequate and timely treatment of this pathology decreases the risk of complications.

ETHICAL CONSIDERATIONS

The patient's guardian (mother) was asked to read and sign the informed consent for the use of the data in this case report.

CONFLICT OF INTEREST

None stated by the authors.

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NEUROMYELITIS OPTICA SPECTRUM DISORDER IN PEDIATRICS. CASE REPORT

Keywords: Neuromyelitis Optica; Optic Neuritis; Antibodies; Aquaporin 4; Methylprednisolone; Rituximab.
Palabras clave: Neuromielitis óptica; Neuritis óptica; Anticuerpos; Acuaporina 4; Metilprednisolona; Rituximab.

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ABSTRACT

Introduction: Neuromyelitis optica is an inflammatory disorder of the central nervous system that accounts for 5% of demyelinating diseases in pediatrics. Its clinical presentation is variable and associated to the involved area of the central nervous system.

Case presentation: This is the case of a 15-year-old patient who consulted several times for nonspecific neurological symptoms. During his last visit to the Clínica Universitaria Colombia in Bogotá, he presented with bilateral optic neuritis, associated with frontal and parietal headache. Immunophenotyping studies were carried out, reporting positive IgG anti-aquaporin 4 antibodies (anti-AQP4 antibody), thus leading to a diagnosis of seropositive neuromyelitis optica spectrum disorder (NMOSD). Management with methylprednisolone pulses was initiated with subsequent outpatient management with rituximab that allowed stabilizing the disease.

Discussion: This is an interesting case due to its insidious and uncertain onset in a pediatric patient. It was possible to evaluate clinical and diagnostic differences in relation to its presentation in adults. NMOSD mediated by anti-AQP4 is rare; brain and bone marrow MRI are essential for diagnosis. The treatment of choice for acute conditions consists of high doses of methylprednisolone.

Conclusion: This disorder may result in irreversible neurological damage; for this reason, high suspicion is required for early diagnosis and timely treatment.

RESUMEN

Introducción. La neuromielitis óptica es un trastorno inflamatorio del sistema nervioso central que representa el 5% de las enfermedades desmielinizantes en pediatría. Su presentación clínica es variable y está ligada al área del sistema nervioso central comprometida.

Presentación de caso. Paciente masculino de 15 años quien consulta en varias oportunidades por síntomas neurológicos inespecíficos y que en su última visita a la Clínica Universitaria Colombia, en Bogotá, presenta un cuadro de neuritis óptica bilateral, asociado a cefalea frontal y parietal. Se realizan estudios de inmunotipificación que documentan positividad para anticuerpos IgG y anti acuaporina 4 (ACS anti-AQP4), permitiendo así el diagnóstico de desorden del espectro de neuromielitis óptica (NMOSD, por su sigla en inglés) seropositivo; se inicia manejo con pulsos de metilprednisolona a dosis de 1g intravenoso cada 24 horas, con posterior manejo ambulatorio con Rituximab, que permiten estabilización de la enfermedad.

Discusión. Se presenta un caso interesante por su inicio insidioso e incierto en un paciente pediátrico. Este caso permite evaluar las diferencias clínicas y diagnósticas en relación a su presentación en adultos. El NMOSD mediado por ACS anti-AQP4 es poco común; para su diagnóstico es esencial la resonancia magnética cerebral y de médula ósea. El tratamiento de elección para cuadros agudos consiste en altas dosis de metilprednisolona.

Conclusión. El NMOSD puede producir daño neurológico irreversible, por esto requiere un alto índice de sospecha para su diagnóstico temprano y tratamiento oportuno.

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease in pediatrics with a chronic inflammatory demyelinating characteristic that affects the central nervous system (CNS) and may or may not be associated with seropositivity of anti-aquaporin-4 antibody (anti-AQP4 antibody). (1,2) 4% of seropositive cases occur during childhood, at a female/male ratio of 3:1, and have a monophasic course. (2,3)

The clinical presentations of NMOSD are optic neuritis and myelitis. The first causes a decrease in visual acuity from hours to days, pain with eye movement and blindness in one or both eyes, while the second may cause motor, sensory or autonomic involvement. (4-7)

Early diagnosis and treatment, and relapse prevention are essential for improving the quality of life of patients with this disorder. The treatment of the acute form of this condition is mainly based on high doses of methylprednisolone and subsequent immunomodulatory management with azathioprine, mycophenolate or rituximab in some cases. (8-11) Most treatments are based on the management given to the adult population; therefore, clinical studies that address the pediatric population are required. (11)

CASE PRESENTATION

15-year-old male patient, student, mestizo, from and resident of Bogotá D.C., belonging to a middle-income family, with a history of Hodgkin's lymphoma diagnosed at 4 years of age, treated with 5 rounds of chemotherapy and remission at age 5. No history of demyelinating neurological diseases in the family was reported.

The child attended a consultation on February 7, 2017 in the city of Tunja due to a slow and insidious clinical profile of 1 week of evolution consisting of hemiparesis on the right half of the body and loss of strength in upper limbs and trunk, which was associated with sensitive alteration at the cervical level and involvement of sphincters. Initially, the condition was investigated outside the institution as it was considered as a conversion syndrome; then, the patient was hospitalized and initial studies were performed to rule out a differential diagnosis of demyelinating disease. Contrast nuclear magnetic resonance (NMR) of the dorsal spine showed alteration of spinal cord signal intensity in the lower cervical segment, so complement studies were indicated.

That same day, the patient was admitted to the Clinica Universitaria Colombia in Bogotá D.C. due to suspicion of transverse myelitis based on a feeling of stabbing pain in the thoracic spine, associated with hemiparesis of the left side of the body with predominance in the upper limb, mild respiratory difficulty, hyporeflexia and non-voluntary loss of 2kg of weight in 1 week. A cervical spine MRI was performed, showing an alteration in spinal cord signal intensity in the cervical segment, correlated with the affected cervical sensory level. This finding allowed diagnosing longitudinally extensive transverse myelitis (LETM) (Figures 1 and 2), so the patient was admitted to the hospital to start therapy with methylprednisolone pulses at a dose of 1g intravenously every 24 hours for 5 days. In addition, immunophenotyping and diagnostic studies were performed, obtaining negative LETM.

The symptoms resolved with the therapy without associated adverse reactions, so he was discharged from hospital on February 27, 2017.

In April 2017, the patient received a new course of methylprednisone at a dose of 1g intravenously every 24 hours due to persistence of gadolinium enhancement in MRI of the cervical spine. On March 14, 2018, at 17:53 hours, he was readmitted to the Clinica Universitaria Colombia due to a clinical profile of 10 hours

of evolution consisting of a decrease in bilateral visual acuity, associated with transient blurred vision, stabbing frontal and parietal headaches and a fall from his own height due to visual disturbance.

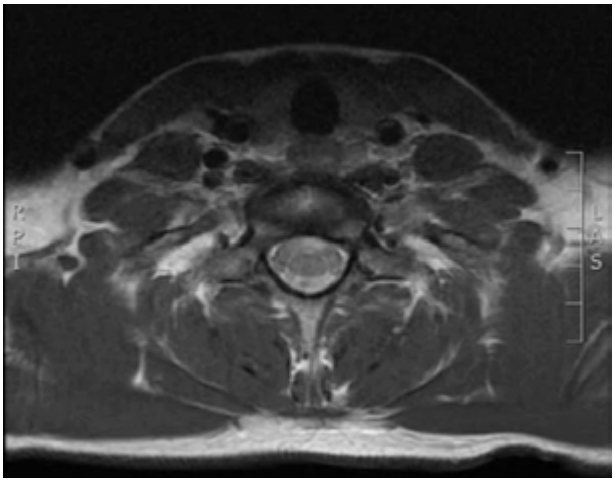

Figure 1. Contrast magnetic resonance imaging (MRI) of the cervical spine (axial plane) that shows spinal cord injury involving anterior horns with abnormal contrast uptake and contrast uptake of the roots, mainly anterior C5, C6, C7 and C8.
Source: Document obtained during the study.

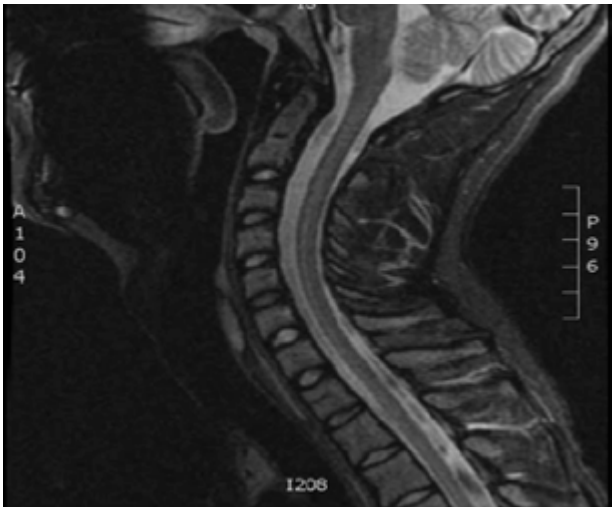

Figure 2. Contrast nuclear magnetic resonance of the cervical spine (sagittal plane) that shows chronic changes in signal intensity and malacia in the anterior cords from level C2 to level C4.
Source: Document obtained during the study.

In April 2017, the patient received a new course of methylprednisone at a dose of 1g intravenously every 24 hours due to persistence of gadolinium enhancement in MRI of the cervical spine. On March 14, 2018, at 17:53 hours, he was readmitted to the Clinica Universitaria Colombia due to a clinical profile of 10 hours of evolution consisting of a decrease in bilateral visual acuity, associated with transient blurred vision, stabbing frontal and parietal headaches and a fall from his own height due to visual disturbance.

On physical examination during admission, the patient was alert, with bilateral 20/20 vision, normal bilateral fundoscopic exam, normal optical coherence tomography and without signs of focalization; the 4 limbs moved with 5/5 strength. Report of studies on cerebrospinal fluid (CSF) showed no pleocytosis or cellularity and normal lactic acid, ruling out encephalitis. The anti-AQP4 autoantibody in CSF taken on February 27, 2018 was positive: 4.53 U/mL with a cut point less than 3 U/mL (Figure 3). Additionally, it reported the presence of three standard oligoclonal bands type 2 in CSF. MRI of the brain and optical nerves following the demyelinating disease protocol were normal.

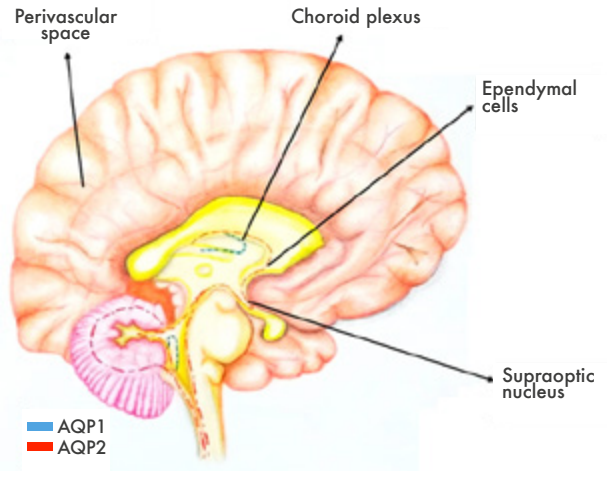

Figure 3. Areas vulnerable to anti-AQP4.
Source: Own elaboration based on Jabob (8).

In the context of this patient, and given his pathological history, a relapse of this condition along with optic neuromyelitis was considered, reason why new boluses of systemic corticosteroid were indicated. Relapse of seropositive NMOSD was diagnosed because it met the criteria of anti-AQP4 autoantibody optical neuritis in positive CSF, acute myelitis with LETM, positive test for AQP4 and exclusion of other diagnoses. Therefore, he received a course of corticotherapy that started on March 15, 2018 for 5 days and was discharged from hospital with prescription of anti-CD20 therapy (Rituximab) at a dose of 375 mg/m^2 of body surface in 4 weeks, with repetition every 6 months (dependent on titration of serum anti-CD20-CD27 every 9-10 weeks), to which he adhered properly.

The symptoms resolved and the disease stabilized thanks to the therapy prescribed, with adequate tolerance to the treatment. At the time of this case report, the boy feels that his condition is adequately controlled, with no associated severe adverse reactions, and has a favorable prognosis without further relapses since management with Rituximab was initiated.

This patient's timeline began with the onset of the symptoms in February 2017, a relapse with transverse myelitis in March 2017 and another relapse with optic neuromyelitis in March 2018, when the NMOSD diagnosis was confirmed. The findings of NMR of the brain ruled out other pathologies, mainly multiple sclerosis (MS) caused by transverse myelitis (not typical of MS) and absence of bright spot in T2 axial sequence. Anti-AQP4 autoantibody biomarkers in CSF were ordered based on these findings.

DISCUSSION

NMOSD, also known as Devic's disease, was first described in the nineteenth century as a monophasic disorder of severe acute transverse myelitis and bilateral optic neuritis. (1) This is a rare disease with a prevalence of 0.52-4.4 per 100 000 inhabitants and an incidence less than 0.05 cases per 100 000 inhabitants per year in the United States. (2,12) The average age of onset is 31 years, but some cases have been reported in the pediatric population. (3,4)

The pathophysiological role of the disease is mediated by a blood cell autoantibody (NMO-IgG, or anti-AQP4 autoantibody) that binds to Aquaporin-4 (water channel found within the CNS) (5), specifically at the astrocyte junction with blood vessels. This antibody plays a key role in neuronal death by astrocytotoxic effect, mainly because of AQP4 dysfunction, complement activation and NK lymphocytes activation in regions with high density of AQP4 (6-8) (Figure 1).

The clinical presentation of patients with NMOSD is highly variable and the symptomatology appears depending on the involvement of various areas of the CNS (optic nerve, spinal cord, area postrema, brain stem, diencephalon and brain). (9,10) The most frequent symptoms are longitudinally extensive optic neuritis, transverse myelitis and area postrema syndrome, consisting of vomiting or intractable hiccups. Other clinical manifestations that may occur with this disease derive from the involvement of the brainstem: vertigo, sensorineural hearing loss, facial paralysis, trigeminal neuralgia, diplopia, ptosis and nystagmus. (10,11,13) Symptomatic forms of narcolepsy or altered states of consciousness, encephalopathy associated with diffuse white matter injury in the CNS, posterior reversible encephalopathy syndrome and manifestations associated with dysfunction of the hypothalamic-pituitary axis such as SIADH have also been described. (14-15)

Diagnostic criteria have changed over the years: an initial proposal was made in 1999 and then revised in 2006. The international

consensus diagnostic criteria for NMOSD made a final proposal in 2015 (16), as follows:

Diagnostic criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic,
2. Positive test for AQP4-IgG using the best available detection method (cell-based assay strongly recommended),
3. Exclusion of alternative diagnoses.

Diagnostic criteria for NMOSD without AQP4-IgG or unknown AQP4-IgG status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:

a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome,
b. Dissemination in space (two or more core clinical characteristics),
c. Fulfillment of additional MRI requirements, as applicable;

2. Negative test for AQP4-IgG using the best available detection method, or testing unavailable;
3. Exclusion of alternative diagnoses.

Core clinical characteristics

The same proposal included optic neuritis, acute myelitis, area postrema syndrome (episodes of hiccup or unexplained nausea and vomiting), acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic syndrome with typical NMOSD diencephalic lesions on MRI, and symptomatic brainstem syndrome with brain lesions typical of NMOSD on MRI as clinical characteristics of NMOSD.

Therefore, an imaging study that includes brain, orbits, single spine and contrast MRI must be performed for diagnosing NMOSD; anti-AQP4 antibody should also be determined. MRI findings are usually >2cm and located in periventricular zones of the third and fourth ventricles, that is, diencephalon and brainstem, supratentorial white matter, midbrain and cerebellum, which are areas where increased expression of AQP4 is observed. (8,9,17) Area postrema and hypothalamic lesions are usual in NMOSD with anti-AQP4 antibody, which is useful to differentiate it from other inflammatory and neurodemyelinating disorders of the central nervous system in the pediatric population. (9,18)

The most common findings of spinal cord MRI is longitudinally extensive transverse myelitis, which is defined as a lesion that involves more than 3 contiguous vertebral segments and predominantly affects the central gray matter in the spinal cord. However, this finding is not as specific in children as it is in adults. (17-19)

Differential diagnoses may include multiple infectious and reactive etiologies, among them, post-infectious and post-vaccinal etiologies, vascular pathologies, nutritional deficiencies — particularly, vitamin B12 deficiency—, compressive tumors, systemic lupus erythematosus, maculopathies and retinopathies. (4,8,11)

Early diagnosis and treatment help prevent relapses, which are the origin of morbidity due to the neurodegeneration caused by this pathology. (4,12) Treatment should be provided early in order to reduce disability and morbidity (8,9,11,20); the therapeutic approach to the acute form of the condition is using high doses of methylprednisolone. (8,9,11) For relapse prevention, first-line immunomodulatory management includes azathioprine, mycophenolate, rituximab, among others; second-line includes metotrexate, mitoxantrone, and cyclophosphamide. (11,21-23)

Regarding prognosis, more than half of the patients will continue to experience acute attacks that will result in possible and potentially permanent neurological disability. (23-24) About 80% of cases have a recurrent course of the disease and relapses are associated with long-term visual and motor disability. (11,19)

This case is relevant due to the low incidence of the disease in pediatrics, the variability of the clinical presentation referred to in the literature, and onset with motor involvement that evolved to optical involvement and finally to seropositivity.

CONCLUSIONS

NMOSD is an entity with particular clinical, immunological and radiological findings that differentiate it from multiple sclerosis. Its diagnosis requires a high rate of suspicion, especially with presentations such as the one described with LETM. Early diagnosis (with a high rate of clinical suspicion) and early treatment help preventing relapses and major neurological sequelae (irreversible brain damage). More descriptive studies in pediatrics are needed to know the population and analytical studies to work on the treatment.

CONFLICT OF INTEREST

None stated by the authors.

FUNDING

None stated by the authors.

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RISK OF REFEEDING SYNDROME. CASE REPORT

Keywords: Hypophosphatemia; Malnutrition; Enteral Nutrition; Refeeding Syndrome.
Palabras clave: Hipofosfatemia; Desnutrición; Nutrición enteral; Síndrome de realimentación.

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ABSTRACT

Introduction: Refeeding syndrome (RS) is an acute metabolic disorder that occurs during nutritional repletion. Although it has been known for years, the early detection of risk factors for its onset and the implementation of measures to prevent it are not common in nutritional care.

Case presentation: 48-year-old male patient, in critical care for 6 days, with suspected Wernicke-Korsakoff encephalopathy and high risk of refeeding syndrome according to criteria of the United Kingdom National Institute of Health and Clinical Excellence. The subject received enteral nutrition with 14 kcal/kg for the first 3 days, with subsequent increases aiming to achieve a nutritional goal of 25 kcal/kg on day 5. He also received daily supplementation of thiamine 600mg, folic acid 5mg and pyridoxine 50mg. Blood phosphorus decreased from 3 mg/dL to 2 mg/dL the day after initiating the nutritional plan and normalized by day 3.

Discussion: The patient did not present severe hypophosphatemia or clinical manifestations of refeeding syndrome. Hypophosphatemia was resolved by maintaining a stable caloric restriction during the first days. Some professionals consider this restriction as very conservative, and others think that it may lead to achieve significant improvements in mortality reduction.

Conclusions: The strategy for assessing the risk of refeeding syndrome, nutritional management and implemented follow-up were successful in preventing the patient from developing a refeeding syndrome.

