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RESEARCH ARTICLE

Children hospitalized for COVID-19 during the first winter of the pandemic in Buenos Aires, Argentina

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Abstract

Background: *Although there are reports on COVID-19 in pediatrics, the characteristics of the population of each country, its health systems, and how the pandemic was addressed could give the disease distinctive features worldwide. We aimed to describe the characteristics of patients hospitalized for COVID-19 in a tertiary pediatric hospital in the City of Buenos Aires, Argentina.* **Methods:** *We conducted a descriptive study, including all patients hospitalized for COVID-19 from 04/26/2020 to 10/31/2020 in a tertiary pediatric hospital. We described the demographic, clinical, and epidemiological characteristics of the patients.* **Results:** *During the period studied, 578 patients were hospitalized with COVID-19. The median age was 4.2 years, and 83% reported close contact with a confirmed COVID-19 case. Regarding severity, 30.8% were asymptomatic, and 60.4% showed mild, 7.4% moderate, and 1.4% severe symptoms. Among symptomatic patients, fever was the most frequent symptom, followed by sore throat and cough.* **Conclusions:** *We reported 578 cases of children and adolescents hospitalized with COVID-19, of which the majority showed mild or asymptomatic disease.*

Keywords: *Coronavirus infection. COVID-19. Pneumonia. Hospitalization. Children.*

Niños hospitalizados por COVID-19 durante el primer invierno de la pandemia en Buenos Aires, Argentina

Resumen

Introducción: *Si bien existen reportes sobre COVID-19 en pediatría, es posible que las características de la población de cada país, sus sistemas de salud y cómo enfrentaron la pandemia hayan hecho que la enfermedad mostrara rasgos distintivos a escala global. El objetivo de este trabajo es describir las características de los pacientes hospitalizados por COVID-19 en un hospital pediátrico terciario de la ciudad de Buenos Aires, Argentina.* **Métodos:** *Se llevó a cabo un estudio descriptivo que incluyó a todos los pacientes hospitalizados por COVID-19 del 26 de abril al 31 de octubre de 2020 en un hospital pediátrico de tercer nivel. Se describen las características demográficas, clínicas y epidemiológicas de los pacientes.* **Resultados:** *Durante el período estudiado fueron hospitalizados 578 pacientes con COVID-19. La mediana de edad fue de 4.2 años y el 83% reportó antecedentes de contacto cercano con un caso confirmado de COVID-19. En cuanto a la gravedad, el 30.8% fueron asintomáticos y el 60.4% mostraron síntomas leves, el 7.4% moderados y el 1.4% graves. Entre los pacientes sintomáticos, el síntoma más frecuente fue la fiebre, seguida de odinofagia y tos.* **Conclusiones:** *Se reportaron 578 casos de niños y adolescentes hospitalizados con COVID-19, de los cuales la mayoría presentó enfermedad leve o fueron asintomáticos.*

Palabras clave: *Infección por coronavirus. COVID-19. Neumonía. Hospitalización. Niños.*

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Introduction

Although the COVID-19 pandemic has caused hundreds of thousands of deaths worldwide, the current information shows that the disease is less severe in the pediatric population[1,2].

Some studies report that the course of the pandemic could be influenced by each country's characteristics, its health systems, and the way it has dealt with the pandemic[3,4].

Argentina faced the pandemic in a particular way, including one of the longest lockdowns[5] and the mandatory hospitalization of affected children[6]. These characteristics could give a distinctive feature to children hospitalized for this disease in Argentina.

We aimed to describe the characteristics of patients hospitalized for COVID-19 in a pediatric tertiary hospital in the City of Buenos Aires.

Methods

We conducted a retrospective study including all patients hospitalized with COVID-19 in a tertiary pediatric hospital in Buenos Aires, Argentina, from April 26 to October 31, 2020. In addition to patients admitted for COVID-19, all cases requiring hospitalization for other reasons were analyzed. Infection was diagnosed by identification of SARS-CoV-2 in nasopharyngeal secretions by RT-PCR.

The study population included subjects who spontaneously attended our hospital for suspected COVID-19 (symptoms or history of close contacts)[7] and subjects who were identified by active surveillance in impoverished neighborhoods[8]. Of these neighborhoods, those symptomatic subjects with SARS-CoV-2 identified by PCR, those under 2 years of age, or those older than that age who could not complete isolation at home were hospitalized[7]. We also included patients who required hospitalization for another reason and whose SARS-Cov-2 infection was identified on admission.

In all cases, we registered demographic characteristics, such as sex, age, place of residence (including whether they lived in an impoverished neighborhood[9]), the onset of symptoms on admission, close contact with a confirmed COVID-19 case, presence of any comorbidity, and duration of hospital stay.

Disease severity was established according to Dong et al.[10]; patients with SARS-CoV-2-related multisystem inflammatory syndrome (MIS-C) were considered severe/critical.

The results of laboratory tests (hemoglobin, differential WBC count, platelets, C-reactive protein, and erythrocyte sedimentation rate) were also recorded.

The Ethics Committee of the institution approved the study.

Statistical analysis

Categorical variables were described by proportions with 95% confidence intervals (95%CI) and continuous variables by the mean and standard deviation or median and interquartile range (IQR), according to the distribution (Kolmogorov-Smirnov test). For the analysis, the IBM SSPS Statistics 20.0 software was used.

Results

During the period studied, 578 children and adolescents were hospitalized for COVID-19. Some characteristics of 191 of these patients were mentioned in a preliminary report at the beginning of the pandemic[9]. Here, we described the characteristics of all patients hospitalized for COVID-19 during the entire cold season (May-October), including laboratory data.

The number of hospitalizations ranged from 2 to 42 per week (median = 30.5; IQR: 21.7-35.7) (Figure 1). The median age was 4.2 years (IQR: 0.7-11.2), and 54.5% of the patients were male. A total of 67.3% were residents within the hospital's jurisdiction (City of Buenos Aires), and, of these, 23.1% lived in a low-income neighborhood.

Also, 83% had a history of close contact with a confirmed case of COVID-19. The onset of symptoms before admission was one day (IQR: 1-3), and 35.3% had a previous or concomitant diagnosis of another disease, with asthma being the most frequent (n = 49) (Table 1).

Disease severity was assessed, and the following results were observed: 30.8% were considered asymptomatic, 60.4% mild, 7.4% moderate, and 1.4% severe. Of the six severe cases, only one required assisted ventilation, and two had SARS-CoV-2-related MIS-C. Other six MIS-C cases were admitted to the hospital, but SARS-CoV-2 tests were negative at that time. In addition, the most frequent initial symptom was fever, followed by sore throat and cough (Table 2).

Regarding laboratory tests results, we found that 9.4% showed lymphopenia (differential lymphocyte count < 20%) and 23.8% had elevated C-reactive protein values (C-reactive protein > 10 mg/dL) in 100% of severe cases and 10% among asymptomatic

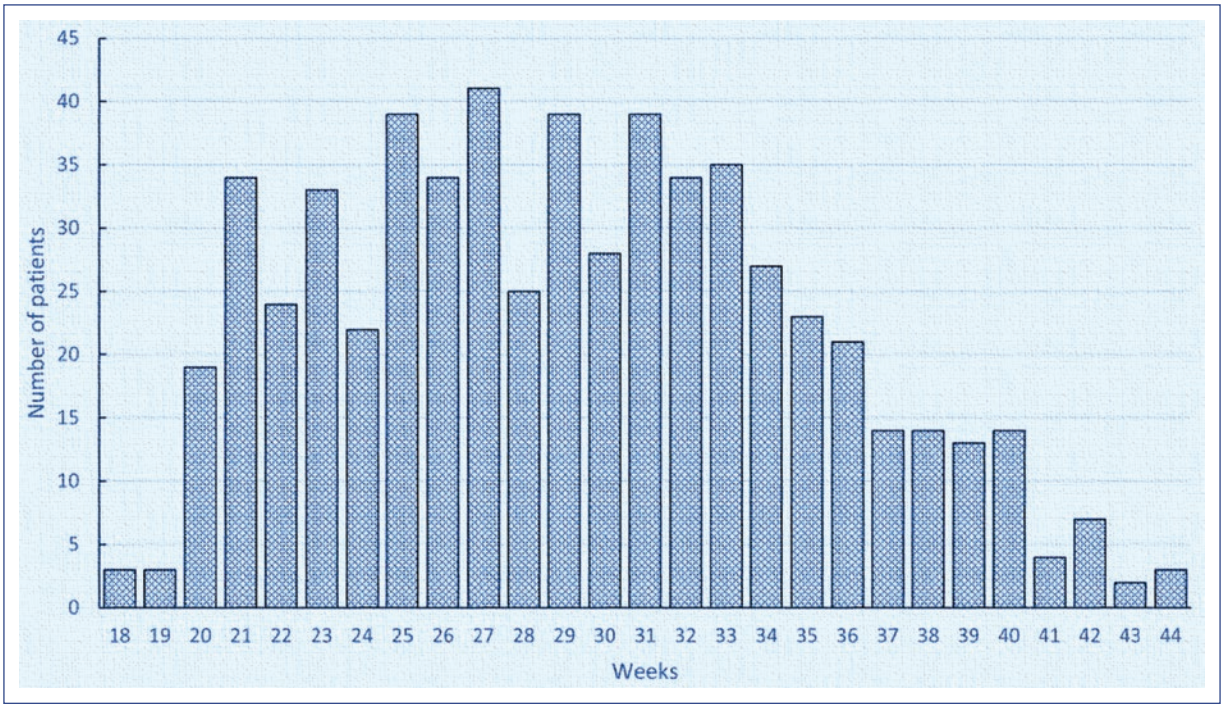

Figure 1. Pediatric hospitalizations for COVID-19 according to the epidemiological weeks.

cases (Table 3). The median length of stay was 6 days (IQR: 2.2-9).

At the time of this report, only one COVID-19 patient died of causes other than the disease, as he had been in end-of-life care for more than a month before infection. All patients were discharged without complications (with phone follow-up), except those whose comorbidity prevented this.

Patients with MIS-C were treated according to local guidelines (including assisted ventilation, systemic corticosteroids, and vasoactive drugs, when necessary)[11]. According to local guidelines, patients received supportive measures and no disease-specific or experimental treatments[12]. When appropriate, patients also received treatment for their comorbidities.

Discussion

The present study reinforces the idea that the manifestations of COVID-19 in pediatrics, in general, are mild. It also supports some characteristics of the disease observed in Argentina, suggested by our group in a previous report[13].

Although the age structure (for example, Argentina has twice as many children under 15 years of age as Italy, the first Western country affected by the pandemic) and the social behavior of the different populations may influence the differences observed[14,15], how local health authorities dealt with the pandemic has generated some particular features in our patients: Buenos Aires reported more pediatric cases than other countries, and we found a higher proportion of asymptomatic patients and with mild symptomatology among those hospitalized.

The City of Buenos Aires adopted a test-and-trace policy. This program was carried out more strongly in poor neighborhoods with a younger population[8]. Mandatory hospitalization of still asymptomatic infants was also established[6,7]. Furthermore, asymptomatic children and adolescents who were unable to comply with out-of-hospital isolation at home were hospitalized during the isolation period[16].

Up to October 31, 2020, the City of Buenos Aires reported 147,363 cases of COVID-19, of which 12.1% were children and adolescents[17]. This proportion was substantially higher than initially reported in China (2.1 %)[18] and Italy[19], but closer to that most recently reported in the United States (9%)[20].

We found a high proportion of asymptomatic patients (30.8%), higher than that reported by Götzinger et al. in Europe in 582 children with SARS-CoV-2 infection (16%)[21]. Despite this high number of asymptomatic children, the

Table 1. Comorbidities in pediatric patients hospitalized for COVID-19 (n = 204/578)

Disease	n
Asthma	49
Surgical conditions (appendicitis, testicular torsion, hernias)	12
Seizures	11
Non-progressive chronic encephalopathy	11
Genetic disorders	9
Tumors	8
Tuberculosis	8
Other infections (otitis, cellulitis, hepatitis)	8
Urinary tract infection	7
Obesity	5
Diabetes mellitus	5
Thrombocytopenic purpura	5
Chronic kidney disease	5
Chronic lung disease/ Bronchopulmonary dysplasia	4
Congenital heart disease	3
Hemolytic-uremic syndrome	2
Hematologic disease (spherocytosis, hemophilia)	2
Human immunodeficiency virus	2
Other	48

Table 2. Initial symptoms of patients hospitalized for COVID-19 (n = 400)

Symptom	n	%
Fever	207	51.7
Sore throat	49	12.2
Cough	40	10
Rhinorrhea	39	9.7
Headache	37	9.2
Diarrhea/vomiting	35	8.7
Dyspnea	17	4.2
Abdominal pain	15	3.7
Loss of smell	13	3.2
Rash	6	1.5
Loss of taste	3	0.7

Table 3. Laboratory results of children hospitalized for COVID-19

	Mean	SD
Hemoglobin (mg/dL)	12.5	1.4
White blood cells count (/mL)	8,062	3,889
Differential lymphocyte count (%)	49	20
Neutrophil differential count (%)	39	20
Platelet count (/mL)	289,544	106,073
Erythrocyte sedimentation rate (mm/h)	13	12
C-reactive protein (mg/dL)	14	38

proportion of those with any comorbidity (35.3%) was similar to other series[22,23]. Our findings are probably related to the test-and-trace and institutional isolation policies adopted by the local health authorities.

As reported[24], we also found a higher proportion of subjects with comorbidities among patients with moderate and severe symptomatology than those with mild disease or asymptomatic. However, this result should be assessed with caution due to our series's low proportion of patients with moderate and severe disease (8.8%).

We found only 7.4% of moderate and 1.4% severe cases. Dong et al. in China reported 5.9% severe and critical cases[10], and Tagarro et al. in Spain reported that 9.7% of the cases in this series were severe[25]. Although a report from the United States showed that 32% of hospitalized pediatric patients with COVID-19 were admitted to a PICU, the limited mean length of stay (2 days) and the limited proportion of subjects requiring assisted ventilation (5.8%) suggest that the admission criteria in this series were broader[23].

The cases of MIS-C (multisystem inflammatory syndrome associated with COVID-19 in children) appeared 4 to 6 weeks after reaching a significant number of cases in our city, as described for the development of this complication[26].

Finally, we found that 83% of our patients had close contact with infected people, supporting the idea that children are usually infected from adults[27].

Our report has limitations that should be mentioned. On the one hand, long-term follow-up of our patients was not carried out, which would have allowed us to identify cases that can be considered "long COVID," although the presence of this condition in children seems to be very infrequent[28]. On the other hand, this study only presents data from a single-center, although

it is probably the public institution that has hospitalized the most pediatric patients with COVID-19 in our country. Moreover, the inclusion of single-center data shows that in winter with no respiratory syncytial virus (RSV)-related hospitalizations, the number of patients hospitalized for COVID-19 is approximately the same as those admitted for RSV disease each year[29], regardless of whether this is related to non-pharmaceutical interventions used to control the pandemic[30].

In this study, 578 cases of children and adolescents hospitalized for COVID-19 in Argentina were reported. The majority presented mild or asymptomatic disease, supporting the idea that the management of pediatric patients with COVID-19 represents more of an organizational challenge than a specific clinical task[31].

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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RESEARCH ARTICLE

Clinical and epidemiological characteristics of COVID-19 in children: experience in two hospitals

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Abstract

Background: *The COVID-19 pandemic is the most significant current public health crisis.* **Methods:** *We conducted a retrospective case series, including patients under 18 years of age admitted to respiratory triage and hospitalized with COVID-19 infection in two hospital centers. Epidemiological, clinical, laboratory and radiological findings were documented. The diagnosis of COVID-19 was confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR). For the analysis, patients were classified into three groups: no comorbidities, immunocompromised, and with chronic disease.* **Results:** *Fifty-four patients with COVID-19 were identified: 40 (74.1%) were admitted through respiratory triage. Of these, 28 (70%) were hospitalized, and 14 (25.9%) were already in the hospital. In addition, 26 (48.1%) presented comorbidities. A mild clinical course was observed in 14 cases (53.7%). The mean age was 6 years, with an interquartile range from 11 months to 13 years. The male sex was more frequent, representing 59.3%. Fever was the most common symptom in 74% of the patients. Lymphopenia was observed in 28.6%, and 69.3% had elevated C-reactive protein. Ground glass injuries were documented in 30.9% of COVID-19 cases; 11.1% of the patients required mechanical ventilation and vasopressor treatment.* **Conclusions:** *Fever was the main symptom, and mild infection was the principal presentation. In hospitalized patients with some comorbidity and COVID-19, the disease was more severe, with a high percentage of mortality.*

Keywords: *COVID-19. Clinical features. Computed tomography. Children.*

Características clínicas y epidemiológicas de la COVID-19 en niños: experiencia en dos centros hospitalarios

Resumen

Introducción: *La pandemia de COVID-19 es la mayor crisis de salud pública actual.* **Métodos:** *Análisis de una serie de casos retrospectiva de pacientes menores de 18 años que ingresaron al triaje respiratorio y de pacientes hospitalizados con COVID-19 en dos centros hospitalarios. Se registraron variables epidemiológicas, clínicas, de laboratorio y radiológicas.*

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El diagnóstico de COVID-19 fue confirmado por reacción en cadena de la polimerasa con transcriptasa inversa en tiempo real (RT-PCR). Para el análisis, los pacientes se clasificaron en tres grupos: sin comorbilidad, inmunocomprometidos y con enfermedad crónica. **Resultados:** *Se identificaron 54 pacientes con COVID-19, de los cuales 40 (74.1%) ingresaron por el triaje respiratorio y, de estos, 28 (70%) fueron hospitalizados y 14 (25.9%) ya estaban hospitalizados; 26 pacientes (48.1%) presentaban comorbilidad. El curso clínico leve se observó con mayor frecuencia, en 14 casos (53.7%). La mediana de edad fue de 6 años (rango intercuartílico: 11 meses a 13 años). El sexo masculino fue más frecuente, con el 59.3%. La fiebre fue el síntoma más común, en el 74% de los pacientes. Se observó linfocitopenia en el 28.6%, y el 69.3% presentaron elevación de la proteína C reactiva. Las lesiones en vidrio esmerilado se documentaron en el 30.9% de los casos y el 11.1% de los pacientes requirieron ventilación mecánica y tratamiento vasopresor.* **Conclusiones:** *La fiebre fue el síntoma principal y la presentación leve de la enfermedad fue la más frecuente. En los pacientes hospitalizados con alguna comorbilidad e infectados por COVID-19, la gravedad de la enfermedad fue mayor, con un alto porcentaje de mortalidad.*

Palabras clave: *COVID-19. Características clínicas. Tomografía computarizada. Niños.*

Introduction

In December 2019, an "unexplained viral pneumonia" outbreak attributed to a new coronavirus (2019-nCoV) appeared in Wuhan, Hubei Province, China[1,2]. In February 2020, it was classified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses; subsequently, the World Health Organization (WHO) officially named this new disease as coronavirus disease 2019 (COVID-19)[3,4]. SARS-CoV-2 is highly contagious and caused a rapid spread of infection throughout China and the rest of the world[5]. The exponential increase in cases prompted WHO to classify this new disease as a public health emergency of international concern, declaring it a pandemic on March 11, 2020[6].

The main routes of transmission of COVID-19 in children are respiratory and close contact with symptomatic and asymptomatic family members[7-9]. So far, case reports in neonates are limited. Only case reports have been published in which vertical transmission has not been confirmed, so transmission of SARS-CoV-2 from mother to newborn is still inconclusive[10-12]. Children present with a milder form of the disease than adults. Asymptomatic infections and mild and moderate forms of the disease comprise more than 90% of the reported cases with a positive COVID-19 test in children[13].

Severe and critical cases in children represent 5.9%, compared to 18.5% in adults[14]. Some hypotheses have been proposed to explain the lower number of COVID-19 infections in children:

1. A difference in the child's immune system compared to that of the adult, both in its composition and in its functional response capacity.
2. The presence of other viruses in the respiratory tract of children could limit the growth of SARS-CoV-2.
3. The difference in angiotensin-converting enzyme 2 (ACE-2) receptor expression, which is necessary for SARS-CoV-2 binding and infection[15-17].

Fever and cough are the most common symptoms in children but occur less frequently than in adults. In general, compared with adults, the clinical expression in this population is modified because a large proportion of those infected is asymptomatic. In addition, laboratory and thoracic imaging findings may not be specific in children with COVID-19[18,19].

The objective of this case series was to describe the clinical and epidemiological characteristics, laboratory results, and tomographic findings of children under 18 years of age with confirmed COVID-19 in two hospital centers in Culiacán, Sinaloa, Mexico.

Methods

We conducted a retrospective cross-sectional study in two pediatric hospitals. All patients under 18 years of age with respiratory triage admission and patients hospitalized between April 1 and June 30, 2020, with a confirmatory COVID-19 test were included in the study. Samples were collected with nasopharyngeal swabs, and COVID-19 diagnosis was confirmed by quantitative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) method at the Laboratorio Estatal de Salud Pública of Sinaloa (Sinaloa State Public Health Laboratory). Clinical, laboratory and radiographic data were extracted from the electronic clinical record and captured in a database. The study was approved by the Ethics and Research Committee of the hospitals that participated in the study: Hospital Pediátrico de Sinaloa Dr. Rigoberto Aguilar Pico (2020 HPS.DI.309) and Hospital General Regional No. 1, Instituto Mexicano de Seguro Social (2020-2506-037) in Culiacán, Sinaloa, México.

Epidemiologic, clinical, laboratory, and radiologic findings were documented using chest computed tomography (CCT). Anthropometric variables were used to classify patients as underweight, normal, overweight, or obese. COVID-19 symptoms were recorded in all patients and classified according to symptomatology as upper respiratory tract infection (URTI) associated with the presence of odynophagia, rhinorrhea, and dry cough; or lower respiratory tract infection (LRTI), in patients with wet cough/rales, tachypnea, shortness of breath, dyspnea, and oxygen saturation less than 92%. CCT findings were classified according to the consensus of the Radiological Society of North America (RSNA), the Society of Thoracic Radiology (STR), and the American College of Radiology (ACR) into four categories:

1. Typical pattern, characterized by ground-glass opacities (GGO) of bilateral and peripheral distribution, characteristic of COVID-19 viral pneumonia.
2. Indeterminate pattern, shows with multifocal, diffuse, perihilar, or unilateral GGO with or without condensation.
3. Atypical pattern, presents single lobar or segmental condensation without GGO, pulmonary cavitation, or pleural effusion.
4. Negative, absence of tomographic findings suggestive of pneumonia[20,21].

Three groups were classified to compare factors that could increase the risk of mortality: patients without comorbidities, immunocompromised children (patients with cancer or chemotherapy treatment), and patients with chronic diseases (patients with medical pathology unrelated to immunodeficiency, with more than one year of evolution or with congenital disease and limitation in physical activity).

According to clinical, laboratory, and CCT findings, the severity of COVID-19 was classified as[22] follows: mild (symptoms of acute URTI, negative CCT, no oxygen treatment); moderate (pneumonia diagnosed clinically or by imaging studies, fever, productive cough, wheezing, oxygen saturation of 95%, and no need for supplemental oxygen); severe (fever and cough accompanied by gastrointestinal symptoms such as diarrhea, evolution of one week, dyspnea, central cyanosis and saturation below 92%, and need for noninvasive supplemental therapy and treatment with inotropic or vasopressors); or critical (rapid progression to acute respiratory distress syndrome (ARDS) or respiratory failure, shock, encephalopathy, heart failure, disseminated intravascular coagulation, acute kidney injury, multiple organ failure, and need for oxygen with mechanical ventilation and support with inotropic and vasopressors).

Laboratory findings were defined as follows: leukopenia (< 5.5 x 10^9/L), neutropenia (< 1.0 x 10^9/L), lymphopenia (< 1.2 x 10^9/L), thrombocytopenia (< 150 x 10^9/L), elevated C-reactive protein (> 3 mg/dL), elevated aspartate and alanine aminotransferase (> 50 U/L).

Statistical analysis

When appropriate, continuous variables were expressed as means or medians and standard deviation or interquartile ranges (IQR). Categorical variables were summarized as absolute values and percentages. The Mann-Whitney U-test was used to compare epidemiological variables and categorical clinical variables. A p-value < 0.05 was considered as significant. We used the SPSS version 22.0 statistical package.

Results

Between April 1 and June 30, 2020, 54 children with confirmed RT-PCR for COVID-19 were identified. The first case occurred in an 8-month-old infant with Down syndrome (April 15, 2020). Figure 1 shows the distribution of the 54 patients with COVID-19 by week and severity of infection. Forty patients (74.1%) were admitted through respiratory triage, of whom 28 (70%) were hospitalized, and the remaining patients (12) were discharged home with symptomatic treatment. Fourteen patients (25.9%) were already hospitalized for another disease; 28 patients (51.9%) were classified as having no comorbidities, 14 (25.9%) with immunodeficiency, and 12 (22.2%) with chronic disease. According to the severity of infection, 29 patients (53.7%) had mild, 14 (25.9%) moderate, 5 (9.3%) severe, and 6 (11.1%) critical disease.

Figure 2 shows the distribution of COVID-19 cases with no comorbidities, immunocompromised, with chronic diseases according to the severity of the disease.

Table 1 summarizes the clinical characteristics of the 54 patients with COVID-19. In the group of patients with no comorbidities, the median age was 5 years (IQR 9 months-12.7 years); in immunocompromised children, the median age was 9 years (IQR 1.7-16 years); in children with chronic diseases, the median age was 5.5 years (IQR 6 months-12.5 years, p = 0.314). The most frequent age group was 1-5 years, with 14 cases (25.9%).

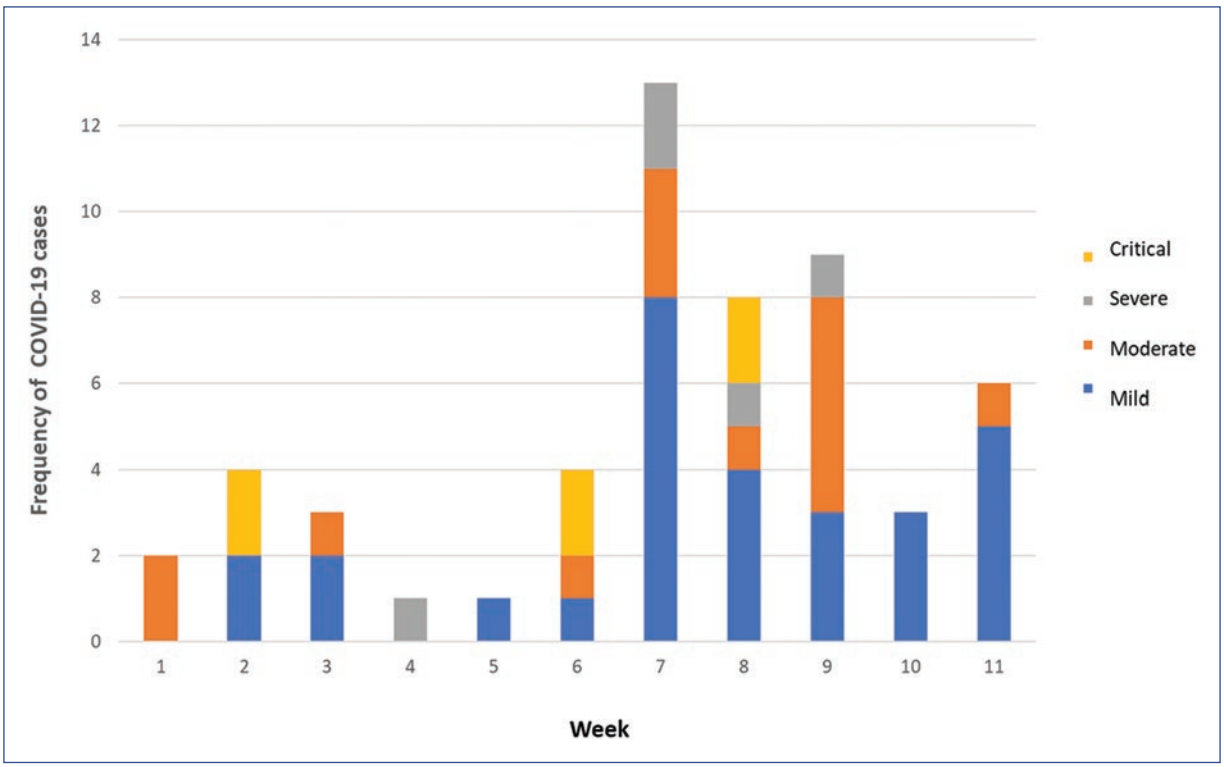

Figure 1. Distribution of patients with COVID-19 (N = 54) by week (April 1 to June 30, 2020) and severity of infection.

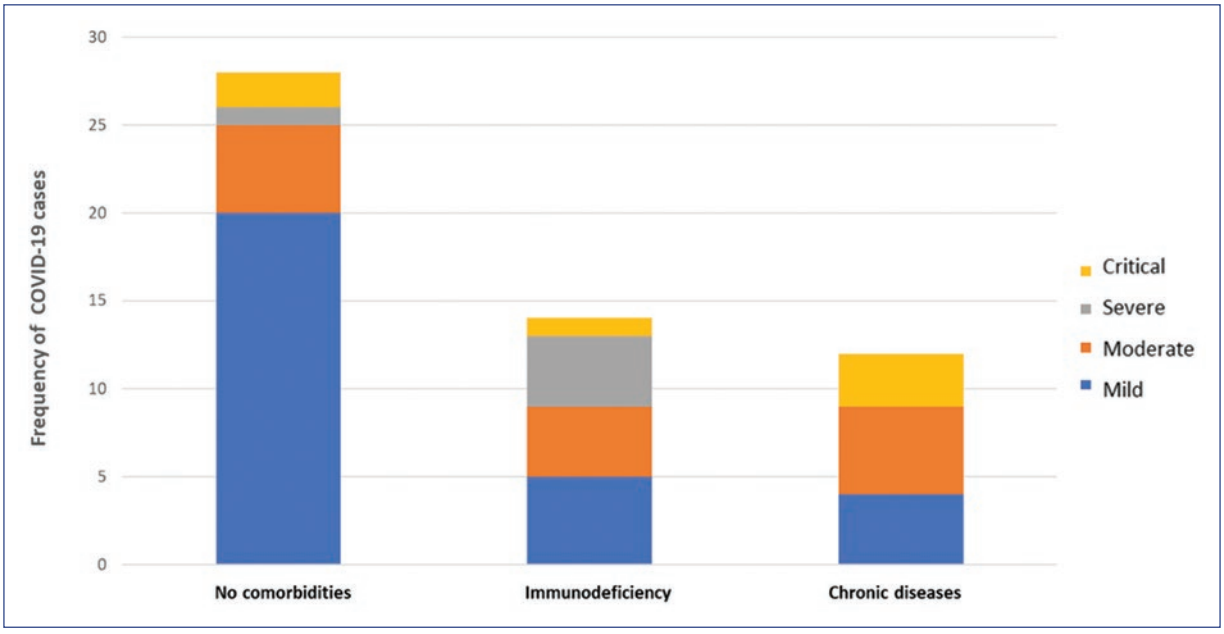

Figure 2. Distribution of the 54 cases with COVID-19 by medical history and disease severity.

Figure 3 describes the distribution of COVID-19 cases by age group and disease severity. The distribution by sex was higher in males, with 32 cases (59.3%; p = 0.672). According to weight, 35 patients (64.8%) were of normal weight. The route of infection in 30 patients (55.6%) was by contact with a non-relative

Table 1. Clinical and epidemiological characteristics of children with COVID-19

Characteristics	Total (n = 54)	No CM (n = 28)	IC (n = 14)	CD (n = 12)	*p*-values
Age (years)*	6 (11 m-13)	5 (9 m-12.7)	9 (1.7-16)	5.5 (6 m-12.5)	0.314
Age groups (years)					
< 1	13 (24.1)	7 (25)	3 (21.4)	3 (25)	0.383
1-5	14 (25.9)	9 (32.1)	2 (14.3)	3 (25)	
6-10	8 (14.8)	3 (10.7)	3 (21.4)	2 (16.7)	
11-15	13 (24.1)	7 (25)	2 (14.3)	4 (33.3)	
> 15	6 (11.1)	2 (7.1)	4 (28.6)	0 (0)	
Sex					
Female	22 (40.7)	10 (35.7)	7 (50)	5 (41.5)	0.672
Male	32 (59.2)	18 (64.2)	7 (50)	7 (58.3)	
Status by weight					
Normal	35 (64.8)	22 (78.6)	6 (42.9)	7 (58.3)	0.189
Underweight	7 (13)	2 (7.1)	2 (14.3)	3 (25)	
Overweight	2 (7.1)	2 (7.1)	4 (28.6)	2 (16.7)	
Obesity	2 (7.1)	2 (7.1)	2 (14.6)	0 (0)	
Route of infection					
Contact with an infected family member	10 (18.5)	9 (32.1)	0 (0)	1 (8.3)	0.023
Contact with a non-relative infected individual	30 (55.6)	16 (57.1)	8 (57.1)	6 (50)	
In-hospital	14 (25.9)	3 (10.7)	6 (42.9)	5 (41.7)	
COVID-19 severity					
Mild	29 (53.7)	20 (71.7)	5 (35.7)	4 (33.3)	0.010
Moderate	14 (25.9)	5 (17.9)	4 (28.6)	5 (41.7)	
Severe	5 (9.3)	1 (3.6)	4 (28.6)	0 (0)	
Critical	6 (11.1)	2 (7.1)	1 (7.1)	3 (25)	
Signs and symptoms					
Body temperature					0.261
< 37.5°C	14 (25.9)	10 (35.7)	1 (7.1)	3 (25)	
37.5-38°C	9 (16.7)	5 (17.9)	3 (21.4)	1 (8.3)	
38.1-39°C	17 (31.5)	5 (17.9)	6 (42.9)	6 (50)	
> 39°C	14 (25.9)	8 (28.6)	4 (28.6)	2 (16.7)	
Symptoms of URTI					
Rhinorrhea/nasal congestion	16 (29.6)	10 (35.7)	3 (21.4)	3 (25)	0.585
Odynophagia	6 (11.1)	3 (10.7)	2 (14.3)	1 (8.3)	0.886
Dry cough	24 (44.4)	12 (42.9)	5 (35.7)	7 (58.3)	0.497
Symptoms of LRTI					
Wet cough/rales	22 (40.7)	11 (39.3)	4 (28.6)	7 (58.3)	0.298
Tachypnea	17 (31.5)	10 (35.7)	1 (7.1)	6 (50)	0.05
Respiratory distress	19 (36.5)	6 (23.1)	4 (28.6)	9 (75)	0.007
Oxygen saturation<92%	17 (31.5)	6 (21.4)	4 (28.6)	7 (58.3)	0.068
Dyspnea	11 (20.4)	2 (7.1)	5 (35.7)	4 (33.3)	0.043
Gastrointestinal symptoms					
Abdominal pain	8 (14.8)	4 (14.3)	3 (21.4)	1 (8.3)	0.641
Hyporexia/anorexia	14 (25.9)	6 (21.4)	4 (28.6)	4 (33.3)	0.709
Nausea	9 (16.7)	4 (14.3)	2 (14.3)	3 (23)	0.680
Vomiting	10 (18.5)	5 (17.9)	2 (14.3)	3 (25)	0.776
Diarrhea	6 (11.6)	4 (14.3)	1 (7.1)	1 (8.3)	0.740
Neurological symptoms					
Headache	14 (25.9)	8 (28.6)	6 (42.9)	0 (0)	0.041
Seizures	2 (3.7)	0 (0)	1 (7.1)	1 (8.3)	0.323
Anosmia	1 (1.9)	1 (3.6)	0 (0)	0 (0)	0.623
Dysgeusia	1 (1.9)	1 (3.6)	0 (0)	0 (0)	0.623
Asthenia	20 (37)	7 (25)	8 (57.1)	5 (41.7)	0.118
Myalgia or muscle fatigue	5 (9.3)	1 (3.6)	4 (28.6)	0 (0)	0.014
Chest pain	5 (9.3)	2 (7.1)	1 (7.1)	2 (16.7)	0.604
Skin rash	3 (5.6)	3 (10.7)	0 (0)	0 (0)	0.229

Data are expressed as n (%) unless indicated otherwise.
*median (interquartile range).
CD, chronic diseases; CM, comorbidities; COVID-19, coronavirus disease 2019; IC, immunocompromise; IQR, interquartile range; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

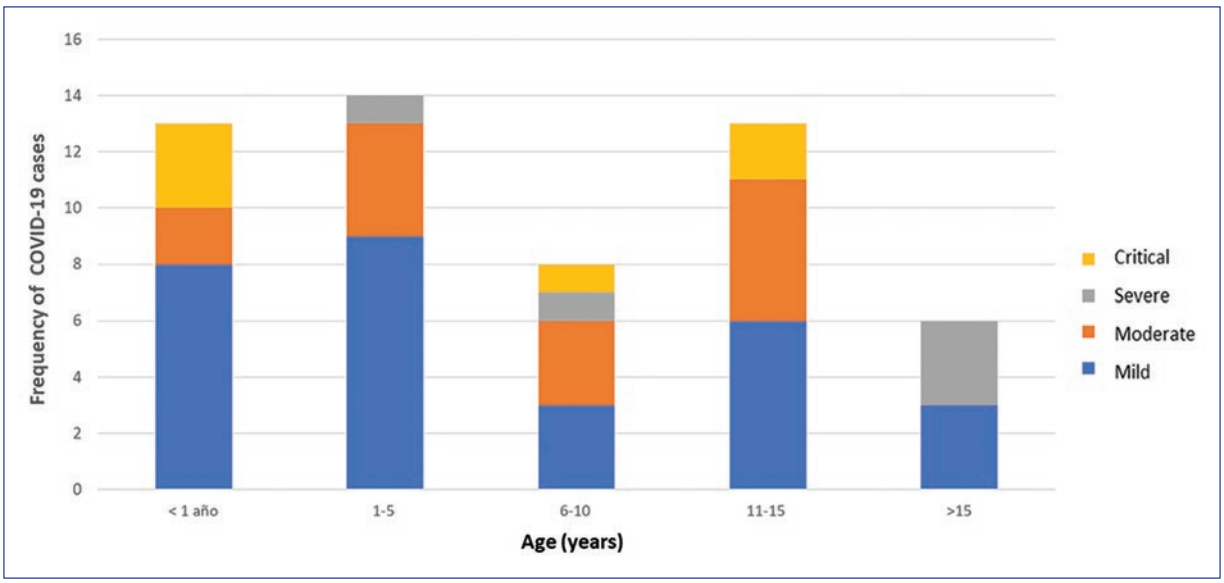

Figure 3. Distribution of the 54 cases with COVID-19 by age group and disease severity.

infected individual; the in-hospital route of infection was high in patients with some immunodeficiency (6, 42.9%) or chronic disease (5, 41.7%; $p = 0.023$). Fever was the most frequent symptom observed in 40 patients (74.1%).

In patients with URTI, dry cough was reported in 24 (44.4%) and rhinorrhea with nasal congestion in 16 cases (29.6%); no significant differences were observed between the study groups. In children with LRTI, wet cough with rales was the most frequent symptom in 22 cases (40.7%). In patients with chronic diseases, respiratory distress was the most frequent sign in nine cases (75%; $p = 0.007$). In 17 cases (31.5%), oxygen saturation was < 92%. Hyporexia was the most frequent gastrointestinal symptom in 14 patients (25.9%). In addition, other symptoms were recorded, such as vomiting (n = 10, 18.5%) and diarrhea (n = 6, 11.6%). Headache was the most prevalent neurological symptom, detected in 14 cases (25.9%); the least frequent were seizures (n = 2, 3.7%), anosmia, and dysgeusia in one case (1.9%), respectively. Among the general symptoms, general malaise was recorded in 20 (37%), myalgia or muscle fatigue in 5 (9.3%), chest pain in 5 (9.3%), and skin rash in 3 patients (5.6%).

Table 2 summarizes the laboratory and CCT characteristics observed in the 42/54 (77.8%) patients with COVID-19 who were hospitalized after respiratory triage or who presented with COVID-19 while hospitalized. Leukopenia (< 5500 total leukocytes) was observed in 9 patients (21.4%), neutropenia (< 1000 absolute neutrophils) in 9 (21.4%), lymphopenia (< 1200 absolute lymphocytes) in 12 (28.6%), and thrombocytopenia (< 150,000 mL) in 14 (33.3%) patients. All alterations were observed more frequently in immunocompromised patients. C-reactive protein (CRP) levels > 3 mg/L were observed in 69.5% (16/23), and serum alanine and aspartate aminotransferase (ALT and AST) levels > 50 U/L were recorded in 61.5% (16/26), respectively.

The alterations observed in 42 CCT scans were heterogeneous. Thirteen patients (31%) showed typical COVID-19 (GGO) images, 14 (33%) showed an intermediate pattern, six (14.3%) atypical pattern, and nine (21.4%) patients had negative or normal CCT scans.

Thirty-nine patients (92.9%) received antibiotic treatment, 32 (76.2%) with antivirals, and 21 (50%) with hydroxychloroquine. Six patients (14.2%) required respiratory support with mechanical ventilation and vasopressor drugs.

The median in-hospital days was 10 days (IQR 7-24 days), and 3/42 (7.1%) patients were still hospitalized at the end of the study.

Comorbidities were reported in 26 (61.9%) patients, and 6 (14.2%) deaths were recorded. In the group of patients with immunodeficiency, one death was recorded in a 6-year-old female patient with Down syndrome and acute lymphoblastic leukemia. In contrast, five deaths were recorded in the group of patients with chronic disease: an 8-month-old male with congenital heart disease and Down syndrome, an 8-year-old male

Tabla 2. Laboratory and CCT results of children hospitalized with COVID-19

Characteristics	Total (n = 42)	No CM (n = 16)	IC (n = 14)	CD (n = 12)	*p*-values
Initial results					
Leukocytes x10^9/L*		13.8 (8.3-21.3)	3.5 (0.2-11.2)	10.4 (8.8-14.3)	0.021
Leukopenia<5.5 x10^9/L	9 (21.4)	2 (12.5)	6 (42.8)	1 (8.3)	0.032
Neutropenia<1.0 x10^9/L	9 (21.4)	1 (6.3)	7 (50)	1 (8.3)	0.003
Lymphopenia<1.2 x10^9/L	12 (28.6)	1 (6.3)	8 (57)	3 (25)	0.004
Thrombocytopenia<150	14 (33.3)	3 (18.7)	9 (64.3)	2 (16.7)	0.004
CRP>3 mg/dL	16/23 (69.5)	5/8 (62.5)	6/8 (75)	5/7 (71.4)	0.856
ALT>50 U/L	16/26 (61.5)	4/8 (50.0)	8/11 (72.7)	4/7 (57.1)	0.580
AST>50 U/L	16/26 (61.5)	4/8 (50.0)	8/11 (72.7)	4/7 (57.1)	0.580
CCT, according to RSNA					
Typical	13 (30.9)	4 (25.0)	7 (50)	2 (16.7)	0.087
Indeterminate	14 (33.3)	4 (25.0)	4 (28.6)	6 (50.0)	
Atypical	6 (14.2)	1 (6.25)	2 (14.3)	3 (25.0)	
Negative	9 (21.4)	7 (43.7)	1 (7.1)	1 (8.3)	
Treatment					
Antibiotic	39 (92.9)	15 (93.8)	13 (92.9)	11 (91.7)	0.537
Antiviral	32 (76.2)	12 (75)	12 (85.7)	7 (58.3)	0.256
Hydroxychloroquine	21 (50)	7 (43.8)	9 (64.3)	5 (41.7)	0.372
Mechanical ventilation	6 (14.1)	0 (0)	1 (7.1)	5 (41.7)	0.005
Vasopressor/inothropic	6 (14.1)	0 (0)	1 (7.1)	5 (41.7)	0.005
Days of hospitalization*	10 (7-24)	12 (5-17)	19 (8-32)	22 (7-30)	0.186
Mortality	6 (14.2)	0 (0)	1 (7.1)	5 (41.7)	0.005

Data are expressed as n (%) unless indicated otherwise.
*median (interquartile range).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCT, chest computed tomography; CD, chronic diseases; CM, comorbidities; COVID-19, coronavirus disease 2019; IC, immunocompromise; IQR, interquartile range; LRTI, lower respiratory tract infection; RSNA, Radiological Society of North America; URTI, upper respiratory tract infection.

with muscular atrophy and chronic lung disease, an 11-year-old male with chronic lung disease and chronic renal failure, a 13-year-old female patient with Turner syndrome and chronic renal failure, and a 14-year-old male with infantile cerebral palsy and chronic lung disease. All patients were treated with vasoactive amines and mechanical ventilation support.

Discussion

This case series describes the spectrum of illness produced by SARS-CoV-2 infection in 54 children during the first three months of the pandemic. The description of this series is based on the experience gained from caring for a group of 54 children with COVID-19. Unfortunately, it was not possible to detect asymptomatic infections because RT-PCR was only performed in children admitted with suspected COVID-19 due to their symptoms. However, we know the potential risk of transmission in asymptomatic patients and the importance of developing pandemic control measures. The relevance of our study is that it describes the experience in two hospitals in a considerable sample of COVID-19 cases representing clinical, laboratory, radiological, treatment, and mortality variables. In our study, the in-hospital transmission of COVID-19 was high, and the transmission source was probably the patients' relatives or healthcare personnel. In a series of 130 pediatric patients, Parri et al.[23] observed that 53.8% of the positive cases had contact with a COVID-19 case, and 95.5% was a family member.

In our study, the group aged 1 to 5 years had the highest prevalence of COVID-19 and a higher frequency in males. According to disease severity, the group with mild symptoms was the most frequent. The results are similar to the report of 31 cases of COVID-19 by Wang et al.[24], which was one of the first studies reported in China. In that report, the average age of the 31 children studied was 7 years. Sixty-eight percent of the cases had contact with confirmed infected adults. The clinical classification was asymptomatic in 13%, mild in 42% of the cases, and moderate in 45%; the male sex was the most frequent, and no severe or critical cases were observed[24].

The most frequent clinical data in our study were fever > 38°C, dry or wet cough, hyporexia, and headache. The results of a systematic review by De Souza et al.[25] described the clinical laboratory and radiological

characteristics of 1124 cases of children with COVID-19 obtained from 38 case series. Fever was the most prevalent symptom, followed by cough, nasal symptoms, diarrhea, nausea, vomiting, fatigue, and respiratory distress.

In another study, Kainth et al.[26] described the clinical characteristics, sociodemographics, hospital course, and disease severity of 65 patients with COVID-19 in the USA. In this series, fever was present in 86% of patients, lower respiratory symptoms or signs in 60%, and gastrointestinal symptoms in 62%. Intensive care was required in 35% of patients.

Laboratory tests alterations observed in our study were leukopenia, neutropenia, lymphopenia, thrombocytopenia, and increased liver enzymes. The results were similar to those reported by Parri et al.[23], who detected leukopenia and lymphopenia in 36.8% and 15.7% of patients, respectively, while increases in ALT and AST were recorded in 18.3% and 11.8%, respectively.

The limitations of this study include those inherent to the case series design, which only describes the clinical characteristics of a group of patients without allowing statistical inferences or causal associations. In addition, the magnitude of the problem was unknown because the results of laboratory tests and imaging studies were only performed in patients with symptoms who attended the hospitals. However, we consider the results obtained from the sample studied to be of great interest because they describe the first cases of COVID-19 in two hospitals with the highest concentration of pediatric population in Sinaloa.

In our study, during the first three months of the pandemic, a high percentage of children became infected with SARS-CoV-2 through contact with infected persons who were not immediate family members; infection was primarily mild, and fever was the main symptom. Conversely, the disease was more severe in patients hospitalized for chronic disease and infected with COVID-19, with a high mortality rate.

Fever is one of the leading causes of consultation to the pediatrician; therefore, pediatricians must have a high level of clinical suspicion to make a timely diagnosis of COVID-19.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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RESEARCH ARTICLE

Antibiotherapy at birth in very low birth weight infants before and after the use of interleukin 6 as an infectious biomarker in a tertiary level unit

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Abstract

Background: *Neonatal sepsis is a condition with high mortality and morbidity that contributes to high rates of antibiotic therapy at birth. In addition, very low birth weight newborns (VLBWN) are particularly vulnerable. Interleukin 6 (IL-6) seems to be an early and effective marker that could help a better selection of patients to be treated. This study aimed to evaluate the use of antibiotics in the first 72 hours of life in VLBW infants before and after using IL-6 as an infection marker. Also, we wanted to analyze the differences in morbidity and mortality during admission and other factors associated with the decision to start antibiotic treatment.* **Methods:** *We conducted a cohort retrospective study. We included VLBWN born in our hospital or admitted before 72 hours of life in two two-year periods (2007-2008 and 2011-2012).* **Results:** *Antibiotics use during the first 72 hours of life was analyzed as the primary variable, which was reduced by 20% on the second period ($p = 0.002$). Regarding the analysis of secondary variables, we found no significant differences in mortality during hospital admission and the incidence of nosocomial sepsis, enterocolitis, or invasive fungal infection. The multivariate analysis indicated extreme prematurity and the study group as the most strongly related factors to the start of antibiotic therapy.* **Conclusions:** *IL-6 was a useful marker of infection to reduce the use of antibiotic therapy in VLBW infants without increasing mortality.*

Keywords: *Interleukin 6. Neonatal sepsis. Antibiotics. Very low-birth weight newborns.*

Antibioterapia al nacimiento en recién nacidos de muy bajo peso antes y después del uso de interleucina 6 como marcador de infección en una unidad de nivel III

Resumen

Introducción: *La sepsis neonatal es una patología con altas mortalidad y morbilidad, lo cual contribuye a las altas tasas de antibioticoterapia al nacimiento. Los recién nacidos de muy bajo peso (RNMBP) son especialmente vulnerables. La interleucina 6 (IL-6) parece ser un marcador precoz y eficaz que podría ayudar a una mejor selección de los pacientes. El objetivo de este estudio fue evaluar el uso de antibióticos en las primeras 72 horas de vida en los RNMBP antes y después de utilizar IL-6 como marcador de infección; en segundo lugar, analizar las diferencias en la morbilidad y la mortalidad durante el ingreso, y estudiar la presencia de otros factores asociados con la decisión de iniciar un tratamiento antibiótico.* **Métodos:** *Se llevó a cabo un estudio de cohortes en el que se incluyeron los RNMBP nacidos en nuestro hospital o admi-*

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tidos antes de las 72 horas de vida en dos periodos de 2 años (2007-2008 y 2011-2012). **Resultados:** *Como variable principal se analizó el uso de antibióticos en las primeras 72 horas de vida, que se redujo casi un 20% en el segundo periodo (p = 0.002). En cuanto a las variables secundarias, no se detectaron diferencias significativas en la mortalidad durante el ingreso ni en la incidencia de sepsis nosocomial, enterocolitis o infección fúngica invasiva. El análisis multivariado señaló la extrema prematuridad y el grupo de estudio como los factores más estrechamente relacionados con el inicio de la antibioticoterapia.* **Conclusiones:** *La IL-6 fue un marcador de infección útil para reducir el uso de antibioticoterapia al nacimiento en los RNMBP, sin aumentar la mortalidad.*

Palabras clave: *Interleucina 6. Sepsis neonatal. Antibióticos. Recién nacido de muy bajo peso.*

Introduction

Neonatal sepsis of vertical transmission constitutes one of the most significant challenges for neonatologists due to its high morbidity and mortality and difficult diagnosis[1].

This pathology affects approximately 9-11 per 1000 very low birth weight newborns (VLBWN), and the mortality can be as high as 8%[2,3]. Also, the pathogenesis is more complicated in preterm infants[4-6]. Intraamniotic infection probably starts before labor and might be the cause—not the consequence—of premature rupture of membranes. In addition, other causes of immune-mediated inflammation may promote rupture and trigger labor. Therefore, it is implied that the same infectious risk factors do not have the same weight on both populations[7,8].

Regarding diagnosis, symptomatology is not specific and is common to other pathologies of prematurity: infection markers are not sensitive and specific enough, and blood culture, considered the gold standard, has a mediocre diagnostic yield, in addition to a long waiting period[9,10]. Furthermore, during the first days of life, the ongoing metabolic, hormonal, and immunological processes complicate determining the standard values of these markers.

These reasons, such as the often fulminant presentation of this type of sepsis and the great difficulty in its diagnosis, often lead to initiate probabilistic antibiotic treatment at birth and prolong it despite negative cultures[11-13]. However, the consequences are not trivial.

The use of antibiotics in the neonatal period leads to a decrease in the biodiversity of the intestinal microbiota, among other things, favoring the appearance of pathogenic organisms and delaying the usual colonization of the gastrointestinal tract[14-16]. In extremely premature infants, this microbiota modification implies an increased risk of late sepsis, ulcerative-necrotizing enterocolitis, and invasive fungal infection[17-19].

Therefore, the challenge is to reduce the use of antibiotics without compromising this vulnerable population. One of the means of improvement to achieve this objective is identifying new biological markers of infection. These include interleukins 6, 8, and 10, nCD64, alarmins, and IP-10, among others[20-23].

The use of interleukin 6 (IL-6) as a marker was introduced in our Unit in 2009. IL-6 is a pleiotropic interleukin of the innate immunity produced by different cell types and recognized as the central mediator of the acute phase response[24]. Also, IL-6 has markedly early kinetics in infections. Importantly, there is no physiological elevation of IL-6 in newborns. Numerous studies support its use as an early marker of sepsis, particularly associated with other markers[25-36].

This study aimed to determine the use of antibiotics during the first 72 hours in VLBWN and analyze whether the introduction of IL-6 as a marker of sepsis reduced this use[37]. As secondary objectives, we wanted to compare the morbidity and mortality of both groups during admission and to study other possible factors associated with initiating antibiotic treatment.

Methods

We conducted a retrospective cohort study. The first cohort corresponded to a period before IL-6 was used as a marker of sepsis in the service (group I or Pre IL-6). The second cohort corresponded to a period after introducing IL-6 (group II or Post IL-6).

We included patients admitted from January 1, 2007, to December 31, 2008 (group I) and from January 1, 2011, to December 31, 2012 (group II). This study was a single-center study in a level IIIb unit (Neonatology Department of the Hospital Universitario Central de Asturias, Spain).

Preterm newborns with birth weight < 1500 g born in our hospital or hospitalized during the first 72 hours of life were selected. We considered the day of admission as the moment of enrollment in the cohort (Figure 1).

The primary outcome variable was the administration of antibiotic therapy during the first 72 hours of life. The

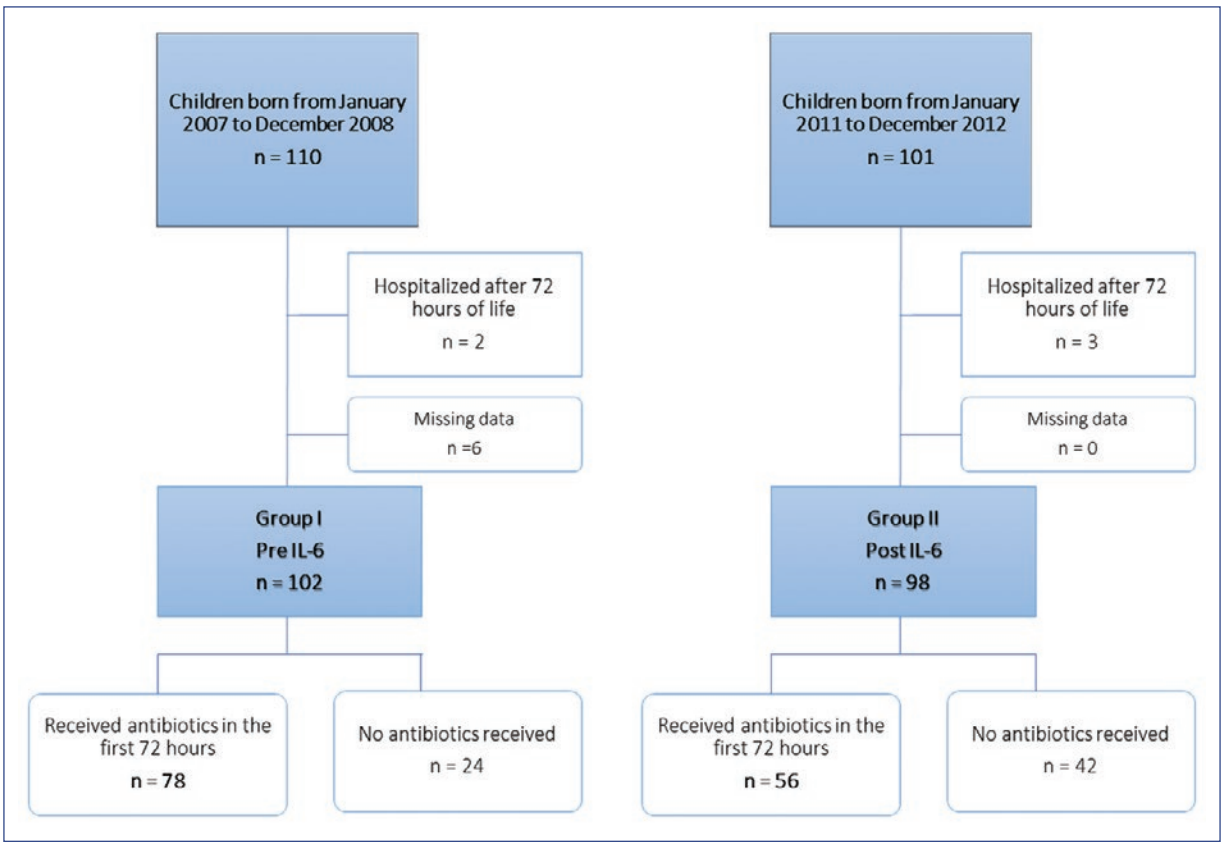

Figure 1. Flow chart of patients from two study periods. IL-6, interleukin 6.

secondary outcome variables were those related to morbidity during admission: nosocomial sepsis, necrotizing enterocolitis, invasive fungal infection, days of hospital stay, and mortality.

We also collected general variables and those related to the diagnosis and treatment of early sepsis (C-reactive protein (CRP) and IL-6 levels in the admission blood test, blood culture results, antibiotic treatment, and duration) to characterize both populations. IL-6 levels at birth are expressed in pg/mL. In group I, the cut-off value in the first 72 hours was 150 pg/mL, and in group II, 300 pg/mL[38,39].

We also collected data on potentially effect-modifying variables such as risk factors for infection or gestational age. Discharge reports, hospitalization clinical course, and nursing charts were used for data collection through the hospital's information software (Cerner Millenium).

Qualitative variables were expressed as percentages. Normal quantitative variables were reported as the mean with a 95% confidence interval (95% CI). In the case of the Apgar test, the median and interquartile ranges were used. As the groups are sufficiently large, we assumed that the distribution of the means followed a normal distribution according to the central limit theorem.

When considered relevant, percentages were compared using the χ^2 test and the odds ratio (OR) with its confidence interval. The Student's t-test was used to compare quantitative variables and the Mann-Whitney's U-test for the Apgar test.

A binary logistic regression was performed (Wald backward stepwise method with PIN 0.05 and POUT 0.10) to determine which variables had a statistically significant effect after the previous analysis. The dependent variable was the antibiotic treatment, and the independent variables were prolonged rupture of membranes (> 18 h), gestational age (< 28 weeks), spontaneous prematurity, and the study group (I or II).

Statistical analysis was performed with SPSS-17 and R packages.

The Regional Ethics Committee (CEIP-Comité de Ética en Investigación de Asturias) approved this protocol.

Table 1. Comparative analysis of initial characteristics of patients in the studied groups

Characteristics of the patients	Group I (n = 102) Jan 2007-Dec 2008 n (%)	Group II (n = 98) Jan 2011-Dec 2012 n (%)	*p*-values
Gestational age (weeks)*	28 (28.4-29.3)	29 (28.3-29.6)	0.738
Birth weight (g)*	1086 (1034-1139)	1085 (1030-1140)	0.983
Spontaneous prematurity	57 (55.9%)	62 (63.3%)	0.288
Rupture of membranes (> 18 h)	7 (6.9%)	20 (20.4%)	0.005
Sex Male Female	 53 (52%) 49 (48%)	 52 (53.1%) 46 (46.9%)	
Multiple birth	40 (39%)	38 (39%)	0.958
Chorioamnionitis	3 (2.9%)	8 (8.2%)	0.105
Type of delivery Cesarean section Normal Instrumental vaginal delivery	 77 (75.5%) 25 (24.5%) 0	 60 (61.2%) 34 (34.7%) 4 (4.1%)	0.025
Gestation obtained through *in vitro* fertilization	8 (7.8%)	23 (23.5%)	0.002
Prenatal corticosteroid therapy Partial Complete	 26 (25.5%) 61 (59.8%)	 46 (46.9%) 40 (40.8%)	0.005
Maternal antepartum antibiotic therapy	16 (16.3%)	38 (39.6%)	0.001
Apgar 1 min**	7 (4)	7 (4)	0.548
Apgar 5 min**	8 (2)	9 (2)	0.883
Intubation in the delivery room	41 (41.8%)	33 (32.4%)	0.132
Received surfactant at some point	55 (53.9%)	52 (53%)	0.972
Diagnosis of hyaline membrane disease	54 (52.9%)	56 (57.1%)	0.492
Persistent *ductus arteriosus*	20(19.6%)	33 (33.7%)	0.030
Pharmacological treatment of persistent *ductus arteriosus* (ibuprofen)	14 (13.7%)	15 (15.3%)	0.706
CRP (mg/dL)*	0.55 (0.39-0.72)	0.10 (0.06-0.15)	0.001
IL-6 > 150 pg/mL	—	18 (37.8%)	
IL-6 > 300 pg/mL	—	15 (31%)	
Inotropes hypotension	22 (21.6%)	22 (22.4%)	0.382
Nasal CPAP/MV at 28 days of life	10 (9.8%)	13 (13.2%)	0.707

CI, confidence interval; CPAP, continuous positive airway pressure; CRP, C-reactive protein; IL-6, interleukin 6; IQR, interquartile range; MV, mechanical ventilation.
*Mean (95%CI); **Median (IQR).

Results

General characteristics of both groups

We had two groups of 102 and 98 patients (group I and II, respectively). Table 1 shows the general variables of both groups. In group I, the mean gestational age was 28 weeks (95% CI 28.4-29.3), the mean birth weight was 1086 g (95% CI 1034-1139), the sex distribution was almost equal (52% male), and the median Apgar 7 and 8 at 1 and 5 min, respectively. In group II, the mean gestational age was 29 weeks (95% CI 28.3-29.6), mean birth weight 1085 g (95% CI 1030-1140), 53% were male, and median Apgar 7 and 9 at

Table 2. Comparative analysis of the primary and secondary outcome variables of both groups

Primary and secondary outcome variables	Group I Jan 2007-Dec 2008 (n = 102) n (%)	Group II Jan 2011-Dec 2012 (n = 98) n (%)	*p*-values
Antibiotic therapy in the first 72 h of life	78 (76.5%)	56 (57.1%)	0.004
Antibiotic therapy in the first 72 h of life in patients with sterile blood culture	69 (75%)	52 (57.7%)	0.052
Result of blood culture at birth Gram-negative Coagulase-negative *Staphylococcus* Another microorganism Sterile	 4 (3.9%) 2 (1.9%) 4 (3.9%) 92 (90%)	 1 (1%) 2 (2%) 1 (1%) 90 (91.8%)	0.348
Invasive fungal infection	4 (3.9%)	0	0.066[b]
Exitus during admission	22 (21.6%)	21 (21.4%)	0.981
Antibiotic cycles Median (IQR) Median (95% CI)	 1 (1) 1.5 (1.3-1.7)	 1 (5) 1.25 (1.0-1.4)	 0.041 0.086
Blood culture result[a] Gram negative Coagulase negative *Staphylococcus* Another microorganism Sterile	n = 50 18 (36%) 15 (30%) 5 (10%) 12 (24%)	n = 44 9 (20%) 23 (51%) 6 (13%) 7 (16%)	0.119
In-hospital stay days in survivors[c] Mean (95%CI)	 89.8 (66.7-112.8)	 51.1 (44.7-57.5)	 0.002

[a]Blood culture extracted in the first episode of nosocomial sepsis; [b]Fisher's exact test; [c]Excluding those who died in the first week of life.
CI, confidence interval; IQR, interquartile range.

1 and 5 min, respectively. No significant differences were found between groups regarding these variables.

We found significant differences between the groups ($p = 0.025$) regarding the birth route: 24.5% of normal deliveries and 75.5% of cesarean sections in group I versus 34.7% of normal deliveries, 60% of cesarean sections, and 4.1% of instrumental delivery in group II.

Concerning infectious risk factors, no statistically significant differences were found in the percentage of spontaneous prematurity or chorioamnionitis. However, significant differences in prolonged rupture of membranes were observed (6.9% in group I vs. 20.4% in group II).

Regarding the antibiotherapy, 76.5% of patients received antibiotics in the first 72 hours of life in group I versus 57% in group II. This difference was statistically significant ($p = 0.004$). When we analyzed the percentage of antibiotic therapy in patients with sterile blood culture, the difference was 17%, but not statistically significant (75% group I and 57.7% group II; $p = 0.052$) (Table 2). We were able to collect this variable in all preterm infants except for four patients from group II. Figure 2 shows the percentage of antibiotic therapy and antibiotic therapy in patients with sterile blood culture by study group.

Mean CRP at birth was 0.55 mg/dL (95% CI 0.39-0.72) in group I and 0.10 mg/dL (95% CI 0.06-0.15) in group II ($p = 0.001$). We were able to collect IL-6 levels in 79 of 98 patients. The mean IL-6 at birth was 501 pg/mL (95% CI -52-1054), and the median was 36 pg/mL. Both markers do not appear to be correlated strongly with CRP at birth (Spearman's correlation coefficient of 0.3) in most patients.

As for the duration of antibiotic treatment, no significant differences were observed in the mean and median between groups (group I, mean 5.9 days (95% CI 5.4-6.5); median of 5.5; group II, mean 5.3 days (95% CI 4.7-5.9); median of 5).

The antibiotics used in both groups were ampicillin and an aminoglycoside in > 95% of the patients. In group I, vancomycin was used in three patients and cefotaxime

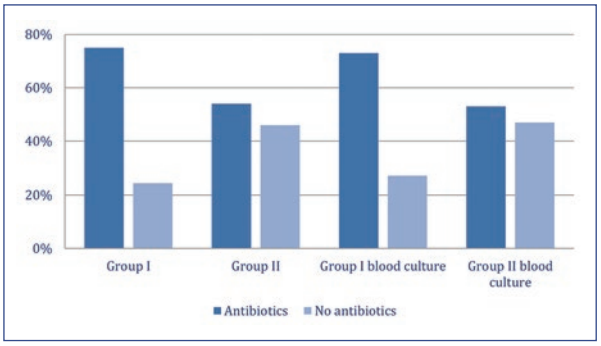

Figure 2. Percentage of antibiotic therapy by study group and percentage of antibiotic therapy in patients with sterile blood culture by study group.
Comparison of the percentage of antibiotic therapy between both groups, $p = 0.002$.
Comparison of the percentage of antibiotic therapy between both groups in patients with sterile blood culture, $p = 0.006$.

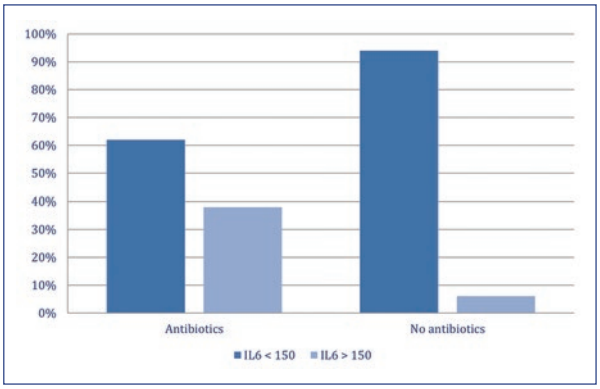

Figure 3. Percentage of patients with IL-6 above and below the cut-off value (150 pg/mL) in the group of patients receiving antibiotic therapy.
IL-6, interleukin 6.

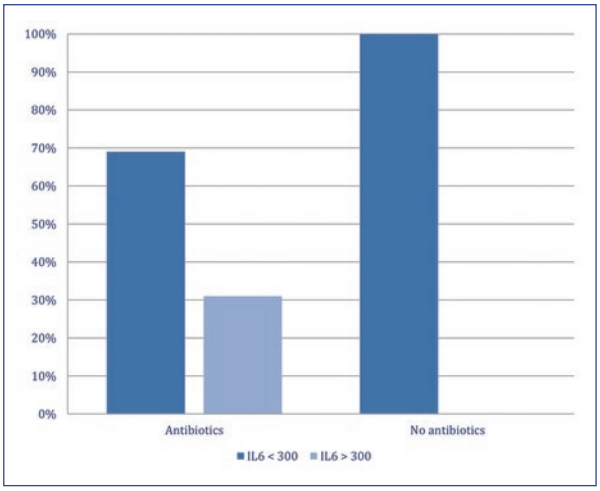

Figure 4. Percentage of patients with IL-6 above and below the cut-off value (300 pg/mL) in the group of patients receiving antibiotic therapy.
IL-6, interleukin 6.

in one patient. In group II, vancomycin was used in two patients and meropenem in one patient with abdominal surgical pathology (neonatal appendicitis).

Regarding the results of blood cultures collected at birth, 90.2% were sterile in group I and 95.9% in group II ($p = 0.348$). Of the remaining, 1.9% of group I and 2 % of group II were positive for coagulase-negative *Staphylococcus*, 3.9% of group I and 1% of group II were positive for a Gram-negative microorganism, and 3.9% of group I and 1% in group II were positive for another microorganism.

In the second study period, we analyzed the percentage of patients who had an IL-6 value above the cut-off level (within the group that had received antibiotics) to find out the importance of IL-6 in the decision to initiate an antibiotic treatment: 37.8% had an IL-6 > 150 pg/mL and 31% had an IL-6 > 300 pg/mL (Table 1). The percentages of patients with IL-6 above and below the cut-off values (150 pg/mL and 300 pg/mL) in the group of patients receiving antibiotic treatment are shown in Figures 3 and 4.

Table 2 shows the variables related to evolution during admission and mortality. No statistically significant differences were found in the percentage of nosocomial sepsis (first episode), necrotizing enterocolitis, invasive fungal infection, or mortality. However, all were slightly higher in group I. In-hospital stay in those who survived beyond the first week of life was significantly longer in group I patients (mean 89.8 days vs. 51.1 days, $p = 0.002$). The median number of antibiotic cycles was 1.5 (95% CI 1.3-1.7) in group I and 1.25 (95% CI 1.0-1.4) in group II.

The result of the blood culture obtained during the first episode of nosocomial sepsis was documented: 24% were sterile in group I and 16% in group II ($p = 0.304$). When analyzing those positive for a Gram-negative microorganism, we found 36% in group I and 20% in group II.

Table 3 shows the bivariate analysis between the patients who received antibiotics (groups I and II) and those who did not. Lower gestational age, lower birth weight, spontaneous prematurity, chorioamnionitis, and belonging to study group I were more frequent in the

Table 3. Comparative analysis of variables related to the risk of developing sepsis of vertical transmission between the patients who received antibiotics in the first 72 hours of life and those who did not receive antibiotics

Variables related to risk	Patients receiving antibiotic therapy in the first 72 h of life (n = 129) n (%)	Patients NOT receiving antibiotic therapy in the first 72 h of life (n = 71) n (%)	*p*-values
Gestational age (weeks)*	27.9 (27.5-28.4)	30.9 (30.4-31.5)	< 0.001
Weight (g)*	1022 (978-1067)	1215 (1155-1275)	< 0.001
Spontaneous prematurity	96 (71.6%)	23 (34.8%)	< 0.001
Chorioamnionitis	11 58.2%)	0%	0.017
Rupture of membranes > 18 h	22 (16.4%)	5 (7.6%)	0.085
Belonging to study group I	78 (58.2%)	24 (36.4%)	0.004

*Mean (95%CI).
CI, confidence interval.

Table 4. Binary logistic regression. Dependent variable: initiation antibiotic treatment in the first 72 hours of life in very-low-birth-weight infants

Risk factors	B	Significance	OR	95%CI	
				Inferior	Superior
Spontaneous prematurity	1.11	0.002	3.28	1.52	7.04
Study group	1.44	< 0.001	4.22	1.96	9.08
Gestational age < 28 weeks	2.80	< 0.001	16.59	4.65	59.23
Constant	1.28	< 0.001	0.27		

CI, confidence interval; OR, odds ratio.

patients receiving antibiotics, with statistically significant differences.

The results of the multivariate analysis are shown in Table 4. Spontaneous prematurity would multiply the risk of receiving antibiotics by 3, extreme prematurity by 16, and belonging to study group I by 4.

Discussion

The use of antibiotics during the first 72 hours of life in VLBWN reached 76.5% of the patients in our Unit, similar to those found in the literature. After implementing IL-6 testing as a biological marker of sepsis in 2009, we observed a 20% reduction in antibiotic therapy. This reduction was almost maintained in the group of patients with negative blood cultures. We have specified this last point because it seems that the negative consequences of this antibiotic treatment would be more pronounced in preterm infants with sterile blood cultures[40]. These data confirm our working hypothesis; however, due to the type of study performed, we cannot conclude that this decrease is exclusively due to the use of IL-6. To analyze the question in more detail, we have examined some of the factors related to initiating antibiotic treatment. As already discussed, this decision is based on three pillars that are not easy to interpret in preterm infants: clinical features, clinical risk factors, and biological markers of infection.