RESUMEN

Introducción. El síndrome de realimentación (SR) es un trastorno metabólico agudo que ocurre durante la repleción nutricional. Aunque ha sido conocido por años, la detección precoz de factores de riesgo para su desarrollo y la instauración de medidas para prevenirlo no son una práctica habitual en la atención nutricional.

Presentación del caso. Paciente masculino de 48 años en cuidado crítico por 6 días, con sospecha de encefalopatía de Wernicke-Korsakoff y riesgo alto de SR según criterios del Instituto Nacional de Salud y Excelencia Clínica del Reino Unido. El sujeto recibió nutrición enteral con 14 kcal/kg los 3 primeros días, con aumentos posteriores que pretendían una meta de 25 kcal/kg al día 5 y suplementación diaria de tiamina 600mg, ácido fólico 5mg y piridoxina 50mg. El fósforo en sangre disminuyó de 3 mg/dL a 2 mg/dL al día siguiente del inicio de la nutrición y se normalizó para el día 3.

Discusión. El paciente no presentó manifestaciones clínicas de SR ni hipofosfatemia severa; esta última se resolvió manteniendo estable la restricción calórica los primeros días. Para algunos profesionales dicha restricción puede ser muy conservadora; sin embargo, para otros puede llevar a mejoras significativas en la reducción de la mortalidad.

Conclusiones. La estrategia para valorar el riesgo de SR, el manejo nutricional y el seguimiento implementado fueron acertados para evitar que el paciente desarrollara el síndrome.

INTRODUCTION

Refeeding syndrome (RS) is a potentially deadly acute metabolic disorder that takes place during nutritional repletion in patients with prolonged malnutrition or starvation. RS commonly occurs with all types of nutritional support, but the risk seems to be higher in patients fed with enteral or parenteral nutrition. (1-3) In addition, it encompasses a set of fluid and electrolyte imbalances that affect multiple organ systems, including neurological, cardiac, hematologic, neuromuscular, and pulmonary functions. (2) Hypophosphatemia is the predominant characteristic of RS and is observed in more than 95% of cases; it also explains a large part of the symptoms of this clinical picture. (4) Other metabolic changes, such as hypomagnesemia, hypokalemia, fluid balance disturbances, and vitamin deficiencies, may also play an important role. (1)

This condition is usually underdiagnosed as it lacks uniform criteria for diagnosis, while symptoms may be wrongly attributed to other clinical diagnoses. (1,5) Reports on critically ill patients show, for example, that the incidence of refeeding hypophosphatemia ranges from 34% to 52%. (1)

In 2006, the UK National Institute of Health and Clinical Excellence (NICE) published recommendations for the detection and management of patients at risk of RS. (6) Some studies (7-9) have evaluated the practices and opinions of health professionals with respect to these recommendations, concluding that some aspects of the risk criteria and feeding initiation doses suggested by NICE have been adopted, although this is not the case worldwide. (8,9) For some professionals, the recommendations are too conservative and are an obstacle to providing adequate nutrition, while others think that they lead to increased costs due to the need for more frequent biochemical analyses, increased electrolyte replacement rates and closer monitoring as suggested by NICE. (7)

RS prevention should be the main guideline when initiating nutritional management. The identification of patients at risk, the establishment of adequate nutritional support, and follow-up may potentially reduce the morbidity and mortality rates associated with the syndrome. (3) The description of this case intends to expose identification strategies and nutritional management of a patient at risk of RS.

CASE PRESENTATION

48-year-old male patient, mestizo, from the northern sub-region of Antioquia (Colombia), with no schooling, unemployed and economically dependent on his siblings, who presented a history of neurocognitive deficit since childhood, cleft palate, heavy daily consumption of ethanol for nearly 7 years (without information on quantity) and recent consumption of antiseptic alcohol and heavy smoking (40 cigarettes a day) since childhood. The subject did not have any surgical history nor reported consumption of medications on an outpatient basis.

The patient attended a secondary care hospital in January 2018 due to a fall under the influence of alcohol. He was discharged and re-admitted 4 days later due to a confusional state and weakness of lower limbs. His neurological condition deteriorated and had convulsive episode 5 days after re-admission; he was subsequently intubated and transferred to a tertiary referral hospital.

The subject was referred with a heart rate of 107 beats/minute, blood pressure of 167/110 mmHg, respiratory rate of 18 breaths/minute, temperature of 36.5°C, 99% $SaO_2$with ventilatory support, 3/15 Glasgow with midazolam and fentanyl infusion, 3mm

isocoric reactive pupils and present stem reflexes. On physical examination the subject was hydrated, with macrocephaly and sarcopenia and no other relevant findings. He entered the intensive care unit (ICU) for ventilatory support and neurological surveillance.

Upon questioning, his relatives stated that the patient had a maximum of one meal per day as he preferred to consume alcohol instead of food and that he had experienced chronic and severe weight loss (approximately 10kg) during the last year; his weight on admission was 45kg, height 155cm and body mass index (BMI) of 18.7 kg^2. According to the nutritional screening tool NRS 2002, the patient had a score of 5, which indicated that he was at nutritional risk; he had a score of 2 for the item 'nutritional status', corresponding to BMI between 18.5 and 20.5 kg/m^2, plus deterioration of the general state or energy intake of 25-60% in the last week, and a score of 3 for the item 'disease severity' since he was a critical patient at the ICU. He was diagnosed with severe malnutrition by the ICU dietitian nutritionist.

The initial paraclinical tests showed chronic hepatopathy by ethanol, without cirrhosis or alcoholic hepatitis on abdominal ultrasound. The paraclinical tests on admission were creatinine: 1.21 mg/dL; urea nitrogen: 49 mg/dL; sodium: 148 mmol/L; potassium: 4.28 mmol/L; calcium: 8.7 mg/dL; chlorine: 112.5 mmol/L; aspartate transaminase: 78 u/L; alanine aminotransferase: 207 u/L; alkaline phosphatase: 192 u/L; gamma-glutamyl transferase: 223 u/L; direct bilirubin: 0.78 mg/dL; total bilirubin: 0.94 mg/dL; hemoglobin: 15 g/dL; hematocrit: 45.1%; magnesium: 2.81 mg/dL; folic acid 2.6 ng/mL; and vitamin B12: 333 pg/mL.

Computed tomography (CT) of the skull showed noncommunicating hydrocephalus, subarachnoid hemorrhage and chronic subdural hygromas without indication of surgical intervention and probably unrelated to the current neurological condition. In addition, status epilepticus was ruled out in electroencephalogram, so it was decided to manage Wernicke-Korsakoff encephalopathy by starting thiamine 200mg intravenously every 8 hours and lorazepam 1mg every 8 hours due to risk of abstinence.

At 24 hours after admission to the ICU, enteral nutritional support was initiated using a gastric tube with the lactose-free polymer formula available in the hospital (protein: 14%, carbohydrates: 66%, fat: 20%, sodium: 84 mg/100mL, fructooligosaccharides: 1g/100mL). It was established that the patient had a high risk of suffering RS according to the NICE criteria (Table 1) (6) and the personal history described above (alcohol abuse, inadequate food intake for more than five days, loss of approximately 18% of weight in the last year and BMI in the lower limit of normality). For this reason, early nutritional support was initiated with maximum 15 kcal/kg, maintaining stable caloric intake the first 3 days and then increasing between 5 and 15 kcal/kg/day, in addition to follow-up laboratory tests during the first 72 hours of nutritional support.

Table 1. Criteria to determine people at high risk of developing refeeding problems

The patient has one or more of these symptoms	BMI<16 kg/m2 Unintentional weight loss >15% in the last 3-6 months Little or no nutritional intake for more than 10 days Low levels of potassium, phosphate or magnesium before feeding
The patient has two or more of these symptoms	BMI<18.5 kg/m2 Unintentional weight loss >10% in the last 3-6 months Little or no nutritional intake for more than 5 days History of alcohol or drug abuse that includes insulin, chemotherapy, antacids or diuretics

BMI: body mass index.

Source: Own elaboration based on NICE criteria

Before starting enteral nutrition, baseline paraclinical tests were taken to monitor RS, being within the normal range: phosphorus: 3 mg/dL (0.97 mmol/L), magnesium: 2.55 mg/dL (1.06 mmol/L) and potassium: 3.6 mmol/L. Then, enteral nutrition was started with a caloric intake of 14 kcal/kg and 13 mL/kg of current weight; this was maintained for the first 3 days of nutritional support. Control paraclinical test taken the day after initiating enteral nutrition showed that the phosphorus value decreased to 2 mg/dL (0.65 mmol/L), without the need for repletion. On the third day of nutritional support, phosphorus was again within the normal range (Figure 1). Regarding potassium, it decreased to 3.3 mmol/L, and was replaced with 0.8 mmol/kg/day; during the following days, it was within the normal range. Magnesium values remained normal during all days of nutritional support.

On day 4, the caloric intake increased to 22 kcal/kg and 21 mL/kg, leading to establish a management plan that consisted of reaching the nutritional goal of 25 kcal/kg on day 5 or 30 kcal/kg on day 7 based on the clinical condition of the patient. In addition, since the first day of nutritional support, the patient received folic acid 5mg every 24 hours and pyridoxine 50mg orally every 24 hours. While fed with enteral nutrition, the subject did not present any gastrointestinal symptoms related to nutrition intolerance or adverse events with the nutritional treatment implemented.

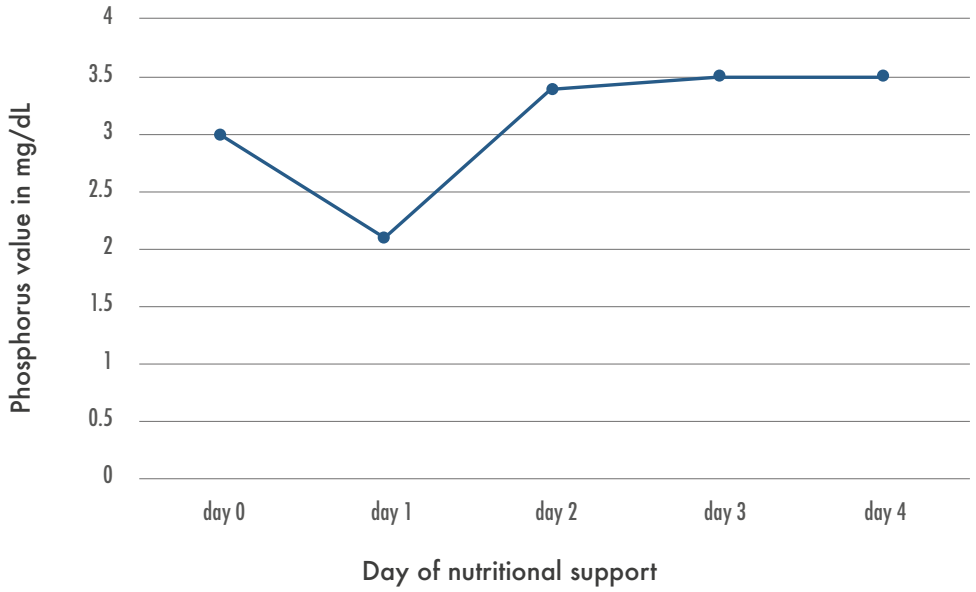

Figure 1. Phosphorus values before and during nutritional support.
Source: Own elaboration.

In order to assess his neurological condition, sedation was suspended 24 hours after admission to the ICU. During the following 3 days, the patient presented eye response without contact with the environment or motor response. He also reported left mydriasis, hypertension and bradycardia. CT scan of the skull showed extensive acute ischemic changes in the right cerebral hemisphere and cerebral edema, so hyperosmolar therapy was initiated.

The patient showed greater neurological deterioration on the fifth day of stay in the ICU.

For this reason, due to his baseline condition and the last identified changes, the subject was considered irrecoverable and minimal baseline support was offered, while the objective of management was redirected to palliative care. The patient died on the sixth day of hospitalization.

DISCUSSION

Although RS is a condition known since the end of World War II and is defined as a life-threatening condition, early detection of risk factors and the implementation of measures to prevent it are not common in the nutritional care process. (7,8) One of the reasons may be that nutritional recommendations emphasize on avoiding high rates of malnutrition: it is reported that the prevalence of malnutrition in critically ill patients can range from 37.8% to 78.1%. (10) In this regard, the concern of health professionals to avoid undernutrition, seek early nutrition, not delay the achievement of nutritional goals, among others, prevails over the concern to implement gradual nutritional treatments in patients at risk of RS.

Another reason is that risk factors for developing RS may be vague. The literature reports very varied and common risk factors among patients admitted to a hospital (2,5,6,11); therefore, there is concern that implementing RS risk prevention measures could put patients at greater nutritional risk, increasing the number of patients who experience a delay in meeting their nutritional goals.

A third reason is the lack of a clear definition of RS, which leads to underdiagnose it and cast doubt on the true relevance of implementing strategies to avoid it. A systematic review including 45 RS-related studies conducted between 1989 and 2015 shows heterogeneous definitions; most studies included hypophosphatemia in their definition, either as a cut-off point or as a relative change from baseline. (5) As it does not have standard criteria for diagnosis, RS goes unnoticed and is attributed to other types of situations such as medical management, basic pathology, clinical complications and drugs action.

One way to avoid imprecision in the classification of RS risk, and thereby prevent over- or underestimation of patients at risk, is the development of care guidelines. The Hospital Pablo Tobón Uribe of Medellín does not have an adult patient RS management guide, although it recognizes the importance of this condition and is working on a care protocol. While own guidelines are generated, the guidelines for RS risk assessment and nutritional management by NICE: nutrition support for adults (Table 1) (6) and the Friedli *et al.* consensus (Table 2) are being used (3) for RS in inpatients.

This last consensus has the added value of detailing the management that should be offered depending on the type of refeeding risk of each subject; patients are classified as low risk, high risk and very high risk (3). This classification could help not to generalize and not to fall into the error of delaying nutritional goals in patients who do not require it.

For the case reported here, nutrition was started at 30 mL/hour, which provided 14 kcal/kg and remained the same for the first 3 days of nutritional support. Although the NICE guidelines usually suggest not exceeding 10 kcal/kg, the expert consensus proposed between 5 and 15 kcal/kg depending on the risk classification. This patient was classified as high risk, a group for which it is recommended not to exceed 10 kcal/kg to 15 kcal/kg during the first 3 days of nutritional support. Some practitioners believe that calorie restrictions become an obstacle to providing adequate nutrition (7); however, a multicenter randomized clinical trial of patients with phosphorus depletion <2 mg/dL (0.65 mmol/L) within 72 hours of initiation of nutrition

determined that calorie restriction at 20 kcal/hour for at least 2 days appears to be an appropriate therapeutic option for critically ill adults. This restriction led to significant improvements in the overall survival time and in the reduction of mortality at day 60 of follow-up. (12)

On the other hand, Friedli *et al.* (3) also propose an algorithm that allows tracking patients at risk and diagnose and treat RS, if applicable. In the reported case, the patient presented phosphorus depletion of over 30%, which is consider by some as a criterion for diagnosing RS; however, the patient did not present severe hypophosphatemia or clinical manifestations, and on the third day of nutritional support the serum phosphorus was normalized without the need for repletion or changes in caloric intake. Therefore, according to the algorithm, this was not considered as RS.

Table 2 shows an adaptation of the work algorithm proposed by Friedli *et al.* (3), which could serve as a guide for health institutions to assess the risk of refeeding and in the nutritional treatment according to the type of risk.

Table 2. Guidelines for nutritional management and prevention of refeeding syndrome.

<table>
<tr><th colspan="4">1. Assessment of risk factors for refeeding syndrome</th></tr>
<tr><td>Low risk factors
▪ BMI<18.5 kg/m²
▪ Unintentional weight loss >10% in the last 3-6 months
▪ Little or no nutritional intake for more than 5 days
▪ History of alcohol or drug abuse that includes insulin, chemotherapy, antacids or diuretics</td><td colspan="2">High risk factors
▪ BMI<16 kg/m²
▪ Unintentional weight loss >15% in the last 3-6 months
▪ Little or no nutritional intake for more than 10 days
▪ Low basal levels of potassium, phosphorus or magnesium before nutrition</td><td>Specific populations of patients at high risk
▪ Severe chronic starvation or diet
▪ History of bariatric surgery, short bowel syndrome
▪ Tumor patients or frail elderly patients with chronic debilitating disease</td></tr>
<tr><th colspan="4">2. Classification of risk factors for refeeding syndrome</th></tr>
<tr><td colspan="2">Low risk
One low risk factor</td><td>High risk
One high risk factor or 2 lower risk factors</td><td>Very high risk
▪ BMI<14 kg/m²
▪ Weight loss >20%.
▪ Starvation for more than 15 days</td></tr>
<tr><th>Nutrition therapy start day</th><th colspan="3">3. Calorie intake according to the type of risk for refeeding syndrome</th></tr>
<tr><td>Days 1-3</td><td>15-25 kcal/kg/d</td><td>10-15 kcal/kg/d</td><td>5-10 kcal/kg/d</td></tr>
<tr><td>Day 4</td><td>30 kcal/kg/d</td><td rowspan="2">15-25 kcal/kg/d</td><td rowspan="3">10-20 kcal/kg/d</td></tr>
<tr><td>Day 5</td><td rowspan="4">Complete requirements</td></tr>
<tr><td>Day 6</td><td>30 kcal/kg/d</td></tr>
<tr><td>Days 7-9</td><td>Complete requirements</td><td>20-30 kcal/kg/d</td></tr>
<tr><td>>10 days</td><td></td><td>Complete requirements</td></tr>
<tr><td>Electrolyte replacement and Supplementation</td><td colspan="3">Depending on the risk, consider:
▪ Substitution of electrolytes if they are below the normal range, with daily adaptation according to serum levels: 1-1.5 mmol/kg/d of potassium, 0.2-0.4 mmol/kg/d of magnesium, 0.3-0.6 mmol/kg/d of phosphate.
▪ Thiamine (200-300mg on days 1-5), multivitamins on days 1-10, specific repletion of trace element deficiencies. No iron substitution within the first 7 days, even in patients with iron deficiency
▪ Sodium restriction (<1 mmol/kg/day) for 1-7 days</td></tr>
</table>

Continues.

<table>
<tr><td>Electrolyte monitoring</td><td colspan="2">Daily evaluation of serum electrolyte levels until day 3, then every 2-3 days</td></tr>
<tr><td colspan="3">4. Diagnosis of refeeding syndrome</td></tr>
<tr><td colspan="3">Change in electrolytes within 72 hours after the initiation of nutritional therapy?
▪ Baseline phosphate reduction >30% or <0.6 mmol/L
▪ Or 2 electrolytes below normal range (Mg <0.75 mmol/L, PO4 <0.80 mmol/L, K <3.5 mmol/L)</td></tr>
<tr><td>NO</td><td colspan="2">YES</td></tr>
<tr><td rowspan="2">Continue with same nutritional management</td><td colspan="2">Associated with clinical symptoms (the most common are tachycardia, tachypnea, and edema)?</td></tr>
<tr><td>NO</td><td>YES</td></tr>
<tr><td></td><td>Imminent refeeding syndrome
Start and/or adapt electrolyte substitution and repeat electrolyte evaluation every 2-3 days</td><td>Evident refeeding syndrome
Increase electrolyte substitution and treat clinical conditions appropriately.
Adapt nutritional therapy as in a high-risk patient, and repeat electrolyte evaluation every day.</td></tr>
</table>

Source: Own elaboration based on Friedli *et al.* (3).

CONCLUSIONS

At the beginning of the nutritional treatment, the patient presented a decrease of phosphorus of more than 30% with respect to its basal value; however, serum phosphorus normalized after maintaining a stable caloric contribution during the first three days of nutritional therapy. Apparently, the patient did not develop RS and the nutritional management offered at all stages (from the detection of RS risk to the implementation of enteral support and follow-up) was successful in preventing the onset of this condition and its complications.

One of the limitations of this case report was the difficulty in accessing anthropometric variables and food background information. Due to his critical condition, the patient was unable to provide information, the anthropometric variables were difficult to establish and his family was unable to provide exhaustive information on food consumption. The subject was classified at high risk of developing RS, but key variables —such as dietary anamnesis— were not obtained, which if known, could have pointed to a greater risk of refeeding and lower initial energy needs.

Prevention is the main recommendation for avoiding the onset of RS and associated complications. It is important to recognize when a patient is at risk, provide adequate management, and monitor the patient to prevent the syndrome from developing. Sometimes it is not possible to prevent RS from happening, but it is possible to prevent the patient from developing serious complications or a fatal outcome. All health institutions should establish the assessment of the risk of refeeding syndrome in their care protocols, as well as a nutritional treatment according to the type of risk.

There is still a wide array of definitions, reported incidence rates, preventive measures and treatment recommendations for RS; therefore, more high quality prospective research is needed to fill this gap.

CONFLICT OF INTEREST

None stated by the authors.

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ZOLLINGER-ELLISON SYNDROME. CASE REPORT

Keywords: Gastrinoma; Zollinger-Ellison Sydrome; Multiple Endocrine Neoplasia Type 1.
Palabras clave: Gastrinoma; Síndrome de Zollinger-Ellison; Neoplasia endocrina múltiple tipo 1.

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ABSTRACT

Introduction: The Zollinger-Ellison syndrome (ZES) is a pathology caused by a neuroendocrine tumor, usually located in the pancreas or the duodenum, which is characterized by elevated levels of gastrin, resulting in an excessive production of gastric acid.

Case presentation: A 42-year-old female patient with a history of longstanding peptic ulcer disease, who consulted due to persistent epigastric pain, melena and signs of peritoneal irritation. Perforated peptic ulcer was suspected, requiring emergency surgical intervention. Subsequently, a tumor lesion in the head of the pancreas was documented and managed with Whipple procedure. The pathology results reported a tumor suggestive of neuroendocrine neoplasm.

Discussion: The Zollinger-Ellison syndrome occurs in 0.1 to 3 people per 1 000 000 inhabitants worldwide and is predominant in women between 20 and 50 years of age. It usually appears as a refractory acid-peptic disease or as a complication of gastric acid hypersecretion. Medical therapy is the standard management, being proton pump inhibitors (PPI) the most effective option. Surgery is recommended for sporadic ZES.

Conclusions: ZES has a low incidence rate. It is rarely considered in the differential diagnosis of chronic epigastric pain and high clinical suspicion is required to achieve adequate management. This article is highly relevant as it presents a confirmed clinical case of ZES in Colombia, highlighting the importance of producing local scientific literature to improve the diagnosis and treatment of this pathology.

RESUMEN

Introducción. El síndrome de Zollinger-Ellison (SZE) es una patología producida por un tumor neuroendocrino habitualmente localizado a nivel duodenal o pancreático, el cual produce niveles elevados de gastrina, derivando en hipersecreción de ácido gástrico.

Presentación del caso. Paciente femenino de 42 años con antecedente de enfermedad ulceropéptica de larga data, quién consulta por epigastralgia persistente y deposiciones melénicas y presenta signos de irritación peritoneal. Se sospecha una ulcera péptica perforada, requiriendo intervención quirúrgica de urgencia. Posteriormente se documenta una lesión tumoral en la cabeza del páncreas, manejada con cirugía de Whipple; en el reporte de patología se detecta un tumor sugestivo de neoplasia neuroendocrina.

Discusión. El SZE se presenta en 0.1-3 personas por cada 1 000 000 de habitantes a nivel mundial, predominantemente en mujeres entre 20 y 50 años de edad. Suele debutar como enfermedad ácido-péptica refractaria o por complicaciones de la hipersecreción gástrica. La terapia médica es el manejo estándar, siendo la más efectiva la que involucra inhibidores de la bomba de protones. En SZE esporádico está recomendada la cirugía.

Conclusiones. El SZE tiene una incidencia baja, raramente se considera en el diagnóstico diferencial de epigastralgia crónica y se requiere alta sospecha clínica para lograr un manejo adecuado. Este artículo es valioso al presentar un caso clínico confirmado de SZE en Colombia, destacando la importancia de producir bibliografía científica local para mejorar el diagnóstico y tratamiento de esta patología.

INTRODUCTION

Zollinger-Ellison syndrome (ZES) is characterized by an increased secretion of gastric acid in the proximal gastrointestinal tract, secondary to the appearance of gastrinomas, which are neuroendocrine tumors located in the duodenum or the pancreas. (1)

The ZES has a wide spectrum of initial presentations and malignancy potentials, so it is important to suspect the presence of the tumor since the first clinical approach. Knowledge about the diagnostic approach and the possible complications and indications to be given to the patient must also be clear. (1) New imaging methods have allowed finding an increasing incidence of this syndrome, which in turn contributes to faster initial treatment. (2)

This paper presents the clinical case of a Colombian patient with ZES, as well as a brief review of the current literature focused on the diagnostic approach to gastric acid hypersecretion and the suspicion of ZES.

CASE PRESENTATION

Female patient of 42 years of age, from Bogotá D.C. (Colombia), housewife, mestizo and from a low-income household, who was admitted to a secondary care hospital due to abdominal pain. The patient presented a clinical profile of 15 days of evolution characterized by epigastric pain associated with multiple episodes of melena; she reported a medical history of refractory ulceroptic disease that appeared 5 years before consultation, which was still pharmacologically treated with omeprazole 20mg every 24 hours, tramadol 50mg every 8 hours and bisacodyl 5mg every 24 hours. She also reported being exposed to wood smoke for 20 years. Her gynecological and surgical history included five pregnancies, four caesarean sections and an ectopic pregnancy that required right oophorectomy.

On physical examination, the patient had tachycardia, but the other vital signs were within normal limits. Hypochromic conjunctiva and dry oral mucosa were found, as well as decreased intestinal sounds and severe abdominal pain in epigastrium on palpation, with signs of peritoneal irritation. Serum hemoglobin was at 9 mg/dL, and electrolytes and glycemia within normal limits.

Perforated peptic ulcer was suspected, so an emergency exploratory laparotomy was performed finding a Forrest III perforated pyloric ulcer. Secondary peritonitis was drained and managed with Graham's patch. Despite the surgery, melena and hematemesis persisted, so a computed axial tomography (CT) and endoscopy of the upper digestive tract were performed, obtaining reports of a mass in the head of the pancreas and Forrest III giant duodenal bulb ulcer, respectively.

Proton pump inhibitors (PPIs) and antibiotic therapy against *Helicobacter Pylori* were initiated. The case of the patient was taken to the surgical board, which decided to perform pancreatoduodenectomy upon concluding that the surgical risk was low and that considering the pathological history, clinical profile, disease evolution and location of the tumor, this was probably a case of gastrinoma that was related to a multiple endocrine neoplasia syndrome (MEN) type 1, so a multifocal nature of the disease was unlikely.

Whipple procedure was performed with usual reconstruction, during which the head of the pancreas, the gallbladder, part of the duodenum, and the lymph nodes located near the head of the pancreas were removed; a mass involving the duodenum, the bowel, the gallbladder, and the lower part of the liver was found (Figure 1).

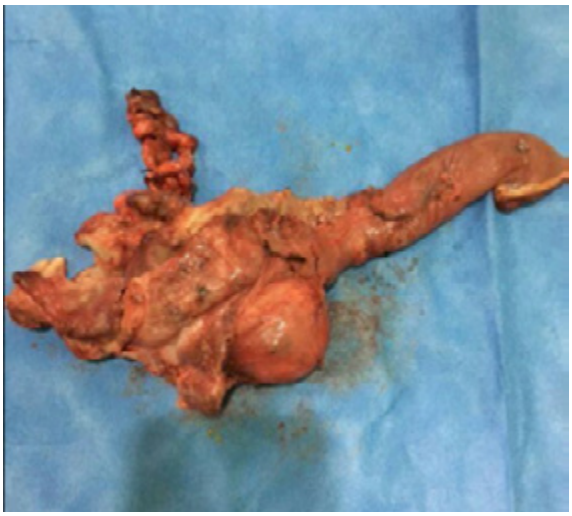

Figure 1. Surgical piece removed –mass involving the duodenum, the bowel, the gallbladder, and the lower part of the liver.

Source: Document obtained during the study.

When the mass was released, a giant ulcer was found in the duodenal bulb with abundant clots and 40% involvement of the duodenal wall and marked fibrosis. Additionally, a 4x3x3cm, regular, soft and apparently encapsulated mass was found on the head of the pancreas immersed in pancreatic tissue and with foci of hemorrhage when cut (Figure 2).

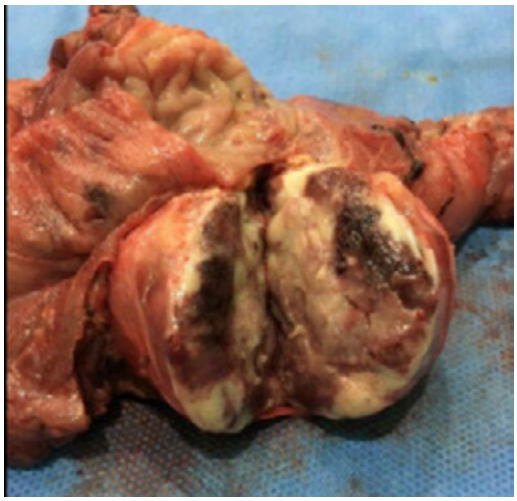

Figure 2. Surgical piece removed: mass in the head of the pancreas with hemorrhagic foci at cut.

Source: Document obtained during the study.

Biopsies were taken from the surgical samples, reporting a histological type of tumor suggestive of neuroendocrine neoplasm, with a solid acinar and trabecular pattern, confined to the head of the pancreas and consistent with gastrinoma. The surgery was successful, there were no complications and the patient had a proper recovery.

Due to administrative procedures, the patient was transferred to a tertiary care hospital in Bogotá D.C., where her treatment continued under the concept of the general surgery service of that institution; this situation prevented an adequate medical follow-up. The prognosis of the patient was considered as favorable in the long term, because besides the satisfactory results of the surgery, not having metastasis of the disease greatly increases survival.

DISCUSSION

The ZES is a pathology caused by a neuroendocrine tumor known as gastrinoma, which is usually located in the duodenum or pancreas. This produces an abnormal increase of the secretion of the hormone gastrin that leads to the hypersecretion of gastric acid in the digestive system in a secondary manner.

The exact incidence of ZES is unknown, but current literature suggests that between 0.1 and 3 people per 1 000 000 inhabitants develop the disease each year. (1) Most patients are diagnosed between 20 and 50 years of age and there is a higher incidence in the female sex.

Gastrinomas originate predominantly in the duodenum and only about 25% occur in the pancreas. (3) About 70-80% of gastrinomas are sporadic, but 20-30% are associated with multiple endocrine neoplasm type 1 (MEN1) with an overall survival rate similar to the sporadic form. (4)

The pathogenesis of gastrinomas remains unknown. Mutations in tumor suppressor genes (p53, retinoblastoma) and oncogenes are rare, and alterations in the m-TOR pathway and abnormal receptor tyrosine kinase activity in tumor growth have also been reported.

Exact cell of origin of gastrinomas remains a controversial issue. Ito *et al.* (5) suggest that pancreatic gastrinomas may originate from islets or duct cells. In the case of duodenal gastrinomas in patients with MEN1, these researchers suggest a higher level of proliferation of duodenal G cells, along with the loss of heterozygosity at the MEN1 locus (11q13) in the G cell. (5)

First of all, it is important to identify the patients with untreated gastric acid hypersecretion, as they can develop complications quickly, and they must be corrected before attempting to establish a diagnosis. (6)

The symptoms of ZES are related to the hypersecretion of gastric acid and the appearance of multiple ulcers distal to the duodenal bulb. In the past, most patients reported refractory peptic ulcers or presented with complications associated with hypersecretion of gastric acid, such as gastric perforation or penetration, bleeding in the digestive tract, and esophageal stricture.

Effective antisecretory drugs, such as PPIs and histamine H2-receptor antagonists (H2Rs), are now available and have led to a significant decrease of this form of presentation.

Symptoms related to ZES are highly variable and include abdominal pain (75%) due to a typical duodenal ulcer or gastroesophageal reflux (GER); diarrhea (73%), being the only manifestation in 3-10% of patients; weight loss (17%); and gastrointestinal bleeding (25%). (7)

Between 1 and 10% of patients with MEN1, especially in metastatic disease, have symptoms associated with a secondary hormonal syndrome (VIPoma, somatostatinoma, glucagonoma, ACTH, etc.) In general, MEN1 patients present with hyperparathyroidism (90-99%), primitive neuroendocrine tumor (PNET) (80-100%), and pituitary adenomas (50-65%) at different ages. The most common functional PNETs are ZES and insulinoma. Hyperparathyroidism can affect the activity of ZES and may even mask its presence if properly controlled, so it is important that all patients with MEN1 are tested for ZES. (5)

The importance of establishing a correct diagnosis of ZES lies in the fact that it requires special treatment. Despite the wide availability of diagnostic tests, there is still a 6-9 year delay in diagnosis. ZES should be suspected in patients with peptic ulcers, ulcers distal to the duodenum, and peptic ulcer disease.

The doses of PPIs and H2Rs antagonists may be different from those generally used in patients with idiopathic peptic disease and may require lifelong treatment. Therefore, in these patients, treatment directed at the gastrinoma should be considered, given its possible malignancy, and should include a periodic evaluation of the location of the tumor and considering surgical resection. (6)

The first study to be performed, if ZES is suspected, is fasting serum gastrin concentration (8), although it is controversial as the literature reports that many of the gastrin assays used worldwide may underestimate or overestimate fasting gastrin concentrations, therefore the results may lead to over- or under-diagnose ZES. In addition, the widespread use of PPIs can mask and delay diagnosis (9-10), as they interferes with the two tests needed to establish it, that is, the measurement of fasting gastrin levels and the evaluation of acid secretion, given their gastric acid suppressor action lasting up to one week.

Hypergastrinemia can be found in many conditions. (2) Hypo/achlorohydria is the most common cause and is frequently observed in patients with atrophic gastritis and chronic pernicious anemia and in whom fasting gastrin levels have been reported even <70 times their normal value or >1000 ng/L. (6)

Shah *et al.* (11) reported the possibility of rapidly developing acid peptic complications associated with ZES by suspending PPIs for at least one week; for this reason, Ito et al. (5) proposed that PPI treatment should be maintained at a lower dose. (6)

The diagnosis of ZES is achieved if the patient has gastrin levels >10 times its normal value or >1000 pg/mL with a gastric pH <2, or fasting gastrin >10 times its normal value with gastric pH <2 and a positive secretin stimulation test. (11,12)

Secretin stimulates the release of gastrin by gastrinoma cells and ZES patients have a significant increase in serum gastrin. In contrast, normal gastric G-cells are inhibited by secretin. A stimulation test with positive secretin in doubtful cases has a sensitivity of 94% and specificity of 100%; however, if the patient is taking PPIs, false positives could be obtained in 15-39% of the cases (12) and false negatives in 6-20%. (13)

This test may also be used to differentiate gastrinomas from other causes of hypergastrinemia, such as atrophic gastritis, kidney failure, or vagotomy. (3) The secretin stimulation test is performed by administering 0.4µg/kg secretin by rapid intravenous infusion for a minute; basal serum gastrin is measured twice before secretin administration and 2, 5, 10, and 30 minutes later. Serum gastrin usually reaches its maximum levels at 10 minutes. Several criteria have been proposed to define a positive test and the most accepted is an increase in gastrin levels of more than 120pg/mL above baseline fasting levels. (14)

On the other hand, 40-90% of gastrinomas are duodenal, both in patients with and without MEN1, and are often so small that they are not clearly seen by imaging tools. They are rarely found in other intra-abdominal sites including lymph nodes, stomach, mesentery, renal capsule, splenic hilum, omentum, ovary, liver, and bile ducts, and may be rarely found in an extra-abdominal location, such as the heart and the lungs. (5) Their location is crucial for surgical management of the organ, active surveillance or modern ablative methods. About 75-90% of gastrinomas are detected in the gastrinoma triangle. (8)

CT and nuclear magnetic resonance with contrast are the most widely used imaging studies; these tools detect 30-50% of primary gastrinomas of 1-2cm; however, their detection rate is low in lesions of size <1cm. Endoscopic ultrasonography has a high spatial resolution, so it is recommended as the method of choice for the detection of very small pancreatic tumors <7mm of diameter. (2,15)

PPIs are the drugs of choice due to their potency and prolonged action, allowing doses of once or twice a day. Intravenous PPIs are the drugs of choice when oral administration cannot be used. RH2 antagonists are also effective, but higher doses and frequencies are required. (5)

Long-term PPI treatment is well tolerated, with <0.1% side effects. Long-term effects of hypoachlorhydria include malabsorption of nutrients and the development of gastric carcinoids by hyperplasia of enterochromaffin cells (EC) of the gastric mucosa. (5)

In patients with sporadic ZES, curative surgery should be attempted if there is no disease that compromises life expectancy or increases surgical risk. The immediate post-operative survival rate is 50-60% and long-term survival rate is 35-40%. (5)

Considering the need for a complete exploration of the abdomen, especially the gastrino-

ma triangle area, the laparoscopic route is not recommended; however, it may be performed in selected cases, such as patients with localized distal pancreatic gastrinoma. (5)

ZES is a disease with a high morbidity and a survival rate of only 50%. The survival of patients, even with active tumors, is >25 years. (16) Between 60 and 90% of gastrinomas are associated with metastasis. Liver metastases are more frequent in patients with pancreatic gastrinomas, and their 10-year survival rate is 15-25%, being one of the most important prognostic factors. Lymph node metastases occur in 43-82% of patients, although lymphadenectomy is routinely recommended in patients with gastrinomas to improve prognosis, prolong recurrence time, and increase survival rates. Metastatic lymphadenopathy has not been shown to have a significant impact on survival. (4)

This case report corresponds to a patient with epidemiological and clinical characteristics frequently reported in the literature, but even so, this is a clinical case that contributes to scientific knowledge as it proposes considering ZES in the differential diagnosis of patients between 20 and 50 years of age who go to the emergency department due to chronic epigastric pain.

CONCLUSIONS

The ZES is a rare entity that requires high clinical suspicion to achieve diagnosis and allow an adequate treatment. Medical therapy is the standard management for patients with this syndrome and the first line of treatment is PPIs at high doses due to their potency and prolonged action. In patients with sporadic ZES without metastases, curative surgery should be attempted, whereas surgical management is not routinely recommended for patients with ZES associated with MEN1, as the multifocal nature of the tumors in this disorder prevents the healing of gastric hypersecretion.

This case report is highly relevant as it presents a confirmed diagnosis in the Colombian environment of a very rare disease, highlighting the importance of producing local scientific literature to improve its diagnosis and treatment. Therefore, it is proposed to consider ZES in the differential diagnosis of patients aged 20 to 50 years who go to the emergency department due to chronic epigastric pain.

The patient received a successful surgical management and achieved a satisfactory early recovery; however, since she was transferred to another institution for administrative reasons, it was not possible to follow her case during hospital stay and long-term medical evolution is unknown.