Regarding the general data that can determine the status of the newborn after delivery (gestational age, weight, Apgar, and others), both groups had similar characteristics.

Although CRP levels at birth differed significantly, no clinical differences were observed. There is no single cut-off value accepted worldwide, but the figures in both groups are clearly below levels suggestive of sepsis. As procalcitonin is only used to diagnose nosocomial sepsis in our department, it was not included in the analysis.

Regarding clinical risk factors, neonatologists do not usually distinguish between term and preterm newborns, although the pathophysiology in both conditions is not the same. Our data support this fact, as prolonged rupture of membranes, one of the most important infectious risk factors in the term newborn, predominates significantly in the second study period without a higher percentage of confirmed sepsis. In these cases, other non-infectious causes of stress might be leading to the initiation of labor and rupture of membranes[41,42].

Following the reasoning of the document published by the American Academy of Pediatrics in 2018, preterm infants with the lowest risk of presenting an early bacterial neonatal infection are those born by cesarean section and those born due to induced prematurity[6]. However, we found a higher percentage of spontaneous prematurity and vaginal deliveries in group II.

We can cite two reasons that might play a role: the change in the Director of Obstetrics in 2010, who clearly wanted to reduce the percentage of cesarean sections, and the progressive change in obstetrics practices—better control of pregnant women and a limitation of the indications for cesarean section in the case of premature delivery[43,44]. After analyzing these items in our sample, no other variable was found that clearly explained the decrease in the use of antibiotic treatment in the second period, except for IL-6.

We also performed a binary logistic regression to determine which variables were significantly related. Our results were consistent with other studies[6]: gestational age < 28 weeks would multiply the risk of receiving antibiotics by 16, spontaneous prematurity (versus induced prematurity) by 3, and belonging to group I of the study by 4. It should be noted that the percentage of extreme prematurity in both samples was similar (35.3% in group I and 37.7% in group II).

Regarding the evolution during admission, we found no statistically significant differences in the percentage of nosocomial sepsis, invasive fungal infection, necrotizing enterocolitis, or mortality. However, the mean in-hospital stay was significantly longer in group I. The complexity of the patients does not seem to justify this fact *a priori* since it was similar in both groups. Conversely, no significant changes were identified between the two periods in the management protocols of these patients in our Unit, especially in the management of neonatal sepsis of vertical transmission or those aspects related to the incidence of nosocomial sepsis, such as catheter insertion, its duration, and the type of feeding, among others.

After analyzing the clinical and paraclinical variables associated with the decision to initiate antibiotic treatment, it seems that the use of IL-6 as an early marker of sepsis in very low birth weight preterm newborns significantly reduces the use of antibiotics in the first 72 hours of life. It is more difficult to conclude subsequent evolution, but it seems that morbidity, length of hospital stay, and mortality are lower in the second period.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on patient data publication.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article requested by their Ethics Committee.

Conflicts of interest

The authors declare no conflict of interest with pharmaceutical companies.

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RESEARCH ARTICLE

Construction and validation of scale factors and attitudes associated with parenting of children with high-risk birth

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Abstract

Background: *High-risk birth is a public health problem that generates atypical parenting practices. This study aimed to identify these practices to construct and validate a scale to measure parenting factors and attitudes in children with high-risk birth parents.* **Methods:** *The instrument was applied to an intentional non-probabilistic sample of 701 parents of children with high-risk births (age range 17-64 years). The scale consists of 56 items, each with five Likert-type response options.* **Results:** *As a result of the factor analysis with Varimax rotation, the final version was divided into two subscales: factors and attitudes associated with parenting skills. In the first, with 36 items and six factors (low educational skills, overprotection, and permissive parenting, dissatisfaction with the parental role, stress in raising a child with a high-risk birth, tri-generational disapproval of the parental role, and positive support from the extended family), a Cronbach's alpha value of 0.90 was obtained, explaining 53.16 of the variance. In the second subscale, with 30 items grouped in four factors (parenting beliefs, negative coping with high-risk birth, self-validation in parenting, and parental resilience to the experience of high-risk birth parenting), a Cronbach's alpha of 0.82 was obtained, explaining 48.08 of the variance.* **Conclusions:** *We suggest that this scale be applied together with others that measure theoretically related variables.*

Keywords: *Parenting. High-risk birth. Overprotection. Stress.*

Construcción y validación de la escala de factores y actitudes asociados con las prácticas de crianza parental de niños con nacimiento de alto riesgo

Resumen

Introducción: *El nacimiento de alto riesgo es un problema de salud pública que genera prácticas de crianza atípicas. El objetivo de este estudio fue identificar estas prácticas para construir y validar una escala para medir factores y actitudes de la crianza en los padres de niños con nacimiento de alto riesgo.* **Métodos:** *La escala consta de 56 reactivos con cinco opciones de respuesta tipo Likert. El instrumento se aplicó a una muestra no probabilística de 701 padres de niños con nacimiento de alto riesgo (rango de edad: 17-64 años).* **Resultados:** *Como resultado del análisis factorial con rotación Vari-*

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max, la versión final se dividió en dos subescalas: factores y actitudes asociados con la crianza. En la primera, con 36 reactivos y seis factores (bajas habilidades educativas, sobreprotección y crianza permisiva, insatisfacción ante el rol parental ejercido, estrés ante la crianza de un niño con nacimiento de alto riesgo, desaprobación trigeneracional en el rol parental y apoyo positivo de la familia extensa), se obtuvo un valor alfa de Cronbach de 0.90, explicando el 53.16 de la varianza. En la segunda subescala, con 30 reactivos y cuatro factores (creencias ante la crianza, afrontamiento negativo ante el nacimiento de alto riesgo, autovalidación en la crianza y resiliencia parental ante la experiencia de la crianza y el nacimiento de alto riesgo), se obtuvo un valor alfa de Cronbach de 0.82, explicando el 48.08 de la varianza. **Conclusiones:** *Se sugiere la aplicación de esta escala junto con otras que midan variables teóricamente relacionadas.*

Palabras clave: *Crianza. Nacimiento de alto riesgo. Sobreprotección. Estrés.*

Introduction

High-risk birth constitutes one of the most critical health problems in society[1], representing the first cause of neonatal and infant morbidity and mortality[2]. The National Institute of Perinatology (INPer, for its Spanish acronym) reported that in infants who survived high-risk birth, the most frequent morbidities were severe bronchopulmonary dysplasia (in 38%), followed by intraventricular hemorrhage grade III/IV (in 20%), and stage 3 retinopathy of prematurity (in 2.6%)[3]. Survivors may have neurodevelopmental sequelae[4-6], as seen in extremely low birth weight infants, who report significantly lower cognitive development and intelligence quotient[7].

Faced with this scenario, families who experience high-risk birth are confronted with different situations: biological vulnerability[8], a change in the expected image of the child, and frustration of the planned family project[9]. Parents also face health problems that can keep the child hospitalized for months, generating alterations in the usual family dynamics and experiencing uncertainty, anxiety, stress, depression, guilt, among other emotions, for not being able to care for their child personally and with the constant fear of his or her death, which generates a tremendous emotional impact. In addition, parents conceive their child as weak, vulnerable, and sick, which generates emotional sequelae, affects their development[4,8], and influences family dynamics and parenting[6,10].

Family attitudes can influence the evolution of the disease, causing a significant burden of stress, time, effort, and costs[11]. Therefore, it is essential to know how parents experience parenting their children when they are born at high risk, help them adapt to these new conditions, know the resources and limitations available for this population, and guide parenting[6,10,12].

Parenting is defined as the knowledge, attitudes, and beliefs that parents assume concerning health, nutrition, the importance of physical and social environment, and learning opportunities for their children at home[13]. Parenting is influenced by different factors: the social group in which the caregivers or parents are immersed, the thoughts they have regarding how to manage their children, the explanations given about education, and the actions towards children[14], which will persist in families through transmission between generations[15,16], while attitudes are the forms that will define the favorable or unfavorable attributions of beliefs[16].

Attitudes are positive or negative affective reactions to a particular situation. Thus attitude is a predisposition to respond emotionally. As attitudes are formed from the accumulation and integration of interrelated experiences, attitudes towards children are the acquired mental states or dispositions that provoke or lead parents to react specifically towards their child. The different components are the following: a cognitive one formed by judgments, beliefs, and values; a reactive one, which is the disposition to act in a certain way; and an affective one, which is the sympathy or antipathy, feelings, pleasant or unpleasant sensations towards the child, as well as the parents' own experience and the characteristics of their personality[17]. Attitudes towards parenting are the thoughts that predispose parents or caregivers to act positively or negatively towards the child, implying the degree of kindness, acceptance, rejection, or detachment that exists in their relationship, which sometimes defines the degree to which parents will be permissive or restrictive in the limits they set with their children[16,18].

Parenting practices are the specific actions and behaviors that parents or caregivers exhibit to form their children and foster their development in different aspects. These practices are influenced by family structure, parents' behaviors towards their children, the number of children, family income, and their perceptions on parenting practices[19-24].

Other conditions that influence parenting are the child's characteristics, illness, temperament, and

high-risk birth, and the characteristics of the parents involved in parenting, such as their personality traits, support networks that favor psychological well-being, and social support[16,25].

Therefore, the factors and attitudes associated with parenting practices in children with high-risk birth allow observing specific behaviors and actions of parents or caregivers, which are determined by external and internal motivations and by the child's characteristics, influenced by the adult's education. Thus, specific attitudes and behaviors towards children with high-risk birth oriented to ensure survival, growth, learning, and psychosocial development in an adaptive manner are generated. The specific needs of these children at each stage of development must be considered, using strategies, skills, tools, and competencies, which have a direct impact on their behavior and establish the co-responsibility of family interaction, beliefs, affections, and emotions, being determined by socio-historical and cultural norms, generating a particular family configuration in the education, stimulation, and socialization of children[14,19,23,25-35].

The effects of medical, biological, and psychoemotional risk on these children promote early interactions in the performance of parental roles and the ability to cope with the stress of the high-risk birth. These effects create a situation between the newborn and the caregiver that has an emotional and unexpected impact on the family experience and parenting. The members of this system may not be prepared to face such a situation, living it as a traumatic experience that will leave its mark over time, despite the child's satisfactory development[8].

It has been observed that there are more alterations in the upbringing of premature children by their mothers since limits and clear rules are not established, resulting in low educational skills due to the stress generated from birth, which, in turn, affects the family dynamics[33,36,37].

Anxiety or stress related to parenting promotes an overprotective attitude and excessive concern for the child's health. Consequently, this conduct generates a series of limitations to develop an independent behavior in the child, violating his or her autonomy, leading to a decrease in feelings of responsibility and, sometimes, promoting learning problems[17].

Several evaluations on parenting have been developed in different countries, starting with the studies of Baumnrid (1971, 1973) and their reformulation (Maccoby and Martin, 1983), as well as those of Darling (1999), who redefined parenting styles and made a distinction between parenting styles and practices, generating a series of scales around these concepts[38].

Different scales on parenting practices have been constructed in Mexico. For example, Gaxiola et al. (2006)[39] reported parenting practices in a Mexican population and evaluated them according to Baumnrid's classification. These authors described three major factors: authoritarian style (reasoning 0.47, participation 0.79, democratic 0.52, and good behavior 0.48), authoritarianism (verbal hostile 0.37, corporal punishment 0.66, punitive strategies 0.47, little directivity), and permissiveness (lack of supervision 0.35). Similarly, Flores and Cortés (2017)[38] conducted a scale on the perception of parenting practices that are significant in a given socio-cultural context. They included the perception of the father's parenting (communication-school support 0.91, positive affect 0.90, punitive control 0.82, control-monitoring 0.59, limits and rules 0.63) and the perception of the mother's parenting (communication 0.87, school support 0.81, positive affect 0.77, punitive control 0.77, control-hostility 0.66, control-monitoring 0.60, limits and rules 0.58). For their part, Robles and Oudhof (2019)[40] addressed parenting duties in Mexican women, measuring the parenting practiced by mothers through seven factors: parent-child communication, acceptance of the child's identity, adequate material resources, control over children's actions, care of physical and mental health, limits and expectations, and environment and coexistence. Also, García-Méndez et al. (2014)[41] conducted a scale on the perception of parental parenting that evaluates the parenting styles used by fathers and mothers through five factors: punishment 0.763, permissiveness 0.702, negative emotions 0.692, behavioral control 0.644, and negative cognition 0.681.

When analyzing the scales of parenting practices in Mexico, we observed different types of scales that assess several factors. However, we did not find a scale that assesses parenting practices in families with high-risk births, and the items of the current scales cannot be used in this particular population. Therefore, this study aimed to construct and validate the Scale of Factors and Attitudes Associated with Parenting Practices toward Children with High-Risk Births.

Methods

Participants

The sample was selected in a non-probabilistic purposive manner. It consisted of parents of children with

high-risk birth who attended their pediatric follow-up at the INPer. Of the participants, 73.2% were women, and the age range was between 17 and 64 years [μ = 35.58, standard deviation (SD) = 8.[18]. The schooling of the majority of the population was high school; the occupation was a housewife in 45.4% of women and various trades in 16.5% of men. In addition, 83.9% of the sample lived with their partner and children with μ= 8.79 (SD= 7.28) years of cohabitation with high-risk birth children.

The Scale of Factors and Attitudes Associated with Parenting Practices toward Children with High-Risk Birth was conducted as follows:

1. The existing literature was reviewed. Based on the findings, a guide for the focus group was constructed.
2. Through the focus groups, the parenting practices exercised by the parents were identified. A discourse analysis was conducted to obtain the main categories of the construct[10,35].
3. Two content analyses were performed. The first yielded three dimensions with 32 categories, resulting in 340 questions with five Likert-type response options. The type of response was then divided into two subscales: the first with frequency responses (never, rarely, sometimes, often, frequently, always) and the second with attitudinal responses (strongly disagree, disagree, sometimes, agree, strongly agree).
4. The response was selected according to the frequency with which parents perform a series of specific behaviors and actions. Although they do not qualify the parenting practices *per se*, they do qualify the factors associated with them so that the subscale was classified as factors associated with parenting practices.
5. In the attitude subscale, responses were classified according to the parents' assessment or conceptualization of the accumulation and integration of experiences and mental attitudes acquired in the face of the high-risk birth, which leads them to react in a specific way to their child on a day-to-day basis.
6. The dimensions were checked for consistency with the theoretical framework. Construct validity was obtained through the participation of five expert judges, who were asked to check the adequacy of the defined dimensions of the questionnaire with the formulation of the proposed items. Subsequently, the scale was subjected to a content validity analysis. Some items were filtered again and eliminated due to the low sensitivity of the statement or the formulation of sensitive and conflicting topics. The result was a shorter version of four dimensions with 24 categories, composed of 202 items that met the approval of the experts; the remaining items were eliminated[10,35].
7. Once the judges had approved the formulation of the items of this first version of the instrument, a pilot assessment was carried out with parents of high-risk birth children, who provided some suggestions regarding certain words and expressions used in the items, without showing any inconvenience regarding the instructions and the mode of response used. Adjustments were made for a better understanding of the items. Thus, the scale version to be validated consisted of 140 items to be applied in the questionnaires to the target population.

Procedure

The instrument was applied when the children with high-risk birth came for a consultation at the INPer. Parents were invited to participate by explaining the objective of the research and how to answer the questionnaire. They were provided with an informed consent form. The mean response time was 40 minutes.

Results

Subscale of factors associated with parenting practices

The psychometric analysis of the items of the instrument was carried out to analyze its performance. In this analysis, the following tests were performed to obtain the levels of validity and reliability of the instrument:

Discrimination analysis of the items was performed according to the method proposed by Reyes-Lagunes and García-Barragán (2006)[42]. Subsequently, construct validity was obtained through an exploratory factor analysis, which allows a more precise exploration of the underlying dimensions of the observed variables, constructs, or latent variables[43]. Given the nature of the items, we performed the analysis by principal components because it allows us to identify the number and composition of the necessary components[44] and reduce the variables by considering the total variance and deriving those factors that contain small portions of unique variance[45]. In addition, orthogonal rotation was used because it assumes the independence of the factors[43], and Varimax rotation was used because the relationship between the factors was unknown, and the aim was to maximize the weights at the factor level. In other words, each item or variable was expected to be

representative in only one of them to reduce the number of variables within each factor[45]. Finally, the internal consistency coefficients were obtained.

For item discrimination, each item was correlated with the total scale. For each subscale, discrimination between the low extreme group and the high extreme group of the item was performed using the Student's t-test. For each subscale, the frequency and bias of the item > 0.5 were analyzed. In the subscale "Factors associated with parenting practices," 11 items out of a total of 140 were eliminated because they did not meet two of the three required criteria. An exploratory principal component factor analysis with orthogonal Varimax rotation was applied to determine the construct validity of each subscale, considering that the Kaiser-Meyer-Olkin (KMO) test revealed that the matrix was factorable (KMO = 0.913). The subscale items obtained communalities > 0.40, indicating that they measure the same construct. Six factors were chosen with an eigenvalue > 1, which explained 53.16% of the variance, with a Cronbach's alpha of 0.90. An orthogonal rotation (Varimax) was performed, and those items with a factorial weight ≥ 0.40 in a single factor were chosen to form the first subscale of the final instrument. The best version of the subscale of factors associated with parenting practices consisted of 36 items (Table 1).

Based on the distribution of the items, the factors that compose the behaviors associated with parenting practices in children with high-risk birth were defined. The definition of each of the subscale factors, "Factors associated with parenting practices," is shown in Table 2.

Finally, a Pearson product-moment correlation was performed between the subscale factors. Table 3 shows the correlations; the factors have a significant correlation, indicating that the subscale measures what was theoretically proposed.

Subscale of attitudes associated with parenting practices

In this subscale, two of a total of 38 items were eliminated because they did not meet two of the three criteria required for discrimination. Subsequently, a factor analysis with orthogonal rotation (Varimax) was performed since the KMO test revealed that the subscale matrix was factorizable (KMO = 0.876). Four factors were obtained with an eigenvalue > 1 that explained 48.08% of the total variance and a Cronbach's alpha of 0.823. The best version of the subscale of attitudes associated with parenting practices consisted of 20 items (Table 4).

Based on the distribution of the items, the factors that compose the attitudes associated with parenting practices in children with high-risk birth were defined (Table 5).

Finally, a Pearson product-moment correlation was performed. Table 6 shows the correlations between the subscale factors. Again, the factors have a significant correlation with each other, which indicates that the subscale measures what was theoretically proposed.

Discussion

The construction and validation of the scale Factors and Attitudes Associated with Parenting Practices of Children with High-Risk Birth were carried out in a Mexican population.

The data from the present study indicate the formation of two subscales. Parenting practices are specific behaviors and actions of parents or adults determined by external and internal motivations and by the children's characteristics influenced by their upbringing, guided by socio-historical and cultural norms[35]. Based on the above, the first subscale was named "Factors associated with parenting practices" and consisted of 36 items distributed in six factors: 1) low educational skills; 2) overprotection and permissive parenting; 3) dissatisfaction with the parental role played; 4) stress due to parenting a high-risk birth child; 5) tri-generational disapproval in the parental role; and 6) positive support from the extended family.

Since attitudes are thoughts resulting from the integration of acquired experiences that provoke or lead parents to react in a specific way towards their child, giving a particular configuration in each family for the education, stimulation, and socialization of children, the second subscale was named[17,35] "Attitudes associated with parenting practices." This subscale consists of 20 items comprising four factors: 1) beliefs toward parenting, 2) negative coping toward high-risk birth, 3) self-efficacy in parenting and 4) parental resilience toward parenting and the experience of a high-risk birth.

The scale does not assess parenting practices *per se*, but rather the factors and attitudes associated with parenting practices mainly used by parents of children with high-risk birth from an individual, family, and social perspective. Thus, the subscales and factors obtained in the exploratory factor analysis describe and explain the experiences of families affected by high-risk births, who face medical, biological, and psychoemotional

Table 1. Items and factors of the subscale "factors associated with parenting practices"

Items	Factor						
	1	2	3	4	5	6	Total
My child has tantrums I would never have imagined	0.681	0.135	-0.012	0.094	0.151	-0.003	
My child blackmails me to get what he wants	0.675	0.054	0.153	0.123	0.117	0.045	
My child tries to get attention; that is why he does not want to obey	0.668	0.072	0.257	-0.105	0.065	0.070	
I try to set rules for my child, but he does not obey; he does not listen	0.644	0.089	0.062	0.204	0.128	0.077	
I consider my child to be very rebellious, and that overwhelms me	0.642	0.075	0.102	0.199	0.206	0.012	
My child challenges me, and I do not know how to behave	0.608	0.170	0.129	0.158	0.148	-0.003	
My child tries to get our attention to get our expression of affection	0.579	0.219	0.287	0.077	0.025	0.026	
My child obeys everyone except me	0.556	0.120	0.134	0.072	0.124	-0.027	
I feel that I have hurt my child by solving all of his problems, but I did not mean it that way	0.497	0.277	0.135	0.154	0.130	-0.044	
I need much patience to avoid yelling at my child or getting desperate	0.485	0.072	0.041	0.277	0.158	-0.013	
I talk to my child, but he does not understand me	0.479	0.180	0.069	0.206	0.020	-0.040	
I have specific considerations with my child because of his condition	0.041	0.749	0.014	0.066	0.050	0.055	
I remember seeing my child so small, so fragile when he was born, makes me not want him to suffer now	0.119	0.708	0.049	-0.097	0.142	-0.165	
I am limited by the fear of my child getting sick when I set limits because of the risk he had at birth	-0.012	0.698	0.144	0.109	0.020	0.095	
I have to take great care of my child because I do not want him to suffer more than he has already experienced	0.085	0.637	0.092	-0.001	0.145	-0.088	
I have a hard time letting my child do activities without my help	0.187	0.593	0.055	0.285	0.038	0.006	
I rearrange the environment for my child's benefit to prevent him from struggling too much	0.176	0.590	-0.049	0.205	-0.004	-0.030	
I prefer to help my child with everything to avoid an accident	0.147	0.569	0.101	0.056	0.026	-0.033	
I try to compensate my child and devote myself entirely to him because of the guilt I feel	0.218	0.498	0.196	0.221	0.136	0.040	
My child is very pampered because of everything he went through	0.361	0.492	0.051	-0.006	0.229	-0.014	
I am so busy with my work that I do not notice what my child is doing	0.145	0.063	0.735	0.125	0.034	-0.020	
I have so much work that I do not pay as much attention to my child as I would like to	0.172	0.090	0.704	0.292	0.067	0.049	
I think I do not see some of my child's accomplishments because I do not have much time with him	0.150	0.133	0.616	0.081	0.165	0.082	
I do not realize what my child wants because I am busy with other things (TV, work, phone, computer, housework)	0.198	-0.003	0.602	0.041	-0.042	-0.032	
I am so busy at work every day, so I try to compensate my child by buying him what he wants, so he knows how much I love him	0.232	0.291	0.537	0.102	0.126	0.034	
My child has me so overwhelmed by how much he demands. He does not let me rest	0.306	0.124	0.139	0.738	0.040	0.032	
My child demands so much of my time, and I feel like I am going to explode	0.303	0.160	0.178	0.703	0.059	-0.026	
I get desperate with parenting my child because I did not imagine that he would have so many problems at birth when I was expecting him	0.255	0.258	0.087	0.578	0.142	0.064	

(continues)

Table 1. Items and factors of the subscale "factors associated with parenting practices" (*continued*)

Items	Factor						
	1	2	3	4	5	6	Total
It is challenging to allocate quality time for my family since my child was born	-0.021	0.053	0.193	0.547	0.178	0.062	
I think that my family does not let me behave freely with my child to educate him	0.232	0.088	0.023	0.143	0.767	-0.039	
There are behaviors that the family has with my child that I do not like; however, I have to tolerate them because they help me with him	0.154	0.101	0.125	0.166	0.725	-0.072	
My family is very overprotective with my child, and it bothers me	0.258	0.168	0.078	0.082	0.687	0.062	
My family and I think differently about how to raise my child	0.190	0.140	0.101	-0.028	0.580	0.131	
I receive the greatest support with my child from my family	0.022	-0.079	0.008	-0.052	-0.055	0.814	
My family has been with me through all the happy and challenging times since my child was born	0.011	0.009	0.051	0.064	-0.011	0.802	
I have a good relationship with my family, and they help me take care of my child	0.042	-0.037	0.021	0.079	0.092	0.786	
Number of items	11	9	5	4	4	3	36
Explained variance (%)	13.35	11.14	7.02	6.54	6.49	2.93	53.16
Eigenvalue	8.8	2.6	1.9	1.7	1.4	1.3	
Cronbach's alpha	0.861	0.831	0.739	0.716	0.742	0.733	0.901
Mean (SD)	3.77 (0.70)	3.73 (0.73)	3.94 (0.70)	4.2 (0.73)	3.7 (0.90)	3.9 (0.94)	
KMO							913

Bartlett's test of sphericity: X^2 (630) = 8206.53, $P < 0.001$.
KMO, Kaiser-Meyer-Olkin test; SD, standard deviation.

risks that generate early interactions in the parental functions[8] and specific parenting practices.

From the subscale "Factors associated with parenting practices," a first factor named "low educational skills" explains the parents' self-perception regarding their poor educational ability to deal with their children's behaviors, such as tantrums, defiance of authority, manipulation, among others. In this regard, Lopez et al.[33] have attempted to conceptualize and delimit the skills parents should master in parenting-related tasks: warmth and affection, recognition of achievements, control and supervision, adequate communication, and confidence-building stimulation and learning support. In addition, these skills favor the adaptability of parents to the characteristics of their children, especially in parents who have faced situations such as fear of their children's death, illness at birth that can keep them hospitalized for up to months, generating alterations in the usual family dynamics[4,8]. As this research shows, these events tend to generate confusion and fear in parents in the face of their children's health problems, impacting their self-control and self-efficacy in their educational skills.

Factor 2, "overprotection and permissive practices," measures the behaviors that occur in parents due to the emotional impact generated by their children's birth, which leads them to exercise permissive and overprotective parenting practices to establish limits poorly. The different stressors generate particular attitudes in parents when interacting with their children and influence parenting. These attitudes are determined by external and internal motivations[17,28,30], ranging from stress to subjective feelings of responsibility in parenting[37] and, therefore, each parent's characteristics[30]. When there is a child with a high-risk birth, the emotional impact experienced and the child's perception as weak, vulnerable, and sick promotes overprotective and permissive parenting practices. This behavior is

Table 2. Definition of factors of the subscale "factors associated with parenting practices"

Factors	Definition
Factor 1 Low educational skills	Parental self-perception of poor educational skills such as tantrums, challenging authority, manipulation
Factor 2 Overprotection and permissive parenting	Parental behaviors result from the emotional impact generated by the birth of their children, leading to permissive, overprotective parenting practices, and poor limit setting
Factor 3 Dissatisfaction with the parental role exercised	It evaluates the dissatisfaction of the parental role on the behaviors exercised, generating guilt (discomfort and displeasure) due to the little interaction and work overload that prevent parents from being part of the development and improvement of their children
Factor 4 Stress of parenting a child with a high-risk birth	Assesses the perceived burnout and overwhelm of parents faced with the demands of raising and caring for a child with a high-risk birth
Factor 5 Tri-generational disapproval in the parental role	Evaluates the intrusive and negative behaviors of the extended family in the exercise of parenting practices and parental role
Factor 6 Positive extended family support	Evaluates the accompaniment conduct provided by the extended family when faced with a high-risk birth and the parenting practices during the child's development

Table 3. Correlation between the factors of the subscale "factors associated with parenting practices"

	F1	F2	F3	F4	F5	F6
F1: Low educational skills	1					
F2: Overprotection and permissive parenting	0.460**	1				
F3: Dissatisfaction with the parental role exercised	0.492**	0.343**	1			
F4: Stress of parenting a child with a high-risk birth	0.532**	0.393**	0.444**	1		
F5: Tri-generational disapproval in the parental role	0.500**	0.363**	0.309**	0.363**	1	
F6: Positive extended family support	0.046	-0.055	0.073	0.074	0.044	1

*$p < 0.05$; **$P < 0.01$.
F, factor.

due to the intention that the child should not suffer more than he/she has already experienced and will depend on how the parents experienced the different stressors[9,30,37] and on the particular motivations of each family.

Factor 3 assesses parental role dissatisfaction and guilt provoked by the discomfort or displeasure after the little interaction with the children and the work overload that restrict parents from being part of the development and improvement of their offspring. According to Webster-Stratton, this discomfort is associated with the influence of parental stress on interactions with their children during parenting[30]. This author notes that non-familial factors, such as socioeconomic and sociodemographic issues, everyday problems, such as work and time-consuming work, can trigger parents' dissatisfaction with their parenting role.

Factor 4 assesses parents' perceived burnout and exhaustion due to the demands of parenting and caring for a child with a high-risk birth. The literature states that when children are hospitalized after birth, parents experience uncertainty, anguish, stress, sadness, anxiety, guilt for not caring for their child personally, and constant fear of death[4,8,12]. All the above influences family dynamics and parenting[6,10], which leads to alterations in the children's behavior because of the anxiety produced in the family[8,46,47], which can promote less independence, development of competencies[48], and parental overwhelm due to the constant demands of their children.

Table 4. Subscale "attitudes associated with parenting practices"

	Factors				
	1	2	3	4	Total
My child has to explore to learn	0.720	0.166	0.161	0.192	
I discovered that I could set limits for my child since he was young because he responds	0.679	0.135	0.150	-0.059	
I understood that despite the conditions present when my child was born, he had to be integrated into regular activities	0.655	0.115	0.111	0.207	
Parenting is about learning and adapting as a family	0.605	-0.074	0.167	0.252	
As time goes on, my child behaviors let me know that things are going well with his development	0.510	0.252	0.231	0.173	
I have had a hard time accepting everything that has happened since I was told my child would be at high risk	0.102	0.734	-0.094	0.067	
It has been hard to face everything I lost when my child was born, and he is living with the consequences of that	0.024	0.718	0.138	0.070	
I have a hard time coping with my child going to school because he is still vulnerable	0.116	0.666	0.000	0.050	
I have not enjoyed raising my child because of the conditions of his birth	0.027	0.663	0.030	0.042	
I wish my child would not grow up because I did not enjoy him enough as a baby	0.109	0.552	0.033	-0.043	
My child's improvement is the result of the discipline of following the specialists' indications	0.198	0.071	0.793	0.033	
The experience of having a child born with high risk gives you maturity, no matter how old you are	0.225	-0.014	0.741	0.082	
I learned from what I was taught in the hospital how to raise my child correctly	0.274	-0.005	0.544	0.318	
With the guidance I have been given at the hospital, I have learned to educate my child differently.	-0.022	-0.015	0.503	0.375	
With the arrival of our child, I learned to prepare myself to face the conflicts that may arise	0.282	0.109	0.496	0.247	
Children are a reflection of their parents	0.060	0.046	0.013	0.691	
When my child was born, I decided to accept the experience and carry him forward despite setbacks	0.264	0.116	0.193	0.628	
The experience of giving birth and raising my child made me an emotionally stronger person	0.053	0.113	0.234	0.607	
I learned to adapt to my child's needs and he to mine	0.257	-0.056	0.109	0.554	
With a high-risk birth child, you have to take away your fear; you have to be decisive and strong	0.397	-0.004	0.277	0.455	
Number of items	5	5	5	5	20
Explained variance (%)	13.08	12.09	11.62	11.28	48.08
Eigenvalue	5.1	2.23	1.17	1.09	
Cronbach's alpha	0.724	0.703	0.720	0.673	0.823
Mean (SD)	4.36 (0.59)	4.12 (0.75)	4.25 (0.64)	4.23 (0.64)	
KMO					0.876

Bartlett's test of sphericity: X^2 (190) = 3277.497, $P < 0.001$.
KMO, Kaiser-Meyer-Olkin test; SD, standard deviation.

Table 5. Definition of factors of the subscale "attitudes associated with parenting practices"

Factors	Definition
Factor 1 Beliefs towards parenting	Parents' beliefs, ideas, or thoughts favor or facilitate the integral development (developmental potential) of the child with high-risk birth
Factor 2 Negative coping toward high-risk births	Assesses parental coping skills in the face of a high-risk birth that harm parenting practices
Factor 3 Self-efficacy in parenting	It assesses the perception of parental self-efficacy that modulates the competencies, beliefs of skills, actions, and specific behaviors that parents have to deal with the different situations that arise and to favor the developmental potential of the child with high-risk birth
Factor 4 Parental resilience towards parenting and the experience of a high-risk birth	Assesses the resilience and coping capacity of parents who experienced high-risk birth and who use positive behaviors for parenting practices

Table 6. Correlation between factors of the subscale "attitudes associated with parenting practices"

	F1	F2	F3	F4
F1: Beliefs towards parenting	1			
F2: Negative coping toward high-risk births	0.273**	1		
F3: Self-efficacy in parenting	0.533**	0.117**	1	
F4: Parental resilience towards parenting and the experience of a high-risk birth	0.509**	0.150**	0.546**	1

*$p < 0.05$; **$p < 0.01$.
F, factor.

Factor 5 evaluates the intrusive and negative behaviors of the extended family in the exercise of parenting practices and the parental role. The literature reports that Mexican families commonly present intrusiveness of the extended family, where family boundaries tend to be diffuse and rigid, the hierarchy is confusing, promoting coalitions rather than alliances[49], which generates confusion and anger in parenting due to perceived parental behaviors.

Factor 6 assesses the companionship provided by the extended family in response to the high-risk birth and parenting practices during the child's development. As mentioned in the literature[27,34], parenting is not an exclusive function of the parents, and they are not the only ones responsible for it; instead, parenting involves a social interweaving that involves several people. Thus, from its social function, the family has co-responsibility in education and upbringing, transmitting a variety of socio-cultural facts, symbolic representations, beliefs, patterns, habits, guidelines, norms, and systems or practices of upbringing in the formative processes of children. As observed in this research, the extended family also supports parenting practices in structure, affection, behavior control, and communication in intrafamily and microsystemic relationships, as well as the transmission of values and external systems[23,24], evidencing the diversification and family configurations in each culture[34]. As shown, parents perceive the intervention of the extended family as supportive.

Regarding the subscale "Attitudes associated with parenting practices," from which four factors were derived, we highlight the following:

Factor 1, named "parenting beliefs," assesses the parents' beliefs, ideas, or thoughts, which favor or facilitate the integral development (developmental potential) of the child with high-risk birth. As mentioned in the literature[17,26,41], these beliefs will motivate adults to guide children to improve their development, quality of life, and well-being. In a child with a high-risk birth family, a series of attitudes and beliefs will modulate parenting in the family's need to adapt to a new life and get the child to make the most of his or her abilities[6,10,11].

Factor 2, named "negative coping towards the experience of parenting and high-risk birth," assesses the coping skills that parents experienced and that impair parenting practices. This factor is associated with reports citing that families are not prepared to face a situation of this type so that they live it as a traumatic experience that will leave its mark despite time, even if the child has a good evolution[8]. As observed in this

study, families may interfere in parenting due to the stress experienced, fostering the child's vulnerability and perceiving that he/she has more significant difficulties in coping with the situation[50].

Factor 3 evaluates the parental perception of self-efficacy. As referred to in the literature[51], self-efficacy depends on the ability one feels to achieve a goal. It also modulates the competencies, strategies, beliefs about skills, actions, and specific behaviors that parents deploy when facing different situations that arise and directly impact the child's behavior, learning, and developmental potential with high-risk birth[19,52].

Factor 4 assesses resilience and coping with the high-risk birth experience through positive attitudes toward parenting practices. As the literature indicates, the resilient potential is the capacity of individuals to cope with adversity and influences different areas of life[53]. As observed in this research, these competencies allow parents to focus on their children, generate real expectations, and enhance their capabilities and strengths[54].

Finally, it is essential to mention that parenting practices differ among parents and their effect on children. The effects depend on the method used to modulate and channel the children's behaviors and on the direction parents intend and wish to value, considering that these practices will be done according to personality. Therefore, some dimensions, such as discipline, the relationship tone, the communication level, and the forms adopted by the expression of affection, are related[23].

Furthermore, this scale allows us to observe the factors and attitudes associated with the parenting practices used by parents of children with high-risk birth from an individual and family perspective, which differ from the practices used in children with no problems at birth.

As being the first version of the scale, a limitation of this study was that a non-probabilistic sampling was used, so the results of this validation are only applicable to similar samples.

For further studies, we suggest applying this scale with others that measure theoretically related variables to determine the convergent and divergent construct validity and corroborating the factorial structure through confirmatory factor analysis.

Based on this instrument, diagnoses can be made in clinical populations to create intervention programs that favor the development of factors and attitudes associated with effective parenting practices and, thus, help children with high-risk birth to achieve more significant integral development.

We can conclude that we obtained a valid and reliable instrument that allows us to identify a common social phenomenon in the population of Mexico City.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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RESEARCH ARTICLE

Outcome of the treatment of hydronephrosis due to congenital ureteropelvic stenosis according to age at surgery

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Abstract

Background: *Congenital kidney and urinary tract anomalies are the most common cause of chronic kidney disease in the first three decades of life. Stenosis of the ureteropelvic junction may cause dilation of the collecting system in the fetal kidney. This study aimed to determine hydronephrosis due to congenital ureteropelvic stenosis treatment outcome according to the age of the intervention.* **Methods:** *We conducted a retrospective descriptive study that included pediatric patients with hydronephrosis secondary to ureteropelvic junction stenosis operated by the Anderson-Hynes open pyeloplasty method from 2010 to 2016. Patients were divided into two groups: group A, children < 1 year of age, and group B, children > 1 year of age. We analyzed ultrasonographic parameters, renal function, and clinical data. Inferential statistics were used with the Mann-Whitney U-test and X^2 test. Intra-group data were assessed with the Wilcoxon test.* **Results:** *We included 52 patients: group A (n = 16, 30%) and group B (n = 36, 70%). The male sex predominated, and mainly the left renal unit. The most important surgical finding was stenotic segment. The median right glomerular filtration rate was 24.1 mL/min (19.0-34.5) pre-surgical and 38.2 mL/min (35.9-41.09) post-surgical in group A (p = 0.028), and 28.4 mL/min (18.5-35.0) pre-surgical and 37 mL/min (35.7-46.0) post-surgical in group B (p = 0.003). The median left glomerular filtration rate was 30 mL/min (21.4-39.0) pre-surgical and 40.0 mL/min (37.7-44.6) post-surgical in group A (p = 0.005) and 18.4 mL/min (14.2-29.2) pre-surgical and 37 mL/min (33.1-38.5) post-surgical in group B (p < 0.001).* **Conclusions:** *Correction of ureteropelvic stenosis before one year of age results in better renal function than a later correction.*

Keywords: *Pyeloplasty. Hydronephrosis. Ureteropyelic stenosis.*

Resultados del tratamiento de la hidronefrosis por estenosis ureteropiélica congénita según la edad de la intervención

Resumen

Introducción: *Las anormalidades congénitas del riñón y del tracto urinario son la causa más frecuente de enfermedad renal crónica en las primeras décadas de la vida. La estenosis de la unión ureteropiélica puede ocasionar restricción del flujo urinario desde la pelvis renal hacia el uréter, y es la causa más común de dilatación del sistema colector en el riñón*

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fetal. El objetivo de este estudio fue determinar los resultados del tratamiento de la hidronefrosis por estenosis ureteropiélica congénita según la edad de la intervención. **Métodos:** *Se llevó a cabo un estudio retrospectivo descriptivo incluyendo pacientes pediátricos con hidronefrosis secundaria a estenosis de la unión ureteropiélica sometidos a pieloplastia abierta de Anderson-Hynes en el periodo 2010-2016. Se formaron dos grupos: A, pacientes < 1 año, y B, pacientes > 1 año. Se analizaron parámetros clínicos, ecosonográficos y de función renal. Se utilizó estadística inferencial con las pruebas U de Mann Whitney, χ^2 y Wilcoxon.* **Resultados:** *Se incluyeron 52 pacientes: 16 en el grupo A (30%) y 36 en el grupo B (70%). Predominó el sexo masculino, y principalmente la unidad renal izquierda. El hallazgo quirúrgico más importante fue el segmento estenótico. La mediana de la tasa de filtración glomerular derecha prequirúrgica fue de 24.1 ml/min (19.0-34.5) y la posquirúrgica fue de 38.2 ml/min (35.9-41.09) en el grupo A (p = 0.028), frente a 28.4 ml/min (18.5-35.0) y 37 ml/min (35.7-46.0), respectivamente, en el grupo B (p = 0.003). La mediana de la tasa de filtración glomerular izquierda prequirúrgica fue de 30 ml/min (21.4-39.0) y la posquirúrgica fue de 40.0 ml/min (37.7-44.6) en el grupo A (p = 0.005), frente a 18.4 ml/min (14.2-29.2) y 37 ml/min (33.1-38.5), respectivamente, en el grupo B (p < 0.001).* **Conclusiones:** *La corrección de la estenosis ureteropiélica antes de 1 año de edad resulta en una mejor función renal que la corrección tardía.*

Palabras clave: *Pieloplastia. Hidronefrosis. Estenosis ureteropiélica.*

Introduction

Congenital anomalies of the kidney and urinary tract are the most common cause of chronic kidney disease in the first three decades of life (40-50% of the cases)[1,2]. Ureteropelvic junction (UPJ) stenosis is considered a cause of restriction of urine flow from the renal pelvis into the ureter and the most common cause of significant dilatation of the collecting system in the fetal kidney[3]. The reported frequency of UPJ stenosis is 1 in 1500 live births[4]. The primary etiology is a narrowed segment of the ureter at the ureteropelvic junction that may result from an interruption in the development of the circular musculature[5]. Traditionally, prenatal hydronephrosis has been classified by the Society for Fetal Urology (SFU) according to ultrasound findings on a spectrum ranging from grade I (standard parenchymal thickness and only division of the renal pelvis) to grade IV (distention of the renal pelvis, calyces, and parenchymal thinning)[6]. Prenatal ultrasound has improved detection of fetal hydronephrosis and timely treatment[7,8].

UPJ stenosis occurs more frequently in males than females, especially in the neonatal period (ratio > 2:1). In addition, left-sided lesions predominate in neonates up to 67%. Bilateral obstruction occurs in 10-40% of cases, with the simultaneous or non-simultaneous occurrence and a tendency in young children < 6 months old. Also, it affects members of more than one generation[3]. Postnatal pathology was detected in only 12% of children with isolated urinary tract dilation during the second trimester of pregnancy; however, it was present in 40% of those with dilation observed during the second and third trimesters of pregnancy[9]. In general, earlier and more frequent postnatal evaluation is recommended in patients with moderate and severe hydronephrosis (SFU grade III and IV) than those with mild dilatation (SFU grade I and II), as moderate and severe cases are associated with an estimated 5-50% risk of requiring surgical intervention[10]. In children with mild hydronephrosis, a functional study by nuclear renography is not imperative to perform. However, surgical intervention in many centers was indicated in children with moderate hydronephrosis with a differential renal function (DRF) < 40% (33% vs. 3%)[9].

Severe hydronephrosis should be evaluated with functional studies. Renography with a diuretic is used to diagnose urinary tract obstruction since it measures the emptying time of the renal pelvis (referred to as washout) and estimates the total and individual function of each kidney[11]. The main indications for surgical treatment are a DRF < 40%, washout time > 20 min, deterioration in renal function, and urinary tract infections[12].

This study aimed to determine open pyeloplasty's functional and morphological results in pediatric patients with hydronephrosis secondary to UPJ stenosis, comparing two age groups: < 1 year and > 1 year of age, considering the early or late time of diagnosis and surgical management.

Methods

We conducted a retrospective descriptive study of 52 pediatric patients with hydronephrosis secondary to UPJ stenosis diagnosed between 2010 and 2016 in the Pediatric Urology service of the Unidad Médica de Alta Especialidad, Hospital de Pediatría, Centro Médico Nacional de Occidente, Instituto Méxicano del Seguro Social, in Guadalajara, Jalisco, Mexico.

Table 1. Clinical characteristics of pediatric patients with hydronephrosis due to UPJ stenosis

Clinical characteristics	Group A (< 1 year of age) (n = 16)	Group B (> 1 year of age) (n = 36)	*p*-values
Gender Male Female	n (%) 10 (62.5) 6 (37.5)	n (%) 27 (75) 9 (25)	0.358
Age at the surgical procedure in months, median (quartiles) < 1 year 1-3 years 4-7 years 8-11 years 12-16 years	10.5 (6.2-12) 16 (100) — — — —	60 (24-93) — 14 (38.8) 13 (36.1) 8 (22.2) 1 (2.7)	< 0.001
Affected kidney Right Left	 6 (37.5) 10 (62.5)	 10 (27.7) 26 (72.3)	0.622
Days of hospital stay, median (quartiles)	4 (4-5)	4 (4-5)	0.454
Follow-up years, median (quartiles)	3 (2-3)	3.5 (2.25-4)	0.052
Pre-surgical classification Grade II Grade III Grade IV	 1 (6) 3 (38) 9 (56)	 1 (3) 10 (28) 25 (69)	0.56
Post-surgical classification Grade I Grade II Grade III Grade IV	 4 (25) 11 (69) 0 (0) 1 (6)	 15 (42) 20 (56) 0 (0) 1 (2)	0.48
Serum creatinine (mg/dL) Pre-surgical, median (quartiles) Post-surgical, median (quartiles) *p*-value	 0.2 (0.2-0.4) 0.3 (0.3-0.5) 0.014	 0.3 (0.2-0.4) 0.5 (0.4-0.6) 0.000	 0.387 0.031

UPJ, ureteropelvic junction.
Intergroup median comparison with Mann-Whitney U-test; intragroup median comparison with Wilcoxon test.

Selection criteria

The ultrasonographic parameters, renal function, and clinical data were extracted and validated from electronic medical records and physical files. All cases were diagnosed with unilateral ureteropelvic stenosis. We only included patients < 16 years of age with complete medical records and ultrasound and renography with penta-acetic acid (DTPA) before and after surgery. Patients with bilateral disease, renal dysplasia, pelvic kidney, single kidney status, and lower urinary tract anomalies were excluded.

Two age groups were compared: group A, patients < 1 year of age, and group B, patients > 1 year of age, considering that those < 1 year had an early prenatal or neonatal diagnosis and could have a better prognosis than those diagnosed later.

Study design

Data were collected from the databases of the pediatric urology service and grouped according to age at the time of surgery into group A and group B, using a non-probabilistic sampling of consecutive cases.

The diagnosis and definition of urinary tract obstruction were made by pre-surgical and post-surgical ultrasound and by pre-surgical and post-surgical scintigraphy. Indications for surgery were ultrasonographic morphologic changes with UFS grade III to IV and those with grade II with functional scintigraphy data of obstruction percentage < 40% and obstructive curve > 20 min. In this study, the radiopharmaceutical used to measure glomerular filtration rate (GFR) by renography was DTPA (Table 1). We corroborated obstruction data through the elimination of the marker (> 20 min)

and the reduction of radioactivity at the renal pelvis (50%) in all the patients. The degrees of renal function varied as follows: function < 10 mL/min: 21 cases, 9 (56. 3%) in group A and 12 (33.4%) in group B; function between 10-20 mL/min: 20 cases, 4 (25%) in group A and 16 (44.4%) in group B; function between 21-40 mL/min: 11 cases, 3 (18.8%) in group A and 8 (22.2%) in group B. A successful outcome was defined with significant macroscopic morphological changes on ultrasound; i.e., going from grade III or IV of the pre-surgical SFU classification to grade I or II of the SFU classification in the post-surgical control measurement. In these cases, an improvement on hydronephrosis, the renogram curves, and percentages of functionality were demonstrated by renal scintigraphy.

The SFU criteria were used to classify the patients since this classification delimits better the morphologic alterations of the kidneys. Therefore, the morphological, anatomical changes could be better evaluated. The SFU system defines the severity of stenosis for the second trimester of the gestational age group according to the renal pelvis anterior-posterior diameter (RPAPD) as mild (4 to < 7 mm), moderate (7 to ≤10 mm), and severe (>10 mm). During the third trimester of pregnancy, mild is defined as RPAPD of 7 to < 9 mm, moderate as 9 to ≤15 mm, and severe as >15 mm.

Post-surgical evaluations were performed during follow-up in the pediatric urology outpatient clinic 6 months after surgery. This period was established to evaluate and reduce the risk of post-surgical edema to influence the functional and morphological results.

An adynamic segment is defined as a narrowing of the ureteral segment that prevents the adequate passage of urine; a stenotic segment refers to macroscopic visualization during surgical exploration and can be documented if peristalsis of the ureter is present.

The glomerular filtration rate was calculated using the renal scintigrams; in the renal scintigraphy, renogram curves and the total of the renal curves were reported separately.

Post-surgical complications included post-surgical ileus, pyelonephritis, ureteral catheter migration, and ureteral stenosis recurrence.

The study was conducted under the principles of the Declaration of Helsinki. Due to the study design, no informed consent signature was required. The protocol was authorized by the Local Research and Research Ethics Committee 1302 with a registration number R-1302-2017-132.

Statistical analysis

Descriptive statistics frequencies and percentages were used for qualitative variables and medians and quartiles for quantitative variables with a non-symmetrical curve. We used statistical inference with Mann-Whitney U-test for intergroup medians and the Wilcoxon test for intragroup medians.

Results

We included 52 patients and divided them into two study groups according to diagnosis and age at the time of surgery: group A (16 patients) and group B (36 patients). The male: female ratio was 3:1, with male predominance in both groups: 10 in group A (62.5%) and 27 in group B (75%) ($p = 0.358$). The left renal unit was affected in 35 children; 10 in group A (62.5%) and 25 in group B (65.6%). Surgical reports confirmed urinary tract obstruction in all patients. The follow-up period started from the surgical event and had a median of 3 years in group A and 3.5 years in group B. We found significant differences in both groups when we compared improvement by a decreased degree of hydronephrosis: from 34 patients with grade IV before surgery, only 2 remained in the same grade after surgery ($p = 0.038$ for group A and $p = 0.032$ for group B) (Table 1). The most frequent surgical finding at the time of pyeloplasty was a stenotic segment of the ureter measuring 0.5 cm, corresponding to 11 patients (68.8%) in group A and 21 patients (65.6%) in group B. Negative outcomes were treated as post-surgical complications. Ureteral catheter migration occurred in two (3.8%) of the 52 patients and was removed by ureterorenoscopy.

Additionally, ureteral stenosis recurrence occurred in four (7.69%) of the 52 patients who underwent new ureteropelvic surgical reparation. Finally, post-surgical pyelonephritis and ileus occurred in only one patient (1.9%) (Table 2). Concomitant urinary tract infections were similar in both groups, showing no statistical differences (Table 3).

Regarding the right renal unit, the pre-surgical GFR showed a median of 24.1 mL/min (quartiles 19.0-34.5) and the post-surgical GFR of 38.2 (35.9-41.0) mL/min ($p = 0.028$) in group A. The difference between both measurements in group A (14 mL/min) was higher than in group B (8 mL/min) after pyeloplasty. For the left renal unit, we found a higher difference in GFR in group B (18 mL/min) compared to group A (10 mL/min), with a mean GFR of 18.4 mL/min (14.2-29.2)

Table 2. Characteristics, surgical findings, and surgical complications of patients with hydronephrosis due to UPJ stenosis

Variables	Group A (< 1 year of age) (n = 16)	Group B (> 1 year of age) (n = 36)	*p*-values
Nephrostomy	n (%)	n (%)	0.393
Yes	4 (25)	13 (27.7)	
No	12 (75)	22 (72.3)	
Surgical findings			0.227
Stenotic adynamic segment (0.5 cm)	8 (50)	7 (19.4)	
Aberrant vessel	0	2 (5.5)	
Adynamic segment	1 (6.2)	0	
High insertion of the ureter	1 (6.2)	2 (5.5)	
Stenotic segment (1 cm)	1 (6.2)	1 (2.7)	
Stenotic segment (1.5 cm)	2 (12.5)	3 (8.3)	
Stenotic segment (0.5 cm)	3 (18.8)	14 (38.8)	
Redundant pelvis	0	3 (8.3)	
Periureteral fibrosis	0	1 (2.7)	
Surgical complications			0.232
None	15 (93.7)	29 (80.5)	
Post-surgical ileus	1 (6.3)	0	
Pyelonephritis	0	1 (2.7)	
Migration of the ureteral catheter	0	2 (5.5)	
Ureteral stenosis recurrence	0	4 (11.1)	

UPJ, ureteropelvic junction.
Comparison of ratios with χ^2.

Table 3. Associated urinary tract infection and etiologic agent isolated from pediatric patients with hydronephrosis in UPJ stenosis

Infection agent	Group A (< 1 year of age) (n = 16)	Group B (> 1 year of age) (n = 36)	*p*-values
Pre-surgical	n (%)	n (%)	0.350
No growth	10 (62.5)	29 (80.5)	
Escherichia coli	3 (18.7)	4 (11.1)	
Enterobacter	1 (6.2)	0	
Proteus mirabilis	1 (6.2)	1 (2.7)	
Morganella morganii	0	1 (2.7)	
Klebsiella pneumoniae	0	1 (2.7)	
Pseudomonas aeruginosa	1 (6.2)	0	
Post-surgical			0.309
No growth	14 (87.5)	31 (86.1)	
Escherichia coli	2 (12.5)	1 (2.7)	
Klebsiella pneumoniae	0	1 (2.7)	
Pseudomonas aeruginosa	0	3 (8.3)	

UPJ, ureteropelvic junction.
Comparison of ratios with χ^2.

pre-surgery and 37 mL/min (33.1-38.5) post-surgery ($p < 0.001$).

Table 4 shows the affected kidneys by the side and the differential by age group. Furthermore, the analysis of the percentage of improvement between baseline and final measurements showed that the stage with the highest percentage of change in morphological recovery that achieved a change to mild dilatation corresponded to grade III in 100% of the patients, with a value of $p = 0.02$ in group A. For grade IV, the overall improvement percentage was 94.1%, with a $p = 0.004$ in group A and $p = 0.008$ in group B, averaging an

Table 4. Glomerular filtration rate in each study group of pediatric patients with hydronephrosis due to UPJ stenosis

GFR (mL/min)	Group A (< 1 year of age) (n = 16)				Group B (> 1 year of age) (n = 36)			
	Pre-op	Post-op	Difference	*p*-values	Pre-op	Post-op	Difference	*p*-values
Right renal unit (n = 16 kidneys)	24.1 (19-34.5)	38.2 (35.9-41.0)	14.05 (n = 6)	0.028	28.4 (18.5-35)	37 (35.7-46)	8.6 (n = 10)	0.003
Left renal unit (n = 36 kidneys)	30 (21.4-39)	40 (37.7-44.6)	10.0 (n = 10)	0.005	18.4 (14.2-29.2)	37 (33.1-38.5)	18.6 (n = 26)	0.000
p-values	0.038	0.808			0.000	0.925		

Data are expressed as median (quartiles).
GFR, glomerular filtration rate; Pre-op, pre-surgical; Post-op, post-surgical; UPJ, ureteropelvic junction.
Intergroup median comparison with the Mann-Whitney U-test; intragroup median comparison with Wilcoxon test.

Table 5. Change of the initial and final grade of hydronephrosis comparing pre-and post-surgical parameters in pediatric patients

	Post-surgical grade, n (%)							
	Grade I (n = 19)		Grade II (n = 31)		Grade III (n = 0)		Grade IV (n = 2)	
Group	A	B	A	B	A	B	A	B
Pre-surgical grade, n (%)								
Grade I (n = 0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade II (n = 2)	1 (50)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade III (n = 16)	2 (13)	4 (25)	4 (25)	6 (38)	0 (0)	0 (0)	0 (0)	0 (0)
Grade IV (n = 34)	1 (3)	10 (29)	7 (21)	14 (41)	0 (0)	0 (0)	1 (3)	1 (3)
Total	4 (21)	15 (79)	11 (35)	20 (65)	0 (0)	0 (0)	1 (50)	1 (50)

overall success rate of open pyeloplasty of 97% (comparing baseline and final) in the recovery of renal morphology (Table 5).

Discussion

Our results are consistent with those reported in the literature regarding a higher incidence of the pathology in males[12]. In the population studied, trans-surgical findings confirmed that the most important causes were intrinsic, such as the stenotic adynamic segment of the ureter of 0.5 cm; in a lower number of cases, extrinsic mechanisms, such as the presence of an aberrant vessel, were the most common[5,13,14]. As an accessible, inexpensive, and initial method, ultrasonography was used in both study groups, with indications varying according to the time of diagnosis. Compared to other series, ultrasonography continues to be the most useful diagnostic method and the one with the most significant impact on timely detection at prenatal age, thus providing a more timely intervention that impacts the morphological recovery of the renal unit[8,10,15,16]. The hydronephrosis severity scale applied was the same reported in other case series, which delimits the ideal candidate for surgical management from the morphological point of view, regardless of age and time of diagnosis[6]. UPJ stenosis may be associated with other genitourinary abnormalities, such as horseshoe kidney, or a component associated with CHARGE syndrome (coloboma, cardiac defects, choanal atresia, growth retardation, genital and ear abnormalities). In this study, we found no association with this type of pathologies[3,17].

Renography with a diuretic is used to diagnose urinary tract obstruction. The preferred radioisotope used is Technetium-99m (99mTc) mercaptoacetyltriglycine (Tc-99m MAG3). However, DTPA with diuretic was used in our study due to its availability in our institution[18]. The use of functional studies provides a path for surgical planning and timely intervention, leading to the recovery of function and prevention of damage, as shown in postnatal patients with borderline kidney function[11,19]. Many clinicians recommend surgery when severe hydronephrosis

(grade IV) is observed by ultrasonography, despite both kidneys' relatively stable function. The argument for surgical intervention is that function can be preserved or improved by correction of the blockage. In the present study, significant differences and essential improvements in kidney morphology and function after pyeloplasty were observed, delaying kidney failure and preventing its progression. Noticeably, there was a more significant impact on grade IV hydronephrosis in both study groups. The rate and type of complications in this study were similar to those reported in the published series.

Moreover, no fatal outcome was observed in our study[20]. In our series, the overall success rate was 97%, consistent with other series, with a higher impact in patients who underwent early intervention[21]. Follow-up after the surgical event was also similar to that reported in other series[22].

The contribution of this work is that renal function can be preserved or improved with the correction of the obstruction (stenosis) if the intervention is performed early (before one year of age). We found significant differences and an essential improvement in renal morphology and function after pyeloplasty, delaying renal failure and preventing its progression. This surgical indication should be considered in cases with obstructive uropathy with impaired renal function. However, this type of management should be avoided in cases with a better prognosis in which surgery has no impact on renal function outcome, and in those cases with preserved renal function, with no gradual deterioration of its function despite UPJ stenosis[23,24].

One limitation of this study is that patient information was based on clinical records, with the disadvantages of obtaining information described in previous documents. We also considered a limitation that we could not differentiate the variables studied by age group, so they were handled uniformly for all age groups. A significant limitation is that the hospital is a tertiary-level medical unit and depends on referrals from secondary-level hospitals, where pediatric patients are treated by adult urologists with little experience in children and are sometimes referred too late.

Finally, we conclude that early correction of UPJ stenosis before one year of age results in better renal function than a later correction.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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RESEARCH ARTICLE

Importance of early endoscopic and clinical evaluation of children with caustics ingestion

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Abstract

Background: *Accidental ingestion of caustics in pediatrics continues to be a frequent problem that can lead to severe injuries and permanent sequelae that require esophageal rehabilitation programs. This study aimed to describe the medical care experience of children who ingested caustic substances in a tertiary hospital in Mexico City.* **Methods:** *We conducted a descriptive and analytical study. We described age, sex, type of caustics, clinical and endoscopic findings, and the radiological evolution of 284 patients who arrived during the acute phase.* **Results:** *The records of 336 children with a history of caustic ingestion were reviewed. The median age was 1.7 years, and the predominant sex was male. Caustic soda was the most accidentally ingested substance. We found an association between the severity of the esophageal injury with the presence of more than four symptoms at diagnosis (χ^2, $p < 0.001$) and with the finding of oral lesions, sialorrhea, and vomiting (χ^2, $p < 0.05$). Forty percent ($n = 114$) showed normal gastrointestinal endoscopy.* **Conclusions:** *In children with caustic ingestion, upper gastrointestinal endoscopy should be performed within 72 hours to evaluate the extent of the lesions. In this study, we found that more than four symptoms at admission, and oral lesions, sialorrhea, and vomiting are associated with the severity of the esophageal injury.*

Keywords: *Caustics. Esophagitis. Esophageal stenosis. Anthropyloric stenosis.*

Importancia de la evaluación clínica y endoscópica temprana de niños con ingesta de cáusticos

Resumen

Introducción: *La ingesta accidental de cáusticos continúa siendo un problema frecuente en pediatría que puede llegar a producir lesiones graves y secuelas permanentes que ameritarán programas de rehabilitación esofágica. El objetivo de este estudio es describir la experiencia en la atención médica de niños con ingesta de sustancias cáusticas en un hospital de tercer nivel en la Ciudad de México.* **Métodos:** *Se llevó a cabo un estudio descriptivo y analítico. Se describieron la edad, el sexo, el tipo de cáustico, los hallazgos clínicos y endoscópicos, así como la evolución radiológica, de 284 pacientes que llegaron en la fase aguda.* **Resultados:** *Se revisaron los expedientes de 336 niños con antecedente de ingesta de cáusticos. La mediana de edad fue de 1.7 años, con predominio del sexo masculino. La sosa cáustica fue la sustancia más ingerida*

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y de tipo accidental. Encontramos asociación entre la gravedad de la lesión esofágica y la presencia de más de cuatro síntomas en el momento del diagnóstico (χ^2, $p < 0.001$,), y con el hallazgo de lesiones orales, sialorrea y vómito (χ^2, $p < 0.05$). El 40% de los niños (n = 114) tuvieron una endoscopia digestiva normal. **Conclusiones:** *En los niños con ingesta de cáusticos debe realizarse una endoscopia digestiva alta en las primeras 72 horas para evaluar la extensión de las lesiones. En este estudio se encontró que tener más de cuatro síntomas al ingreso, así como la presencia de lesiones orales, sialorrea y vómito, se asocian con la gravedad de la lesión esofágica.*

Palabras clave: *Cáusticos. Esofagitis. Estenosis esofágica. Estenosis antropilórica.*

Introduction

Ingestion of a caustic substance in pediatric patients is a frequently observed accident in emergency departments and poses a risk of potentially severe and irreversible injury to the upper gastrointestinal tract. This accidental or intentional ingestion represents a public health problem observed mainly in developing countries due to social, economic, and educational variables[1,2]. The highest incidence is observed in infants and preschoolers. It is accidental and occurs with substances found at home due to easy access to them because of their location. Additionally, these substances may be mislabeled or placed in inadequate containers[3]. The following have been identified as risk factors for intake: male gender, attention-deficit/hyperactivity disorder, lower educational level of parents, young maternal age, lack of supervision of children, and rural residence[4].

Mortality is rare, but morbidity is devastating and, in some cases, lifelong, with short- and long-term complications, such as prolonged and multiple hospital admissions, esophageal or pyloric stenosis, as well as an increased risk of esophageal cancer in the long term[5,6]. This study aimed to present the experience of a tertiary pediatric hospital in the care of children with caustic substance ingestion.

Methods

We conducted a descriptive, analytical, retrospective study. We reviewed the biostatistical database of the Hospital Infantil de México Federico Gómez, a national referral center (Mexico City, Mexico). Clinical information was obtained from 336 pediatric patients (age < 18 years) with a diagnosis of admission due to caustic ingestion between 1989 and 2009. We analyzed sociodemographic variables (age and sex), type of substance ingested, signs and symptoms (oral lesions, sialorrhea, vomiting, irritability, nausea, odynophagia, dysphonia, and dysphagia). We also registered those patients who underwent an initial endoscopic study (hospital admission < 72 hours after ingestion) and a control esophagogram. The Zargar esophagitis classification[7] was used to establish the degree of esophageal injury at initial endoscopy; in those where the gastric injury was documented, the Sakita-Miwa classification[8] was used.

The endoscopic control study was performed in the third week after ingestion to define the finding of esophageal or pyloric stenosis. In addition, those children admitted 72 hours after ingesting the caustic substance, in whom the initial endoscopy was not performed, were registered as late admission.

Statistical analysis

We used descriptive statistics with measures of central tendency. For categorical variables, χ^2 and risk tests were performed. Statistical significance was established with a p-value < 0.05.

Results

We included 336 patients with a median age of 1.7 years (range: 6 months to 15 years) at the time of hospital admission; 57% were male. Most patients were admitted to the hospital for accidental ingestion; only three adolescents were admitted for attempted suicide. Alkali ingestion predominated, with 81.5% (n = 274) of patients. Caustic liquid soda was the main substance ingested among other substances (Table 1).

After ingestion, 116 children (34.5%) received some liquid or medication intended to neutralize the caustic administered by parents or first contact medical personnel. Gastric lavage was performed in 14 cases (4%). The main clinical examination finding was oral lesions in 222 children (80%). The most frequently observed signs and symptoms are described in Table 2.

Of the 336 patients, 52 were referred late, so they did not undergo endoscopy but only esophagogram in search of complications. In the 284 children who underwent endoscopic evaluation within 72 hours after ingestion, no esophageal lesions were observed in 40% of the patients (n = 114). In turn, esophageal lesions compatible

Table 1. Type of ingested caustic substances and initial endoscopic findings in the esophagus and stomach

	n (%)	Grade of esophagitis according to Zargar					Gastric lesion
Ingested substance		0	1	2A	2B	3	
Liquid soda	210 (62.5)	54	24	34	35	20	44
Solid soda	25 (7.5)	12	1	4	3		3
Soda gel	24 (7.1)	9	5	6	3	1	
Chlorine	14 (4.1)	10	3	1			2
Hydrochloric acid	13 (3.8)	5	1	3	1	2	3
Salicylic acid	12 (3.6)	3	2	4	3		1
Ammonia	10 (3)	5	2	3			3
Dishwasher	3 (0.9)	3					
Floor cleaner	3 (0.9)	3					
Podophyllin	2 (0.6)		1		1		
Disinfectants	2 (0.6)	2					
Alkaline battery fluid	2 (0.3)	1					
Merthiolate	1 (0.3)		1				1
Calcium hydroxide	1 (0.3)	1					
Thinner	1 (0.3)	1					
Formaldehyde	1 (0.3)	1					
Styrene monoxide	1 (0.3)		1				1
Potassium permanganate	1 (0.3)			1			1
Not identified	10 (3)	4			2	2	2
Total	284	114	41	56	48	25	61

with grade 1 Zargar esophagitis were observed in 14% (n = 41); grade 2A in 20% (n = 56); grade 2B in 17% (n = 48) and grade 3 in 9% (n = 25). Regarding gastric injury, 79% (n = 223) presented normal results, while gastric lesions were found in 21% of the cases, of which 70% (n = 43) were classified as Sakita-Miwa A1 and 30% (n = 18) as Sakita-Miwa A2 ulcers. There were no complications associated with the endoscopic procedure.

A significant association ($p < 0.001$) was identified between the presence of more than four symptoms at diagnosis (Table 2) with severe esophageal injury (Zargar 2B and 3). Oral lesions, sialorrhea, and vomiting indicated a risk for developing Zargar esophagitis 2B and 3. However, we should consider that most patients had concomitant symptoms. No severe degree of burning was documented in asymptomatic patients.

After treatment with antibiotics, corticosteroids, antisecretory agents, and enteral tube feeding, an esophagogram was performed to look for complications in the third week after ingestion. If stenosis was found, upper gastrointestinal endoscopy was performed to pass an endless string and subsequently perform dilatations with Tucker bougies. Esophageal stricture was documented in 21% of patients with Zargar 2A lesion (n = 12), 75% of patients with Zargar 2B (n = 36), and 88% of patients with Zargar 3 lesion (n = 22).

One patient with a history of ammonia ingestion and grade 2B Zargar esophagitis and three patients with caustic soda ingestion and grade 3 Zargar esophagitis developed pyloric stenosis (Table 3).

Discussion

Accidental ingestion of caustic substances and foreign bodies continues to be a critical medical-social health problem[9]. This study describes the clinical and

Table 2. Signs and symptoms observed on admission to the emergency department in children with caustic ingestion and odds ratios for developing Zargar esophagitis 2B and 3

Sign or symptom	n (%)	Odds ratio	95% CI	*p*-values
Oral lesions	222 (80)	9.05	2.74-29.89	< 0.001
Sialorrhea	207 (74)	4.42	2.14-9.09	< 0.001
Vomiting	152 (54)	2.47	1.40-4.37	0.001
Irritability	70 (25)	1.70	0.95-3.01	0.071
Nausea	51 (18)	1.52	0.79-2.93	0.201
Odynophagia	47 (17)	1.63	0.83-3.19	0.152
Dysphonia	6 (2)	2.97	0.58-15.06	0.169
Dysphagia	5 (1.8)	4.47	0.73-27.35	0.077

CI, confidence interval.

Table 3. Initial endoscopic findings in 284 patients and percentage of esophageal stricture and pyloric stenosis development

Zargar grade	Initial endoscopy n (%)	Esophageal stricture n (%)	Pyloric stenosis n (%)
0	114 (40)	0	0
1	41 (14)	0	0
2A	56 (20)	12 (21)	0
2B	48 (17)	36 (75)	1 (2)
3	25 (9)	22 (88)	3 (10)
Total	284	70	4

endoscopic characteristics and evolution of pediatric patients with caustic ingestion. It has been reported that most ingestions occur in children < 5 years of age[4]. In Mexico, a previous study reported a mean age of 3.2 years and male predominance[10]. A meta-analysis that included more than 8,000 children reported that the most frequent age was 2 years[11]. We observed a mean age of 1.7 years, with a male-to-female ratio of 1.3:1. As previously reported, the vast majority of these ingestions occurred accidentally due to children's curiosity or attempt to obtain food, whereas, in adolescents, it occurs intentionally. In this study, intentional ingestion was documented in < 1% of cases.

After ingesting a caustic substance, the initial clinical manifestations are diverse: vomiting, dysphagia, sialorrhea, abdominal pain, and hematemesis[11,12]. A multicenter observational study involving 162 children reported that the number of symptoms allowed physicians to predict the presence of severe esophageal injury[13]. The most useful clinical signs and symptoms to predict the presence of esophageal injury are vomiting, dysphagia, abdominal pain, and the presence of lesions in the oral cavity. If two or more of these signs and symptoms are present, the probability of finding esophageal lesions is higher, with a positive predictive value (PPV) of 43% and a negative predictive value (NPV) of 96%[14]. However, as a single finding, oral lesions have shown a PPV of only 31% and a relatively low NPV of 79% for detecting esophageal lesions[15]. Our study found an association between four or more of the symptoms listed in Table 2, the presence of oral lesions and esophageal lesions Zargar 2B and 3, which should be considered when evaluating children with caustic ingestion. Also, we found that if children were asymptomatic, they did not have severe esophageal lesions; only a small proportion of children without oral lesions (n = 3) had severe esophageal lesions. These findings differ from the series published by Temiz et al.[16], who reported that 12-26% of asymptomatic children show severe lesions on endoscopic evaluation. Therefore, it is recommended to perform upper endoscopy in patients with a history of caustic ingestion, even if they are asymptomatic[1,16].

The ideal time to perform endoscopic evaluation after ingestion of caustic substances in children remains controversial[17]. Most studies recommend that it be performed in the first 24 to 48 hours after ingestion to assess the extent of the lesions and their severity, establish the prognosis, and guide treatment[13,18]. Endoscopy is not recommended more than four days after ingestion, as it increases the risk of esophageal perforation[19]. Currently, the Ibero-Latin American Clinical Practice Guide (Guía de Práctica Clínica Ibero-Latinoamericana) on caustic esophagitis in pediatrics recommends performing this study in the first 24 to 48 hours[1,16]. Endoscopic evaluation is performed during the first 72 hours in the Endoscopy Service of the Hospital Infantil de México Federico Gómez. In this study, the percentage of stenosis was similar to that published by Zargar et al. and other series[19,20]: for grade 2A lesions, 21% vs. <15%; for grade 2B lesions, 75% vs. 70-90%; and for grade 3 lesions, 88% vs. 83-100%, respectively, in patients in whom endoscopy was performed in the first 72 hours. All late referral patients already had an esophageal stricture.