CONFLICT OF INTEREST

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CASE REPORTS
REPORTES DE CASO

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MALIGNANT AMELOBLASTOMA: MULTIPLE LOCAL RECURRENCE AND METASTASIS IN THE SCALP. CASE REPORT

Keywords: Ameloblastoma; Mandibular Neoplasms; Neoplasm Metastasis; Mandibular Osteotomy; Radiotherapy.
Palabras clave: Ameloblastoma; Neoplasias mandibulares; Metástasis de neoplasia; Osteotomía mandibular; Radioterapia.

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ABSTRACT

Introduction: Ameloblastoma is a neoplasm usually found in the maxilla and mandible with progressive intraosseous growth and a tendency to local recurrence. Malignant or metastatic ameloblastoma is one of its rare variants; a histopathological study is required for diagnosis confirmation. The common sites of dissemination are the lungs and cervical lymph nodes. The treatment is surgical and radiotherapy or chemotherapy are palliative options.

Case report: A case of malignant ameloblastoma was reported in a 39-year-old man with metastasis to the scalp and multiple local recurrences. The patient required mandibular osteotomy, multiple local resections, partial maxillary resection, free flap reconstruction, local scalp resection and free flap coverage. Due to a new relapse that could not be treated with a surgical approach, radiotherapy was ordered.

Discussion: The site most frequently affected by malignant ameloblastoma due to hematogenous dissemination is the lung. This paper reports the case of a patient with compromised scalp. To date, according to a search conducted, only one case report about this type of metastatic neoplasm has been published.

Conclusion: Histopathological diagnosis of ameloblastoma associated with surgical resection of the primary tumor and the metastatic tumor is the only approach that can offer disease-free survival.

RESUMEN

Introducción. El ameloblastoma es una neoplasia maxilomandibular con crecimiento progresivo intraóseo y tendencia a la recidiva local. El ameloblastoma maligno, o metastásico, es una de sus variantes raras y para su diagnóstico se requiere confirmación con estudio histopatológico. Los sitios frecuentes de diseminación son el pulmón y los ganglios cervicales. El tratamiento es quirúrgico y la radioterapia o quimioterapia son paliativas.

Presentación del caso. Paciente masculino de 39 años con ameloblastoma maligno que hace metástasis a cuero cabelludo y quien requirió osteotomía mandibular, resecciones locales, resección parcial de maxilar, reconstrucción con colgajo libre, resección local en cuero cabelludo y cubrimiento con colgajo libre. Por nueva recaída no susceptible de abordaje quirúrgico, se ordenó radioterapia.

Discusión. En ameloblastoma maligno por diseminación hematógena, el sitio más frecuentemente afectado es el pulmón. En el caso reportado se presenta un paciente con compromiso del cuero cabelludo, lo que lo hace inusual, pues, según la búsqueda realizada, hasta la fecha solo se encontró un reporte de caso publicado con este tipo de metástasis.

Conclusión. El diagnostico histopatológico del ameloblastoma asociado a una resección quirúrgica del tumor primario como del tumor metastásico es lo único que puede ofrecer una supervivencia libre de enfermedad.

INTRODUCTION

Ameloblastoma is a rare benign intraosseous neoplasm that originates in the odontogenic epithelium. It is of unknown etiology and is characterized by expansive growth with a tendency to recurrence. (1) This pathology represents 10% of maxillary and mandibular tumors, with equal affectation by sex, with average age of onset at 35 years. (2) 80% of ameloblastomas originate in the jaw and most often affect the posterior region, followed by the anterior region. The maxilla is the second most common site of presentation, while the involvement of the sinuses and nasal cavity is rare. (3)

The clinical picture of this pathology is characterized by a mass of slow growth that is not painful at the beginning, but complications such as dental loss, dental malocclusion, paresthesia, pain, soft tissue invasion, facial deformity, limitation of mouth opening, difficulty chewing and airway obstruction can be observed as size increases. (1) Diagnosis requires imaging studies, such as panoramic radiography and computed tomography (CT), as well as biopsy of the lesion for histopathological studies. (2)

Ameloblastoma rarely evolves into malignancy and develops hematogenous spread (3); although the benign histology of ameloblastoma is the same, the malignant histology is characterized by the presence of metastases and is associated with cytologic atypia with or without metastases. (3)

The current treatment is wide local excision, which should include adequate resection margins. Radiation and chemotherapy are reserved for palliative purposes only.

CASE PRESENTATION

Male patient of 39 years of age, mestizo, from Zapatoca (Santander, Colombia), high school graduate, freelance trader, non-smoker, with no relevant medical history nor previous ameloblastomas or neoplastic diseases. The subject had a history of 11 years of evolution, which began with the appearance of a mass of progressive growth in the left mandibular region, associated with pain in the mandibular and dental areas with left irradiation to the mastoid. The physical examination revealed an alteration of the facial contour due to the presence of a mass of about 7cm of anteroposterior diameter occupying the maxillary sinus and the left mandibular region.

A contrasted CT scan of the neck and paranasal sinuses was performed, identifying a mass involving the left mandibular region and the pterigopalatine fossa with associated bone destruction; a biopsy with histopathological study report was also performed, showing follicular and plexiform ameloblastoma. Taking into account the findings of the tomography and the reports from the pathologist, ameloblastoma was diagnosed without a doubt. Extension studies were also performed with chest CT and cervical lymph node puncture biopsy, ruling out distant disease. The case was discussed during a multidisciplinary meeting where a left partial mandibulectomy, mandibular condyle reconstruction with plaque and fibula free flap were established as management. The pathology of the surgical specimen showed tumor-free edges and surgical margins of 10mm (Figure 1).

The patient underwent medical check-ups and contrasted sinus and chest CT every six months during the first year and then every year. After three years of follow-up, in an outpatient control consultation, the patient was found in good general condition, with adequate Weber–Fergusson's approach facial scar, left peripheral facial palsy, adequate mouth opening, island flap of the skin with vital and integrated fibula, left hemifacial induration of soft tissues and scalp lesion in left temporal region that extended to the parietal region with anteroposterior diameter of 7cm, without further pathological findings.

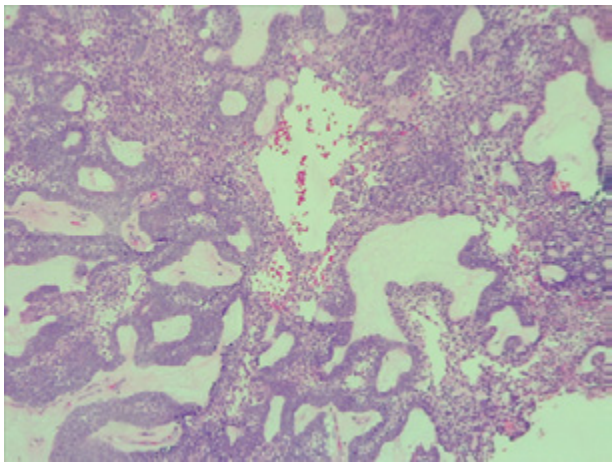

Figure 1. Histopathology of mandibulectomy with evidence of follicular ameloblastoma and odontogenic epithelial islands with peripheral columnar cells.
Source: Document obtained during the study.

Biopsy was performed on the lesion of the scalp revealing ameloblastoma metastases; the subject was taken to surgery with wide local excision and free flap reconstruction. Surgical specimen pathology confirmed metastatic ameloblastoma and reported tumor-free section borders with margins of 14mm (Figure 2).

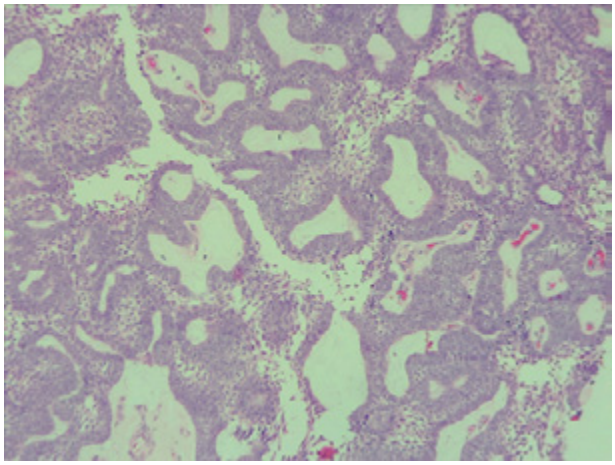

Figure 2. Histopathology study of resection of scalp metastases, follicular ameloblastoma without changes in the cell type of the primary tumor.
Source: Document obtained during the study.

The patient assisted to annual medical check-ups with contrasted CT scans; in the sixth year of follow-up, local relapse was observed, so he was taken to partial resection of the left maxilla with extension to infratemporal fossa and reconstruction with anterolateral thigh free flap. The pathology of the surgical specimen confirmed ameloblastoma and reported tumor free section borders with margins of 9mm.

Eleven years after the initial surgery, and after 3 surgeries, a new local relapse was discovered. On physical examination, the patient was found in good condition, with left facial palsy and mass in left masticator space with extension to hard and soft palate, in addition to left submandibular ganglion conglomerate. Contrasted CT showed a mass that involved the left masticator space, lobed, of heterogeneous density with extension towards the skull and average cranial fossa of 36.7x53.6x42mm in anteroposterior section (Figures 3 and 4); biopsy and histopathological study confirmed ameloblastoma.

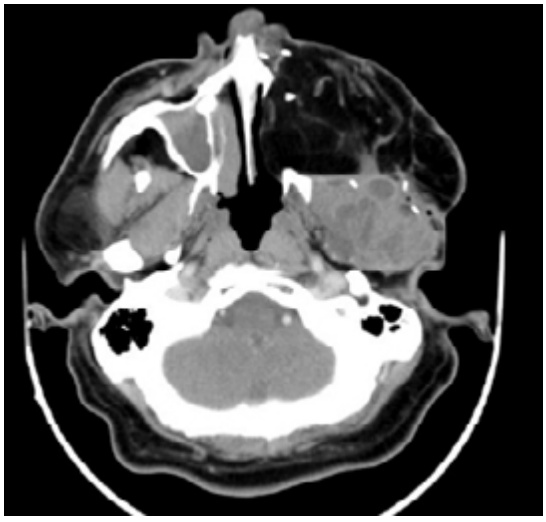

Figure 3. Computed tomography of paranasal sinuses with evidence of heterogeneous and hypotensive mass in the left masticator space of lobed contours with dimensions of 36.7x53.6x42.7mm.
Source: Document obtained during the study.

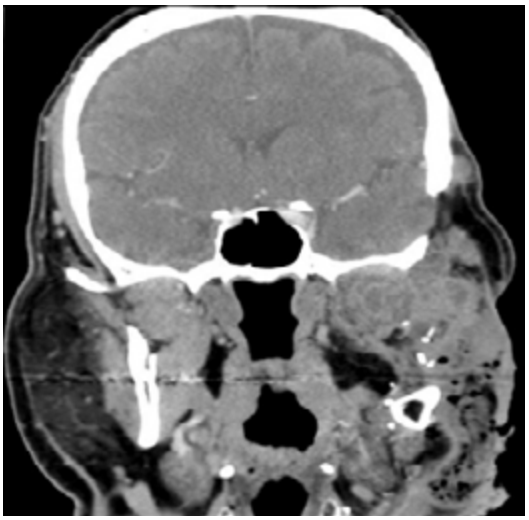

Figure 4. Computed tomography of paranasal sinuses showing heterogeneous mass in left masticator space with extension to the base of the skull and middle cranial fossa.
Source: Document obtained during the study.

The patient was assessed by a multidisciplinary team, which concluded that it was not possible to perform new surgical interventions due to the extent of the disease; instead, palliative management with intensity-modulated radiation therapy (IMRT) was ordered. After simulation, planning and delimitation of the area to irradiate, a total of 66 Gray (Gy) in fractionation of 2 Gy was indicated, for a total of 33 sessions during 44 days. During session 12, the patient presented an episode of mucositis treated with a master formula for topical use with appropriate resolution, allowing the radiotherapy to continue without suspending it.

Two months after completing the radiotherapy sessions, the patient was in good general condition but reported xerostomy; the physical examination showed clinical decrease of the mass in the masticator space and palate with changes in the left hemifacial and cervical skin secondary to radiodermatitis. There were no clinical signs of lesion progression.

Follicular cystic ameloblastoma and plexiform ameloblastoma were identified in all the pathologies analyzed since the initial biopsy and in the different surgical specimens (Figures 3 and 4), both from the local resections and the scalp lesion. No genetic profile of BRAFV600E mutation was performed, since it was not requested during the period when the samples were processed and it is not a routine test performed in the institution.

Although the surgeries performed were useful to completely resect the tumor with negative and proper surgical margins and without failures in the surgical technique or in the choice of the surgical approach, the ability of ameloblastoma to recur was demonstrated.

DISCUSSION

Ameloblastoma is a benign but aggressive intraosseous odontogenic neoplasm with progressive growth, large local expansion, bone destruction, dental resorption and a high tendency to recurrence. (1-3) Although rare, with an annual incidence in the general population of 0.5 cases per 1 000 000 inhabitants, ameloblastoma is the most common odontogenic tumor, excluding odontomas. (4,5) Peak incidence is between the fourth and the fifth decade of life, with an age range of 8 to 92 years and no sex predilection. (4,6,7) For cases associated with BRAFV600E mutation, the mean age of diagnosis is 34, with a more aggressive presentation. (8) 80% of all ameloblastomas are found in the mandible, most frequently in the posterior region, followed by the anterior portion of the mandible, the posterior maxillary segment and the anterior maxillary segment (4,6,9-11) as observed in this case, where the entire left mandible was involved with extension to the ipsilateral pterygopalatin fossa, associated with bone destruction.

Ameloblastoma presents as a slow-growing, expansive lesion, which may exhibit late, accelerated growth. (12) As size increases,

it is associated with complications such as dental loss, dental malocclusion, paresthesia, pain, invasion of soft tissues, facial deformity, limitation of mouth opening, difficulty chewing and airway obstruction.

Radiologically speaking, it is common to find a multilocular radiolucent image of soap bubble or honeycomb appearance in the cortex, buccal and lingual expansion, and resorption of the involved dental roots. (13,14)

The diagnosis of ameloblastoma is achieved based on physical examination, including examination of the head and neck and imaging studies, which in turn include panoramic radiography, contrasted computed tomography and biopsy of the lesion.

The pathological types of this disease can be varied: solid, multicystic, unicystic, desmoplastic and peripheral ameloblastoma. (15,16) Solid and multicystic ameloblastomas have been identified as the most aggressive subtype, with a high rate of recurrence after local excision. (17) The most common histological type is the follicular, followed by the plexiform; other histological types are the acanthomatous, granular and basaloid. (1) The case presented here had a histopathological diagnosis of follicular and plexiform ameloblastoma, which is the most frequently reported. (1)

Since 2015, the World Health Organization classification system made a clear distinction between ameloblastoma, malignant ameloblastoma and ameloblastic carcinoma. (1) Malignant ameloblastoma differs from ameloblastoma in the presence of distant metastases, although both have the same benign histology. A metastatic malignant ameloblastoma tumor, by definition, should have the same histological characteristics as a primary mandibular tumor. (18)

The histopathological comparison between the different surgical specimens of the reported case, which had the same characteristics between samples, was fundamental for the diagnosis of malignant ameloblastoma. Ameloblastic carcinoma combines some characteristics of ameloblastoma and cytological atypia with or without metastases. (18)

Most ameloblastomas have predominantly follicular and acanthomatous patterns and are rarely mistaken for other lesions if adequate tissue is provided for histopathological examination. Desmoplastic ameloblastoma may cause some initial confusion, but knowing about this unusual and particular pattern that occurs in a jaw tumor should not cause diagnostic difficulties as long as adequate material is available for the pathologist to study. (19)

Since there is a time gap between the diagnosis of the primary tumor and the occurrence of metastasis, whether regional or distant (10 to 12 years on average), at least one chest x-ray per year is recommended for follow-up because it is the most frequent site of distant metastasis, in addition to clinical progression and imaging studies of the neck and primary site of surgical resection. (20)

In the US, the annual incidence of malignant ameloblastoma and ameloblastic carcinoma is 1.79 cases per 10 000 000 inhabitants. (1) In a literature review conducted by the Mayo Clinic of publications made between 1923 and 2009, only 101 possible cases of metastatic ameloblastoma were identified. (21) According to Houston et al. (22), most reported cases of metastatic ameloblastoma suggest hematogenous or lymphatic spread. Another mechanism of metastasis described by Vorzimer & Perla (23) is the aspiration of tumor cells from the primary lesion during surgery, which may contribute to pulmonary, lymphatic, or hematogenous spread. The most common site of ameloblastoma metastasis is the lung (72.7%), followed by cervical lymph nodes, brain, and bone. (23) The scalp is a rare site of

metastasis of malignant ameloblastoma: only one case has been reported in the literature. (24)

The primary and optimal treatment for ameloblastoma is surgery, in other words, total excision of the lesion with radical resections and margins of 1.5cm to 2.0cm. (25) The surgical options for tumors in the jaw are hemimandibulectomy, segmental mandibulectomy or mandibulectomy; for very small, well-defined lesions that can be resected through the oral cavity, marginal mandibulectomy is indicated, but curettage of the lesion is not useful because lesions always recur; for lesions in the upper jaw, depending on the area involved and the extent of the tumor, infrastructure, medial, partial, subtotal or total maxillectomy are indicated (26); cystic ameloblastomas, which have less aggressive biological behavior and less recurrence compared to multilocular ameloblastomas, can be treated by decompression and subsequent enucleation of the lesion. (27)

Treatment of metastatic lesions is not yet uniform, as sometimes surgical resection is not possible due to their anatomical location or extension; furthermore, no clear chemotherapy or radiotherapy protocols have been established for these lesions. (28) So far, surgical treatment is the only one option that increases disease-free survival.

The effectiveness of adjuvant treatment is not clear because few cases have been described. The case reported by Jain et al. (29) showed partial response of an ameloblastoma with pulmonary metastases treated with pazopanib.

In the multivariate analysis of Yang et al. (30), in 87 cases of recurrent craniofacial ameloblastoma, the associated risk factors for recurrence and ameloblastic carcinoma were evaluated. The conclusion was that the most important factors are size and stage of the tumor: stage I, maximum tumor diameter ≤6cm; stage II, maximum tumor diameter >6cm or tumor invading the maxillary sinus, orbital floor or soft tissues; and stage III, tumor invading the base of the skull or metastatic tumor in the cervical lymph nodes. Tumors >6cm and involving soft tissues and adjacent anatomical structures are associated with early recurrences, regardless of the surgical treatment. (30)

Freignani et al. (31) examined the clinical, pathological and histological findings of 121 patients treated in a single institution and diagnosed with ameloblastoma from 1953 to 2003. The study aimed to establish predictors of recurrence, and the results suggested that the presence of a multilocular lesion with rupture of the basal cortical bone and a histological follicular tumor have poor prognosis.

The case reported here allows approaching a pathology that, although rare, has great impact on the health state of the patients who have it due to its tendency to local recurrence and distant involvement, making ameloblastoma a complex entity. For this reason, a clear, accurate and timely diagnosis of ameloblastoma, paying utmost attention to its histopathological characteristics and complete radical surgical resection with oncological resection margins, is considered as the best option for adequate survival in patients presenting with this rare entity. Curettage of the lesion only or multiple resections due to recurrence increase the risk of metastasis.

Surgery is the best alternative for the treatment of metastases; even though chemotherapy and radiotherapy have also been described, they have been recommended for palliative management. For lesions that cannot be treated surgically, radiotherapy and chemotherapy are the only options currently available; however, the recurrence rate with these techniques is high.

Here, in consequence, the treatment currently available for ameloblastoma was used, which consists of extensive surgical resection of the initial

tumor, as well as of recurrent tumors and distant lesions. When new resections cannot be done, implantation of radiotherapy with IMR technique is used, which was the case of this patient.

CONCLUSIONS

Malignant ameloblastoma is a rare entity and its timely histopathological diagnosis, associated with radical surgical resection of both the primary tumor and the metastatic tumor, is the only option that can offer disease-free survival with adequate quality of life. Non-surgical alternatives, such as chemotherapy and radiotherapy, are only recommended as a palliative option for lesions that cannot be approached surgically or in unresectable tumor recurrence.

The case of malignant ameloblastoma with scalp metastases presented here, which is one of the few reported in the medical literature, stresses the need for adequate treatment planning, timely and regular follow-up in all patients with this pathology, as well as the implementation of the genetic profile in the histopathological study, which allows predicting a more aggressive behavior of this entity. It is worth noting that multiple surgical interventions or recurrences are a risk factor for malignant or metastatic ameloblastoma.

CONFLICT OF INTERESTS

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CASE REPORTS
REPORTES DE CASO

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GIANT CELL TUMOR OF THE DORSAL VERTEBRAE. CASE REPORT

Keywords: Carcinoma; Giant Cell; Dyspnea; Thorax; Lung Neoplasms.
Palabras clave: Células gigantes; Disnea; Tórax; Neoplasias pulmonares.

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ABSTRACT

Introduction: Giant cell tumors are rarely observed in the thoracic vertebrae. They appear between the ages of 20 and 50, more often in women. The purpose of this case report is to make known the clinical characteristics, the presentation and the treatment used to solve this pathology.

Case presentation: 37-year-old female patient who presented a clinical picture of seven days of dyspnea, cough with white expectoration, high temperature, paraparesis, loss of control in the sphincters and weight loss. High-resolution computed tomography of the thorax showed a right paraspinal mass located in posterior mediastinum at T8-T9 level. Surgical excision of the tumor was decided by right posterolateral thoracotomy at the seventh intercostal space and free surgical margins. The histopathology report described giant cell tumor grade II. The patient did not require chemotherapy and had a satisfactory evolution.

Discussion: This case has a non-specific presentation, as it shows evidence of pain, tumor and functional impotence of the involved region. Surgery is the best treatment and consists of tumor excision, leaving wide margins to prevent recurrences.

Conclusions: Giant cell tumors involving the lungs and thoracic vertebrae are underdiagnosed due to their nonspecific symptoms and the limited literature currently available.

RESUMEN

Introducción. Los tumores de células gigantes son de presentación rara en las vértebras torácicas: ocurren entre los 20 y 50 años y con más frecuencia en mujeres. La presentación de este caso tiene por objeto dar a conocer las características clínicas, la presentación y el tratamiento que se tomó para la resolución de esta patología.

Presentación del caso. Paciente femenino de 37 años quien presentó cuadro clínico de siete días de disnea, tos con expectoración blanquecina, alza térmica, paraparesia, pérdida de control en esfínteres y pérdida de peso. En la tomografía computarizada de tórax de alta resolución se evidenció masa localizada en el mediastino posterior, paravertebral derecha, a la altura de T8-T9. Se decidió resección quirúrgica del tumor por toracotomía posterolateral mayor derecha a nivel de séptimo espacio intercostal y márgenes quirúrgicos libres. El estudio histopatológico reportó tumor de células gigantes grado 2. La paciente no requirió de quimioterapia y tuvo evolución satisfactoria.

Discusión. La presentación de este caso es inespecífica: se evidencia dolor, tumor e impotencia funcional de la región comprometida. El tratamiento óptimo es el quirúrgico, que consiste en la resección del tumor dejando amplios márgenes para evitar las recurrencias.

Conclusiones. Los tumores de células gigantes con afectación en pulmón y vértebras torácicas son sub diagnosticados por la sintomatología inespecífica que presenta y por la poca literatura que existe en la actualidad.

INTRODUCTION

Although locally aggressive, unpredictable and rare in bone tissue, giant cell tumors (GCT) are increasingly common today, mostly affecting young adults, especially women, between 20 and 50 years of age, with a higher incidence in the Eastern population. GCTs account for 3-5%

of bone tumors and 20% of benign tumors. (1-3) In Latin America they are more common in women and are more frequently located in the epiphyseal regions of long bones; however, they can also affect small bones of the hands and feet or, rarely, flat bones such as the skull. (4) This type of neoplasm involves mainly femoral condyles, tibial plateau, humerus head and distal radius but it could also be found in the vertebrae. If it manifests, the lumbar and sacral regions are involved. (5)

X-rays show eccentric osteolytic metaphyseal lesion, whose edges may be either limited by sclerotic margin or ill-defined with destruction of the cortex and invasion of neighboring structures. GCT do not usually lead to periosteal reaction nor show trabeculation inside.

Other diagnostic methods, such as nuclear magnetic resonance, may be used to assess the tumor and possible soft tissue involvement. (6) Surgical treatment is necessary in all cases due to a possible metastatic disease depending on several risk factors still under study (7), but its high rate of recurrence, influenced both by the expression of certain genes and the neoplastic grading on the Campanacci scale (8), means that there is no consensus about its management. Incomplete resection of the tumor when the cortex is destroyed with invasion of nearby tissues causes recurrence in 2% to 25% of cases. People with GCT rarely develop lung metastases. (9)

CASE PRESENTATION

37 year-old female patient, mestizo, from Quevedo (Ecuador) and low socioeconomic level who entered the emergency service after being transferred from another health center of less complexity. Relevant medical history includes a spinal tumor six months earlier.

The patient presented with a clinical picture of seven days of evolution characterized by dyspnea during moderate efforts, cough with white expectoration, unquantified fever, loss of sensitivity in lower limbs (paraparesis), loss of sphincter control and weight loss. Physical examination revealed blood pressure of 110/60 mmHg, heart rate of 104 beats per minute, respiratory rate of 20 per minute, temperature of 38°C and oxygen saturation of 95%. Pale fascies, dry mucous membranes, symmetrical thorax, lung fields with abolished sounds in right pulmonary base, rhythmic and tachycardic heart sounds, atrophy of the muscles in the lower limbs, loss of sensitivity and soft, depressible and not painful abdomen on palpation were also observed. Complementary blood tests, tumor markers —considering her six-month history of spine tumor— and diagnostic imaging were requested (Table 1).

Table 1. Blood tests on admission.

Blood tests	Results
Leucocytes	7.04
Neutrophils	74%
Lymphocytes	16.5%
Red blood cells	3.20 M/uL
Hemoglobin	9 g/dL
Hematocrits	27.2%
Platelets	381
CA 72-4	5.18 UI
CA 19-9	4.05 U/mL
CA 125	20.64 U/mL
Alpha-fetoprotein	2.94 ng/mL
Carcinoembryonic antigen	1.32 ng/mL

Source: Own elaboration.

All blood tests were within normal parameters. Diagnostic imaging (Figure 1) showed a right paraspinal tumor in posterior mediastinum at the level of the eighth and ninth thoracic vertebra,

with calcifications involving bone structures, posterior arch and expansive osteolytic lesions; a decrease in the vertebral bodies of T8-T9 was observed in bone window.

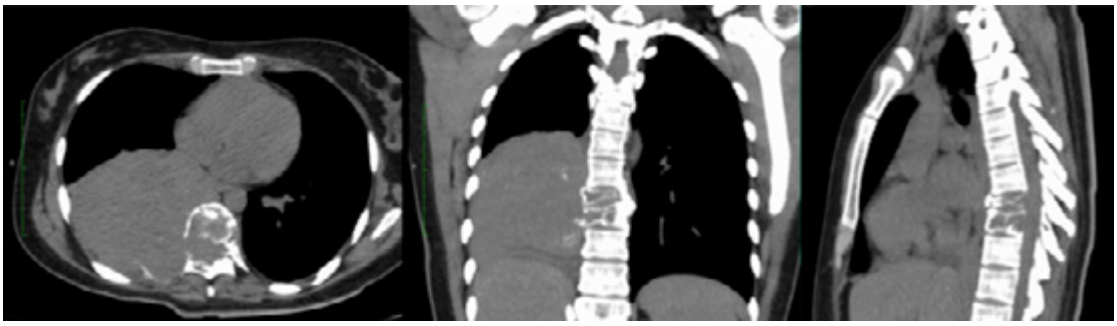

Figure 1. High resolution computed tomography (CT) of the thorax in axial, coronal and sagittal planes.
Source: Document obtained during the study.

A magnetic resonance (MRI) of the dorsal spine was requested (Figure 2), revealing a right paravertebral mass of 9.9x10x9.4 cm that caused an osteolytic lesion in the vertebral body and lateral antlers of T8 and T9 topography, infiltrating through an intervertebral foramen into the medullary canal, and expansive lytic lesion in the topography of the posterior region of the ninth costal arch diaphysis.

Based on the above data, the patient was scheduled for surgery, and entered the operating room for thoracotomy. During the perioperative period, right posterolateral thoracotomy was performed at the level of the seventh intercostal space; dissection was performed by planes until reaching the pleural space where a tumor was observed in the lower right pulmonary lobe with limited edges that involved the posterior part of the seventh to the tenth rib and T8-T9 vertebral bodies. A right inferior lobectomy plus partial resection of the costal wall, which includes the ribs mentioned above, was performed (Figure 3).

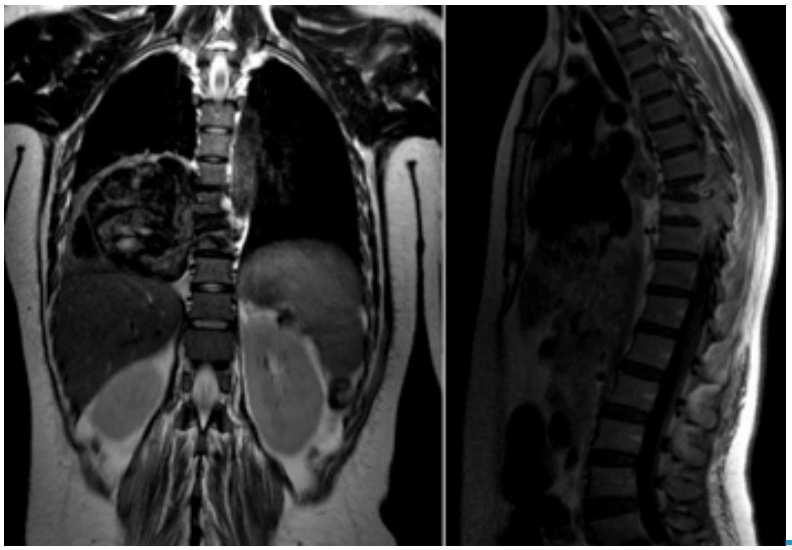

Figure 2. MRI of the dorsal spine, T2-weighted coronal plane and T1-weighted sagittal plane.
Source: Document obtained during the study.

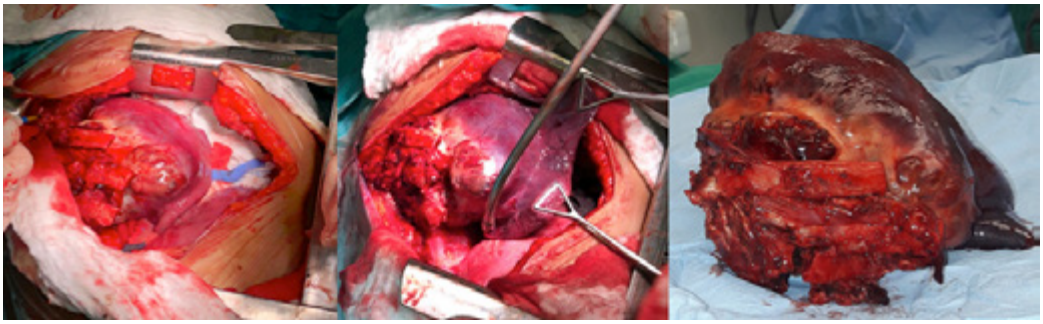

Figure 3. Resection of the seventh, eighth and ninth rib plus right inferior lobectomy.
Source: Document obtained during the study.

Skeletonization of vertebral bodies T8-T9, lower vertebral endplate of T7 and upper vertebral endplate of T10 was performed, revealing the involvement of the T8-T9 vertebral bodies and disc space. Resection of vertebral bodies T8-T9, disectomy in T7, T8 and T9, mesh placement with bone substitute over corpectomy space, closing of thoracic wall by planes and placement of polypropylene mesh (Figure 4) at the level of wall defect by costal resections were also performed.

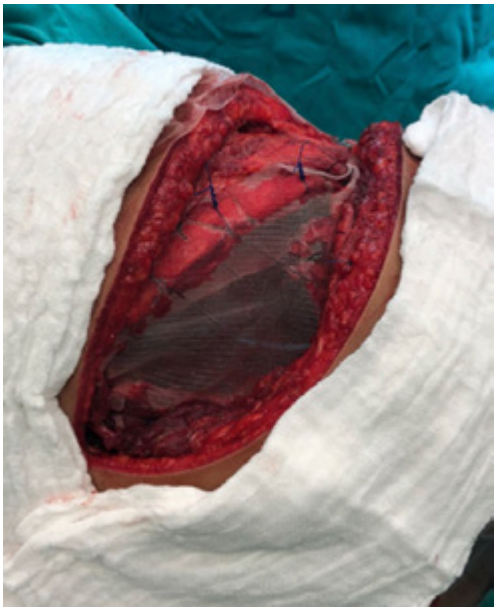

Figure 4. Placement of polypropylene mesh on wall defect after costal resections.
Source: Document obtained during the study.

After the procedure, the woman entered the intensive care unit hemodynamically unstable and with vasopressor support, no evidence of bleeding and mechanical ventilation with PaO2/FiO2 ratio of 350 and metabolic acidosis. On the fourth post-operative day, the patient was extubated; she woke up without vasopressor support, although she did not move actively her limbs and sat with assistance. The histopathology report described neoplastic proliferation characterized by mononuclear stromal cells, some with atypia, low mitotic count in stroma and multinucleated giant cells with 10 to 50 nuclei, reactive metaplastic bone and lymphovascular invasion. Immunostaining was positive for Ki-67 in 5% of stromal cells; CD 68 immunostaining was positive in giant cells. Vimentin was positive in stromal cells and giant cells; the histopathological diagnosis was locally aggressive GCT grade II.

On the tenth post-operative day, the patient was taken to intermediate care, where she remained calm, awake, with symmetrical thorax, surgical wound in good condition, hypoventilated pulmonary fields in right pulmonary base, paraparesis in lower limbs, muscle strength 2/4, and bilateral and hyporeflective anesthesia. A control CT was taken (Figure 5) showing pulmonary expansion and small amounts of pleural fluid with elevation of the right hemidiaphragm.

Furthermore, 14 days after inpatient surgery, a chest x-ray was performed (Figure 6), showing

expanded right lung, small pleura effusion and adequate ossification process in the corpectomy space where the mesh was located. After six months, at the time of this publication, the patient fully recovered her strength, had full sensitivity and performed her daily activities.

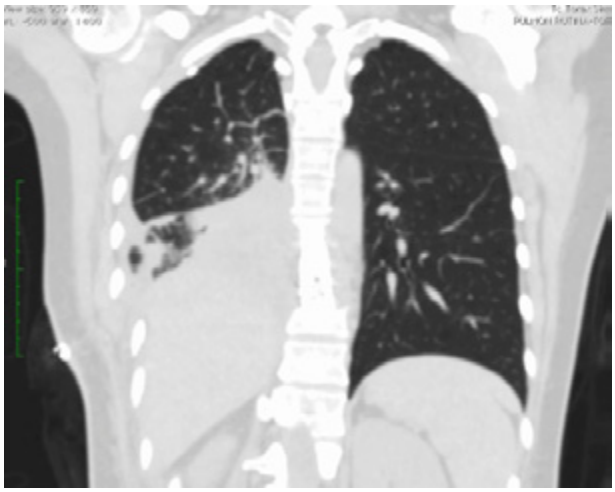

Figure 5. Control CT scan that shows lung parenchyma window 10 days after surgery.
Source: Document obtained during the study.

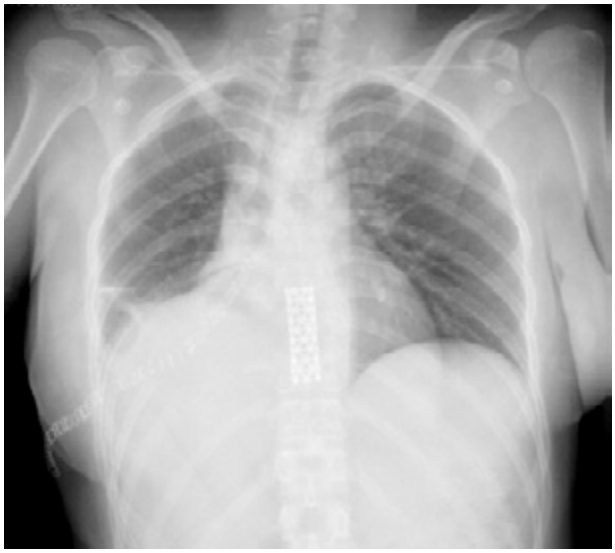

Figura 6. Anteroposterior chest x-ray 14 days after surgery.
Source: Document obtained during the study.

DISCUSSION

GCTs of bone are rare and aggressive lesions (10) that mainly affect the metaphysis of long bones; they may involve the lumbar and sacral vertebrae on specific and infrequent occasions. According to sex and regarding the contextual approach in Latin America, this type of tumors affects more frequently women between 30 and 40 years of age. When the cortical bone is involved, it can also affect the soft tissues near the lesion due to continuity (11), and cause possible metastasis in <2% of the cases. (12,13)

This was the case of a 37-year-old patient with a tumor mass in the thoracic vertebral bodies 8 and 9 of six month evolution, with invasion to the lower lobe of the right lung and to the diaphysis of the ninth rib. In this case, tumor activity is still under study considering that there is still pain in the area and rare consequences such as alterations in the functional performance of the affected limb. (14) Predominant symptomatology may include pain or neurologic deficit, which were observed in this patient as she suffered from back pain and lower limb paraparesis. However, as stated in other studies, it is evident that pain may last for a long time, even up to a year later. (15) The approaches reported in the literature describe total tumor resections (16), based on the Capanacci system, as the most frequently implemented. It consists of identifying and performing 1) intralesional curettage of intramedullary lesion confined to the bones, 2) wide excision of the cortex and 3) rupture of cortical bone.

This classification is necessary because treatment consists of intralesional excision by curettage plus bone graft and cement at stages I and II, and en bloc resection and reconstruction at stage III. (17) According to Sanerkin, GCTs are classified as follows:

Grade – I. Benign. Normal mitotic count, less than 5 mitoses per field, little or no nuclear atypia, no neoformed or scarce vascular tissue and no sarcomatoid cells are evident.

Grade II. Benign. Some abnormal mitoses, more than 5 mitoses per field of greatest increase, moderate nuclear atypia, moderate vascularization and absence of sarcomatoid cells.

Grade III. Malign. Abundant abnormal mitosis and nuclear atypia, great vascularization and presence of sarcomatoid cells.