In conclusion, the morbidity caused by caustic ingestion indicates that it is necessary to develop more effective prevention measures to avoid this type of accident. Furthermore, any patient with a history of ingestion of a caustic substance, even without symptoms, should undergo an endoscopic procedure within the first 24 to 72 hours since it is not possible to rule out some injuries. If the patient presents with more than four signs/symptoms, or oral lesions, sialorrhea, or vomiting, severe esophageal damage should be suspected.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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RESEARCH ARTICLE

Parental satisfaction with health care during child hospitalization at a social security facility in Mexico

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Abstract

Background: *The Service Quality in Hospital (SERVQHOS) assesses quality and satisfaction with hospital care received. This study aimed to determine the quality and satisfaction of parents in a tertiary-level pediatric public facility in Mexico.* **Methods:** *We conducted a cross-sectional study in which 425 anonymous surveys were distributed during the discharge of children. The questionnaire evaluates the individual (subjective) and organizational (objective) quality of service: reliability, tangibles, assurance, responsiveness, and empathy, as well as satisfaction on a 5-point scale from 1 (much worse) to 5 (much better).* **Results:** *A total of 401 questionnaires were returned (94%). The mean quality score was 3.6 ± 0.7. The best-rated aspects were the medical equipment technology (3.6 + 0.8), the confidence that the staff transmits to patients (3.6 ± 0.8), and the friendliness of the staff when attending patients (3.6 ± 0.8). The worst-rated aspects were the condition of the rooms (3.4 ± 0.8), the waiting time to be attended by a physician (3.3 ± 0.8), and the timeliness of internal consultations (3.3 ± 0.8). The overall population rated as satisfied in 97% of cases.* **Conclusions:** *A high rate of satisfaction was observed concerning both objective and subjective factors. However, the negative aspects of objective quality, such as reliability, should be addressed organizationally without implying economic investment in their resolution.*

Keywords: *Children. Healthcare. Quality of care. Health facility survey. Mexico. Patient satisfaction.*

Satisfacción de los padres con la atención médica durante la hospitalización de sus hijos en una institución de seguridad social en México

Resumen

Introducción: *La prueba de Calidad en el Servicio de Hospital (SERVQHOS) evalúa la calidad y la satisfacción con la atención hospitalaria recibida. El objetivo de este estudio fue determinar la calidad y la satisfacción de los padres de familia en un hospital público pediátrico de tercer nivel en México.* **Métodos:** *Se realizó un estudio transversal en el que se distribuyeron 425 encuestas anónimas durante el alta de los pacientes. El cuestionario evalúa la calidad individual (subjetiva) y de la organización (objetiva) del servicio: fiabilidad, tangibles, garantía, capacidad de respuesta y empatía, y satisfac-*

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ción en una escala tipo Likert de 5 puntos, de 1 (mucho peor) a 5 (mucho mejor). **Resultados:** *Se recibieron 401 encuestas respondidas (tasa de respuesta del 94%). El 97% de los padres calificaron la satisfacción global como satisfechos o muy satisfechos. Los aspectos mejor calificados fueron la tecnología de los equipos médicos (3.6 ± 0.8), la confianza que el personal transmite al paciente (3.6 ± 0.8) y la amabilidad del personal en su trato al paciente (3.6 ± 0.8). Los aspectos peor valorados fueron el estado de las habitaciones (3.4 ± 0.8), el tiempo de espera para ser atendido por un médico (3.3 ± 0.8) y la puntualidad de las interconsultas (3.3 ± 0.8).* **Conclusiones:** *Se observó un alto índice de satisfacción relacionado tanto con los factores objetivos como con los subjetivos. Sin embargo, los aspectos negativos de calidad objetiva, tales como la fiabilidad, deben ser atendidos por la organización sin que ello implique una inversión económica para su resolución.*

Palabras clave: *Niños. Cuidado de la salud. Calidad de la atención. Encuesta sobre centro de salud. Satisfacción del paciente. México.*

Introduction

In western societies, the quality of public and private healthcare services is commonly evaluated by measuring user satisfaction[1]. The interest in seeking the opinions of users has at least a triple justification: first, from the point of view of social participation, emphasis has been placed on citizens being an integral and central part of the system, participating actively in the evaluation, planning, and redefining of healthcare policies[2]; second, it is the users who can monitor and ultimately judge the quality of service since the subjective perception of the user speaks of the quality of the service combining their needs with their expectations[3]; and third, measuring satisfaction of the users is of great importance because it is proven that a satisfied patient is more disposed to following medical advice and treatment, and thus, to improve their health[4].

Over 120 million Mexicans are potential users of healthcare services in one of Mexico's health subsystems. These subsystems can be classified into three groups: the social security institutions, the institutions that provide services to the population without social security, and the private sector. The formal sector workers and their families obtain healthcare services mainly through one social security entity called the Mexican Social Security Institute (IMSS, for its Spanish acronym). The IMSS is responsible for providing healthcare services to approximately 62 million potential clients, and it is financed by the earmarked employee, employer payroll taxes, and legally mandated government contributions[5].

Patient satisfaction with care has been described as a multidimensional concept. Parasuraman et al. developed the Service Quality Questionnaire (SERVQUAL) for its use by service and retail organizations. According to these authors, there are five dimensions to service quality: reliability (the ability to carry out the promised service reliably and accurately), tangibles (equipment, physical facilities, and staff appearance), assurance (employee courtesy and knowledge, and their ability to inspire confidence and trust), responsiveness (the effort to help customers and provide fast service), and empathy (individualized attention the firm provides its clients)[6]. Although SERVQUAL was initially designed for application within financial service areas, the model is intended for a wide range of services, and its potential usefulness in a hospital environment has been evaluated and proven[7,8]. By using SERVQUAL as a guide, the Service Quality in Hospital Questionnaire (SERVQHOS) was developed for its use in the healthcare sector in Spanish-speaking countries[9]. We have chosen SERVQHOS as the measurement tool for assessing satisfaction because it is a brief questionnaire that is easy to complete, and it is broadly used in Spanish-speaking countries as a validated questionnaire[10]. This study aimed to describe parental satisfaction with healthcare during their child's hospitalization in a pediatric social security facility in Mexico.

Methods

Study population

This cross-sectional study consisted of parents of pediatric patients hospitalized in an academic, tertiary care pediatric medical facility in western Mexico. The facility offers care for children < 16 years of age. In 2018, the capacity of the pediatric and surgical wards was 250 beds, with 8,834 admissions, 3,979 surgical procedures, and 92,847 outpatient visits. The questionnaire was given between February and May 2019 to all parents who consented to participate and could read and write in Spanish.

Measurements

The SERVQHOS questionnaire is divided into three sections. The first section included 19 items measuring

perception of several factors that influence the *quality of assistance* rated on a 5-point Likert scale, where 1 = much worse than expected; 2 = worse than expected; 3 = as expected; 4 = better than expected; 5 = much better than expected. Patients had to answer the question, "How did you find the quality of assistance on the following aspects?", rating from 1 to 5. The 19 aspects included the five dimensions of service quality: reliability, tangibles, assurance, responsiveness, and empathy. The items could also be divided into subjective quality (human assistance) and objective quality (organizational and facility issues)[9].

The second section included questions regarding *overall satisfaction* (rated on a 4-point Likert scale, where 1 = very dissatisfied, 2 = dissatisfied, 3 = satisfied, and 4 = very satisfied). For example, if the length of stay was appropriate, if they would recommend the hospital, if the hospitalization was scheduled or urgent, the number of hospital admissions in the last year, whether the information received was adequate, and whether they knew the name of the doctors and nurses.

The third section included socio-demographic data like sex, age, marital status, educational level, and employment status. In the end, free space was provided for feedback. The SERVQHOS is a generic, non-surgery-specific questionnaire. The instrument showed a Cronbach's alpha for the domains ranging from 0.89 to 0.95 (overall scale: 0.92)[9,10].

Procedure

The questionnaires were delivered to the parents during child discharge. A trained social worker informed the parents about the purpose and the importance of their participation and gave an informed consent form to be signed. The questionnaire was provided with a blank envelope. Parents answered the questionnaire, placed it inside the envelope, and sealed it. The time to complete the questionnaire was 10 minutes. The social worker was available for clarifications as needed while parents responded to the questionnaire. One member of the team collected the sealed envelopes daily. Neither the questionnaire nor the envelope contained any questions or distinguishing signs leading to the identification of the participants. Regardless, the anonymity of the participants was ensured. No material or financial compensation was provided to participants. The local Research and Ethics Committee of the Mexican Social Security Institute approved the study protocol (CLIS R-2019-1302-011).

Statistical analysis

A pre-analysis power calculation gave the study > 84% power, $\alpha = 0.05$, with a sample size of 425. Initially, 425 questionnaires were delivered, but parent surveys with more than 50% of unanswered questions were excluded from the analysis, which occurred in 24 (5.6%) of the surveys. Data were presented as mean ± standard deviation (SD), median, or percentages as appropriate. We performed logistic regression analyses in those factors statistically associated with overall satisfaction when comparing the very satisfied group vs. the other categories, including marital status (having a couple vs. not having a couple), level of education (secondary education or less), scheduled hospital admission, and have received enough information about child health status. The standardized regression coefficient and R^2 determination coefficients were calculated. Data were analyzed with the SPSS Statistical Software Package (version 20.0 for Windows; SPSS, Inc., Chicago, IL). A value of $p<0.05$ was considered statistically significant.

Results

Demographics and quality evaluation

The population consisted of 401 parents (401 pediatric patients). The parents' mean age was 33 ± 8 years old, most of the participants were women 302 (75%), 322 (80%) had a couple (including married and common law), 218 (54%) completed at least secondary school education, and 204 (50%) were homemakers. The demographic characteristics of the parents are summarized in Table 1.

The results of the *quality* first section of the SERVQHOS questionnaire are presented as a mean and SD of a 5-point Likert scale rate (Table 2). Among the best-rated aspects were those related to objective quality (tangibles dimension): modern equipment technology, 3.68 ± 0.86; hospital employee appearance, 3.65 ± 0.84; and subjective quality (assurance dimension), including the ability to inspire trust and confidence (3.66 ± 0.83), employee courtesy (3.65 ± 0.83), and nursing staff interest in patients (3.65 ± 0.85). However, the aspects that users rated worst were those related to objective quality (reliability dimension): waiting time for services (3.37 ± 0.82) and timeliness at the doctor's visit (3.34 ± 0.80), as well as (tangibles dimension) room conditions (3.46 ± 0.82) and ease of getting to the hospital (3.40 ± 0.85).

Table 1. Demographic characteristics of responders

Total population		Comparison between groups		*p*-values
		Very satisfied	Others	
	n = 401 (%)	n = 78 (%)	n = 323 (%)	
Age				
Mean ± SD	33 ± 8	33 ± 8	34 ± 8	0.34
Sex				
Female	302 (75)	55 (70)	247 (76)	0.344
Male	97 (24)	22 (28)	75 (23)	
Not available	2 (0.5)	1 (1.2)	1 (0.3)	
Marital status				
Having couple	322 (80.2)	55 (70.5)	267 (82.6)	0.056
Not having couple	75 (18.7)	20 (25.6)	55 (17.0)	
Not available	4 (0.9)	3 (3.8)	1 (0.3)	
Education level				
Secondary or less	218 (54.3)	52 (66.6)	166 (51.3)	0.016
Preparatory or higher	181 (45.1)	25 (32.0)	156 (48.2)	
Not available	2 (0.4)	1 (1.2)	1 (0.3)	
Occupation				
Homemaker	204 (50.8)	42 (53)	162 (50)	0.563
Student	6 (1.4)	2 (2)	4 (1)	
Employed	187 (46.6)	33 (42)	154 (47)	
Retired	2 (0.4)	0 (0)	2 (0.6)	
Not available	2 (0.4)	1 (1)	1 (0.3)	

SD, standard deviation.

Satisfaction evaluation

The results of the *satisfaction* second section of the questionnaire are shown in Table 3. The overall satisfaction with care was rated on a 4-point Likert scale as follows: very dissatisfied (0%), 8 dissatisfied (1.9%), 315 satisfied (78.5%), and 78 very satisfied parents (19.4%); additionally, 388 parents (96%) would not hesitate to recommend the hospital to others. Also, 382 parents (95%) believed that their child stayed in the hospital necessary length of time, and 394 parents (98%) responded that their child did not undergo medical tests without permission. However, 39 parents (9%) did not know the name of the doctor who treated their child during hospitalization, and 29 parents (7%) did not know the nurse's name. The free space for feedback was used by 96 parents (23.9%) who gave one or more comments or suggestions: 27 acknowledgments/words of gratitude (28%), and 69 complaints (72%) about the facilities, catering services, the care received by staff, and the lack of personnel.

Comparisons between groups

To know which factors determined *satisfaction* in our population, we grouped the parents into two groups: those who rated the attention as 'very satisfied' 78 (19.4%) and those who rated the rest of the categories as dissatisfied and satisfied 323 (80.5%). We did not observe any significant differences in age, sex, and occupation upon comparing the demographic characteristics. In contrast, we observed a tendency concerning having a couple or not (including married and common law) ($p = 0.056$) and a statistically significant difference regarding the level of education (secondary education or less) ($p = 0.016$) (Table 1). When comparing the first section of the SERVQHOS questionnaire results between the very satisfied group and the rest of the categories, we observed statistically significant differences ($p = 0.001$) in the 19 questions of that section. Conversely, for the seven questions that comprise the second section of the questionnaire, we only observed a significant difference for the question "Did you get enough information?" ($p = 0.001$) (Table 3).

With this information, we performed a multiple logistic regression analysis, considering the level of satisfaction of 'very satisfied' as a dependent variable and the variables that were found to be significant in the bivariate analysis as predictors: not having a couple ($p = 0.056$), secondary level of education or less ($p = 0.016$), having received enough information

Table 2. SERVQHOS (Service Quality in Hospital) parental quality evaluation with care—Part 1

Evaluation	Score	Much worse/Worse		Much better/Better
	Mean ± SD	n (%)	n (%)	n (%)
Total satisfaction with care	3.63 ± 0.79	6 (1.4)	208 (51.8)	187 (46.6)
Objective quality				
Tangibles				
Modern equipment technology	3.68 ± 0.86	6 (1.4)	209 (52.1)	186 (46.3)
Hospital employee appearance	3.65 ± 0.84	7 (1.7)	213 (53.1)	181 (45.1)
Location directions	3.54 ± 0.81	11 (2.7)	227 (56.6)	163 (40.6)
Room conditions	3.46 ± 0.82	20 (4.9)	223 (55.6)	158 (39.4)
Ease of getting to the hospital	3.40 ± 0.85	26 (6.4)	229 (57.1)	146 (36.4)
Reliability				
Accomplishment of promised services	3.59 ± 0.81	10 (2.4)	215 (53.6)	176 (43.8)
Waiting time for service	3.37 ± 0.82	28 (6.9)	238 (59.3)	135 (33.6)
Timeliness of doctor's visit	3.34 ± 0.80	34 (8.4)	231 (57.6)	136 (33.9)
Subjective quality				
Responsiveness				
Sincere interest in solving problems	3.55 ± 0.80	12 (2.9)	218 (54.3)	171 (42.6)
Provision of prompt services	3.47 ± 0.78	19 (4.7)	226 (56.3)	156 (38.9)
Willingness to help patients	3.62 ± 0.84	11 (2.7)	209 (52.1)	181 (45.1)
Assurance				
Ability to inspire trust and confidence	3.66 ± 0.83	9 (2.2)	200 (49.8)	192 (47.8)
Employee courtesy	3.65 ± 0.83	5 (1.2)	212 (52.8)	184 (45.8)
Employees professional skills	3.62 ± 0.82	9 (2.2)	212 (52.8)	180 (44.8)
Nursing staff interest in patients	3.65 ± 0.85	6 (1.4)	215 (53.6)	180 (44.8)
Empathy				
Individual personal attention	3.62 ± 0.83	9 (2.2)	213 (53.1)	179 (44.6)
Understanding of specific patients' needs	3.56 ± 0.79	8 (1.9)	225 (56.1)	168 (41.8)
Objective quality				
Others				
Information about treatments	3.58 ± 0.86	18 (4.4)	208 (51.8)	175 (43.6)
Information to relatives/families	3.56 ± 0.84	15 (3.7)	220 (54.8)	166 (41.3

SD, standard deviation.

(p = 0.001), and type of hospital admission (p = 0.056). This model achieved an explanatory power on the variable 'very satisfied' from 53% to 83% (R squared of Cox and Snell: 0.52; and R squared of Nagelkerke: 0.83, respectively); however, the variables not having a couple and secondary level of education or less were not statistically significant in this model (Table 4).

Discussion

The Mexican health care system seems to be overstretched, and healthcare quality has remained unsatisfactory for most of the population. A 2006 national survey found substantial heterogeneity in healthcare quality assessments across healthcare subsystems, favoring private providers over social security institutions.

Moreover, 76% of Mexicans thought their health system needed fundamental changes[11]. As a result of the healthcare system overhaul, the quality of care has become increasingly important. Furthermore, experts emphasize that the results of patient satisfaction questionnaires will be required by insurance companies and care providers[12-14].

Methods that measure patient satisfaction are not well applied in specific populations like children, who have difficulties expressing their views directly[15]. In contrast, a quality assessment of parental satisfaction with service provision is particularly challenging and rarely undertaken[16]. Parental satisfaction has been used successfully to measure quality for pediatric patients' attention as it is closely linked to the adequacy of children's treatment and staff performance in pediatric practice[17]. A thorough review of the literature

Table 3. SERVQHOS (Service Quality in Hospital) parental satisfaction evaluation with care—Part 2

Total population		Comparison between groups		*p*-values
		Very satisfied	Others	
	n = 401 (%)	n = 78 (%)	n = 323 (%)	
Would you recommend this hospital?				
Yes, no doubt	388 (96.4)	78 (100)	310 (96)	0.197
I am not sure	12 (3.2)	0 (0)	12 (3)	
Never	0 (0)	0 (0)	0 (0)	
Information unavailable	1 (0.2)	0 (0)	1 (0.3)	
Your patient underwent a medical test without your permission?				0.423
No	394 (98.2)	78 (100)	316 (98)	
Yes	6 (1.4)	0 (0)	6 (1)	
Information unavailable	1 (0.2)	0 (0)	1 (0.3)	
Do you believe the length of stay of your child was				
Shorter than necessary				
Adequate	5 (1.2)	2 (2)	3 (0.9)	0.432
Longer than necessary	382 (95.2)	75 (96)	307 (95)	
Information unavailable	13 (3.2)	1 (1)	12 (3)	
	1 (0.2)	0 (0)	1 (0.3)	
Do you know your doctor's name?				
Yes	361 (90)	69 (88)	292 (90)	0.742
No	39 (9.7)	9 (11)	30 (9)	
Information unavailable	1 (0.2)	0 (0)	1 (0.3)	
Do you know your nurse's name?				
Yes	371 (92.5)	70 (89)	301 (93)	0.098
No	29 (7.2)	7 (8)	22 (6)	
Information unavailable	1 (0.2)	1 (1)	0 (0)	
Do you get enough information?				
Yes	347 (86.5)	75 (96)	272 (84)	0.001
No	53 (13.2)	2 (2)	51 (15)	
Information unavailable	1 (0.2)	1 (1)	0 (0)	
Hospital admission				
Emergency	222 (55.3)	34 (43)	188 (58)	0.056
Scheduled	173 (43.1)	42 (53)	131 (40)	
Information unavailable	6 (1.4)	2 (2)	4 (1)	
Number of admissions during the last year				
Mean	1.9±2.7	1.7±1.3	2.1±2.5	0.055
Hospitalization service evaluated				
Cardiac surgery	4 (0.99)	0 (0)	4 (100)	
Cardiology	58 (14.4)	7 (12)	51 (88)	
Maxillofacial surgery	1 (0.2)	0 (0)	1 (100)	
Pediatric surgery	36 (8.9)	4 (11)	32 (89)	
Plastic surgery	9 (2.2)	3 (33)	6 (67)	
Endocrinology	5 (1.2)	0 (0)	5 (100)	
Gastroenterology	23 (5.7)	5 (22)	18 (78)	
Hematology	32 (7.9)	6 (19)	26 (81)	
Infectology	3 (0.7)	0 (0)	3 (100)	
Internal medicine	6 (1.4)	2 (33)	4 (67)	
Nephrology	8 (1.9)	1 (12)	7 (88)	
Neonatology	7 (1.7)	1 (14)	6 (86)	
Respirology	11 (2.7)	2 (18)	9 (82)	
Neurosurgery	10 (2.4)	0 (0)	10 (100)	
Neurology	35 (8.7)	3 (8)	32 (92)	
Oncology	28 (7.2)	2 (7)	26 (93)	
Otorhinolaryngology	3 (0.7)	1 (33)	2 (67)	
Orthopedics	6 (1.4)	2 (33)	4 (67)	
Pediatrics	17 (4.2)	7 (41)	10 (59)	
Rheumatology	3 (0.7)	2 (67)	1 (33)	
Emergency	48 (11.7)	15 (31)	33 (69)	
Urology	13 (3.2)	5 (38)	8 (62)	
Information unavailable	35 (8.7)	10 (29)	25 (71)	

Table 4. Parents' satisfaction with healthcare—logistic regression

Variable	*p*-values	β coefficient	Confidence interval 95%	
			Lower	Upper
Enough information received	0.009	0.149	0.035	0.626
Scheduled hospital admission	0.015	0.526	0.314	0.882
Secondary educational level or less	0.115	0.552	0.263	1.155
Not having a couple	0.224	1.396	0.815	2.390

revealed a lack of studies that have examined a broader perspective of parents' views on the quality of pediatric ward healthcare. Previous studies have been focused on specific areas such as emergency care[18], intensive pediatric care[19], neonatal intensive care[20], and pain management[21] or parental involvement in the care of their child[22].

This study analyzed the perceived parental quality and satisfaction with healthcare in tertiary care, social security, pediatric facility. We achieved a participation rate of 94% in our study, which is quite similar to the Arrebola-Pajares et al. study in Spain, with a participation rate of 92% using the same SERVQHOS questionnaire but in adult patients with urological conditions[23]. In our unit, the quality issues rated worst by parents were aspects concerning objective quality (waiting time for service, punctuality of doctor's visit, room conditions, and ease of getting to the hospital); this situation has also been highlighted in other surveys using SERVQHOS[23,24]. The best-rated aspects were objective quality (modern equipment technology) and subjective quality (ability to inspire trust and confidence, employee courtesy, and nursing staff interest in patients). Similar results but higher mean scores were reported in the study of Gomez et al. applied to adult patients from a burn unit in Spain[24]. Our results demonstrate a high level of overall parental satisfaction: 78% satisfied and 19% very satisfied, while dissatisfaction rated as 'not very satisfied' was only 2%, similar to that published by Perez et al., where they referred to dissatisfaction ranging from 2.9% to 2.5% when comparing a public healthcare center vs. a private institution[25]. To the best of our knowledge, this is the first time the SERVQHOS questionnaire has been applied to parents of pediatric patients. Therefore, we cannot make specific comparisons at this time, unfortunately.

Few of the parents did not know the name of the doctor who attended their child (9%), while the name of the nurse was unknown to a slightly lower percentage (7%). This lack of awareness could be caused by staff rotations: a high percentage of its eventuality occurs in our facility, which did not allow identification of a nurse as a point of reference. Knowing the name of the person who provides services improves the achievement of treatment in patients. Our results are better than those published by other authors, where the percentages varied from 20% to 40%. However, this aspect should be improved[24,25]. Regarding the number of previous hospitalizations, our results are consistent with the study performed by Ygge et al., where parents whose child was hospitalized several times in the past expressed lower levels of satisfaction[26].

In the logistic regression analysis, we observed that the variables of having received enough information and pre-scheduled hospitalization were the most influencing factors on the overall satisfaction in parents, achieving an explanatory power from 52% al 83%. In contrast to other studies, we did not observe a significant difference in marital status variables and level of education[27]. In the present study, the questions regarding treatments and information to relatives/families were scored low (3.58 and 3.56 points, respectively). Moreover, 13% of the parents referred not having received enough information, a result lower than Tolosa et al. study in a public hospital in Colombia, where 31% of parents referred dissatisfied with the information provided[28].

In the free space for feedback, the parents mainly complained about not having enough information about the illness, the resolution of doubts in an everyday language, and uncertainty about the outcome of the illness and the evolution of the patient. These grievances fit into the three domains proposed in the taxonomy of Reader et al.[29], in which communication is a common complaint issue. This finding agrees with previous publications that report significant problems in staff-patient relationships and communication between staff and patients[30].

The limitations of our study include that it was conducted at a single-center tertiary level facility, which limits the generalizability since the experiences of parents of children admitted in other contexts may vary. The use of questionnaires to evaluate the level of satisfaction is a simple and effective tool, but it depends on the expectations of the parents: if parental expectations are low, their perceptions of the quality received will be better. Although the hospital from which the sample was drawn is the most extensive pediatric facility in the northwest of Mexico, the results should be interpreted with caution because it is unclear how these findings represent parental satisfaction in other pediatric wards of the IMSS healthcare network.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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RESEARCH ARTICLE

Neutrophilic-lymphocytes and platelet-lymphocytes ratios as predictors for acute perforated appendicitis in children

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Abstract

Background: *This study aimed to evaluate the neutrophil-lymphocyte (NLR) and platelet-lymphocyte (PLR) ratios as markers of perforated appendicitis.* **Methods:** *We conducted a cross-sectional analytical study. We performed a secondary analysis of a population of pediatric patients who underwent appendectomy between 2017 and 2019 at the Regional Hospital of Ayacucho, Peru. Logistic regression models were used to analyze markers (NLR and PLR) and perforated appendicitis. Later, ROC (receiver operating characteristic) curves were constructed, and sensitivity, specificity, and likelihood ratios were estimated.* **Results:** *We identified 31% of perforated appendicitis in 203 patients. A significant association was observed between perforated appendicitis and NLR values > 10.4 (odds ratio [OR]: 2.53; 95% confidence interval [95% CI]: 1.27-5.05) and PLR > 284 (OR: 2.11; 95% CI: 1.09-4.08) in the adjusted analysis. For these models, the areas under the curve were 0.74 (95% CI: 0.67 - 0.81) for both variables. With a cut-off point of 30% probability of perforated appendicitis, we observed sensitivity of 77.78% for both NLR and PLR (likelihood ratio +2.37 and +2.14, respectively), and specificity of 67.14% and 63.57% for NLR and PLR (likelihood ratio –0.33), respectively.* **Conclusions:** *Our study showed a significant association between NLR and PLR and acute perforated appendicitis. Future studies should validate the model and corroborate the performance of these markers.*

Keywords: *Appendicitis. Pediatrics. Neutrophils. Blood platelets. Lymphocyte count.*

Relación neutrófilos-linfocitos y relación plaquetas-linfocitos como predictores para apendicitis aguda perforada en niños

Resumen

Introducción: *El objetivo del estudio fue evaluar la relación neutrófilos-linfocitos (RNL) y la relación plaquetas-linfocitos (RPL) como marcadores de apendicitis perforada.* **Métodos:** *Se llevó a cabo un estudio analítico transversal. Se realizó el análisis secundario de una población de pacientes pediátricos sometidos a apendicectomía, entre 2017 y 2019, en el Hospital Regional de Ayacucho, Perú. Para el análisis de los marcadores (RNL y RPL) y la apendicitis perforada se utilizaron modelos de regresión logística, de los cuales se construyeron curvas ROC (Receiver Operating Characteristic) y se estimaron la sensibilidad, la especificidad y la razón de verosimilitud.* **Resultados:** *Se identificó apendicitis perforada en el 31% de un total de 203 pacientes. Se observó una asociación significativa entre la apendicitis perforada y los valores > 10.4 de RNL (razón de momios [RM]: 2.53; intervalo de confianza del 95% [IC 95%]: 1.27-5.05) y > 284 de PLR (RM: 2.11; IC 95% 1.09 - 4.08) en el análisis ajustado. Para estos modelos, las áreas bajo la curva fueron de 0.74 (IC 95%: 0.67 – 0.81) para*

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ambas variables. Con un punto de corte del 30% de probabilidad de apendicitis perforada se observa una sensibilidad del 77.78% tanto para RNL como para RPL (razón de verosimilitud +2.37 y +2.14, respectivamente), y una especificidad del 67.14% y el 63.57% para RNL y RPL (razón de verosimilitud –0.33). **Conclusiones:** *Este estudio mostró una asociación significativa de RNL y RPL y la apendicitis aguda perforada. Futuros estudios deberán validar el modelo elaborado y corroborar el desempeño de dichos marcadores.*

Palabras clave: *Apendicitis. Pediatría. Neutrófilos. Plaquetas sanguíneas. Recuento de linfocitos.*

Introduction

Acute appendicitis (AA) is the most common diagnosis requiring emergency surgery in the pediatric population[1], with a prevalence of 69% in this age group[2], of which 30-75% of cases progress to perforated appendicitis[3].

According to some reports, the risk of progression from acute to perforated appendicitis in children is high[4], with a mortality risk of ≈50%. This risk is higher than in the general population[5,6], mainly due to the difficulty in diagnosing the complication, difficulties in physician-patient communication, and the absence of classic symptoms, resulting in delays in early treatment[7,8].

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are emerging as simple, low-cost markers that provide information on the action of two immune and inflammatory pathways[9,10]. These parameters have even been proposed as potential markers for predicting perforated appendicitis[11-13] because they relate to innate immunity, which has an initial action on the inflammatory process and the long-term response of the immune system. Although studies have been performed in adult and elderly populations, there is uncertainty about using these markers in the pediatric population.

In countries with scarce health resources, such as Peru, these markers could help to identify patients at potential risk of perforated appendicitis in order to prioritize their admission to surgical wards, considering that surgical care times for appendicitis are usually long, which could lead to worse outcomes in this group of patients[14,15]. Therefore, this study aimed to evaluate the potential clinical utility of NLR and PLR as markers for the early diagnosis of acute perforated appendicitis in the pediatric population.

Methods

Study design

We conducted an observational, analytical cross-sectional study in which we performed a secondary analysis of a database of pediatric patients attended at the Regional Hospital of Ayacucho.

Study population, sample, and selection criteria

The study population consisted of all pediatric patients under 16 years of age at the time of diagnosis and who underwent appendectomy for acute appendicitis at the Regional Hospital of Ayacucho between January 2017 and December 2019.

For the present analysis, we obtained a non-random sample, in which we included all patients with an intraoperative diagnosis of acute appendicitis. We excluded those patients < 5 years of age (due to the essential physiological differences in lymphocyte counts below this age)[16] who reported having pathologies that altered the NLR and PLR[17], who had consumed any drug before admission, and who did not have any of the variables of interest reported.

Procedures

The necessary permissions were requested for access to the patient database and patient medical records. An author verified the data reliability by contrasting the information collected with the clinical history of each patient. Considering previous research, we also included variables that were not initially included but were necessary for the study and added them to the database[11,18].

Outcome: perforated appendicitis

The diagnosis of non-perforated appendicitis was defined as congestive or catarrhal, phlegmonous or suppurative, gangrenous or necrotic appendicitis, and without macroscopic perforations or free fluid. In contrast, perforated appendicitis was defined by the presence of macroscopic perforations in the appendix and the presence of free intra-abdominal fluid. This variable was assessed based on the intraoperative report of each patient.

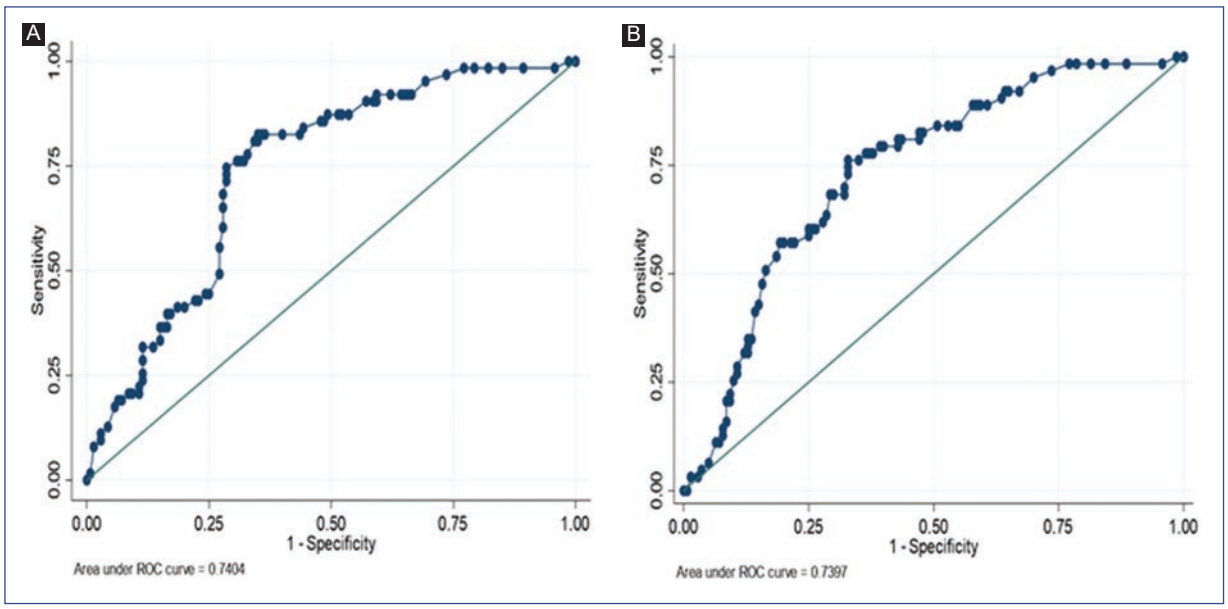

Figure 1. Receiver operating characteristic (ROC) curves of the predictive models. **A.** Predictive model for acute appendicitis and neutrophil-to-lymphocyte ratio, adjusted for age, sex, and leukocytes. **B.** Predictive model for acute appendicitis and platelet-to-lymphocyte ratio, adjusted for age, sex, and leukocytes.

Independent variables

The leading independent variables were the NLR and PLR ratios. To obtain the NLR value, we divided the absolute number of neutrophils by the absolute number of lymphocytes, and for PLR, the absolute number of platelets by the absolute number of lymphocytes, as recommended elsewhere[16]. We decided to categorize the NLR and PLR variables considering the established cut-off points for the pediatric population proposed in published studies[18]. Therefore, categorical variables were obtained for both cases (NLR: ≤ 10.4 and > 10.4; PLR: ≤ 284 and >284).

Other variables were also evaluated, such as sex (male and female) and age (years), and clinical characteristics, such as fever, abdominal pain, nausea, vomiting, and diarrhea. Also, laboratory values such as leukocytes (≤ 15000 and > 15000 cells/mm^3), neutrophils, lymphocytes, and their absolute values from the complete blood count were performed when the patient was admitted to the hospital. All the laboratory values were processed at the Regional Hospital of Ayacucho.

Statistical analysis

We used the Stata v.15 statistical software for data analysis. A descriptive analysis of the study population was performed using absolute and relative frequencies for categorical variables and central tendency and dispersion measures for numerical variables. The distribution of the variables was evaluated using quantiles plots.

The relationship between NLR and PLR and perforated appendicitis was calculated using logistic regression models, in which the odds ratio (OR) and their respective confidence intervals (95%CI) were obtained. To develop multiple models, we considered including known variables that could affect the primary relationship, such as age, sex, leukocytes >15 000 cells/mm^3, as reported previously[5,19]. In addition, a sensitivity analysis was performed to compare the model created, including the confounding variables and the NLR/PLR vs. the model without the NLR/PLR variables, to determine the contribution of the primary variables NLR and PLR.

For the selected multiple regression models, receiver operating characteristic (ROC) curves were plotted, and their respective areas under the curve (AUC) were estimated. A cut-off point of 0.29 was chosen as the probability of having the outcome because it reports a better balance between its sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR-) values (Figure 1).

Ethical aspects

The present study is based on secondary analysis. No individuals were contacted, so the risks were minimal. Anonymity and confidentiality of the participants' data were maintained by coding each one of the individuals.

Table 1. Clinical characteristics of the patients with appendicitis (n = 203)

Variable		Perforated appendicitis		
	n (%)	No 140 (68.97)	Yes 63 (31.03)	*p*-values
Sociodemographic characteristics				
Sex Male Female	 110 (54.19) 93 (45.81)	 67 (60.91) 73 (78.49)	 43 (39.09) 20 (21.51)	0.007
Age	10.98 ± 3.10*	11.39 ± 3.04*	10.08 ± 3.07*	0.005
Clinical features				
Fever No Yes	 137 (67.49) 66 (32.51)	 104 (75.91) 36 (54.55)	 33 (24.09) 30 (45.45)	0.002
Abdominal pain No Yes	 1 (0.49) 202 (99.51)	 1 (100) 139 (68.81)	 0 (0) 63 (31.19)	0.501
Vomiting No Yes	 4 (46.31) 109 (53.69)	 70 (74.47) 70 (64.22)	 24 (25.53) 39 (35.78)	0.116
Nausea No Yes	 170 (83.74) 33 (16.26)	 112 (65.88) 28 (84.85)	 58 (34.12) 5 (15.15)	0.031
Diarrhea No Yes	 185 (91.13) 18 (8.87)	 129 (69.73) 11 (61.11)	 56 (30.27) 7 (38.89)	0.451
Laboratory values				
Leukocytes ≤ 15000 cells/mm^3 > 15000 cells/m^3	12.97 ± 5.28* 126 (62.07) 77 (37.93)	11.73 ± 5.05* 99 (78.57) 41 (53.25)	15.73 ± 4.73* 27 (21.43) 36 (46.75)	< 0.001
Neutrophils	79.20 ± 13.20*	76.16 ± 14.12*	85.97 ± 7.28*	< 0.001
Absolute value of neutrophils	10.73 ± 5.28*	9.42 ± 5.11*	13.64 ± 4.46*	< 0.001
Lymphocytes	14.67 ± 11.80*	17.49 ± 12.65*	8.40 ± 6.09*	< 0.001
Absolute value of lymphocytes	1.49 ± 0.83*	1.62 ± 0.85*	1.20 ± 0.73*	0.001
Neutrophil-to-lymphocyte ratio ≤ 10.4 > 10.4	10.81 ± 10.32* 124 (61.08) 79 (38.92)	8.40 ± 7.93* 99 (79.84) 41 (51.9)	16.16 ± 12.78* 25 (20.16) 38 (48.1)	< 0.001
Platelet-to-lymphocyte ratio ≤ 284 >284	269.45 ± 183.98* 134 (66.01) 69 (33.99)	233.96 ± 139.00* 103 (76.87) 37 (53.62)	348.32 ± 240.43* 31 (23.13) 32 (46.38)	< 0.001

Results

Of the 232 pediatric patients surgically intervened for AA at the Regional Hospital of Ayacucho between 2017 and 2019, we excluded 25 due to the absence of data on the variables under study, and four medical records were reported as missing. The final population study was of 203 patients with AA (mean age 10.9 ± 3.1), of which 31.0% presented perforated appendicitis.