Finally, the reported patient was diagnosed with GCT grade II according to the histological classification scale, identifying moderate benignity, vascularization and absence of sarcomatoid bodies. (18)

For the case described here, based on CT findings, this was a stage III tumor with ruptured cortical cells, so radical corpectomy was performed with complementary stabilizations plus en bloc resection of the tumor. Refai *et al.* (19) published a similar case in which the patient was treated for the first time with arterial embolization of the hypervascular region observed in angiography. Then, the patient underwent a transthoracic corpectomy in T7 in one stage, followed by reconstruction and stabilization of the anterior spine. According to the pathology report, this was a GCT grade II according to the Sanerkin classification, so the decision taken was the best for this case; in addition, radiotherapy was not required because the sample yielded a benign result.

On the other hand, it is worth mentioning that intervention variables were analyzed taking into account a series of GCT in adults treated with surgery plus radiotherapy and surgery alone, showing better prognosis. (20) Complementary radiotherapy should be considered, since the possibility of recurrence is 46% in patients who use this technique compared to 45% with radiotherapy only. There is a report with favorable results in which the lesion was treated with cryosurgery combined with radiotherapy. (21)

CONCLUSIONS

GCTs are rare in the dorsal vertebrae. In some cases, when there is cortical involvement, metastasis can develop and complicate the patient's prognosis; therefore, a timely diagnosis is required to improve it.

The treatment for GCT should be determined based on the patient's clinic and the radiological study according to the Campanacci classification and also to the histological study according to the Sanerkin classification. Recommendations are en bloc resection for benign tumors, and resection plus radiotherapy for malignant tumors.

CONFLICT OF INTEREST

None stated by the authors.

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CASE REPORTS
REPORTES DE CASO

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INTUSSUSCEPTION SECONDARY TO INFLAMMATORY MYOFIBROBLASTIC TUMOR OF THE SMALL INTESTINE. CASE REPORT

Keywords: Intussusception; Intestinal Obstruction; Intestinal Neoplasm.
Palabras clave: Intususcepción; Obstrucción intestinal; Neoplasia intestinal.

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ABSTRACT

Introduction: Intussusception occurs when part of the intestine slides into an adjacent intestinal segment. Inflammatory myofibroblast tumor is a rare cause of this condition, and is observed in 5% -16% cases in adults.

Case presentation: A 41-year-old woman presented with abdominal pain and distension. A exploratory laparoscopy was performed, finding ileocolic intussusception into the transverse colon. Due to uncontrollable bleeding, the procedure was converted to laparotomy; resection and latero-lateral ileocolic anastomosis were performed. Histopathology reported inflammatory myofibroblastic tumor, with a favorable postoperative evolution. The patient was discharged on the sixth postoperative day.

Discussion: When located in the small intestine, 57% of the tumors that cause intussusception are benign, including the myofibroblastic tumor in this patient. The symptoms and signs associated with this neoplasm are cramp-like abdominal pain, nausea and vomiting. Although imaging studies may lead to suspect this diagnosis, in most cases it is made intraoperatively. Surgical resection of the affected intestinal segment is curative, with favorable prognosis.

Conclusions: This case is considered as a rare cause of intussusception. It had a benign course and is still under study since its pathophysiology has not been fully understood.

RESUMEN

Introducción. Se denomina intususcepción a la introducción de un segmento intestinal a otro distal, siendo esta la causa posterior del tumor miofibroblástico inflamatorio en el 5-16% de los adultos.

Presentación del caso. Paciente femenino de 41 años con presencia de dolor y distensión abdominal. Se practica exploración quirúrgica laparoscópica, observando intususcepción ileocólica hasta colon transverso. Por sangrado no controlable se realiza conversión a laparotomía, se reseca y se realiza anastomosis ileocólica latero-lateral. La histopatología reporta tumor miofibroblástico inflamatorio, con evolución postquirúrgica favorable. Se da de alta al sexto día postquirúrgico.

Discusión. En el intestino delgado, 57% de los tumores que originan intususcepción son benignos, como el tumor miofibroblástico que presentó la paciente reportada. Los síntomas y signos de esta neoplasia son dolor abdominal tipo cólico, náusea y vómito. Aunque los estudios de imágenes pueden dar una sospecha del diagnóstico, en la mayoría de los casos se hace intraoperatorio. La resección quirúrgica del segmento intestinal afectado es curativa, con pronóstico favorable.

Conclusiones. El presente caso representa una causa poco frecuente de intususcepción intestinal, de curso benigno, la cual continúa en estudio ya que no se ha logrado entender por completo su fisiopatología.

INTRODUCTION

Intussusception occurs when a part of the intestine and its mesentery slide into an adjacent intestinal segment. (1) It is most frequently observed in children, and only 5% to 16% of the cases occur in adults. (2) Currently, this neoplasm represents 1% of all causes of intestinal obstruction. (3,4)

Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal neoplasm caused by the multiplication of spindle cells in variable inflammatory patterns. (5-8)

Although the etiology of intussusception is unknown, previous surgeries, infections, trauma, immune reactions, radiation therapy and steroids have been suggested as probable causes. (9-11) The onset of this condition in 52% of cases is associated with malignant tumors and exacerbation of acute abdominal pain; in addition, data on pathological involvement have been obtained in the small intestine and, less frequently, in the colon and the gastroduodenal portion. Imaging studies help to make the diagnosis; however, exploratory laparotomy supports the diagnosis in 68% of cases. (12,13) It is worth mentioning that it can be confused with cancer due to similar clinical and imaging characteristics, causing difficulties in its subsequent treatment. (5,12)

IMTs that extend through the gastric wall and into neighboring organs such as the esophagus, duodenum, pancreas, peritoneal cavity, and liver are known as inflammatory infiltrates and simulate malignancy in endoscopy and imaging. (7,13) Regarding management, despite pathological findings, it has been proven that complete resection is possible; this is the treatment of choice and is considered as a cure as symptoms and even recurrences tent to decrease. (6,14-16)

CASE PRESENTATION

Female patient of 41 years, of mixed race, from the rural area of Babahoyo (Ecuador), housewife and of a low-income household who consulted for pain and abdominal distension associated with vomiting, constipation and diarrhea of three months of evolution prior to admission.

No relevant medical history was reported. Initial care provided found normal vital signs, and physical examination revealed general abdominal pain with response to deep palpation in mesogastrium and hypogastrium, abdominal distention and increased hydro-aeric sounds, accompanied by nausea that led to vomiting and diarrheic stools. Finally, laboratory results showed anemia and leukocytosis without additional blood tests.

Anteroposterior abdominal x-ray, in standing position and supine decubitus position, showed accentuated distension and dilatation of thin intestinal loops and hydro-aerial levels (Figure 1).

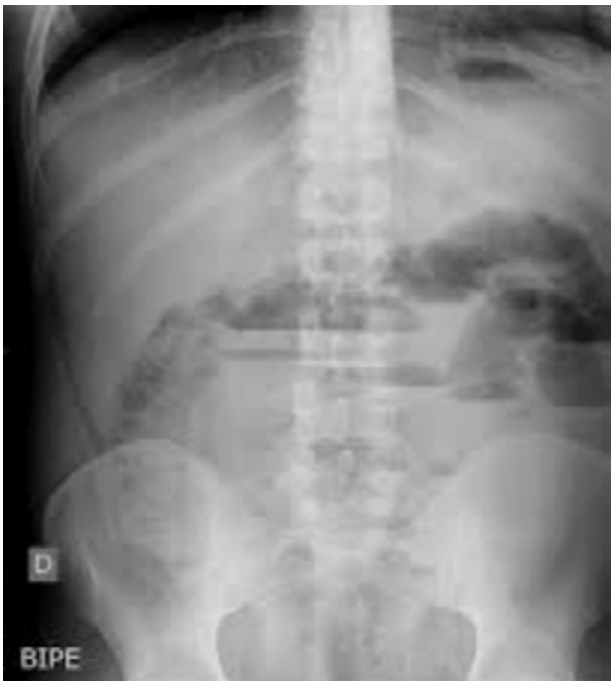

Figure 1. X-ray of abdomen in standing position showing thin bowel loops with hydro-air levels.
Source: Document obtained during the study.

Likewise, abdominal ultrasound reported concentric thickening of the wall of the ascending and transverse colon with preservation of the visualization of its layers (Figure 2).

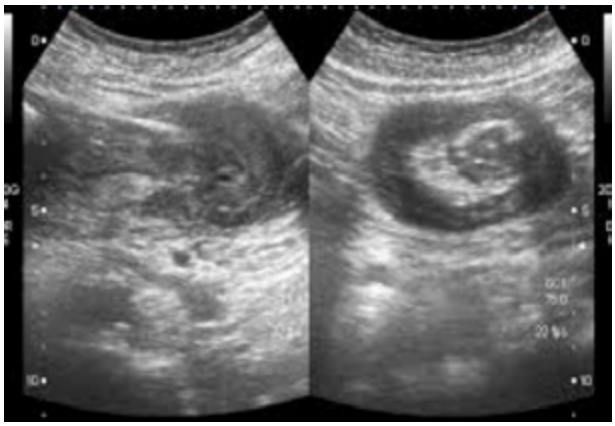

Figure 2. Concentric thickening of the colonic wall compatible with endoluminal tumor or intussusception.
Source: Document obtained during the study.

Diffuse wall edema of the transverse ascending colon and splenic angle, image of invaginated appearance and space-occupying lesion at this level can be observed in abdomen and pelvis tomography (Figures 3 and 4).

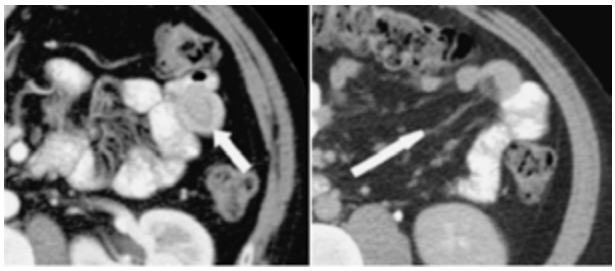

Figure 3. Crescent in doughnut sign. Imaging of oral phase showing enteroenteric intussusception. The arrow points the external muscularis of intussusception.
Source: Document obtained during the study.

Based on the result of the admission examination, a diagnostic exploratory laparoscopy was performed to identify the location, causality and correct procedures of the treatment. During surgery, dilation of the small intestine was observed and the diagnosis of ascending intestinal intussusception was confirmed; due to uncontrollable bleeding, the procedure was converted to laparotomy (Figures 5 and 6).

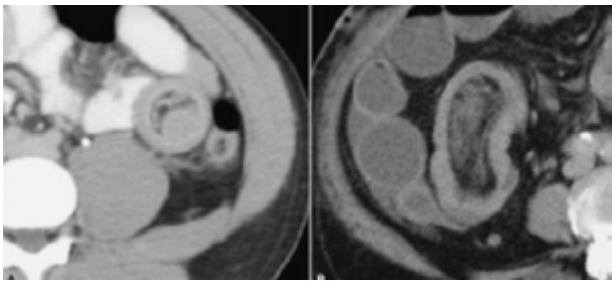

Figura 4. A. Sausage pattern with alternate areas of low and high attenuation. B. Intraluminal lesion as the lead point of intussusception.
Source: Document obtained during the study.

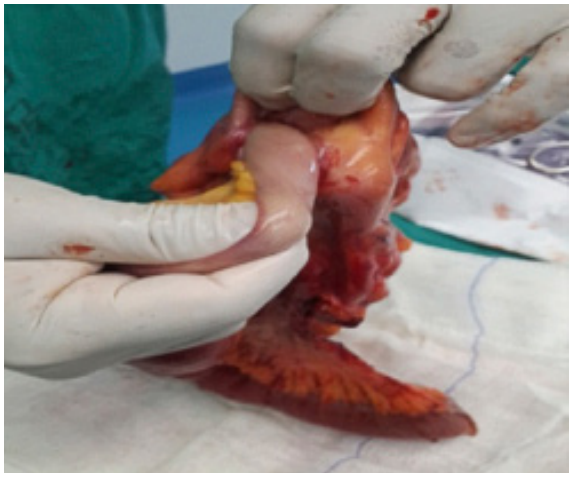

Figure 5. Ileocolonic intussusception.
Source: Document obtained during the study.

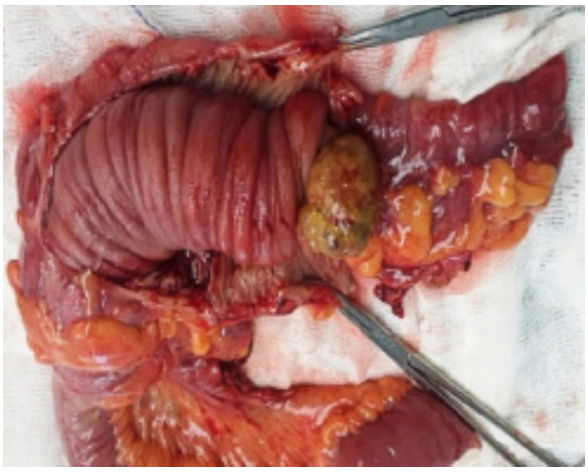

Figure 6. Intussusception of ascending bowel to transverse colon.
Source: Document obtained during the study.

Resection of the segment of terminal ileum affected by the tumor mass and bowel transit reconstruction were performed by means of termino-terminal ileocolic anastomosis (Figure 7).

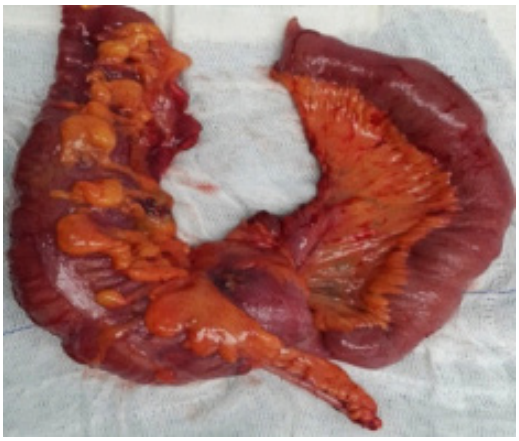

Figure 7. Affected bowel segment.
Source: Document obtained during the study.

When analyzing the sample collected during surgery, a polypoid formation of 6cm of diameter, on a pedicle and ulcerated that occupied of 85% the lumen, with smooth and whitish external surface was observed. A homogeneous and elastic hard consistency was evident after cutting.

Then, histological cutting was performed (Figure 8) and taken to a laboratory where proliferation of spindle cells (which surround the vessels) and abundant inflammatory infiltrate were identified.

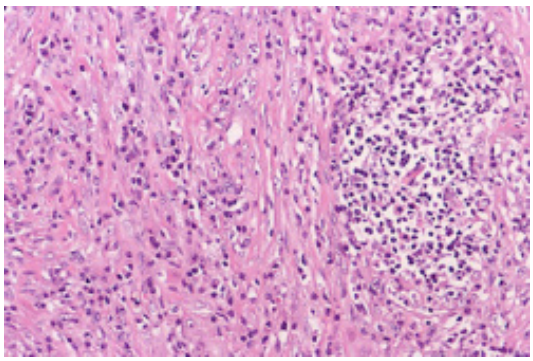

Figure 8. Microscopy of the tumor segment in sectioned terminal ileum.
Source: Document obtained during the study.

The definitive treatment in this case was surgical, that is to say, resecting the segment of intestine that had the tumor and restoring intestinal transit with termino-terminal ileocolic anastomosis. The patient had a good post-operative evolution and no adverse reaction; she was discharged six days after surgery, with favorable prognosis and without complications.

DISCUSSION

Intussusception in adults occurs after an aggression in the intestinal wall causes alteration of peristalsis, in turn leading to a proximal segment sliding into a distal segment. If the mesentery is involved, it causes vascular compression, wall edema and necrosis of the intestinal loop. Its etiology in 70-90% of cases is an organic lesion of malignant origin, frequently in the colon and small intestine. (17) 57% of tumors that cause intussusception are benign, including myofibroblastic tumor, also known as granuloma; 30% of cases are malignant. The most common malignant tumor is melanoma and its metastases (18). Other less frequent causes are Meckel's diverticulum, adhesions or hematoma of the wall. (19)

Nevertheless, adhesions are the most common extraluminal lesions; they originate after being pulled into an intestinal segment, which causes a fold and invagination into the segment that produces the pulsation due to the intestinal movement. (20) According to the location of the adhesions, and of intussusception in general, the lesions are classified into four categories: 1) enteroenteric (75% and with greater recurrence), 2) colocolic (14% recurrence), 3) ileocecal (8% recurrence) and 4) ileocolic (5% recurrence). (17,21)

If the alteration is caused by the colon, the most common cause of intussusception is adenocarcinoma, followed by leiomyosarcoma, liposarcomas, reticular cell sarcoma and metastases. (22)

It is important to assess symptoms and signs; those related to intestinal obstruction, according to frequency, are: colicky abdominal pain (75%-85%), nausea (50%), vomiting (30%) and constipation. Other less common symptoms include diarrhea, weight loss, melena, fever, and palpable abdominal mass. (17) The case reported here presented with abdominal pain and bloating. Because of these symptoms, diagnosis is made preoperatively only in a third of the cases, of which 50% are diagnosed as intestinal obstruction, 11% as abdominal tumor and 2-5% as bleeding in the digestive tract. (17)

This correlates well with the ultrasound studies of the abdomen performed worldwide; target sign imaging have shown that it is possible to identify multiple thin, parallel, hypo-echoic and ecogenic layers in longitudinal planes. (23)

Pathognomonic findings in tomography include bowel thinning, space-occupying lesion and an area of fat and vessel hyperdensity. The computed tomography (CT) performed on the reported patient showed diffuse edema of the transverse ascending colon wall and splenic angle, image of invaginated aspect and space-occupying lesion. (24) Nuclear Magnetic Resonance Morphology is similar to CT and consistent with other studies. (25)

It is worth noting that surgical exploration is the main means of diagnosis and that, despite other simpler methods, it is the only one that allows providing a definitive treatment by intestinal resection and primary anastomosis with restoration of the intestinal transit. This is mostly curative and to some extent coincides with the literature and the surgical treatment provided to this patient, which was resection of the affected ileal segment and termino-terminal ileocolic anastomosis. (26)

CONCLUSIONS

This case corresponds to a very rare cause of intussusception due to the specificity of the clinical presentation, the diagnosis and the immediate need for resection. It should be noted that the definitive diagnosis is made through a histopathological study. The pathophysiology of this disease is not correctly established yet, so this neoplasm is still under study.

CONFLICT OF INTEREST

None stated by the authors.

FUNDING

None stated by the authors.

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PEDIATRIC DIABETIC KETOACIDOSIS IN A PATIENT WITH DOWN SYNDROME. CASE REPORT

Keywords: Diabetic Ketoacidosis; Down syndrome; Type 1 Diabetes; Pediatrics.
Palabras clave: Cetoacidosis Diabética; Síndrome de Down; Diabetes Mellitus Tipo 1; Pediatría.

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ABSTRACT

Introduction: Patients with Down syndrome (DS) have an increased risk of developing autoimmune diseases. This is a rare case of a pediatric patient with DS with an initial clinical profile of diabetic ketoacidosis.

Case presentation: 6-year-old male patient with symptoms suggestive of diabetes mellitus type 1 (DM1) of 15 days of evolution (polyuria, polydipsia, polyphagia and loss of 2 kilos of weight), who was admitted to the emergency department of the Hospital de San José, in Bogotá, Colombia, with uncontrollable vomiting and dehydration. The tests performed confirmed moderate ketoacidosis: glycometry: 592 mg/dL, pH: 7.19, HCO3: 10 mmol/L, PCO2: 45, PO2: 95 and lactic acid: 1.4 mmol/L. Management with isotonic fluids and intravenous insulin therapy was initiated and the patient was transferred to the pediatric intensive care unit, where ketoacidosis was controlled in approximately 10 hours. Subcutaneous insulin schedule was initiated without complications.

Discussion: This case highlights the importance of monitoring possible autoimmune complications in patients with DS, since the risk of developing them is 4.2 times higher than in the general population.

Conclusion: This case calls on to contemplate autoimmune complications in patients with DS during clinical practice. Although they are not part of the most frequent reasons for consultation, they cannot be underestimated and should be suspected and treated in a timely manner.

RESUMEN

Introducción. Los pacientes con síndrome de Down (SD) tienen mayor riesgo de enfermedades autoinmunes. A continuación, se presenta un caso inusual de un paciente pediátrico con SD quien debuta con un cuadro de cetoacidosis diabética.

Presentación del caso. Paciente masculino de 6 años con síntomas sugestivos de diabetes mellitus (DM) tipo 1 de 15 días de evolución (poliuria, polidipsia, polifagia y pérdida de 2 kilos de peso), quien ingresa al servicio de urgencias del Hospital de San José, en Bogotá, Colombia, con vómito incoercible y deshidratación. Se realizan exámenes que confirman cuadro de cetoacidosis moderada, glucometría: 592 mg/dL, pH: 7.19, HCO3: 10 mmol/L, PCO2: 45, PO2: 95 y ácido láctico: 1.4 mmol/L. Se inicia manejo con líquidos isotónicos e insulinoterapia endovenosa y se traslada a la unidad de cuidado intensivo pediátrico, donde se controla la cetoacidosis en un aproximado de 10 horas. Se da inicio de esquema de insulina subcutáneo sin complicaciones.

Discusión. Este caso resalta la importancia del seguimiento de posibles complicaciones autoinmunes en pacientes con SD, ya que el riesgo de estas es 4.2 veces mayor en población con SD.

Conclusiones. El presente caso invita a contemplar las complicaciones autoinmunes en pacientes con SD durante la práctica clínica. Si bien no hacen parte de los motivos de consulta más frecuentes, no se pueden subestimar, sino que deben sospecharse y tratarse oportunamente.

INTRODUCTION

Patients with Down syndrome (DS) are at high risk of developing autoimmune diseases, including diabetes mellitus type 1 (DM1), one of the most common endocrine autoimmune diseases. The risk of presenting this type of disease is 4.2 times higher in patients with DS compared to the general population (prevalence of 0.38% in DS vs. 0.09% in the general population), with a peak incidence before 2 years of age and a second peak in early adolescence. (1)

Blood studies show a high frequency of glutamic acid decarboxylase (Anti-GAD) antibodies in patients with DS presenting with DM1; they are also associated with other autoimmune disorders, mainly thyroid and celiac disease. (2) This report presents the case of a patient with DS, with no history of thyroid or celiac disease with an initial clinical profile of diabetic ketoacidosis.

CASE PRESENTATION

6-year-old male patient, from Puerto López (Meta, Colombia), mestizo, student, with a history of DS, who required endovascular closure of a patent ductus arteriosus 3 years before consultation; he also had a history of pneumonia at 6 months of age, which required in-hospital management. The mother reported continuous medical checkups and no abnormal events.

The patient visited the emergency department of the Hospital de San José, in Bogotá D.C., due to a clinical profile of 1 day evolution, consisting of 10 emetic episodes of food at first, which progressed to biliary content associated with generalized abdominal pain; he did not presented with dysthermias, nor diarrheal episodes or respiratory symptoms. The patient's mother stated that he had presented other symptoms in the last 15 days such as polyuria, polydipsia, polyphagia and loss of 2 kilos of weight.

Physical examination revealed a normocephalic eutrophic patient with flat nasal bridge, low-set ears and clinodactyly. Vital signs were: blood pressure: 94/79 mmHg, heart rate: 129 beat/min, respiratory rate: 26 breaths/min, temperature: 36.7°C, and pulse oximetry saturation: 92%. The only additional findings of importance were signs of dehydration (dry oral mucosa, tachycardia, and hypotension), drowsiness and soft abdomen without abdominal guarding. Glucometry reported values >592 mg/dL and venous blood gases that evidenced metabolic acidosis (pH: 7.19, HCO3: 10 mmol/L, PCO2: 45, PO2: 95, lactic acid: 1.4 mmol/L). No antibodies test was taken, since it is not a routine practice at the hospital.

The child presented with polyuria, polyphagia, polydipsia and weight loss suggestive of diabetes, in addition to laboratory tests that showed hyperglycemia and metabolic acidosis, symptoms compatible with a diagnosis of moderate diabetic ketoacidosis (DKA). He was transferred to resuscitation for monitoring, and intravenous isotonic fluids (bolus of 10 mL/kg) and insulin infusion (0.1 U/kg/hour) were initiated. Follow-up continued in the pediatric intensive care unit.

In the pediatric intensive care unit, insulin infusion was maintained and isotonic fluids were administered at 120 mL/hour (160 mL/kg/day) with 40 mEq/L of potassium chloride. Additional admission tests reported elevated urea nitrogen (BUN) (35mg/dL); high level of serum sodium at 150mEq/L; normal serum potassium (4.9 meq/L); elevated level of chlorine at 110 mEq/L, but adequate sodium level; total serum calcium (9.7mg/dL); phosphate of 7.5 mg/dL, unusually high for DKA; and glycosylated hemoglobin (HbA1c) at 8.17%, slightly elevated. These results confirmed the recent nature of the disease.

Furthermore, a partial urine test was performed, which did not suggest an infectious profile, although it showed the presence of ketones; consequently, no complete blood count was required. Other tests were taken, including thyroid hormone profile, TSH 0.4 mU/l and T4L 16.8 pmol/L, which were not suggestive of active concomitant thyroid disease. DKA correction was achieved 10 hours after initiating the treatment, with adequate clinical evolution; the scheme was switched to subcutaneous insulin with doses of 0.8 U/kg/day with 7 UI of insulin determir and 2 UI of insulin aspart with each meal.

Multidisciplinary in-hospital management continued together with nutrition for input management and food education, physical activity and psychotherapy. DKA successfully resolved and no adverse reaction to the established treatment was observed during hospital stay.

DISCUSSION

DS was first described in 1986 by J.L Down (1) and is considered the most common chromosomal aneuploidy and at the same time the main cause of cognitive retardation worldwide. In Colombia, it is in the fourth most common congenital malformation, more frequently found in male patients. (3) Its incidence is around 1/700 to 1/1500 live births, which increases with maternal age. 95% of cases are caused by nondysjunction in meiosis I. (4,5)

Compared to the general population, patients with DS have a significantly higher risk of developing DM1 and autoimmune thyroiditis, which is why multiple studies have been conducted to identify immune alterations. (5-8)

About 25% of DM1 cases present with an initial clinical profile of DKA. Children, especially those under the age of 5, are at high risk for DKA, and its severity is also inversely related to the age at which it occurs, with a mortality rate of 0.15% to 0.3%. (9)

Pathophysiology

DKA is a metabolic disorder caused by the absolute or relative deficit of insulin associated with a concomitant rise in counterregulatory hormones. Excess counterregulatory hormones and insulin deficit induce lipolysis, which in turn increases non-esterified fatty acids in the bloodstream. These acids are the base for ketogenesis and are transformed into Acyl-CoA; once they reach the mitochondria by means of carnitine, beta-oxidation takes place, transforming into Acetyl-CoA, which under normal conditions will be completely oxidized. However, many derivatives of acyl-CoA are observed in DKA, which saturate the pathway and are partially oxidized, giving rise to three β-hydroxybutyrate and acetoacetates known as ketone bodies. This is considered as the extreme manifestation of deterioration in carbohydrate metabolism. (10-13)

It has been demonstrated that patients with DS older than 5 years have excessive IgA and IgG, with high levels of IgG1 and IgG3, low levels of IgG2 and IgG4 and decreased levels of IgM, which would generate an exaggerated response with a marked decrease in the production of natural antigens that worsens from infancy to adulthood. (12-15)

Moreover, it is evident how genetic polymorphisms generate a reduced thymic output that targets insulin, the A chain of the acetylcholine receptor and the TSH receptor, in turn generating an alteration in the extracellular adenine nucleotides and nucleosides that participate in the regulation of inflammation by stimulating the pro-inflammatory pathway and the anti-inflammatory cytokines that contribute to immune deregulation in patients with DS. (2,13-15)

The genotype most frequently associated with DM1 in the general population is HLA class II DR4/DQ8/DR3-DQ2, which is also found in patients with DS, generating a common pathogenesis. (16) People with DS are usually treated with simple insulin regimens for better therapeutic adherence; this, added to a simple lifestyle and the acceptance of routine, leads to less complications. (17)

As has been shown, the clinic of DKA can be variable, overlooked and even mistaken for other pathologies. This was the case of a patient who attended periodic medical checkups during which no glycemic alterations had been observed, making this pathology more insidious. Cognitive delay in these patients is also a factor that contributes to the underestimation of the symptomatology. (18)

The symptoms of patients with DS presenting with DKA may manifest through hyperglycemia, polyuria, polydipsia, weight loss and dehydration; in addition, this clinical profile may lead to acidosis, vomiting, extreme thirst, tachycardia, hypotension, drowsiness and hyperventilation. In the presence of these symptoms, it is necessary to take into account the following diagnostic criteria to initiate a timely treatment. (19)

Diagnostic criteria

Diagnostic criteria include glycemia >200-250 mg/dL, pH <7.3, bicarbonate <15 mEq/L and ketonemia >3 mmol or ketonuria.

Once DKA has been diagnosed, timely management should be initiated. Both in patients with DS and healthy patients, management is performed by starting with rehydration using isotonic solutions to restore the circulating volume and the glomerular filtration rate, and avoid cerebral edema. In case of shock or severe dehydration, boluses at 10 mL/kg may be used for an estimated time of 10 to 30 minutes (19,20); this intervention should be carried out with caution due to the danger of worsening the risk of cerebral edema. Maintenance fluids should be supplied by calculating a deficit that is usually close to 10%. (19-22).

On the other hand, insulin therapy as treatment should be initiated in order to correct hyperglycemia, ketogenesis and glycogenolysis; to inhibit lipolysis; and to counteract excessive levels of counterregulatory hormones. Thus, a dose of 0.5 to 0.1 IU/kg/h will be started and corrected according to the glucometries. (9,23) These patients will benefit from continuous monitoring until acidosis is corrected.

CONCLUSIONS

Patients with DS have significantly higher rates of developing autoimmune disorders than the general population. This chromosomal aneuploidy is considered a risk factor for the onset of DM1 and autoimmune thyroiditis; therefore, patients suffering from this syndrome should be monitored periodically. This should also be done to make early diagnoses, start early treatment, and decrease the occurrence of complications. These patients will have a better control of their disease given the simplicity of the indicated insulin schemes and their adherence, which reduces the presentation of complications compared to the general population.

This case report calls on to contemplate autoimmune complications in patients with DS during clinical practice, which should be suspected and treated in a timely manner. Although DM is a multifactorial and polygenic disease, hypothesis suggest that patients with DS have an alteration in the mutated chromosome 21 that predisposes them to have a higher rate of autoimmune diseases. This must be confirmed through genetic studies in larger populations.

CONFLICT OF INTEREST

None stated by the authors.

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CASE REPORTS
REPORTES DE CASO

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BEYOND PROSODY: FOREIGN ACCENT SYNDROME IN A SPANISH-SPEAKING PATIENT. CASE REPORT

Keywords: Foreign Accent Syndrome; Aphasia, Language Disorders; Psychogenic; Speech Disorders; Case Reports.
Palabras clave: Síndrome de acento extranjero; Afasia; Trastornos de lenguaje; Trastornos del habla; Informes de casos.

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ABSTRACT

Introduction: Foreign accent syndrome (FAS) is a rare speech disorder. It is becoming increasingly common to find reports of cases about alterations different from the suprasegmental aspects of speech, although these reports are not frequent in Spanish-speaking patients.

Case presentation: 48-year-old female patient from Colombia diagnosed with FAS, segmental and suprasegmental speech alterations, and changes in cognitive domains (executive functions and language). The woman also presented with motor and affective changes. Brain imaging studies ruled out structural involvement and follow-up at one year did not show significant changes in speech.

Discussion: This case presents the neurological, neuropsychological and speech features of a Spanish-speaking patient with FAS. Greater alteration in vowels than in consonants, alteration in pronunciation time, variation in rhythm and intonation of words and phrases, decrease of time between syllables, and insertion of vowels are common elements between this patient and other cases of FAS in non-Spanish speaking subjects.

Conclusions: FAS is essentially a speech alteration; however, it can be accompanied by other physical and psychological signs. This case report allows recognizing the essential components for the definition, diagnosis and intervention of this syndrome.

RESUMEN

Introducción. El síndrome de acento extranjero (FAS por su sigla en inglés) es un trastorno infrecuente del habla. Cada vez es más usual encontrar reportes de casos con alteraciones diferentes a los aspectos suprasegmentales del habla; estos no son frecuentes para pacientes hispanohablantes.

Presentación del caso. Paciente femenino, colombiana, de 48 años de edad, con FAS y alteraciones segmentales y suprasegmentales del habla y en dominios cognoscitivos (funciones ejecutivas y lenguaje). La mujer también presentó cambios motores y afectivos. Las imágenes cerebrales descartaron compromiso estructural y el seguimiento a un año no evidenció cambios significativos en el habla.

Discusión. El caso presenta las características neurológicas, neuropsicológicas y del habla de una paciente hispanohablante con FAS. La mayor alteración en vocales, la alteración en el tiempo de pronunciación, la variación en el ritmo y entonación en palabras y frases, la disminución en el tiempo entre sílaba y sílaba y la inserción de vocales son elementos que esta paciente comparte con otros casos de FAS en sujetos no hispanohablantes.

Conclusiones. El FAS se constituye esencialmente por alteración del habla; sin embargo, puede acompañarse de otros signos físicos y psicológicos. El presente reporte de caso permite reconocer los componentes esenciales para la definición, diagnóstico e intervención de este síndrome.

INTRODUCTION

Foreign accent syndrome (FAS) is a disorder characterized by an affectation in speech automatism. This affectation, since it is expressed with certain motor patterns, is perceived in a biased way by the listeners as a “foreign” accent, although is not associated with previous experience with a second language. (1,2) This

interpretation depends on the stereotypes of the listeners regarding particular foreign pronunciations. (3)

The syndrome was first described in 1907 by Pierre Marie, who reported the case of a Parisian patient that developed a strong Alsatian accent, along with right hemiplegia. (4,5)

The most famous case of FAS is the patient described by Monrad-Krohn in 1947 (2,6,7): a 30-year-old woman who developed hemiplegia and global aphasia with agrammatism after suffering from a head trauma with right frontal lesion. During speech therapy, the patient presented an accent that was similar to French, with fluent speech, but without a history of exposure to other languages or learning other languages; her cognitive examination did not reveal any involvement in domains other than language.

Regarding its etiology, the onset of FAS follows cerebrovascular accidents (8) (ischemic or hemorrhagic) or may be a consequence of traumatic brain injuries (9), progressive primary aphasia (10) or multiple sclerosis. (11) In some cases, it begins with total mutism, followed by a limited capacity to moan that leads to articulatory difficulty, described as foreign accent (12), or a clinical profile of prosody alteration, as in cases of cranioencephalic trauma. (9)

Despite the heterogeneous presentation of FAS, the cases reported in the literature show some common elements such as distorted prosody, characteristic by which the syndrome receives its name, and awareness of the difficulties experienced, specifically as far as speech production is concerned. (12)

Perceived changes in prosody are the result of particular alterations in pitch (6,13), intonation (12,13), duration (14) or other characteristics such as stress (15) and elongation. (16) However, alterations are not limited to prosody; phonetic deviations have been described such as changes in the articulation of consonants or vowels (13,15,17), reduction or simplification of consonant clusters (13,17), and elimination of consonants or vowels. (5,18) Motor aspects of speech are also involved, such as the reduction of production speed. (13,16)

The name FAS was coined by Whitaker in 1982. (4) He proposed a set of diagnostic criteria that define neurogenic FAS, where structural injury is the underlying condition. This variation has been especially associated with brain involvement in the dominant hemisphere for language (left hemisphere) (15,19) and subcortical areas (20-22); however, some cases have reported injury in the right hemisphere. (14,23).

Although these criteria shed some light on the diagnosis, they are not always met; consequently, FAS is classified as a neurogenic condition when these criteria are met and as psychogenic (24) or mixed when they are not.

The characteristics of neurogenic FAS are: 1) the patient, their the acquaintances and researchers perceive that the accent has changed, 2) the accent is different from the patient's native dialect before brain involvement, 3) the change in the accent is clearly related to central nervous system damage and, 4) there is no evidence that the patient speaks a foreign language. (4,7,25)

Psychogenic, functional or non-organic FAS (13) includes cases in which structural alterations that could explain the symptoms are not observed in the patient. These symptoms occur within the framework of psychiatric disorders such as depression (5), anxiety, conversion disorder (13,26,27), bipolar disorder (28) and schizophrenia. (29,30)

Besides these two diagnostic categories, the mixed variant refers organic damage that generates reactive psychological effects such as the emphasis of the new accent. (13)

FAS is a complex syndrome that involves multiple levels of speech and that should be approached in a transdisciplinary manner to achieve a better characterization of its presentation and to avoid diagnostic inaccuracies, considering that initial diagnoses such as transient aphasia, larynx disorders or conversion disorder are frequent (1,31) and delay the initiation of interventions.

Speech, language, and neurological and neuropsychological findings of Spanish-speaking patients with this syndrome have not been characterized in detail, unlike the case of English or French-speaking patients. (32,33) Therefore, having such information is essential for clinical and academic purposes.

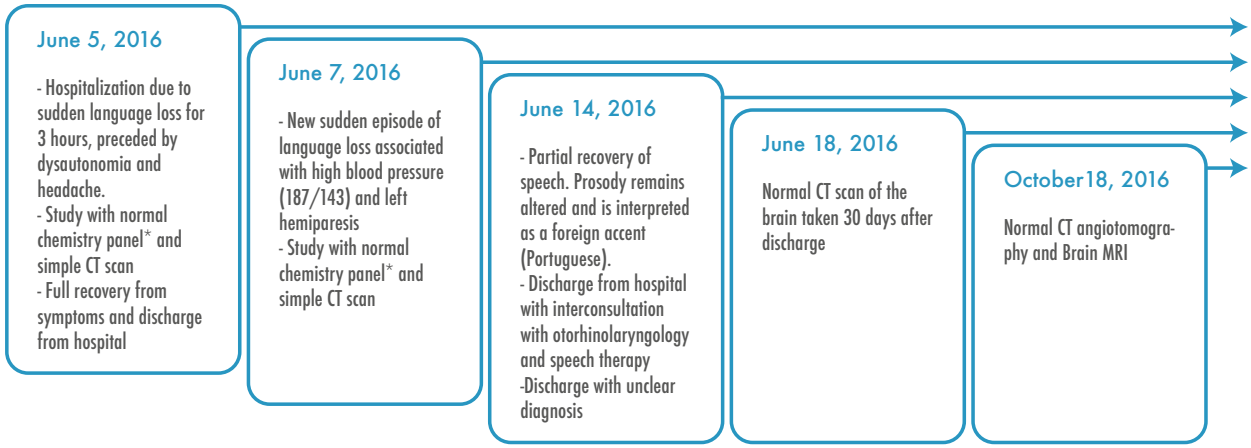
The following case describes the main neurological, neuropsychological, speech and language findings involved in a Spanish-speaking patient with FAS from a multidisciplinary approach.