Of this population, 32.5%, 99.5%, 53.7%, 16.3%, and 8.9% presented with fever, abdominal pain, vomiting, nausea, and diarrhea, respectively. Furthermore, within the laboratory values we obtained a mean of 10.7 ± 5.3 neutrophils (absolute value) and 1.5 ± 0.8 lymphocytes (absolute value) (Table 1). We observed that 37.9% showed values >15000 cells/mm^3 of leukocytes, 38.9% values >10.4 in NLR, and 33.9% values >284 in PLR.

Table 2. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as predictors of acute perforated appendicitis

	Bivariate analysis		Multiple regression*		AUC	Cut-off point**	Sensitivity	Specificity	LR+	LR-
	OR	95%CI	OR	95%CI						
Model for NLR										
NLR										
≤ 10.4	Reference		Reference		0.74 (0.67-0.81)	0.29	77.78%	67.14%	2.37	0.33
> 10.4	3.67	1.97-6.84	2.53	1.27-5.05						
Age	0.87	0.79-0.96	0.90	0.81-1.00						
Sex										
Female	Reference		Reference							
Male	0.43	0.23-0.80	0.45	0.23-0.88						
Leukocytes										
≤ 15000	Reference		Reference							
> 15000	3.22	1.74-5.97	2.01	0.26-3.54						
Model for PLR										
PLR										
≤ 284	Reference		Reference		0.74 (0.67-0.81)	0.29	77.78%	63.57%	2.14	0.33
>284	2.87	1.54-5.34	2.11	1.09-4.08						
Age	0.87	0.79-0.96	0.91	0.82-1.02						
Sex										
Female	Reference		Reference							
Male	0.43	0.23-0.80	0.48	0.24-0.92						
Leukocytes										
≤ 15000	Reference		Reference							
> 15000	3.22	1.74-5.97	2.71	1.42-5.18						

*Adjusted for sex, age, and leukocytes. **Cut-off point for probability.
The estimation of the area under the curve, sensitivity, specificity, and likelihood ratio was performed using the multiple regression model.
AUC, area under the curve; CI, confidence interval; LR, likelihood ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; OR, odds ratio.

Also, a statistically significant difference was found between the variables sex, age, fever, nausea, leukocytes, neutrophils, lymphocytes, NLR, and PLR, with perforated appendicitis (Table 1).

Predictive model

In the bivariate analysis, we found a significant association between NLR (> 10.4; OR: 3.67; 95%CI 1.97 - 6.84) and PLR values (> 284; OR: 2.87; 95%CI 1.54 - 5. 34) with perforated appendicitis, which was maintained when performing the adjusted analysis, where values > 10.4 and > 284 of NLR (OR: 2.53; 95%CI 1.27 - 5.05) and PLR (OR: 2.11; 95%CI 1.09 - 4.08), respectively, were associated with an increased risk of perforated appendicitis (Table 2).

When comparing the multiple regression models with and with no NLR and PLR variables, we observed an improvement in the values of the likelihood ratios and pseudo R^2 when adding the NLR (with no variables: log-likelihood = -113.25, pseudo R^2 = 0.099; with variables: log-likelihood = -109.76, pseudo R^2 = 0.127) and PLR (with no variables: log-likelihood = -113.25, pseudo

R^2 = 0.099; with variables: log-likelihood = -110.82, pseudo R^2 = 0.118). Considering that NLR and PLR variables contributed significantly to the multiple regression models, we decided to select the models that included the main variables.

Both models created for NLR and PLR performed well as markers of perforated appendicitis with an AUC of 0.74 (0.67 - 0.81) for both variables.

Finally, for a cut-off point of the probability of having perforated appendicitis of 30%, we observed sensitivity of 77.78% for both NLR and PLR (likelihood ratio +2.37 and +2.14, respectively), and a specificity of 67.14% and 63.57% for NLR and PLR (likelihood ratio -0.33), respectively.

Discussion

Our study evaluated a population of patients with AA to assess two potential markers for the diagnosis of perforated appendicitis. Besides abdominal pain, we found that vomiting was present in more than half of the children with AA, consistent with a previous study conducted in Turkey, where 100% and 56% of the children indicated abdominal pain and presented vomiting, respectively[18]. In contrast, another study in the United States reported absent symptoms in children with pathologically established appendicitis[8].

While it is true that these symptoms and their severity could be helpful for diagnosis, we must consider that many of the clinical data are referred by the patient, which makes them of little use in young children due to their limited ability to communicate their symptoms[20]. Furthermore, there is no typical pattern in the clinical features of AA in children, so complementary diagnostic tools are required to diagnose appendicitis and detect complications such as perforation[8].

Perforated appendicitis

We found perforated appendicitis in more than one-third of the population studied. Similar figures have been reported in Turkey[21] and the United States[7], where approximately 30% and 24% of children, respectively, presented with perforated appendicitis. The percentage found is higher than other age groups, which may be because the diagnosis of appendicitis in children is generally difficult and may progress to perforated appendicitis[6,20,22].

Perforated appendicitis occurs more commonly in young children because they are less able to understand or articulate their developing symptomatology compared with adolescents. Therefore, it impacts low diagnostic accuracy in this age group[5] and is associated with a delay in inpatient surgical treatment, subsequently leading to a potential risk of perforation[3]. Our findings corroborate this fact, as the patients with perforation were young.

A higher frequency of perforation was observed in males (39.09% vs. 21.51%), similar to a study in Germany, in which males presented with perforated appendicitis more frequently (66%)[23]. This higher frequency could be mainly due to differences in the immune response and differences in the characteristics of the intestinal connective tissue between males and females[24,25]. In this regard, it has been observed that women have higher levels of immune activation and higher gene expression associated with inflammation in intestinal mucosa samples, which, in theory, could translate into a lower incidence of perforated appendicitis cases.

Consistent with a study in China[13], we also found that leukocytes (> 15000 cells/mm^3), neutrophils, and lymphopenia were significantly higher in those patients with perforated appendicitis. As both leukocytes and neutrophils are part of the acute inflammatory response, their increase would be involved in the appendix inflammation process and, consequently, its perforation[9]. Lymphopenia is a marker of stress[26] and infectious pathologies[27], and its reduction is associated with the progression of appendicitis infection, especially after 6 hours[28].

Markers for perforated appendicitis

NLR is a commonly available biomarker that conveys information about inflammatory conditions[10] because neutrophils signal and are part of the immune response, which helps the body initiate and maintain a sustained response[9]. Therefore, it would be expected that the higher the NLR value, the more excessive and uncontrolled the immune response will be due to tissue destruction mediated by the inflammatory process, leading to perforation[29]. In this case, predictive models have reported that NLR values > 10.4 would more precisely indicate the development of perforated appendicitis[18].

We evaluated the NLR considering a cut-off point of 10.4 and found a statistically significant association between NLR and perforated appendicitis, with a sensitivity of approximately 78% and a specificity of 67% for a probability of perforated appendicitis of 29%.

Although the use of NLR as a diagnostic marker in perforated appendicitis has been previously studied, primarily adult and elderly populations have been included[11-13]. Higher sensitivities were found in a South Korean (78%), and a Turkish (81%) study, whereas a lower sensitivity was reported in another study conducted in Turkey (64%). Additionally, these three studies reported lower specificity (66%, 53%, and 64%, respectively). These results may be because NLR measurement can potentially be impaired in adults and elderly individuals due to increased NLR when one of the following pathologies is present: high blood pressure, diabetes mellitus, metabolic syndrome[30], left ventricular dysfunction, acute coronary syndrome, valvular heart disease, abnormal thyroid function, renal or hepatic dysfunction, malignancy[31,32], local or systemic infection, previous history of infection (< 3 months), inflammatory disease, any medications related to the inflammatory condition and obesity[17,33]. In contrast, these conditions are not commonly found in pediatric patients. For this case, we found only one study that evaluated the NLR as a predictor of complicated AA in the pediatric population, which reported similar sensitivity (61%) and specificity (73%) values to those in our population[18]. Therefore, these findings could suggest that the use of this marker would be reproducible in different populations.

We also found a good performance of the final model, including NLR (AUC = 0.74) with relatively higher values than those reported in studies from Turkey[12] and Korea[11], which may be a consequence of the differences in the included population[17]. However, the values were similar to those reported in a pediatric population in Turkey[18], with an NLR performance of only 0.71. If adjusted for other known predictors, this value could have been higher or even equal to that observed in our population.

Furthermore, we found a higher probability of perforated appendicitis for PLR values > 284, with a sensitivity of 77% and a specificity of 64% in the final model. These percentages are far from those reported in studies conducted in Turkey, both in adult[13] and pediatric populations[18]. In general, PLR can be affected by the lymphocyte count, which is influenced by physical and psychological stress, smoking, pregnancy, and others[16], or even by the platelet count, due to the sampling time, processing, and equipment used for blood analysis[34]. Therefore, the performance of this marker may vary under these circumstances and could present changes in sensitivity and specificity. Regardless, these values demonstrated that PLR could be a good marker for perforated appendicitis.

The hypothesis of the usefulness of this marker originates from the fact that platelets accumulate at sites of vascular injury or inflammation to maintain the leukocytes recruitment necessary for immunopathological responses. Therefore, in the presence of a more significant inflammatory response, platelets increase[35] and, consequently, the PLR ratio. In this case, we found a good performance of the obtained model, including PLR (AUC = 0.74).

The adequate performance of both NLR and PLR as markers in the development of perforated appendicitis has been demonstrated. However, future studies are required to validate the proposed models, especially in longitudinal designs, for the sole purpose of verifying the performance of these markers.

Strength and limitations

The present work is one of the few studies exploring markers of appendix perforation in a pediatric population from blood tests, which are commonly used and available in emergency departments. Furthermore, NLR and PLR analysis are affordable and easy to calculate in the clinical setting, making it an effective clinical assessment tool, a valuable complement, and an aid to risk stratification.

As these markers could be used to indicate appendix perforation, which would allow determining antibiotic coverage and timely use of laparoscopic surgery, further research based on these markers should be continued.

However, some limitations should be considered. First, patients < 5 years of age were not included, so our results cannot be extrapolated to the entire pediatric population. In addition, as this was an analysis of a secondary database, some critical variables could not be included in the final model, such as the time elapsed since symptom onset.

In future research on this topic, we recommend a prospective study with a larger sample, considering some methodological, physiological, and pathological confounding factors, which could make the significance of NLR and PLR analysis in pediatric perforated appendicitis more powerful.

The present study evidenced an adequate performance of NLR and PLR as markers of perforated appendicitis. NLR values >10.4 and PLR > 284 were significantly associated with perforated appendicitis in pediatric patients. Future studies should validate the

proposed models, including variables not contemplated in this study and longitudinal designs.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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RESEARCH ARTICLE

Comparison of growth and psychomotor development in daycare centers attended by professionals

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Abstract

Background: *Growth and development reflect the child's health condition. Currently, child care is supported in daycare centers. In this context, this article aimed to identify the differences in growth and psychomotor development in children according to their attendance at daycare centers.* **Methods:** *We conducted an analytical cross-sectional study in children aged 25 to 48 months. Two groups were identified: 68 children attended daycare, and 68 children did not attend daycare. Growth was assessed with weight-for-height curves, and psychomotor development was evaluated with the child developmental assessment instrument (psychosocial, language, psychomotor, and cognitive area). The* X^2 *test was used for statistical analysis.* **Results:** *The percentage of daycare children with ideal weight was higher than those not attending in daycare (p = 0.035). Psychomotor development was significantly higher in daycare children: in the psychosocial (p = 0.000), language (p = 0.000), motor (p = 0.000), and cognitive development (p = 0.000) areas.* **Conclusions:** *The psychomotor development of children attending daycare centers is superior to that of children not in daycare centers.*

Keywords: *Growth. Psychomotor development. Preschool child. Child care. Daycare center.*

Comparación del crecimiento y desarrollo psicomotor en guarderías atendidas por profesionales

Resumen

Introducción: *La salud del niño se puede evaluar a partir de su crecimiento y desarrollo. En la sociedad actual, el cuidado de los hijos se comparte con las guarderías infantiles. En este contexto, el objetivo del artículo fue identificar las diferencias de crecimiento y desarrollo psicomotor en niños de acuerdo con su asistencia a las guarderías.* **Métodos:** *Se llevó a cabo un estudio transversal analítico en niños de 25 a 48 meses de edad. Se identificaron dos grupos: 68 niños atendidos en guarderías y 68 niños no atendidos en guarderías. El crecimiento se evaluó con las curvas de peso para la talla y el desarrollo psicomotor, con el instrumento de evaluación del desarrollo del niño (área psicosocial, lenguaje, psicomotriz, y cognitiva). Se utilizó la prueba de* X^2 *para el análisis estadístico.* **Resultados:** *El porcentaje de niños de guardería con peso ideal es superior al de los no atendidos en guardería (p = 0.035). El desarrollo psicomotor es significativamente mayor en los*

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niños de guardería: en el área psicosocial (p = 0.000), en lenguaje (p = 0.000), en el área motriz (p = 0.000) y en desarrollo cognitivo (p = 0.000). **Conclusiones:** *El desarrollo psicomotor de los niños atendidos en guardería es superior al de los niños no atendidos en guardería.*

Palabras clave: *Crecimiento. Desarrollo psicomotor. Preescolar. Cuidado del niño. Centros de día.*

Introduction

In traditional families, the mother and father are responsible for the care of the children. However, in practice, specific roles have been assigned: the father is identified with the role of provider, and the mother is responsible for the daily care of children. In today's society, these roles have been reassigned. As women have been incorporated into the workforce, the initial role of caregiver has lost its validity. However, it does not mean that the child's need for care has disappeared. Therefore, the social response resulted in the creation of centers responsible for the care and attention of the children of working mothers. Subsequently, this condition was modified by law to include any children, regardless of the mother's occupation, and recently was extended to include the children of working fathers[1-4]. In addition to being a physical place, this initiative aims to represent a space that fosters psychomotor development and growth of the child[5-8].

Today, depending on the institution to which they belong, these centers are identified as childcare, child development assistance, or daycare centers staffed by health and education professionals. The child stays in these centers 8-10 hours a day[9].

As a program derived from a health policy, daycare centers require periodic evaluation to generate feedback to determine the program's validity and propose supportive or corrective measures. Within daycare centers, health professionals have designed and coordinated activities oriented to the growth and psychomotor development of the child without becoming an early stimulation program.

Psychomotor development is understood as the acquisition or improvement of biological, psychological, or social functions that reflect cognitive, behavioral, or socialization processes and determine the degree of development as a reflection of the child's health status[10-13].

Several instruments are used to assess the psychomotor development of the child. Some institutions have constructed instruments taking others as a reference and respecting the psychomotor development evaluation expected for the age. These instruments are applied at the national level in all daycare centers belonging to the same system[2,14-17].

In addition to psychomotor development, growth is another indicator of a child's health conditions. Child growth is a biological process that corresponds to the increase in body weight or volume[18]. The instruments for assessing growth are diverse, including height-for-age, weight-for-age, and weight-for-height. In this regard, the World Health Organization has proposed weight-for-height curves, a method institutionally adopted as a standard for assessing the nutritional status of children[19].

In this context, daycare centers follow a specific program implemented by professionals in education, nutrition, and child health derived from a health policy that can be evaluated. The literature is abundant regarding the effectiveness of these programs on children's growth and development. However, ongoing evaluation of public policies is mandatory. In addition, these publications reinforce the proposal to extend the daycare program in specific centers to all infants[20,21]. Therefore, the study aimed to identify differences in growth and psychomotor development between children attending daycare centers and those receiving home care.

Methods

From September to October 2019, we conducted a cross-sectional analytical study with children aged 25 to 48 months belonging to families of factory workers, merchants, and office workers affiliated[22] to a Social Security Institution in the City of Querétaro, Mexico.

According to daycare attendance, two groups of children were identified:

- The daycare group included children who received care in centers designed to promote adequate growth and psychomotor development of the child and attended by professional staff with specific training (educators, nurses, and nutritionists). The evaluation of psychomotor development and growth upon leaving the daycare center (mean age 38.29 months) was carried out in children who remained in the center for 32.11 months.
- The non-daycare group included children who did not attend daycare and were cared for at home by their

parents or relatives. This group was evaluated at 39.16 months of age.

Both groups were located in the same geographical area and belonged to the same socioeconomic level.

The professionals responsible for the care of children in the group of daycare centers included those with training oriented to education (educators), health (nurses), and nutrition (nutritionists). The program applied in daycare centers included pedagogy (developmental stimulation for habit formation, integration, and community life), health promotion (medical evaluation, early detection of pathologies, vaccination, and growth monitoring), and nutrition (healthy, varied, and sufficient diet administered at defined times)[15,16].

The daycare group included children attending a center for at least one year, and information on their growth and psychomotor development was available. For the non-daycare group, we considered children identified in the waiting room of the medical unit who attended as companions, whose mothers were willing to provide information and allow the evaluation of the child. For both groups, children whose medical history indicated any congenital pathology, food allergy, or underlying pathology that could interfere with growth and psychomotor development were excluded.

The sample size (68 per group) was calculated using the mean formula for two populations, with a confidence level of 95% ($Z\alpha = 1.64$) and a test power of 80% ($Z\beta = 0.84$), assuming that adequate or normal cognitive development in the daycare group was 62.7% ($p_1 = 0.627$) and adequate or normal cognitive development in the non-daycare group was 41.8 % ($p_2 = 0.418$). To estimate the percentages, we used as a reference what has been published in the literature[23]. This value was modified based on empirical evidence from daycare center personnel and researchers. The sample size was calculated for the four areas (psychosocial, language, cognitive, and motor), and we adopted the largest size resulting from the estimation of cognitive development.

The sampling technique was performed non-randomly by consecutive cases. In the daycare group, the sampling frame used was the list of children registered in the daycare information and administration system. In the non-care group, sampling was performed on children accompanying their parents who came to request a health service at the medical unit.

Data on the age and sex of the children were included. Regarding nutritional status, we used the World Health Organization charts for girls and boys, which include weigh-for-length in children < 2 years of age and weight-for-height from 2 to 5 years of age (severe wasting, < 3 standard deviations (SD); wasting, < 2 SD; normal, < 1 SD; ideal, mean value; normal with a possible risk of overweight, > 1 SD; overweight, > 2 SD; obesity, > 3 SD)[24].

Psychomotor development was measured with the Child Development Evaluation instrument proposed and validated by the Head of Daycare Centers of the Institution. For the evaluation, the children were divided into four age groups: 25 to 30 months, 31 to 36 months, 37 to 42 months, and 43 to 48 months. Psychosocial, language, psychomotor, and cognitive development were evaluated in each group. The expected development for each age group was used as a reference, and it was verified whether they complied with it. The instrument had three possible responses: yes (with a score of 1), sometimes (with a score of 0.5), and no (with a score of 0). For each area and age group, the number of items evaluated ranged from 4 to 11. According to each one of the age groups, the number of items was as follows: psychosocial area, 6, 8, 8, and 8 items, respectively; language area, 8, 8, 8, and 6 items, respectively; motor area, 8, 11, 8, and 8 items, respectively; and cognitive area, 4, 4, 10, and 11 items, respectively. The score obtained in each area was added up and multiplied by 100 and then divided by the number of items in the respective area. The result obtained on a scale from 0 to 100 was considered normal when the score was ≥ 75[15]. In this regard, the results of children in non-daycare centers were similar to those reported in the literature.

The fieldwork was carried out by a third-year physician of the Family Medicine Specialty. Before data acquisition, the nursery staff (nurses and educators) trained the researcher to collect the information and standardize the procedures[16].

To collect the information on the daycare children, the responsible researcher went to the daycare center, accessed the Daycare Information and Administration System, identified and reviewed the file of each of the children. From this, children were individually evaluated, and the database was constructed. To collect information on non-daycare center children, the researcher went to the medical unit located in the same geographic area as the daycare center. Once in the waiting room, children who attended as companions of the parents were identified, and the parents' authorization was requested to carry out the evaluation and answer the questionnaire. Parents who agreed to participate were invited to come to the office designated for the research, where the researcher applied the Child Development Evaluation instrument. In addition, the weight and measurements of each child were recorded using the same scale (Royal) and the same stadiometer (BAME).

Statistical analysis included means, standard deviation, percentages, t-test for two independent populations, z-test for two independent populations, and X^2 test.

The protocol was registered with the Institution's Research Committee and Bioethics Committee, and informed consent was obtained from the mother or father of the children. When alterations in growth and development were identified, children were referred to the Institution's Family Physician to initiate the study and treatment protocol.

Results

The study included 68 children in the daycare group and 68 children in the non-daycare group. The mean age of the daycare children was 38.29 ± 4.93 months, and that of the non-daycare children, 39.16 ± 5.73 months (t = 0.94, *p* = 0.34). In the daycare group 50% were female, and in the non-daycare group, 51.1% (z = 0.02, *p* = 0.86).

All children who attended the daycare center presented normal development in the psychosocial area. In contrast, 77.9% of the children who did not attend a center presented adequate or normal development in the same area (*p* = 0.000) (Table 1).

Of the children who did not attend a daycare center, 79.4% showed normal language development, while this area was shown in 100% of children who attended daycare centers (*p* = 0.000) (Table 1). Concerning motor development, 100% of the children who attended daycare presented adequate or normal motor development, but only 75.0% in children who did not attend daycare (*p* = 0.000) (Table 1). All children who attended daycare centers presented adequate or normal cognitive development, and in the group that did not attend daycare centers, the percentage was 69.1% (*p* = 0.000) (Table 1).

Differences between groups were observed in all four areas when the developmental assessment was performed on a discrete scale. For example, on the cognitive development scale, daycare children scored 95.25 ± 5.37, and children who did not attend daycare scored 78.95 ± 22.52 (difference of 16.30 points, t = 5.80, *p* = 0.00). The information for the other areas is shown in Table 2.

According to the weight-for-length and weight-for-height anthropometric indexes proposed by the World Health Organization, we identified that 89.7% of the children in the daycare group presented ideal growth, while the percentage was 69.1% in the non-daycare group (X^2 = 10.34, *p* = 0.035) (Table 3).

Table 1. Comparison of psychosocial, language, motor, and cognitive development of children according to daycare attendance

Development	Percentage		χ^2	*p*-values
	Daycare (n = 68)	Non-daycare (n = 68)		
Psychosocial development				
Adequate or normal	100.0	77.9	16.86	0.000
Abnormal	0.0	21.1		
Language development				
Adequate or normal	100.0	79.4	15.60	0.000
Abnormal	0.0	20.6		
Motor development				
Adequate or normal	100.0	75.0	19.42	0.000
Abnormal	0.0	25.0		
Cognitive development				
Adequate or normal	100.0	69.1	24.83	0.000
Abnormal	0.0	30.9		

Discussion

As an organized group, society responds to the population's needs by implementing effective public policies or policies that require adjustments for their proper functioning. One of these is the response to children's care and development needs when parents join the workforce. In this case, daycare centers or kindergartens can be evaluated as health services. In this context, the present study evaluated the growth and development of children attending these centers.

There are reports in the literature related to the psychomotor development of children attending daycare centers. However, when the effectiveness of public policies is questioned, science has the academic obligation to issue positions from an objective point of view, based on a rigorous analysis using the scientific method. Childcare centers have incorrectly adopted the term daycare centers. Therefore, it must be recognized that continuing to use this term stigmatizes the activity performed in these places and the health care workers, the children, and society itself. The concept of daycare has been surpassed in practice. Consequently, institutions must understand the notion to be named according to their functions and the great responsibility they bear.

Table 2. Comparison of psychomotor development scores of children according to daycare attendance

Group	Score			t	*p*-values
	Mean	SD	Difference		
Psychosocial development					
Non-daycare (n = 68)	84.28	16.37	13.20	6.37	0.00
Daycare (n = 68)	97.48	4.87			
Language development					
Non-daycare (n = 68)	80.60	20.24	10.99	4.28	0.00
Daycare (n = 68)	91.60	6.25			
Motor development					
Non-daycare (n = 68)	81.19	17.56	14.85	6.79	0.00
Daycare (n = 68)	96.05	4.54			
Cognitive development					
Non-daycare (n = 68)	78.95	22.52	16.30	5.80	0.00
Daycare (n = 68)	95.25	5.37			

SD, standard deviation.

Table 3. Comparison of children's growth (weight for height) according to daycare attendance

Nutritional status	n (%)		χ^2	*p*-values
	Daycare (n = 68)	Non-daycare (n = 68)		
Normal	2 (2.9)	2 (2.9)	10.34	0.035
Ideal	61 (89.7)	47 (69.1)		
Normal with risk of overweight	4 (5.9)	16 (23.5)		
Overweight	1 (1.5)	2 (2.9)		
Obese	0 (0.0)	1 (1.5)		

World Health Organization charts for boys and girls include weigh-for-length in children under two years of age and weight-for-height from 2 to 5 years of age. Normal (< 1 standard deviation), ideal (mean), normal with the possible risk of overweight (> 1 standard deviation), overweight (> 2 standard deviations), obese (> 3 standard deviations).

To guarantee an objective evaluation and use the same criteria for comparison between groups (daycare and non-daycare), health personnel who assessed the daycare group trained the person responsible for assessing the non-daycare group. This scenario can be considered a strength of the study. The Child Development Evaluation instrument was created when the daycare system was implemented in the institution and is still valid for the entire system at the national level; however, it should be recognized as a limitation of the study. When comparing the results presented in the non-daycare group with those reported in the literature, the values are very similar: in the non-daycare group, the prevalence of inadequate development fluctuates between 25% and 30%. In this regard, the clinical practice guideline on specific psychomotor development disorders identifies a prevalence of 11% and 16% and suggests that the prevalence in Mexico is unknown. However, other reports identify a prevalence between 11% and 35%, depending on the area evaluated[25-27].

Admittedly, the research was conducted in two groups with a specific socioeconomic stratum, limiting the results' generalizability; in this case, extrapolation of the results can be made to the socioeconomic stratum analyzed. This scenario, which initially could be considered a limitation, allows us to measure the impact of the actions generated by the daycare center since it controls for factors that can be indirectly confounding when comparing members of different socioeconomic strata, including the difference in feeding patterns at home. It could be assumed that growth and development will behave differently in other socioeconomic strata, mainly due to the characteristics of the risk factors inherent in the environment. It is likely that the difference between daycare and non-daycare children is more pronounced in the low socioeconomic status and is more similar in the high socioeconomic status, but this is only a hypothesis that corresponds to another research project.

Our findings identified differences in psychomotor development in the four areas studied between the daycare and non-daycare groups. The most significant difference was observed in cognitive development and the least significant difference in language development. Claiming that children's development is better when they attend daycare centers has implications. Therefore, there must be a logical argument to support this claim. This observation can be possible because the programs implemented in the daycare centers, without being an early stimulation program, include continuous and systematized actions that favor the child's development, a scenario described in the literature consistent with our findings[6,28]. To sustain this statement would mean that the child who does not attend daycare is at a disadvantage, and consequently, there should be a public policy to address this problem. However, this is only a

hypothesis since the research design does not allow us to be conclusive. Therefore, a causality study is necessary to be able to conclude on this issue.

Despite finding a statistically significant difference in growth between the groups, it was not the same magnitude as that identified in psychomotor development. A possible explanation would be to consider susceptibility and constancy of stimulation for nutrient intake. When addressing the nutritional aspect, greater vulnerability is identified; in this aspect, the periodicity of adequate nutrient intake and overstimulation by unnecessary nutrients play a determining role. It is a reality that children who attend daycare centers, upon returning home, are exposed to the family's eating habits, so the control of the diet implemented in the daycare center fails. However, differences in the growth of children between groups were present and statistically significant.

In conclusion, growth and psychomotor development in psychosocial, language, motor, and cognitive areas in children enrolled in a daycare program and cared for by healthcare, nutrition, and education professionals are different from the growth and psychomotor development of children not enrolled in these programs.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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REVIEW ARTICLE

How intrauterine growth restriction due to nutritional stress changes the function of key proteins in brain serotonin metabolism during development

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Abstract

This review aimed to describe and comment on how experimental intrauterine nutritional stress in animals produced some changes in tryptophan-5-hydroxylases (TPH) 1 and 2 in the brain and other key proteins such as plasma albumin, and how the intrauterine nutritional stress could produce long-lasting alterations in serotonin function in the brain of human infants.

Keywords: *Intrauterine growth restriction. Undernourishment. Serotonin neurons. Tryptophan-5-hydroxylases. Plasma albumin.*

Cómo la restricción del crecimiento intrauterino debida al estrés nutricional cambia la función de proteínas clave en el metabolismo de la serotonina cerebral durante el desarrollo

Resumen

El objetivo de esta revisión es describir y comentar cómo el estrés nutricional intrauterino experimental en animales produjo algunos cambios en las triptófano-5-hidroxilasas 1 y 2 en el cerebro y en otras proteínas clave, como la albúmina plasmática, y de qué manera el estrés nutricional intrauterino podría producir alteraciones duraderas en la función de la serotonina en el cerebro de lactantes.

Palabras clave: *Restricción del crecimiento intrauterino. Desnutrición. Neuronas serotoninérgicas. Triptófano-5-hidroxilasas. Albúmina plasmática.*

Introduction

The present work reviews the results from a long-lasting research project on prenatal undernutrition and brain development. For a long time, biomedical researchers have been interested in early developmental negative influences on the brain of mammals, particularly humans, due to secondary prenatal stress or restricted nutrition, acting together or separately to influence different brain processes during the early

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development[1]. In addition, the effect of protein-calorie undernutrition has been thought to profoundly affect human brain development[2,3], given its general appearance worldwide, particularly in regions that continue to confirm the "Malthusian Principle of Population Growth," related to food production inequality[4].

Early malnutrition affects some general functions of the human brain, but these observations have always been challenging to interpret, particularly regarding the basic mechanisms underlying these effects[5], such as protein content, number of brain cells, and lipid metabolism. Also, other general unspecific biochemical parameters have been studied, for example, specific brain functions[5-11].

More recently, Morgane et al.[12] reported functional alterations of the hippocampus in early protein-deficient undernourished rats, related explicitly to stressful early conditions. Barros et al. (2006)[13] reported a decrease in dendritic development in early-life stressed rats[13]. Interestingly, Monk et al. (2013)[1] reported a decrease in DNA, RNA, and mRNA coding for neural and glial structural proteins after maternal prenatal distress in animal models, decreasing neurotransmitter peptides, independently from the nutritional condition[1].

Serotonin and its function in the brain

During intrauterine life, increased serotonin production in the fetal brain due to nutritional stress or after the gene knock-out (KO) of the enzyme in charge of serotonin inactivation (*MAOA*) produces structural changes and delayed development in the somatosensory cortex S1[14-17].

Serotonin (5-HT, 5-hydroxytryptamine) is an amine produced by a group of brainstem neurons. Axons from these neurons innervate various important areas of the central nervous system (CNS)[18-22]. 5-HT has been implicated in regulating brain development before it assumes its role as a neurotransmitter and neuromodulator in the mature brain[23-29]. During the fetal period, 5-HT is involved in neuronal growth and differentiation processes, axogenesis[25,27,28], maturation of target neurons[26], the final expression of specific 5-HT receptors[30], and modulation of its synthesis[31]. As a neurotransmitter, 5-HT controls numerous physiologic functions (food intake, temporal control, sleep patterns, nociception)[32-36]; also, in some psychiatric disorders such as anxiety and depression[37] in the adult brain. Serotonin functions in the brain are mediated by activating at least 15 different types of receptors that belong to the G protein-coupled superfamily (except for the 5-HT_3 subtype)[23,31,38,39].

One relevant fact is that 5-HT is synthesized from an essential nutrient, L-tryptophan (L-Trp), its metabolic precursor. There are two known fractions of plasma L-Trp, one bound to albumin and one free (FFT, free fraction of L-Trp)[40]. FFT crosses the blood-brain barrier (BBB) to the brain[41,42], where it is hydroxylated by the action of the tryptophan-5-hydroxylase (TPH), decarboxylated, and transformed into 5-HT[43].

Nutritional stress and intrauterine growth restriction

As our group has long pointed out, pre-, peri-, and postnatal undernourishment also cause alterations in specific brain systems during the prenatal to postnatal developmental periods, which is the case of the serotonin neurotransmission system. These alterations activate the brain's serotonergic biosynthetic system and metabolic processes, with an elevation of the FFT, 5HT metabolic precursor.

Furthermore, it has been demonstrated that plasma albumin changes its ability to bind L-Trp[44-52]. FFT crosses from plasma to the brain through the BBB and is taken up by brainstem serotonergic neurons to activate serotonin synthesis[41,43,46,49,51,53,54]. FFT significantly increases in the plasma and the brain of rats with intrauterine growth restriction (IUGR), reaching levels higher than those of normal controls, showing that the activity of TPH, the limiting enzyme system in the brain's serotonin biosynthetic pathway[55-58], is upregulated in IUGR brains exhibiting significant changes in its kinetics: increased affinity (lower K_m) for its substrate, no changes in the V_{max}, and increased activity under phosphorylation conditions. These changes were considered responsible for the chronically increased serotonin synthesis in the brain of IUGR animals secondary to undernourishment[59,60].

Two TPH isoforms have been described, TPH1 and TPH2[61]. According to the authors who described these TPH isoforms, TPH1 is localized only in peripheral tissues, while TPH2 is present, supposedly only in the CNS[62-66]. Thus, alterations produced by IUGR induce an activation of the brain's serotonergic biosynthetic system and its metabolic correlates, with an elevation of the FFT and the plasma albumin's ability to bind L-Trp[52]. These findings suggest that chronic elevation of 5-HT synthesis in the brain of IUGR rats might be due to a significantly higher amount of TPH1 isoform above that of TPH2. This relation is possibly due to

changes in the molecular regulatory mechanisms of enzyme expression and regulation of its activity, secondary to early nutritional stress during fetal life, with possible mediation of the *Pet-1* regulatory molecular system[67-69].

In contrast, when the undernourished offspring were subjected to a nutritional recovery (NR) regimen during the neonatal period, a satisfactory recovery was demonstrated in their growth curves and FFT and other plasma biochemical markers, which returned to control values[70-74]. Despite this impressive recovery, the whole TPH activity and TPH1 protein levels remained significantly elevated in the animal brainstems, while a significant increase in brain 5-HT levels and its functional activity also prevailed up to adulthood in IUGR rats[70-74].

As an attempt to integrate our knowledge about the consequences of IUGR on the brain's neurochemistry and functions in rats, this review considered all published results, as well as the results of previous studies in human infants related to the capacity of another essential protein, plasma albumin, to bind to the precursor amino acid L-Trp, which appears to be a critical regulatory system of the brain's serotonin synthesis. In this manner, we attempted to provide more information on the neurometabolic mechanism implicated in the persistently increased synthesis of 5-HT in the brain of IUGR subjects.

Experimental models of intrauterine growth restriction

The methods considered in this review were taken from published studies[44,45,48-50]. However, it is worth mentioning that an experimental model of gestational protein-calorie deprivation and early ligation of one branch of the uterine artery in rats was used in an attempt to reproduce conditions of protein-calorie malnutrition and placental insufficiency present in humans. These two experimental procedures would mimic the clinical conditions in pregnant women giving birth to IUGR products. These two methods are complementary in their effects: one involves nutritional and endocrine maternal imbalance, while the other would exclude these variables[44,45]. In a previous study, we evaluated the tracing of thalamocortical fibers in the offspring of IUGR rats and controls on postnatal days 1, 3, and 5. We also evaluated the immunostaining pattern of the serotonin transporter (SERT) and the serotonin receptor 5-HT_{1B} with the specific antibody for each molecule[17,75].

All experimental procedures performed on animals followed the Care and Use of Experimental Animals guidelines published by the Mexican Ministry of Health (NOM-062-ZOO-1999; August 22, 2001). Additionally, the Research Ethics Committee of the National Scientific Research Committee of the Mexican Institute of Social Security (IMSS, for its Spanish acronym), Mexico City, Mexico, authorized all human and animal research protocols (registry numbers: 2005-785-078; 2006-3604-07; 2006-2605-08; 2007-3604-12; 2014-785-052).