CASE PRESENTATION

48-year-old female patient, Colombian, from the urban area of the north of the country, mestizo, from a middle-income household, arts teacher, whose mother tongue and only domain is Spanish. Relevant medical history includes hyperlipidemia and hypertension pharmacologically treated with valsartan, hydrochlorothiazide and amlodipine.

In 2016, the patient presented with a sudden clinical picture of language loss and prosody compromise, with an accent that was recognized as "foreign". The woman was initially treated with speech therapy without having a clear diagnosis. The main symptoms and the clinical evolution are detailed chronologically in Figure 1.

Figure 1. Timeline: establishment of the clinical profile and initial approach.



CT: computed tomography; MRI: magnetic resonance imaging.
* Chemistry panel: blood count, kidney function, glucose, sodium, potassium, chlorine, calcium.
Source: Own elaboration.

In January 2017, the patient was referred for assessment by the interdisciplinary neurosciences team of the Universidad Nacional de Colombia (neurology, neuropsychology, phonoaudiology, internal medicine, psychiatry and neuroradiology). The results are detailed in Table 1.

Table 1. Results of clinical assessment carried out by neurology, psychiatry and radiology.

Physical and neurological examination	Psychiatric assessment	Radiological examination*
Patient alert, attentive and oriented in the three spheres, with signs of high blood pressure (146/92 mmHg), normal breath sounds, regular rhythmic heart sounds and physiologic splitting of S2. Left hemihypoesthesia and left brachiocrural strength 4+/5.	Affection involvement, with tendency to depressive symptoms, apparently reactive to the clinical condition.	No objective structural alterations were identified in brain size, morphology or signal. Fractional anisotropy had no modification.

* Multiplanar sequences in 1.5T PHILIPS MULTIVA, TSE T2, SE T1, GRE T1 and T2, including volumetric acquisitions in addition to tractography of 32 directions.

Source: Own elaboration.

The neuropsychological evaluation showed altered performance (22 points) in tasks included in the Moca Test (34), a high subjective memory complaint of the patient and family members (35), and borderline performance (19,5) in the INECO Frontal Screening executive function screening scale. (36) On the other hand, there was evidence of preservation of functionality (score: 14-14), which was measured using the modified Lawton's scale. (37) The evaluation of the cognitive domains attention, memory, language, praxis and executive functions was carried out using the NEURONORMA Colombia battery (38) (Figure 2); language was further evaluated using the guidelines for the assessment of grammatical transformations in Spanish-speaking patients (spontaneous language, evaluation of grammatical elements, agreement with suggested responses, grammatical transformations, construction of sentences, and handling of passive-active constructions and complex structures), and analysis of tasks with linguistic implication and conversational language to establish the state of the different components of language.

Praxis and attentional skills were preserved, although a decrease in processing speed that interfered with the outcome of tasks assessing attention and inhibitory capacity was observed. Memory capacity was also compromised, since the retrieval of information, both free form and with key, was found to be lower than expected for her age and educational attainment. In addition, the patient presented semantically-related intrusions (4 intrusions).

Further tests were made regarding the language sphere, this being the domain with the most altered report. Figure 2 details the evaluation tests for this domain. Alterations were found in articulation and prosody at the expressive level; speech was abbreviated in short phrases, but it was informative and not telegraphic. Speech was deautomatized, aspect that persisted for automatisms and did not improve in singing tasks. Phonological verbal fluency was diminished and comprehension was correct, as well as denomination. Regarding repetition, reading and writing presented difficulties similar to those observed in oral expression. In addition, writing showed discreet agrammatism, characterized by inappropriate use of adjectives ("my literature is displaced"), difficulty in identifying the right preposition ("there's only time to turn on the forms today") or to preserve singular and plural concordance ("my word are exsaggerated"), and slight alterations of grammatical transformation tasks such as turning nouns into verbs (Beauty-beautiful).

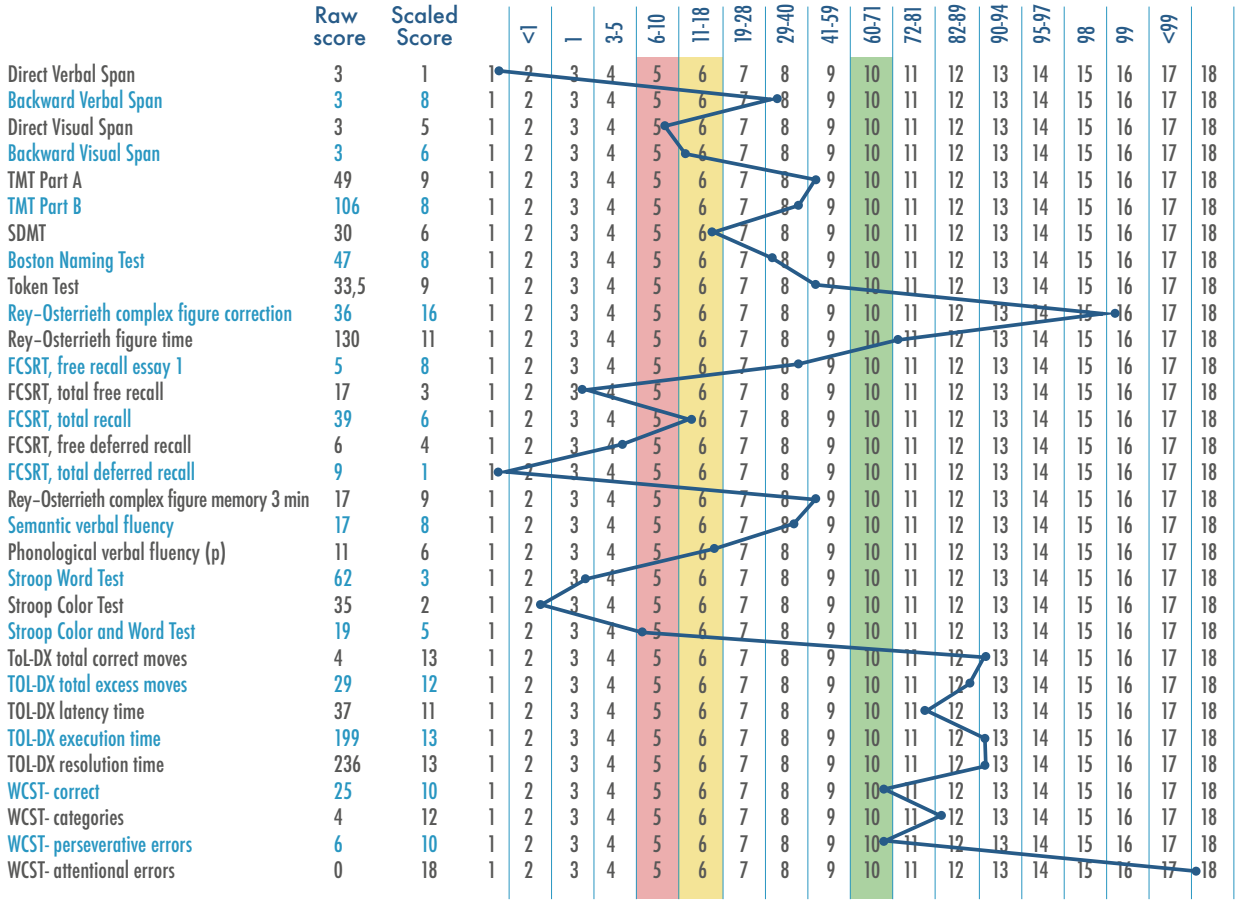


Figure 2. Performance scores in psychometric tests measured using the Neuronorma Colombia battery.

Attention: Direct Verbal Span, Direct Visual Span, Trail Making Test (TMT) Part A and B, Symbol Digit Modalities Test (SDMT), Stroop Color and Word Test, Wisconsin Card Sorting Test (WCST) attentional function. **Language:** Boston Naming Test, Token Test, Semantic and phonological verbal fluency (p). Memory: Colombian version of the Free and Cued Selective Reminding Test (FCSRT) free recall essay 1, total free recall, total recall, free deferred recall, total deferred recall, Rey-Osterrieth complex figure memory 3 minutes. **Building skills:** Rey-Osterrieth complex figure correction, Rey-Osterrieth figure time. **Executive functions:** Backward Verbal Span, Backward Visual Span, TMT B, Phonological Verbal Fluency, (p) Token Test, Stroop Interference Test, Tower of London (ToL-DX) total correct moves, excess moves, latency time, execution and resolution, correct Wisconsin Card Sorting Test (WCST), categories, perseverative errors.

Scores were transformed to scaled measures based on Colombian scales. Decreased performance starting at 1.5 SD (Scaled score 6), indicates alteration if below average. Two or more tests of the same domain below 1.5 SD indicate alteration.

Source: Own elaboration.

Phonetic analysis

Speech subprocesses were evaluated in detail in the phonetic analysis, finding compromise in different segmental and suprasegmental levels (Table 2).

Table 2. Findings of the phonetic examination per evaluated level.

Evaluated level	Findings of the phonetic examination			
Breathing pattern	Costoclavicular, with nasal-oral cycle at rest and oral-oral when speaking			
Phonation	Tone of voice	Phonation time		Comments
	Fluctuating, with occasional tone breaks and intensity variations	Maximum phonation time of 4 seconds in phoneme production of prolonged /a/		An increase of audible aspirations was identified during phonation, which was confirmed by PRAAT software. (39)
Speech articulation	Articulatory movements	Programming of movements		Comments
	Inaccurate articulatory movements, with slow movements and modification of the point and manner of some phonemes and syllables.	1) difficulty to start the production of labiodental occlusive phonemes /p/ - [bga)], 2) glide /p - t - k/ - [b_es ges ga] and / pronda/ - [oan_sé] / /paisa/ _ [baii_sa] 3) Change of point in phonemes with anteriorization /t/ - [d], /k/ - [g].		Frequent jargon (+) before repetition and moderate to severe alteration of prosodic aspects.
Fluency	Rhythm	Speech rate	Disfluency Index	Comments
	Monotonous rhythm during spontaneous speech with blockages that decreased throughout the conversation and were frequent while reading polysyllabic words and during stressful situations.	Spontaneous speech rate: 0.65 words per second. Reading speed: 0.91 words per second.	Spontaneous speech: 0.13% (blocks) Reading output: 0.27% (blocks)	Rhythm: stressful situations such as the first communicative approach with another person. Speed: concomitant aspects such as tension in the face and neck and increased blinking were observed. Index: characterized by prolongation of initial sound, repetition of initial syllables (not suggestive for diagnosis of stuttering) and oral inspiration in the middle of words (audible).
Suprasegmental features	Tone of voice	Syllabic and phonemic sequence	Intrasyllabic duration	Comments
	It did not match the articulatory model and inclusion of compensatory sounds was observed such as / piego/ - [miá_su].	Altered: involvement of the syllabic and phonemic sequence /saen/- [saáá_em] / /pronda/ - [oan_sé].	Increased	Intrasyllabic pauses were found with increased frequency.
Speech intelligibility	Involved by 65%, with an evident increase depending on kinship and knowledge of the situation.			

+: present.

Source: Own elaboration.

Diagnostic consensus

From a neurolinguistic and phonoaudiological perspective, and considering that these findings are similar to those reported in the literature (4,15,32,40,41), FAS was diagnosed. MRI and tractography reports helped ruling out structural lesions, neoplasms, ischemic lesions, demyelinating lesions or others brain lesions as a probable etiology of this disorder.

Interventions and recommendations

Controlling comorbidities was the first step in the treatment of the patient. Acetylsalicylic acid was indicated and antihypertensive therapy was adjusted with spironolactone. Rehabilitation included speech therapy for the correction and rehabilitation of movement and coordination of orofacial musculature (tongue, lips, jaw) and diction: point and manner of articulation, allophonic substitutions and variations, and systematic vocal articulation exercises. A plan was designed with self-implemented exercises and supervised therapy; it was advised not to resort to group therapy to avoid anxiety.

Cognitive activities were recommended to exercise the involved domains and management with music therapy and permanent intervention by psychiatry and psychotherapy was proposed. In addition, the patient was advised not to abandon her work activities in order to avoid social isolation, although switching to activities that required less oral communication was suggested. Finally, it was proposed to attend control appointments with the treating group.

Follow-up

In the third month of follow-up, speech intelligibility increased by 15% compared to the first measurement, but there was an increase in laryngeal tension and hyperfunctional dysphonia. It was found that the patient maintained the point and manner in the production of occlusive alveolar phonemes, so that instead of /d/ she produced [t], giving silent characteristics to a sonorous phoneme. There was also hypernasalization of the dorsal nasal phoneme (/n/), frontalization of the palatal occlusive phoneme /c/ instead of the alveolar occlusive /t/, omission of the simple vibrant /r/ and centralization of the vowels /dolores/ [doooes].

The maximum phonation time was 4 seconds and expressive language was slightly altered before repetition and denomination. Stereotypes were identified in the production of bilabial occlusive phonemes /b/ and /p/, followed by elongated vowels. A high frequency of phonemic paraphasias /cabeza/ - [aBeta], alterations in melody, segmental pauses (syllabic) and prolongations of vowel sounds with low intensity were observed.

Listening was preserved, although there was evidence of contrasting phonological paraphasias with identified articulatory errors. Mild agrammatism was also evident, but, according to analysis with PRAAT, no variations were identified in the formants F1 and F2.

Alterations persisted between February and April 2017, although there were changes in the accent of the mother tongue with a slight improvement in intelligibility with respect to the initial assessment.

Poor adherence to the intervention recommendations made by the group was documented at 6 and 12 months; this was secondary to the unavailability of specialized management in the patient's place of residence. The assessment made by the treating group did not reveal significant improvement in the clinical condition or in the aspects of speech of the patient during this period.

DISCUSSION

This case reports the neurological and neuropsychological characteristics of language and speech in a Spanish-speaking patient with FAS. The neurological manifestations that come along with this syndrome in the reported cases are not exclusive to this condition and are mainly associated with brain injury or organic compromise. Motor alterations such as hemiparesis, hemiplegia, facial paralysis (19) and dysarthria (8,42) stand out in this group. However, other alterations such as buccal-facial apraxia (22), gait apraxia (28), ataxia (42), spasticity and lack of coordination (28) have also been described. These signs should be taken into account at the time of conducting a neurological evaluation of a FAS patient.

In the reported case, mild hemiparesis and left hemihypsesia were documented in the absence of structural brain injury in imaging studies; however, it was not possible to rule out functional involvement (28) due to limited access to specialized equipment.

The exploration of speech and language in FAS must be deep and contemplate all the segmental, suprasegmental (speech) and linguistic aspects (32), since all of them may be altered. (41)

In this case, there was also evidence of fluctuations in the tone of the voice with occasional tonal breaks and variations in intensity; intrasyllabic duration and frequency of intrasyllabic pauses were increased, similar to what the literature reports. (32,33,43) Articulatory movements were imprecise, slow and with changes in the point and manner of some phonemes and syllables.

In patients with FAS, vocabulary may be restricted, slow production and attenuated prosody may be observed (3), and speech may be similar to mild speech apraxia. (1,16,43) Therefore, in general, verbal expression is characterized by articulatory distortions that affect it (3,32,33), leading to errors that are predominantly phonemic substitutions, laborious articulation, sequential errors and unsuccessful efforts in self-correction. (32,33) These errors are always present and do not depend on the task, so there is no improvement when the patient recites, repeats, reads or exclaims. (13)

In this case, the patient showed dissociation between good performance in language tasks that do not directly involve speech and difficulty in tests that evaluate expressive language, compatible with the reported findings (32,33,43) and contrary to what some authors state about the absence of deficits at the level of expressive language, phonetic deformations or lack of fluency, which is usual in motor aphasia. (31)

Another sign that may be observed is agrammatism. (3,28,44) Individuals with agrammatism fail to make changes in verb tenses, conjugate verbs, make grammatical transformations and use complex structures. (31) In the study patient, these difficulties were evident mainly at the written level, in addition to disortography and alteration in grammatical compositions such as conjugations, identification of propositions and use of singular and plural.

Regarding the cognitive level, presentation spectrum is variable, while failures may not be observed at all (8) or one or more altered cognitive domains may appear. (19,22,25,28,31,45) The main tasks involved are related to verbal fluency (28,45) and semantics, although failures are reported in tasks such as Stroop (exact but slow performance) (28), backward digit span, problems with tasks that require sustained and alternating attention (TMT A and B) (19,25,45), moderate deficit in reading, slight failures in tests such as Mini-Mental (19) and difficulties in memory tasks. (25,28,46) Specific cognitive tasks such as denomination

(Boston test), shortened version of the Token test, repetition of sentences, listening and written comprehension and praxis usually have a normal performance. (12)

Cases that show cognitive profiles with failures in tasks that require speed of information processing and working memory have been described (25,28), including those in which FAS develops after cerebrovascular events that present with symptoms that are both dysexecutive and memory-related (28), and whose profile greatly differs from those cases in which FAS is a consequence of injury to the brain stem. (42)

Considering FAS as a condition that implies more than an alteration of prosody is fundamental for a proper approach to treatment and rehabilitation. Treatment is specific for each case and should be oriented towards the management of the causes. It is also essential to make a diagnosis of all the cognitive domains involved, without leaving aside the affective and psychosocial sphere of the patients, which should be interpreted according to their context. Considering the absence of structural lesions and the general preservation of cognition, the impact of this condition on quality of life may be deemed as a guide to the objectives that the intervention should address.

In the reported case, an improvement in speech intelligibility was achieved, similar to what is reported in the literature (41); nevertheless, many of the suprasegmental and segmental alterations remained after one year. This could be the result of the lack of adherence to the recommendations due to the difficult access to specialized care in the place where the patient resides, aspects that should also be considered as a factor associated with the prognosis of recovery.

In all cases, a comprehensive management should be ensured from a multidisciplinary and multilevel perspective, in such a way that the personal, family, occupational and social contexts are addressed. (41)

CONCLUSIONS

FAS is a complex and rare entity that generates change beyond prosody. Its diagnosis is clinical and based on the manifestations and results of an exhaustive phonetic assessment, but not limited to it.

Other alterations in cognitive functions are present in FAS, especially regarding language, memory and executive functions, and in neurological and affective aspects that should be considered as part of a complete assessment.

Imaging studies and other paraclinicals are not the central axis of the diagnosis and their use is convenient to establish a possible etiology in cases where neurogenic or mixed FAS is suspected.

Clinical characterization is essential for approaching patients with FAS; however, there are psychosocial aspects (47) that should not be neglected, such as the work context or occupation, the place of residence and the support network, as they can become barriers or facilitators to the recovery process.

With respect to this case, it is necessary to highlight the deep linguistic, neuropsychological and clinical exploration carried out in the context of a Spanish-speaking patient. The detailed description of speech elements makes this an interesting case in clinical and academic settings. One of its limitations is the lack of functional studies that could specify the etiology of the condition and guide the classification by type of FAS.

ETHICAL CONSIDERATIONS

The patient accepted the support provided by the research team in order to know the etiology

of her clinical condition. She manifested her interest in having her case studied in depth and shared with the scientific community and the general public, as she perceived an inadequate approach to her case as a result of the lack of knowledge of the syndrome by the health personnel during the previous clinical assessments. She is currently undergoing a process of neuropsychological and language rehabilitation aimed at recovering the characteristics of her speech and resuming her work and social dynamics. Additionally, she decided to take courses that allowed her to interact and learn from other activities that promote biopsychosocial well-being.

The patient granted her consent for performing each of the studies, for using the information and publishing the case by signing the informed consent.

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CONFLICT OF INTEREST

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