Intrauterine growth restriction in newborns

All procedures in infant patients, diagnoses, and clinical care were closely followed by experienced specialists[76-78]. The general conditions of how this review was organized for the various studies conducted in human infants can be wholly reviewed in Hernandez et al.[45,52] and Manjarrez et al.[46,47,49,51].

For the human segment of the whole project, we include a representative summary of the procedure followed in a case-cohort study in 37 newborns during the first 3 months of postnatal life. At birth, two groups were formed; the first group (IUGR group) included 20 term newborns with the antecedent of IUGR, with bodyweight < 10^{th} percentile of intrauterine growth curves[79] and with a fetal growth ratio (FGR) of < 0.90[80]. The control group comprised 17 newborns with bodyweight between the 10^{th} and the 90^{th} percentiles and an FGR of > 0.90. Interestingly, at 30 days of age, nine infants of the IUGR group demonstrated a return to normal physical growth; subsequently, these infants formed the nutritionally recovered group (NR group) (Table 1). Free, bound, and total L-Trp were measured in blood micro-samples. These samples were freed of fatty acids and tested under "mole-to-mole" conditions of the sample components of the IUGR, NR, and control groups to assess the binding kinetics of L-Trp to albumin.

Serotonergic activity in the brain

In animal models, the variables analyzed generally used included the following in each one of the experimental groups: serotonergic activity, L-Trp, TPH whole activity, and 5-HT concentration expressed as mean and standard deviations (SD). Also, the number of TPH1 or TPH2-immunopositive neurons in each age group was determined in six 4 μm-thick sections, in an area of 83 μm^2 with a 40X objective (Infinity 1-Lumenera camera equipped with a 10X objective, aided with an

Table 1. Representative clinical data of infants of the various groups

	Controls	Intrauterine growth restriction	Nutritionally recovered
Gestational age (weeks)	39.5 ± 0.7	39.1 ± 1.20	–
Ponderal index	2.38 ± 0.26	2.10 ± 0.29€	–
Fetal growth ratio	98 ± 0.09	68 ± 0.05€	–
Body weight (g)			
1 day	3,165 ± 326.9	2,125 ± 234.5€	–
30 days	4,093 ± 322.3	3,316 ± 332.3€	3,839 ± 193.9€
90 days	5,703 ± 438.2	4,671 ± 387.1¥	5,571 ± 333.9€
Body length (cm)			
1 day	51.06 ± 1.0	46.63 ± 1.6€	–
30 days	56.33 ± 2.9	51.06 ± 1.5€	54.00 ± 2.9€
90 days	62.60 ± 2.4	58.38 ± 1.0€	61.86 ± 2.1€
Body mass index			
1 day	12.15 ± 1.13	9.90 ± 1.10 €	-
30 days	14.23 ± 1.23	12.46 ± 0.84 €	13.89 ± 1.02 ¥
90 days	15.36 ± 1.02	12.74 ± 1.30 ¥	15.28 ± 1.28 ¥

Data are expressed as mean values ± standard deviation of 17 controls, 20 intrauterine growth restriction, and nine nutritionally recovered infants.
Body weight (Treatment: SS = 11340, Df = 7, MS = 1610. Residual SS = 7320, Df = 76, MS = 96320). Body length (Treatment: SS = 2226, Df = 7, MS = 317.9. Residual SS = 286.7, Df = 70, MS = 4.096). Body mass index (Treatment: SS = 292.5, Df = 7, MS = 4178. Residual SS = 101.6, Df = 79, MS = 1.286). Differences were determined by Mann-Whitney U, ANOVA and Tukey's multiple comparison tests.
¥$p < 0.01$, €$p < 0.001$[52].
SS, the sum of squares; MS, mean square; Df, degrees of freedom.

Table 2. Representative serotoninergic activity in the brainstem of rat pups of various groups

Age (days)	L-Trp (μMol/g wet tissue)			TPH (whole activity) (nmol 5-HTP/mg protein/h)			5-HT (nmol/g wet tissue)		
	C	IUGR	NR	C	IUGR	NR	C	IUGR	NR
1	45.50 ± 0.50	58.70 ± 0.68*	57.70 ± 0.68*	0.217 ± 0.010	0.310 ± 0.030*	0.308 ± 0.030*	0.720 ± 0.070	1.185 ± 0.019*	1.067 ± 0.010*
15	12.70 ± 0.28	21.30 ± 0.21*	13.60 ± 0.10	0.337 ± 0.050	0.510 ± 0.030*	0.512 ± 0.030*	1.670 ± 0.050	2.370 ± 0.031*	2.400 ± 0.010*
21	12.70 ± 0.28	22.30 ± 0.20*	11.60 ± 0.20	0.376 ± 0.030	0.500 ± 0.010*	0.517 ± 0.010*	1.840 ± 0.040	2.750 ± 0.070*	2.180 ± 0.060*

Each point corresponds to mean values ± standard deviation of six experiments in duplicate.
Differences were determined by two-way ANOVA and post-hoc analysis conducted using the Tukey test.
*$p < 0.05$ (C vs IUGR; IUGR vs NR; C vs NR). Days = Days after birth[70,74,87]
C, controls; IUGR, *in-utero* undernourished; NR, nutritionally recovered; L-Trp, L-tryptophan; TPH, tryptophan-5-hydroxylase whole activity; 5-HT, 5-hydroxytryptamine.

Olympus microscope). The relative densities of the bands observed in the dorsal raphe nucleus (DRN) (ages 1, 15, and 21 days) were determined. Afterward, the groups were compared by two-way ANOVA (nursing time 1, 15, and 21 days, and maternal nutritional status in control and undernourished groups), and *post hoc* analyses using the Tukey comparison test were conducted; *p*-values < 0.05 were considered statistically significant.

In general, these findings confirmed previous results, showing that malnourished offspring showed higher L-Trp concentration, 5-HT content, and TPH whole activity in the brainstem. In contrast, L-Trp concentration in the brain returned to normal values in the NR groups. Regardless of their physical and biochemical recovery, TPH whole activity remained significantly elevated, accompanied by an increased synthesis of 5-HT up to the end of lactation and even during adulthood (Table 2).

The identification of TPH1 and TPH2 in the brainstem from the different groups was obtained by Western Blot (Figure 1A and 1B). The expression of TPH1 remained increased in the IUGR group from birth, and TPH2 expression predominated and subsequently showed a significant decrease during the lactation period in controls. Interestingly, TPH1 expression remained increased, while TPH2 returned to normal values in the NR group.

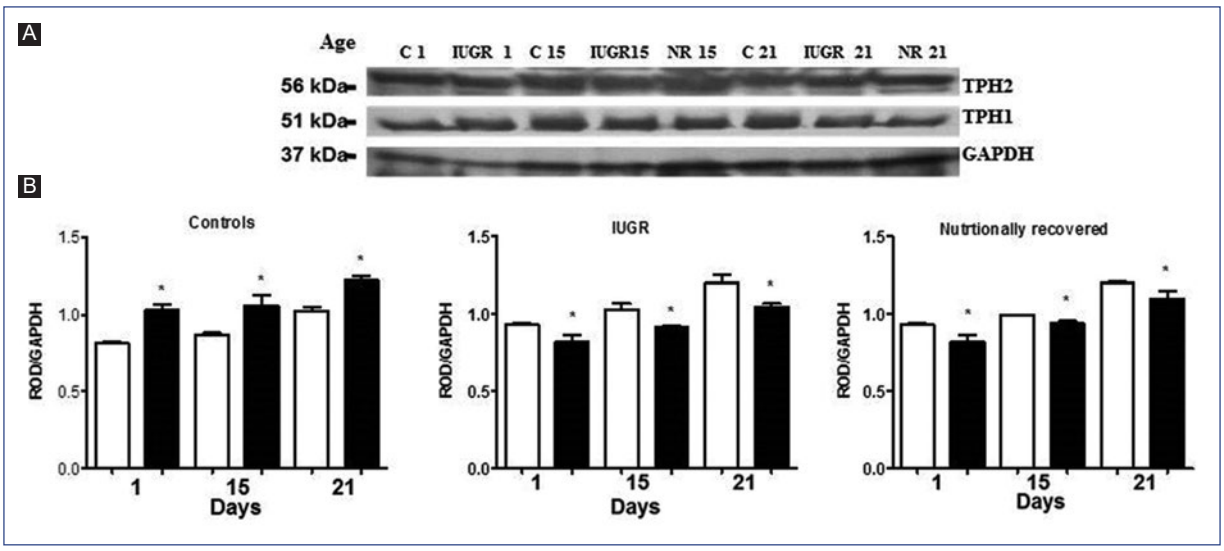

Figure 1. Identification of tryptophan-5-hydroxylases 1 and 2 (TPH1 and TPH2) in the brainstem of the offspring by electro-transference with specific antibodies to each isoform. **A.** Three bands were observed, one of 51 kDa (TPH1), another of 56 kDa (TPH2), and another of 37 kDa (GAPDH). **B.** Relative optical density (ROD) of each isoform; □: TPH1 y ■: TPH2.
Each bar corresponds to mean values of ROD ± standard deviation of six experiments in duplicate of each isoform. *$p < 0.05$. (C vs IUGR; IUGR vs NR; C vs NR).
A two-way ANOVA and post-hoc Tukey test analysis were conducted.
C, controls; Days, days after birth[87]; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; IUGR, intrauterine growth restriction; NR, nutritionally recovered.

A population of 5-HT neurons from the DRN was immunolabeled for TPH1 and another for TPH2 (Figure 2 and 3). Interestingly, the IUGR group showed fewer 5-HT immune-positive neurons (TPH1 and TPH2) than controls during the nursing period. It is essential to highlight that pups of the NR group exhibited a return from a decreased neuronal population to control values (Figure 4). Some morphological differences in the serotoninergic neurons between controls and the IUGR group, including the NR group, were having small neurons with little cytoplasm, small nuclei, and more space between them. In addition, immunolabeled serotoninergic neurons that express TPH1 increased in the IUGR and NR groups. Interestingly, the opposite was noted in neurons that expressed TPH2, in which the immunolabeling was lower than controls.

The study in human infants confirmed that IUGR newborns exhibited a delay in physical growth. Remarkably, when they were fed only with maternal milk from birth, they demonstrated an appropriate recovering that allowed them to reach the growth rate of controls during the nursing period[52]. Also, IUGR infants showed significantly lower plasma albumin levels at birth, restored after 30 days of nutritional recovery. Furthermore, the FFT was significantly elevated in IUGR 3-month-old infants but returned to normal values on day 30 of postnatal life in the NR group. Another remarkable finding was that IUGR infants showed the following kinetic constants of albumin-L-Trp binding: high K_D and low B_{max}, both remaining unchanged up to postnatal day 90, even after NR[52].

Discussion

We reviewed data derived from a long-lasting project confirming that undernourishment-related IUGR induces essential changes in the brain's serotonergic-metabolic pathway during early development and that this pathway is overactivated with a concomitant increase in 5-HT levels and functions.

In the related literature, data describes the importance of early alterations on the brain's serotonergic system in laboratory animals. Haydon et al. (1984)[25,81] reported a strong effect on *in-situ* alterations induced by 5-HT excess. These 5-HT levels altered the axonal growth cone in cultured neurons, significantly inhibiting their growth, hence altering their developmental pattern. Also, early inhibition of the activity of the limiting

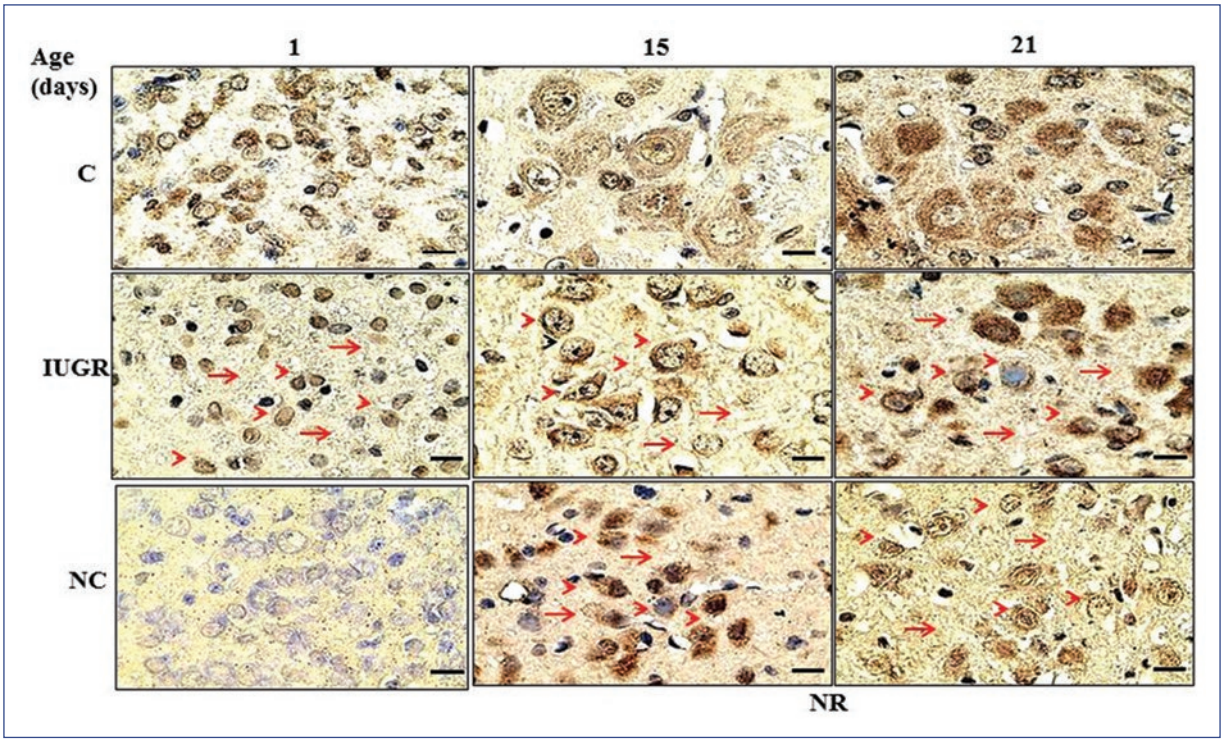

Figure 2. Coronal sections at the level of the DRN show immunoreactive neurons to tryptophan-5-hydroxylase 1. Sections were incubated with enzyme-linked monoclonal antibodies (1:1000), and immunoreactivity was detected with peroxidase-conjugated secondary antibodies and revealed with 3,3-diaminobenzidine on days 1, 15, and 21 after birth[87]. Scale bar in each panel = 100 X, 4 μm.
Arrowhead = small neurons with little cytoplasm and small nuclei. Arrow = more space between neurons.
C, controls; DRN, dorsal raphe nucleus; IUGR, intrauterine growth restriction; NC, negative control; NR, nutritionally recovered.

enzymes by PCPA (*P*-chlorophenyl alanine) altered the maturation pattern of neurons innervated by 5-HT in different brain regions[82]. Fillion et al. observed that the early chemical lesion of serotonergic neurons by the intraventricular administration of 5,7-dihydroxytryptamine at birth increased the final number of 5-HT binding sites in rats developing brain[30]. Also, we observed that extra doses of L-Trp to gestational rats increased TPH whole activity, not only in the mother's brain but also in the fetal brain and serotonin synthesis[83]. Other authors have also reported a harmful effect of increasing serotonin levels in the brain during postnatal development[84]. Concerning prenatal brain differentiation, essential participation of 5-HT has been well known for some time in several aspects of this function[26]. For instance, we observed essential functions of 5-HT in the axonal growth cone particles (AGCP) isolated from rat fetal brain of 17 days of gestation[27]. These organelles are mainly responsible for axogenesis and synaptogenesis, among other functions. 5-HT produces serotonin uptake in a Na^+-dependent manner, which is subsequently released in a K^+ and Ca^{++}-dependent-manner in the AGCP[27,28], supporting the functional role of serotonin in brain neurodifferentiation.

Based on the experimental data published by our group, it is possible to state that fetal neurons have all the necessary elements to produce and use serotonin as follows: a) a regulatory plasma mechanism to obtain the precursor amino acid through FFT kinetic binding to plasma albumin, therefore regulating the amino-acid precursor availability[52]; b) a complete set of molecules to synthesize the neurotransmitter to take it up and release it physiologically; c) a set of specific high-affinity receptors, also identified in axonal growth cones[85]; and d) a molecular signaling cascade that transduces the 5-HT message to the target cells[86]. All these data illustrate how 5-HT works within the fetal brain (Figure 5).

Unexpectedly, the elevated enzymatic activity in IUGR brains appeared to be mainly mediated through

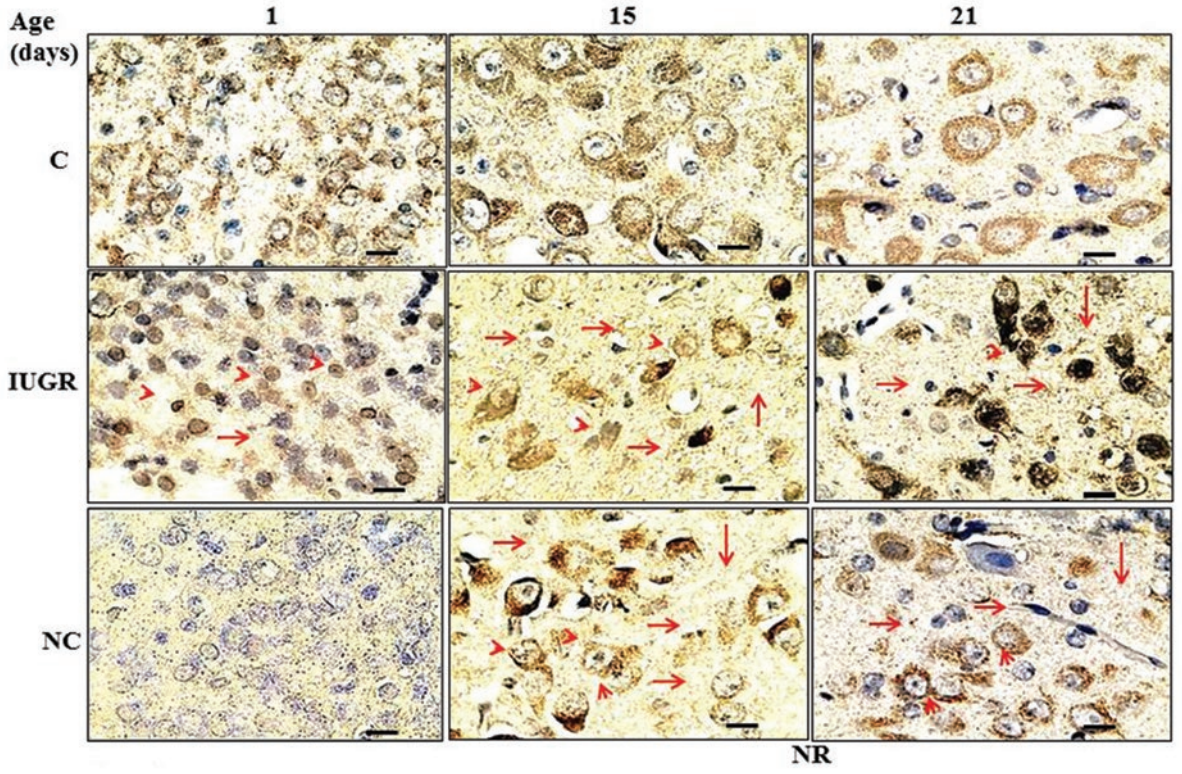

Figure 3. Coronal sections at the level of the DRN show immunoreactive neurons to tryptophan-5-hydroxylase 2. Sections were incubated with enzyme-linked monoclonal antibodies (1:1000), and immunoreactivity was detected with peroxidase-conjugated secondary antibodies and revealed with 3,3-diaminobenzidine on days 1, 15, and 21 after birth. Scale bar in each panel = 100 X, 4 μm.
Arrowhead = small neurons with little cytoplasm and small nuclei. Arrow = more space between neurons[87].
C, controls; DRN, dorsal raphe nucleus; IUGR: intrauterine growth restriction; NC, negative control; NR, nutritionally recovered.

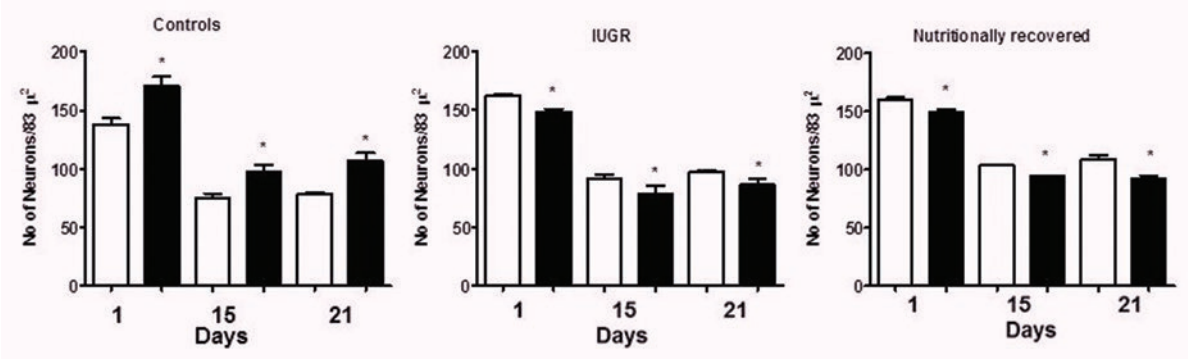

Figure 4. Tryptophan-5-hydroxylase-immunoreactive neurons in the DRN of the offspring. Each bar corresponds to the mean ± standard deviation of six pups of the groups. □TPH 1 and ■TPH 2.
*$p < 0.05$. (C vs IUGR; IUGR vs NR; C vs NR).
A two-way ANOVA and post-hoc Tukey test analysis were conducted.
C, controls; Days, days after birth[87]; DRN, dorsal raphe nucleus; IUGR, intrauterine growth restriction; NR, nutritionally recovered.

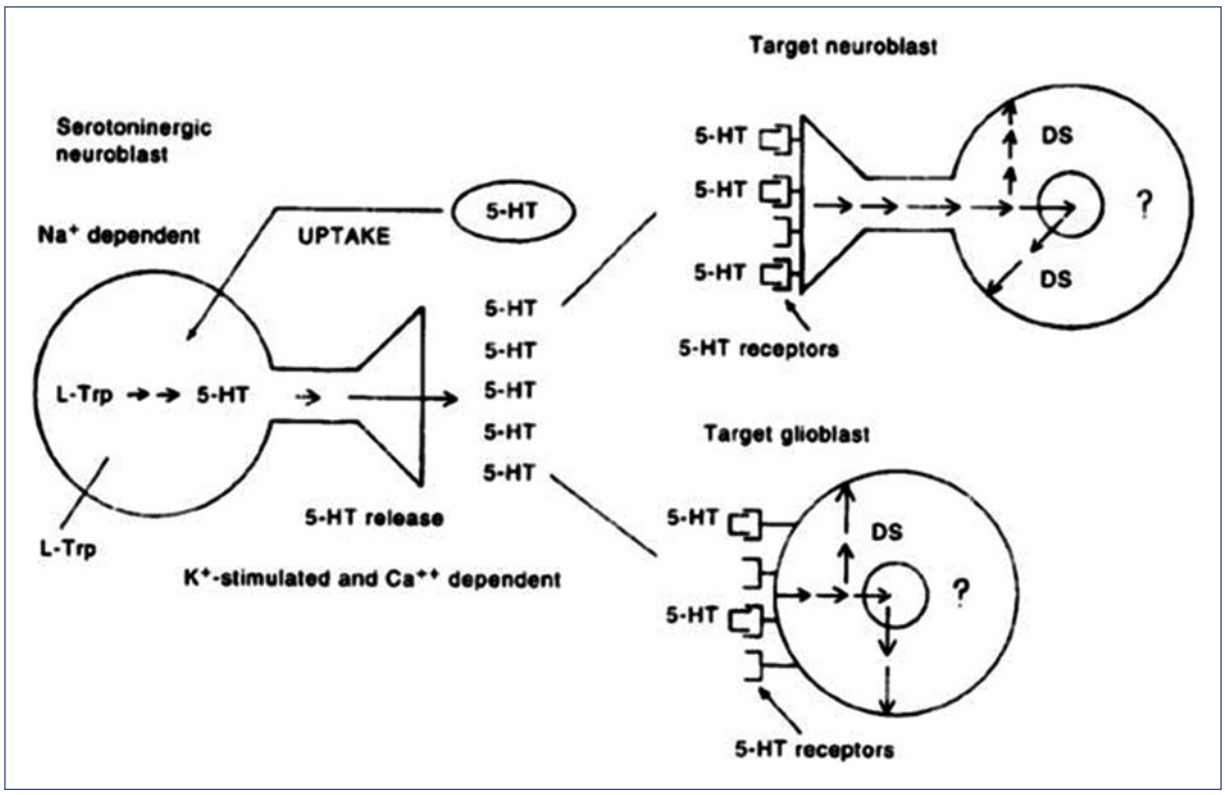

Figure 5. Proposed model of the physiological role of 5-HT in the fetal brain. Serotoninergic neuroblasts (left) synthesize and release 5-HT in a K^+ and Ca^{2+} dependent way. Target neuroblasts (upper right) or glioblasts (lower right) would have 5-HT recognizing sites of a specific receptor that receive a differentiation signal whose sequence is unknown (?). 5-HT could be inactivated by a reuptake system dependent on Na^+ and fluoxetine.
DS, differentiation signal; 5-HT, 5-hydroxytryptamine[65].

the activity of TPH1, which was significantly elevated. TPH2 was also present, but its identification by western blot was less evident than TPH1, although still higher than controls, as confirmed later[87]. Therefore, it appears that TPH1 activity in this area of the brain may play an essential role in the overactivation of the brain-serotonin pathway in both IUGR and normal brainstems, which could significantly alter the brain's morphogenetic processes, previously referred to in IUGR-malnourished rats[44,45,50,59,60]. By Western-blot analysis, both TPH isoforms (1 and 2) were expressed in serotonergic neurons in IUGR rats from birth[61]. In this context, it is important to mention that the intensity of the immunolabeling was significantly higher in neurons labeled with the specific anti-TPH1 monoclonal antibody. Interestingly, TPH2 neurons demonstrated a decreased immunopositive intensity at the end of the nursing period compared to the one exhibited by the TPH1 isoform[61].

According to the literature, TPH1 expression in the brainstem of IUGR infants or normal eutrophic controls would not be expected because TPH2 predominates in the brain. Thus, the presence and activity of the TPH1-isoform in the brain of IUGR and controls require an acceptable explanation. This observation may be due to changes in the TPH regulatory expression exerted by the *Pet*-1 genetic regulatory system[67-69]. Alternatively, this metabolic modification consisting of the expression of TPH1 activity in the brain—higher than that of TPH2, which was supposed to be the only one active in the brain—could be secondary to hormonal changes due to the early profound stressful conditions exerted by the severe prenatal undernourishment.

Corticoids, other hormones, and nutritional changes may produce a *de novo* synthesis of enzymatic proteins. For example, it was reported that the genetic system of glucose-6-phosphate dehydrogenase responds to hormonal and dietary manipulations[88]. Thus, the enzymatic changes in the biosynthetic

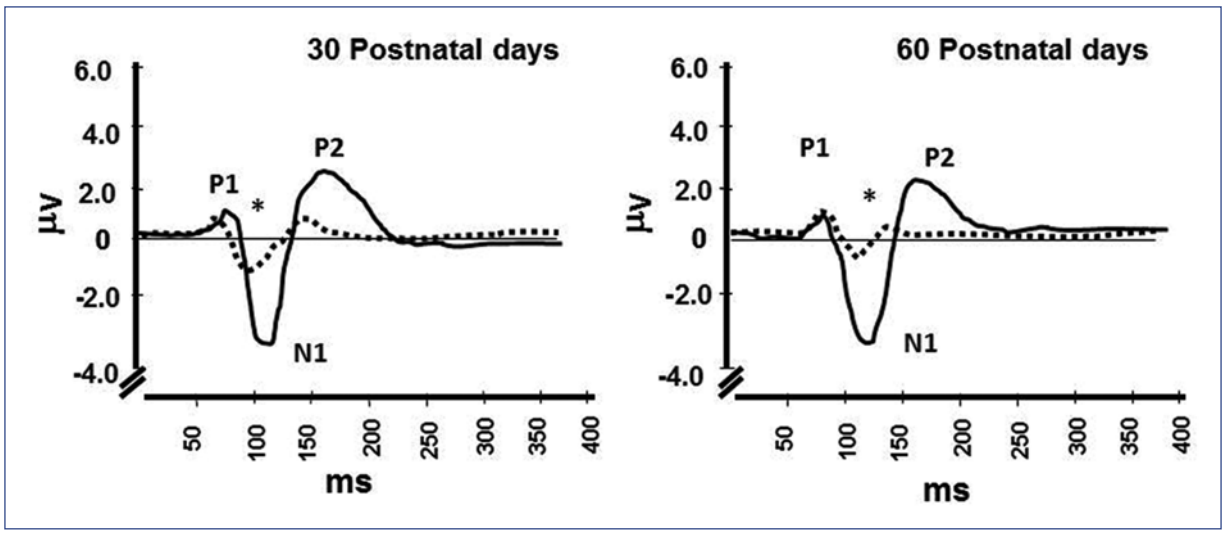

Figure 6. Auditory evoked potentials obtained from Cz reference electrode at a stimulation intensity of 60 dB in human controls (—) and infants with IUGR (---). Each recording represents the mean values from 12 and 13 infants in each group, respectively.
*p< 0.001. Wilcoxon test, comparing N1/P2 component amplitude of IUGR with controls[47]. IUGR, intrauterine growth restriction

serotonin-brain pathway could also result from intense early nutritional stress during the prenatal period and subsequent effects on the genetic regulatory system at transcriptional and posttranscriptional levels. Therefore, it appears that activation of the involved gene's systems could be related to the unexpected presence of an enzyme that has been reported to function only in peripheral tissues[62-66], inducing the expression of different enzymatic isoforms that are generally not present in the brain, as is the case of TPH1 in IUGR subjects. Alternatively, nutritional stress could activate a separate isozyme with an antigenicity like the one of TPH1. This phenomenon has been observed with other metabolic pathways, in which their limiting control rate can be reached in a tissue-specific manner by an adaptive regulatory process of a system of two genes, each one encoding a specific isozyme. Also, mRNA expression may be modified under fasting and re-feeding conditions, and dietary limitation of any essential amino acid may initiate a signaling cascade leading to an increase in the translation of a "master regulator" activating transcription factor, leading to the regulation of the DNA-RNA-protein pathway[88,89]. The functional overactivation of the serotonergic neuronal system in some brain areas, such as the sensory cerebral cortices, increases its function during the perinatal and nursing periods. This effect lasts up to adulthood in rat brains[73,74] and up to 3 months in the postnatal life of infants who underwent IUGR (measured through indirect methods), affecting mainly the sensory cortices' normal responses to specific stimuli[46,47,51,52].

Given that 5-HT has an important morphogenetic function in the process of neurogenesis[15,26,86,90-93] and other differentiating events such as synaptogenesis[27,28,81], we can also propose that disturbances may originate harmful effects exerted by IUGR nutritional stress in the prenatal serotonin functions. We also observed significant alterations not only in brain serotonin metabolism but also in the process of corticogenesis, particularly in thalamocortical connectivity during somatosensory (S1) cortex formation, adding evidence on how changes produced by IUGR stress on fetal serotonergic function are reflected in morphogenetic processes, with an abnormal morphologic S1 development[16,17].

By non-invasive methods, we detected sensory cortex responses directly associated with serotonergic regulation in infants: N1/P2 auditory intensity-dependent recordings. These recordings provide information on the auditory cortex's responses to specific stimuli. In our experience[47] and that of Hegerl et al.[94,95], an inverse correlation was found between the amplitude and intensity of the N1/P2 component of the auditory evoked potential response that the cortical serotonergic activity could produce on the auditory cortex (A1), rich in 5-HT innervation, regulating its responses to specific

stimuli. Consequently, we obtained interesting and significant information on the sensory cortex function indicators and plasma biochemical indicators of brain-serotonin metabolism in IUGR infants. These parameters were markedly abnormal in IUGR rats and IUGR infants born from mothers diagnosed with placental insufficiency and, thus, malnourished[45-47,49].

When allowed to NR, early undernourished subjects showed a good catch-up to normality on their physical parameters. However, functional and biochemical changes were not recoverable despite NR and remained up to adulthood in the rat brain compared to controls[70-74] and up to 3 months in infants[52] (Table 1). This observation suggests the permanence of the alterations observed in the auditory cortex responses to specific stimuli, dramatically abnormal in infants who underwent prenatal stress with IUGR[47] (Figure 6).

Another interesting question is why albumin capacity to bind L-Trp decreased significantly in IUGR patients' plasma. Plasma albumin from IUGR infants exhibited different binding properties than normal controls: a significantly higher K_D and lower B_{max}, indicating a lower affinity for the ligand (L-Trp) and a lower number of binding sites[52,96]. This kinetic behavior could explain higher FFT levels in the plasma of IUGR malnourished individuals, leading to an imbalance between plasma-free L-Trp and other neutral amino acids and the L-Trp/neutral amino acid ratio favoring the FFT[45,49]. In turn, high levels of FFT are transported across the BBB, activating the 5-HT biosynthetic pathway and, thus, reaching higher levels in the brainstem of IUGR individuals than controls. Unfortunately, there is no data on this binding phenomenon in humans, which possibly plays a relevant role in the serotonin metabolic pathway in the brain since FFT functions as a precursor for the synthesis of this brain neurotransmitter.

Authors who argue against albumin-L-Trp binding determinations have claimed that FFT is increased because plasma albumin concentration is decreased in malnourished individuals. However, *in vitro* binding experiments demonstrated that this is not the case because albumin concentration was the same, mole-to-mole, in plasma derived from eutrophic control infants and derived from IUGR subjects and free of fatty acids (FFA). Therefore, under these assay conditions, differences in L-Trp binding kinetics are not dependent on differences in plasma albumin concentration. These differences would be present if binding experiments were performed directly on whole plasma albumin samples with no prior FFA. Undoubtedly, if the kinetics of albumin binding to L-Trp were measured directly, not only would its concentration be variable, but other factors would probably interfere[52]. Therefore, our findings suggest a possible structural difference in human IUGR albumin that allows this protein to change its conformation[97] in response to prenatal malnutrition stress. Thus, there is a different kinetic behavior for its binding to L-Trp in the plasma of human IUGR infants. In the context of serotonin metabolism in the brain, this phenomenon represents an essential peripheral regulatory mechanism for synthesizing this brain neurotransmitter, acting through the modulation of substrates for neurotransmitter synthesis. To our knowledge, this is the first time this has been described in newborns with IUGR and normal controls.

These findings support the notion that undernourishment distress during pre-, peri-, or postnatal development causes significant growth restriction and a possible change in TPH protein and plasma albumin structure, based on modifications in their kinetics and phosphorylation capacity[52,59,60]. Moreover, the decrease in TPH1-expressing serotonergic neurons coincides with a predominant enzyme expression compared with controls. A significant decrease of TPH2-immunoreactive neurons and a lower concentration of the enzyme suggest that stressful early conditions may induce epigenetic influences on the corresponding genes, as discussed previously, which shifts TPH expression toward TPH1 predominance, through a mechanism that, at present, is unclear, particularly concerning the presence of isoform 1 in controls.

Based on these results, it can be proposed that prenatal nutritional stress may significantly influence the brain's 5-HT biosynthetic pathway through mechanisms that may not necessarily be dependent on the genes encoding the enzymes but by epigenetic changes caused by intense nutritional stress and abnormal neurological changes induced by early undernourishment[98-100]. These remarkable enzymatic changes could be produced by modifications in the *Pet-1* molecular apparatus, which appear to be essential in regulating enzyme expression in the serotonergic biosynthetic pathway from very early stages of brain development[67-69,101]. According to some authors, *Pet-1* is also required to maintain TPH enzymes in the developing brain. Thus, significant alteration of the *Pet-1*-related molecular apparatus can be studied to gain further insight into the effects of early undernourishment on TPH enzymes activity in the developing brain. Another exciting possibility that would add information to this research project would be to establish the heritability of functional changes in tryptophan-5-hydroxylases

and plasma albumin[52,59,60,61] and their metabolic consequences on brain serotonin biosynthesis, which mainly affect the brain sensory function of IUGR infants. However, this phenomenon would be related to an epigenetic explanation.

In conclusion, our experimental data allowed extrapolation to human infants under similar pre-and perinatal developmental conditions. On this basis, the proposal of a psychopathological alteration of the brain-serotonin in these patients was supported, reinforced by the significant morphological, neurobiochemical, biochemical, and electrophysiological alterations affecting the serotonergic functions of the brain from the prenatal stage. These alterations could favor abnormal cognitive development or a predisposition to psychiatric abnormalities related to brain serotonergic function.

Experimental work continues in our group to obtain more information on this exciting and relevant topic.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors declare no conflict of interest.

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REVIEW ARTICLE

Cystic fibrosis: current concepts

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Abstract

Cystic fibrosis is an autosomal recessive genetic disease, mainly in Caucasian children and young adults. It is caused by pathogenic variants in the CFTR (cystic fibrosis transmembrane conductance regulator) gene, which results in increased viscosity and difficult mucus clearance. The main organ affected is the lung, the pancreas, sweat glands, intestine, liver, nasal mucosa, salivary glands, and reproductive tract. The clinical manifestations vary, ranging from the most frequent pulmonary symptoms of obstructive disease to gastrointestinal manifestations related to malabsorption secondary to pancreatic insufficiency. Although there are multiple diagnostic tests for cystic fibrosis, neonatal screening to identify increased immunoreactive trypsinogen, chloride sweat test, and the detection of pathogenic variants in the CFTR gene allow the diagnosis to be integrated. Cystic fibrosis management consists of three main strategies: firstly, to keep the airway free of secretion; secondly, to keep the airway free of infection; and finally, to maintain an optimal nutritional status. Therapies that seek to correct alterations in the CFTR gene are focused on avoiding a pathogenic nonsense variant, correcting folding, increasing trafficking to the plasma membrane, or increasing the function of the CFTR channel. Other therapies still under development include gene therapy, genome editing, and antisense oligonucleotides to modify the expression of this gene.

Keywords: *Cystic fibrosis. CFTR gene. Gene therapy.*

Fibrosis quística: conceptos actuales

Resumen

La fibrosis quística es una enfermedad genética autosómica recesiva que se presenta principalmente en niños y adultos jóvenes caucásicos. Está causada por variantes patogénicas en el gen CFTR (regulador de la conductancia transmembrana de la fibrosis quística), lo que ocasiona un aumento de la viscosidad y un difícil aclaramiento del moco. El principal órgano afectado es el pulmón, seguido del páncreas, las glándulas sudoríparas, el intestino, el hígado, la mucosa nasal, las glándulas salivales y el aparato reproductor. Las manifestaciones clínicas son variables y van desde las más frecuentes, que son los síntomas pulmonares de enfermedad obstructiva, hasta manifestaciones gastrointestinales relacionadas con la malabsorción secundaria a la insuficiencia pancreática. Aunque existen múltiples pruebas diagnósticas para la fibrosis quística, el tamiz neonatal, el aumento en el tripsinógeno inmunorreactivo, la prueba de cloro en sudor y la detección de variantes patogénicas en el gen CFTR permiten integrar el diagnóstico. El manejo consta de tres niveles principales: el primero, mantener la vía aérea libre de secreción; el segundo, mantener la vía aérea libre de infección; y por último, mantener un estado nutricional óptimo. Las terapias que buscan corregir las alteraciones en el gen CFTR están enfocadas en evitar una variante

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patogénica sin sentido, corregir el plegamiento, aumentar el tráfico a la membrana plasmática o incrementar la función del canal CFTR. Otras terapias aún en desarrollo incluyen la terapia génica, la edición del genoma y los oligonucleótidos antisentido para modificar la expresión de este gen.

Palabras clave: *Fibrosis quística. Gen CFTR. Terapia génica.*

Introduction

Cystic fibrosis (CF), a monogenic disease transmitted in an autosomal recessive pattern, is multisystemic and chronic and originates as a consequence of pathogenic changes in the *CFTR* gene located on the long arm of chromosome 7 (locus 7q.31) that encodes for the protein known as the CF transmembrane conductance regulator (CFTR). Dysfunction of this protein causes altered ion transport in the apical membrane of epithelial cells in different organs. This dysfunction becomes evident in the early stages of life (infant stage). It is a complex and highly pleomorphic disease whose classic phenotype is a progressive obstructive pulmonary disease, exocrine pancreatic insufficiency, and elevated sweat chloride and sodium levels in 90% of patients[1].

Epidemiology

CF is the most common inherited genetic disease among Caucasians; however, any ethnic group can be affected. Prevalence ranges from 1:1400 in Ireland to 1:3500 in the United States, while rates are much lower in geographic regions such as Asia and Africa[2,3]. In Latin America, the prevalence is 1:1600-14,000 live newborns (LNB), and in Mexico, 1:8500 LNB, with a detection rate of pathogenic variants of 41.6%[4,5].

Mortality in childhood is due to complications of recurrent respiratory infections and malnutrition due to pancreatic insufficiency[6]. However, in Mexico and Latin America, life expectancy in the early 1990s averaged only 9 years. With the use of new therapies and better control of the disease, the average survival is 18 years[1]. In developed countries, life expectancy exceeds 40 years; these “long survivors” have a mean survival of 52.1 years of age in Canada, 47.4 years in the United States, and 47.3 years in the United Kingdom[1,7].

Etiopathogenesis

CF is caused by pathogenic variants in the *CFTR* gene (locus 7q31.2) and is inherited in an autosomal recessive (AR) manner[8-10]. More than 2000 variants have been identified in the *CFTR* gene, but the most common variant is the phenylalanine deletion at position 508 (p.F508del, ΔF508)[11,12]. The pathogenic variants and their effects have been grouped into seven classes (Table 1)[12-14].

Structurally, CFTR is a membrane-bound glycoprotein with a typical 12-helix architecture comprising two pseudosymmetric transmembrane domains (MSD) and two nuclear binding domains (NBD) that bind and hydrolyze ATP. Between both NBD units is a single regulatory domain (R) consisting of many charged amino acids (Figure 1)[15]. The CFTR protein is expressed mainly in the lung and the pancreas, sweat glands, intestine, liver, nasal mucosa, salivary glands, and reproductive tract[16]. Under normal conditions, CFTR works like a gate tightly coupled to ATPase cycles (Figure 1) through NBD dimerization, which subsequently induces the formation of a transmembrane domain cavity that opens towards the extracellular side to allow the flow of selective anions as chlorine (Cl-) and bicarbonate (HCO3-)[11].

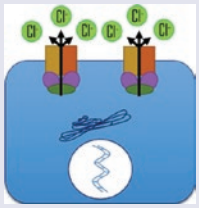
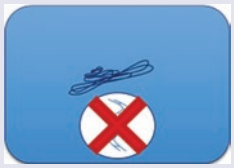
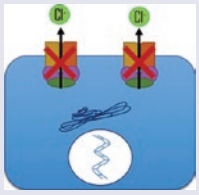
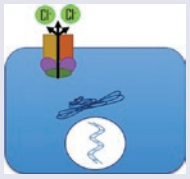
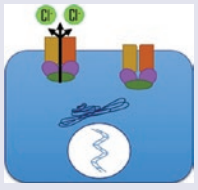
Particularly in the airway, CFTR regulates the local pH by allowing Cl- and HCO3- to flow out of the cell; in addition, it causes the epithelial sodium channel ENaC to transport sodium into the cell (Figure 2). Normal airway surface fluid (ASF) has a pH around 7.0[17]. However, in CF, the pH is eight times more acidic due to the lack of adequate secretion of Cl- and HCO3- anions into the extracellular space (Figure 2). The loss of chloride secretion due to CFTR deficiency results in changes in osmotic pressures and electroneutrality, which probably lead to excessive sodium and water absorption[18].

Pulmonary alterations are due to the addition of a considerably more acidic pH (caused by the lack of secretion of Cl- and HCO3- anions) and the excessive absorption of Na+ and water that cause an increase in mucus viscosity and a difficult clearance of mucus in the airway. In the other organs and systems, CF produces obstructions at different levels, causing extrapulmonary symptoms.

Clinical manifestations

Respiratory, gastrointestinal, and metabolic alterations are present in CF, some associated with inadequate nutrient uptake related to intestinal pathology.

Table 1. Classification of *CFTR* gene mutations. The most common mutations in each class and the type of defect are described

Classification of CFTR mutations		Description	Examples
Normal		The CFTR protein is found on the cell surface and functions properly, allowing chloride and water transfer	—
Class I		No protein production: No CFTR protein synthesis	p.G542X p.W1282X p.R553X
Class II		Traffic defects: CFTR protein is created but is misfolded, preventing it from reaching the cell surface	p.F508del p.N1303K p.I507del
Class III		Defective regulation: CFTR protein is created and reaches the cell surface, but there is a defect in the channel opening	p.G551D p.S549N p.V520F
Class IV		Decreased conductance: There is a defect in ion transport through the CFTR protein, resulting in a poor outflow of ions from the cell	p.R117H p.D1152H p.R347P
Class V		Reduced amount: CFTR protein is created but in insufficient quantities, resulting in decreased ion transport	c. 621+1G>T c. 3849+10C>T c. 2780+5G>A p.A455E c. 3140-26A>G
Class VI		Increased turnover: A decrease in the half-life of the CFTR protein occurs, causing accelerated turnover of the CFTR protein	c. 4326delTC p.Gln1412X
Class VII		No mRNA: No mRNA is synthesized, no CFTR protein is formed	Dele2,3 (21kb)

CFTR, cystic fibrosis transmembrane conductance regulator; mRNA, messenger ribonucleic acid.

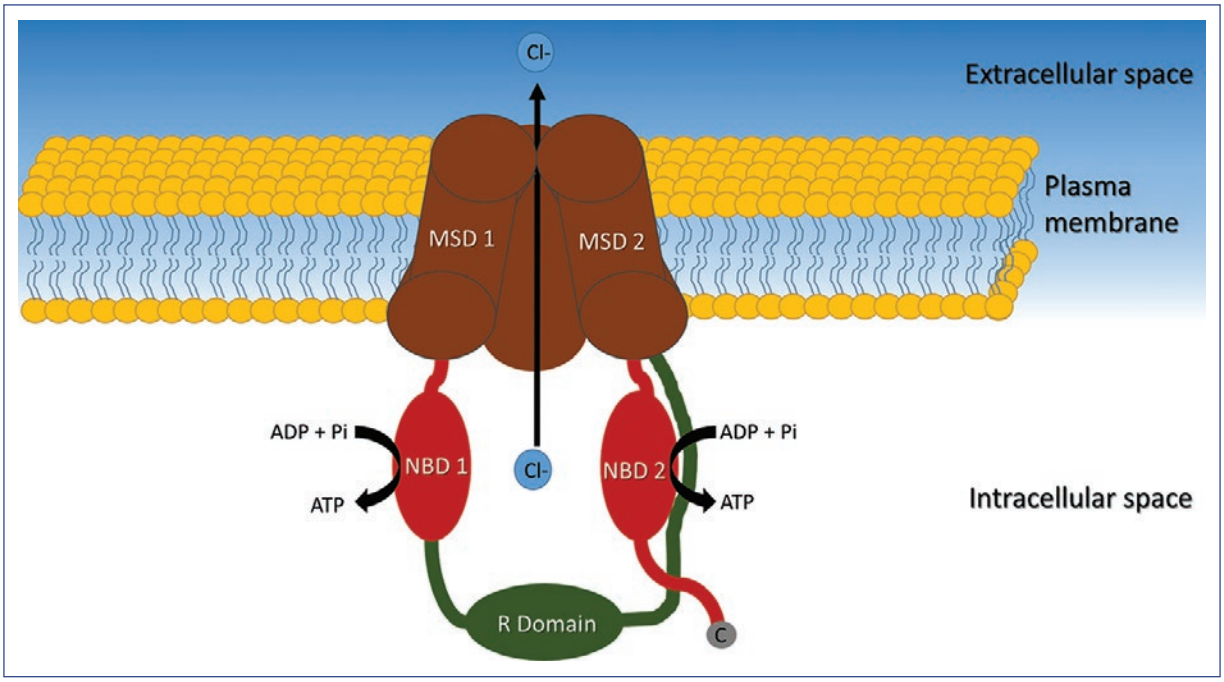


Figure 1. Representation of the CFTR protein channel, composed of two transmembrane domains (MSD 1 and 2), each bound to a nucleotide-binding domain (NBD 1 and 2). NBD1 is connected to MSD2 by a regulatory domain (R). NBD 2 has a carboxyl end.
CFTR, CF transmembrane conductance regulator; MSD, transmembrane domain; NBD, nucleotide-binding domain; R, regulatory domain.

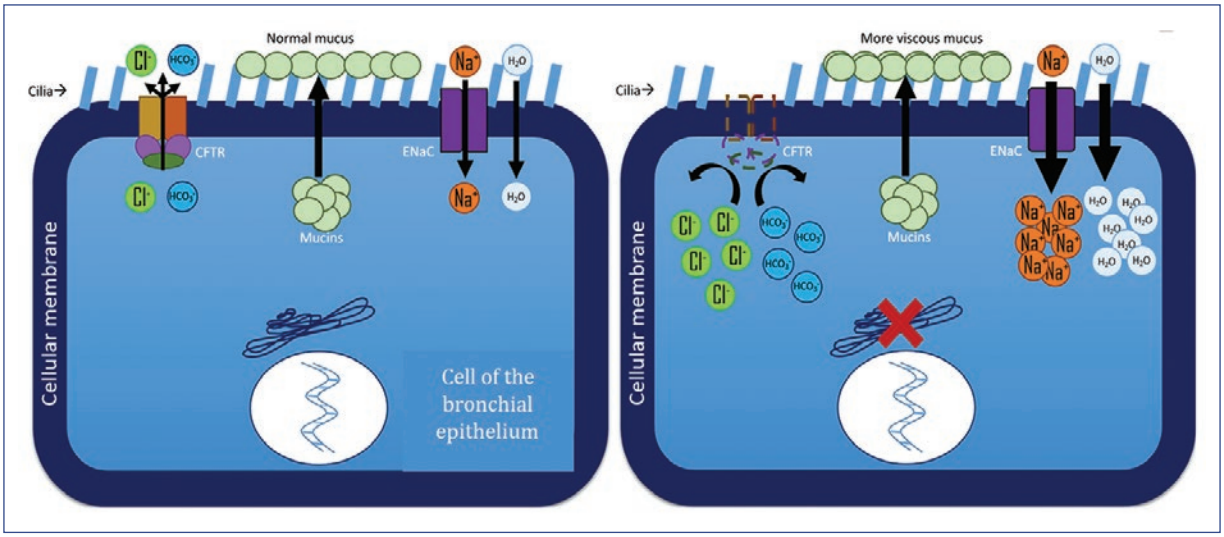


Figure 2. The function of the CFTR channel, the function of the ENaC channel, and mucin secretion for the formation of normal airway surface fluid are illustrated. **A.** Cell dynamics in a healthy context. **B.** Cell dynamics in CF in the context of the p.F508del mutation. The intradomain defect affects full-length CFTR protein assembly and post-translational stability, whereby deletion of phenylalanine at position 508 in NBD1 leads to a CFTR trafficking defect.
CFTR, cystic fibrosis transmembrane conductance regulator; ENaC, epithelial sodium channel.

The presenting symptoms may vary according to age at diagnosis and are sometimes related to genotype. Prior to the implementation of newborn screening in the United States, the diagnosis of CF in

infants and preschoolers was integrated after presenting with one or more of the following symptoms[19]: respiratory symptoms (45% of patients), inadequate weight for age (28%), or meconium ileus (20%). In addition, the clinical presentation in adults with atypical features is better in the long term than those diagnosed in childhood[19].

Signs and symptoms can be grouped according to the age group or location of the damage. According to age group, meconium ileus, prolonged neonatal jaundice (cholestatic), edema, anemia, malnutrition, steatorrhea, malabsorption syndrome, inadequate weight gain, and recurrent vomiting may be found in newborns and young infants. There is often recurrent or chronic coughing or wheezing in infants that do not improve with treatment, recurrent or chronic pneumonia, growth retardation, chronic diarrhea, rectal prolapse, salty skin taste, and chronic hyponatremia, and hypochloremia. Preschool children may show chronic cough with purulent expectoration and chronic recurrent unexplained wheezing (both with no response to treatment), poor weight and height gain, recurrent abdominal pain, rectal prolapse, intussusception, chronic diarrhea, clubbing of the fingers, chronic hyponatremia, and chronic hypochloremia, hepatomegaly or unexplained liver disease, and nasal polyps. Schoolchildren present with chronic unexplained respiratory symptoms, *Pseudomonas aeruginosa* in bronchial discharge, chronic sinusitis, nasal polyposis, bronchiectasis, chronic diarrhea, distal intestinal obstruction syndrome, pancreatitis, rectal prolapse, and hepatomegaly. Moreover, adolescents and adults often present with chronic unexplained suppurative lung disease, digital clubbing, recurrent abdominal pain, pancreatitis, distal intestinal obstruction syndrome, liver cirrhosis and portal hypertension, growth retardation, male sterility with azoospermia, and decreased fertility in women[20]. These symptoms are characteristic in patients with chloride concentrations > 60 mmol/L (discussed later). However, a subgroup of patients with chloride concentrations in the intermediate range is diagnostically challenging. As mentioned by Jorquera[21], these patients may develop minimal symptoms or other symptoms related to defects in the *CFTR* gene in non-respiratory organs, making diagnosis difficult. Symptoms usually range from clubbing toes, recurrent respiratory infections, and isolation of *P. aeruginosa* and *Staphylococcus aureus*. Less common symptoms are pancreatic insufficiency, meconium ileus, distal intestinal obstruction syndrome, and liver disease[21].

Respiratory symptoms

Respiratory alterations can be found in 80% of infants and preschoolers[19]. In children under one year of age, dry and repetitive cough is frequent. Also, persistent tachypnea, a slight increase in the anteroposterior diameter of the thorax, decreased expansion of the upper thorax, persistent intercostal retraction, and bronchial obstruction may be observed. Older children may present with bronchial obstruction and cough with purulent mucous secretions as constant symptoms. There are variable degrees of thoracic deformity with increased anteroposterior diameter. In the thoracic auscultation, in general, there is no added noise in intercrisis periods, and crackles in infectious exacerbations are present in children with severe compromise. In advanced disease, bronchiectasis, with or without hemoptysis, watch glass nails, and clubbing fingers may be present, while cyanosis is a late sign[20].

Sinus disease is also present in most patients and manifests as chronic nasal congestion, headache, cough, chronic posterior nasal discharge, and sleep disorders[19].

With increased viscosity and difficult clearance, respiratory secretions obstruct the airways and promote infection, leading to tissue destruction and, eventually, bronchiectasis. In chronic airway obstruction, *Haemophilus influenzae*, *S. aureus*, *P. aeruginosa*, and *Burkholderia cepacia* are the main pathogenic bacteria[22].

Some germs have been implicated in the infection that occurs in CF. Before the antimicrobial era, few children with CF survived beyond the age of 2 years. Children died primarily from failure to thrive, along with bacterial pneumonia. The organism found in the lungs at autopsy in these children was almost always *S. aureus*, which remains the predominant pathogen of CF from birth to adolescence, with 80% of children infected in preadolescence and early adolescence. Moreover, the critical pathogen in chronic lung disease is an unusual morphotype of *P. aeruginosa* termed mucoid. Although this germ is comparatively avirulent, it induces a chronic inflammatory response, apparently responsible for the lung damage that leads to the patient's demise. This process may occur over years or decades, which would explain why 60-75% of adults in the United States are infected with this organism. In other cases of CF, a double count of glucose non-fermenting bacilli that are *B. cepacia* complex organisms, *Achromobacter* and *Stenotrophomonas*, are more frequently found in the patient. The latter is found in

approximately 10% to 20% of CF patients, while *Achromobacter* is found in 5% to 10%. The incidence of these organisms increases with age and probably reflects patients who have received multiple rounds of antipseudomonal antimicrobial therapy[23].

In the case of *P. aeruginosa*, responsible for morbidity and mortality in CF, a prevalence of 25-30% has been reported in infants aged 0-1 year, 38-40% in children aged 2-6 years, and can reach 80% in patients > 18 years. Infection is mainly caused by rough strains with high sensitivity to antibiotics. However, in the case of CF, this infection is not completed and acquires a mucoid phenotype in response to alteration of the *CFTR* gene epithelium. Therefore, the stagnation of mucus due to dehydration helps form an ideal culture medium and a layer around the bacteria that makes the immune system and antibiotics less effective. Consequently, endobronchial infection becomes chronic and can no longer be eliminated[24].

The most frequently detected symptoms in the more advanced stages are pulmonary hypertension, bronchiectasis, and *cor pulmonale*. Progressive lung disease remains the leading cause of morbidity and mortality in these patients[22].

Signs and symptoms that evidence pulmonary exacerbation are increased cough, changes in sputum (consistency or volume), decreased appetite, or weight loss. Exacerbation also shows changes in respiratory examination and respiratory rate. However, the number and variability of signs and symptoms may alter the exacerbation pattern[25].

Extra-respiratory symptoms

Digestive system and nutrition. About 3.9% of patients do not present extrapulmonary manifestations related to pancreatic, gastrointestinal, and hepatobiliary dysfunction[26,27]. Defects in the *CFTR* gene result in abnormalities affecting organs such as the liver, gastrointestinal tract, and pancreas. Nutritional failure in CF is multifactorial. Malabsorption of lipids, protein, and fat-soluble vitamins results from insufficient pancreatic enzyme production, which bile salt abnormalities may aggravate in the presence of concurrent liver disease. Because of the predisposition to pulmonary infection, a relationship has been found with increased breathing, reduced appetite, and increased calories at the expense of inflammatory catabolism. Approximately 85% of patients develop pancreatic insufficiency between 1-2 years of age. In the context of CF, pancreatic insufficiency is a risk factor for recurrent pancreatitis, which is the presentation for the diagnosis of CF[26].

Gastrointestinal tract manifestations are related to mucosal dysmotility and include meconium ileus, constipation, distal intestinal obstruction syndrome, gastroesophageal reflux disease, and small intestinal bacterial overgrowth. The hepatobiliary disease has a prevalence of 10-15%, with peak onset in preadolescence.

In exclusively breastfed infants, the triad of anemia, hypoalbuminemia, and edema—secondary to malnutrition—and some specific deficiencies due to malabsorption caused by CF are common[20].

CF-related liver disease. Approximately 20-40% of people with CF develop clinically detectable CF-related liver disease (CFLD)[19,26].

Hypovitaminosis. CFLD and pancreatic dysfunction lead to lipid malabsorption, predisposing to deficiencies of fat-soluble vitamins (A, D, E, and K)[28].

CF-related diabetes (CFRD). The main cause is an insulin deficiency related to the destruction of pancreatic islets[29]. Two percent of CF patients have CFRD in childhood, increasing to 20% of adolescents and reaching 40-50% of CF patients in adulthood. This increasing proportion suggests multifactorial, complex, and progressive pathogenesis of CFRD. Excessive protein catabolism is problematic in CF lungs, associated with an imbalance between catabolic and anabolic enzymes.

Studies in adults have shown that insulin depletion contributes to an inflammatory catabolic state, compromising lung function[30]. It has been suggested that CFRD patients with no impaired basal glycemia do not require treatment because they are asymptomatic. However, the nutritional consequences of insulin deficiency may impair their quality of life. In the case of patients with altered basal glycemia, microalbuminuria was observed in 14%, retinopathy in 16%, neuropathy in 55%, and gastropathy in 50%. Therefore, from the age of 5 years, it is advisable to monitor annually for microvascular complications from the diagnosis of CFRD[31].

Recurrent venous thrombosis. CF seems to be a risk factor for the development of recurrent venous thrombosis. Of 120 children and young adults with acute venous thromboembolism, 19 showed recurrent thrombosis. Among them, six had CF, of which five were infected with *B. cepacia*[32].

Anemia. It occurs in 10% of children but is more frequent in older adults or those with decreased pulmonary function. Although its causes are diverse, the relationship with CF remains unclear, especially in infants, in whom it may occasionally be a presenting sign. Mechanisms involved include dysregulation of

iron metabolism, anemia due to chronic disease, blood loss, renal failure, or bone marrow suppression after transplantation[28].

Bone disease. Bone disease, characterized by decreased mineral density and increased rates of fracture and kyphosis, is rare in children under 10 years of age but increases in prevalence with age. In addition, vitamin D deficiency decreases intestinal absorption of calcium and produces secondary hyperparathyroidism, which leads to increased bone resorption and fragility[1].

Infertility. Most male CF patients (> 98%) have a congenital bilateral absence of the *vas deferens* (CBAVD) and are infertile, but < 2% remain fertile and usually carry CFTR genotypes. It has been proposed that reduced CFTR activity impairs ion exchange within the male genital ducts and predisposes to increased intraluminal viscosity and obstruction by accumulated secretions and mucus, ultimately leading to obliteration of epididymis and *vas deferens*[33,34]. In contrast, women with CF experience more pulmonary exacerbations after puberty than men and increased colonization with the mucoid form of the commonly acquired CF pathogen *P. aeruginosa*. Gonadal hormones may contribute to these sex differences. Female sex hormones (estrogen and progesterone) are expressed in lung tissue and their hormone receptors. There is a 35% subfertility and infertility rate in women with CF trying to conceive (mean age 30.4 years). In the cervix, the defective CFTR in the epithelium promotes the production of thick, dehydrated cervical mucus. This mucus blocks the cervix and impairs the entry of spermatozoa. In the endometrium, defective CFTR in the epithelium can alter bicarbonate secretion, reducing uterine fluid volume and impairing sperm fertilization capacity. Finally, women with CF may have a lower ovarian reserve compared to age-matched controls[35].

Nephrolithiasis and nephrocalcinosis. CF has been associated with nephrolithiasis and nephrocalcinosis due to factors that promote calcium deposition.

Diagnosis

New challenges have emerged in both the diagnosis and clinical management of children with CF, as various forms of terminology for the disease have been introduced in recent years. During the development of the Cystic Fibrosis Foundation guidelines, newborns diagnosed with CF were identified by screening through the analysis of sweat chloride levels with values ≥ 60 mmol/L[36].

The primary test for confirming the diagnosis of CF is the sweat chloride test, performed according to the guidelines and standards recommended by the Cystic Fibrosis Foundation committee, which places this test as the current gold standard for diagnosing CF. Moreover, it is appropriate to maintain the cut-off values recommended by the committee based on the available data from chloride testing in healthy and CF-affected infants with the following ranges for infants up to 6 months of age: ≤ 29 mmol/L, unlikely CF; 30 to 59 mmol/L, intermediate; ≥ 60 mmol/L, indicative of CF[37,38].

Currently, the extensive use of immunoreactive trypsin (IRT) neonatal screening has aided in diagnosing CF in asymptomatic or low symptomatic patients in approximately 64% of new diagnoses in the United States. Current guidelines on early diagnosis recommend sweat chloride testing by the Gibson and Cook technique in patients with positive screening[37]. There is a low probability of CF diagnosis if the result is < 30 mmol/L. However, in the case of an intermediate-range (30-59 mmol/L), the test should be repeated two to three weeks later, or consider extended *CFTR* gene analysis or CFTR functional analysis to classify the case as CFTR-related metabolic syndrome (CRMS)/CF-screening positive, inconclusive diagnosis (CFSPID). When in both occasions the result is > 60 mmol/L, the diagnosis of CF is confirmatory, always being careful to interpret false positives (caused by conditions such as malnutrition or Down syndrome, among others) or false negatives (due to technical errors, hypoproteinemia, or sampling of the newborn in the first days). Generally, these false results are due to technical errors. Further CF functional tests, such as nasal potential difference or intestinal absorption tests, can be performed. However, these should be performed in specialized centers certified by the CF foundation[36].

Newborn screening for CF depends on the initial identification of elevated immunoreactive trypsinogen (IRT) values in the blood of the newborn. Since normal IRT reference values vary slightly, after identifying an abnormal IRT value, most programs perform DNA testing to detect known *CFTR* gene mutations (IRT/DNA strategy). This strategy provides a sensitivity of approximately 90-95% and identifies newborns at risk for a broad spectrum of disease severity[36].

Once the screening result is positive, sweat chloride analysis should be performed in newborns > 36 weeks of gestation and > 2 kg of weight. Genetic testing should be performed as soon as possible when available[38]. The definitive diagnosis is based on the criteria listed in Table 2[33].

Table 2. Diagnostic criteria for cystic fibrosis

Presence of clinical criteria (at least one):
Organ with consistent symptoms of cystic fibrosis
Chronic sino-pulmonary disease
Characteristic gastrointestinal and nutritional abnormalities
Salt loss syndromes
Obstructive azoospermia
Sibs with cystic fibrosis
Positive test result at birth (positive neonatal screen)
Tests showing CFTR dysfunction (at least one):
CFTR dysfunction indicated by elevated levels in sweat chlorine analysis (> 60 mmol/L) in two tests
Nasal potential difference consistent with cystic fibrosis
Presence of two pathogenic variants in *CFTR* in different alleles

CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator.
Adapted from Brennan et al.[33]

The diagnostic algorithm proposed in the guidelines of the CF Foundation (2017)[38] (Figure 3) and the one proposed by the clinical practice guideline in Mexico[5] (Figure 4) are published and available for review.

Pulmonary function tests help assess disease severity and progression. Spirometry can be performed in children aged 3-6 years using modified acceptability criteria, and most children aged ≥ 6 years can perform reliable lung volume tests[39]. Most patients with cystic fibrosis develop an obstructive pattern. The first manifestations of early obstruction are an increase in the ratio of residual volume to total lung capacity ratio and a decrease in forced expiratory flow of 25-75% of lung volume. Later, in advanced disease, there is a decrease in forced expiratory volume in one second (FEV1) and FEV1/FVC (forced vital capacity) ratio[40].

Chest X-rays and computed tomography are the imaging studies used in CF. Patients are usually monitored with chest X-rays every 2 years. Radiographic findings change according to the progression of the disease: hyperinflation, which later becomes persistent, can be observed. Bronchovascular markings are also visible and may progress to a pattern of bronchiectasis and cyst formation. Also, a progressive flattening of the diaphragms is present. The alterations usually appear first in the upper lobes.

CT is used when detailed knowledge of the extent of lung disease is required. High-resolution CT is useful in asymptomatic children who are small for pulmonary function testing; findings may include peribronchial thickening, air trapping, bronchiectasis, centrilobular nodules[41]. Pulmonary function changes may not be closely related to abnormalities found on CT (progressive).

When inconclusive results are not obtained with sweat chloride and DNA testing, the nasal potential difference can be measured to assess CFTR dysfunction[33]. The potential difference is measured by placing electrodes in the nasal cavity and comparing the voltages between baseline and administration of amiloride to block sodium transport and after nasal perfusion with a chloride-free solution, such as isoproterenol, to stimulate the CFTR-dependent chloride transporter. There is a potential difference in individuals with CFTR abnormalities at baseline, which decreases after amiloride and shows a minimal response to perfusion with chloride-free isoproterenol[42].

Finally, a gut malabsorption study can be performed. The pancreatic exocrine function can be assessed indirectly by measuring fecal elastase. A low fecal elastase level suggests pancreatic insufficiency and consequent gut malabsorption[43].

Management

The management of CF is multidisciplinary and involves both the patient and family members, who will facilitate follow-up and optimization of treatment. The following are the three pillars of treatment that should be considered a guideline for all CF patients.

Keep the airway clear of secretions

Maintaining a clear airway at all times can be achieved through various techniques and schemes that can be combined according to the specific characteristics of each patient. They can be divided into two main groups:

a. Physical therapy. It seeks to clean the airways and drain the accumulation of thick, viscous secretions that can harbor bacteria and their products. Respiratory physiotherapy is performed in two or more daily sessions depending on the severity and complications, separated by a minimum of 2 hours after meals[44]. It has been shown that the application of this therapy can have short-term benefits for patients with CF. However, there are as yet no conclusions on the long-term benefits[45].

Techniques vary and depend on age: in children < 3 years of age, passive chest percussion maneuvers, blocks, vibrations, and postural drainage are used. After 3 years of age, forced expiration techniques can be added, inducing the child to exhale slowly and progressively, to bring secretions into the central airway. In children > 6 years, autogenic drainage maneuvers are taught[37].

Active cycle of breathing techniques, autogenic drainage, and Vojta approach can be combined with respiratory reeducation exercises to improve diaphragmatic function by reducing the number of respiratory cycles

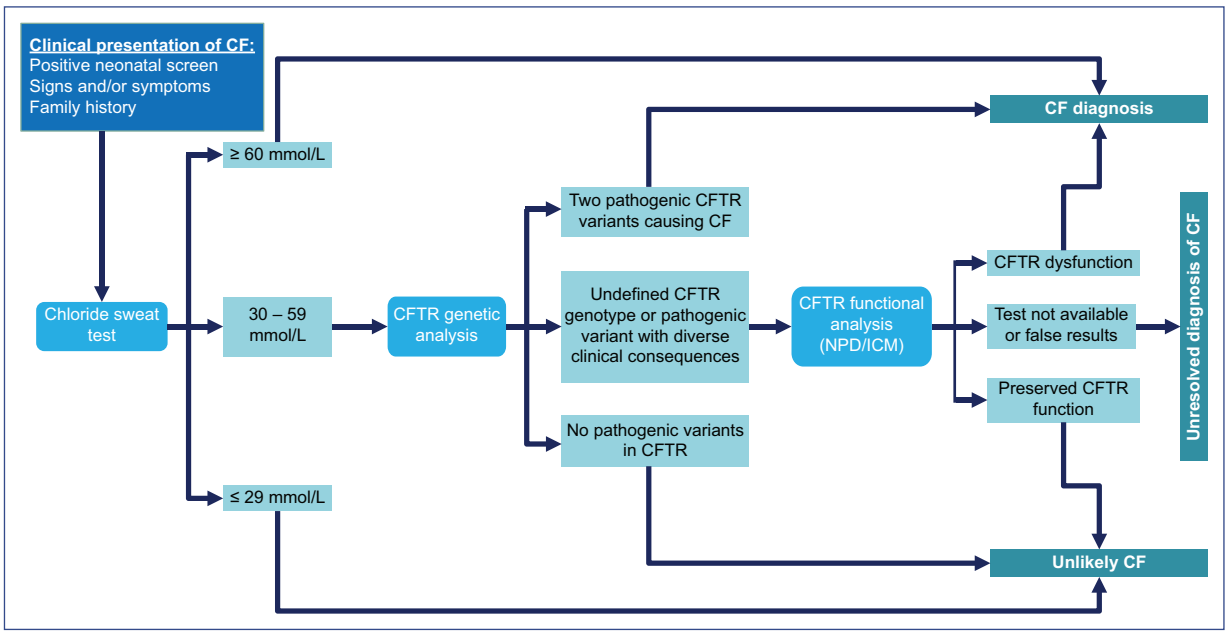


Figure 3. Diagnostic algorithm for individuals with high suspicion of cystic fibrosis.
CFTR, CF transmembrane conductance regulator; NPD, nasal potential difference; ICM, intestinal current measurement.

but with a higher tidal volume. In addition, physical activities that stimulate respiratory training, such as swimming, cycling, or athletics, can be implemented. One of the advantages of using specialized techniques such as physiotherapy in poorly treated patients with or patients with little or no physical activity is that it has helped to find new independent and effective ways of managing respiratory secretions. Physical exercise of different types influences the quality of life, sensitivity, and resistance to lung infections[46].

In addition to physical therapy, there are mechanical aids for the elimination of secretions. Among them, the following stand out:

a) Positive expiratory pressure (PEP) mask. This mask is resistant to expiration.
b) Oscillating positive expiratory pressure (Flutter) devices. These devices combine both PEP and oscillation, generating vibrations that separate bronchial secretions throughout the airway.
c) High-frequency chest compression. This percussion vest generates pressure on the thorax through a pump, but it is costly.
d) Percussive intrapulmonary ventilator. This ventilator includes the administration of a continuous aerosol together with internal percussion of the thorax through small bursts of air at 200-300 cycles per minute[44].

b. Pharmacological therapy

a) DNase I (alpha dornase). This endonuclease breaks the DNA chains released by neutrophils responsible for the high viscosity of secretions in CF. It has been shown to improve lung function, increasing FEV1 by 6% in CF patients > 6 years and decreasing the frequency of pulmonary exacerbations. The usual dose is 2.5 mg to nebulize every 24 hours, daily and permanently, after using aerosol bronchodilators (albuterol) to prevent bronchoconstriction[47].
b) Hypertonic saline solution at 7%. Pre-glucocorticoid nebulization with saline has been used to overcome hydration failure of the aqueous layer of the bronchial mucosa. This treatment reduces the frequency of exacerbations in symptomatic respiratory patients > 12 years. In children < 12 years of age, insufficient evidence has been found to justify its routine use since, in children > 6 years of age, no improvement in the frequency of exacerbations was observed. However, in tracheostomized pediatric patients, cleaning with 5% saline solution before initiating nebulizations reduces the occurrence of exacerbations[37]. The use of inhaled hypertonic saline is suggested in young children based on randomized trials in which lung clearance index is measured and compared to placebo (isotonic saline)[48]. In a randomized trial in infants < 4 months, Stahl et al. found that inhaled hypertonic saline twice daily for 52 weeks

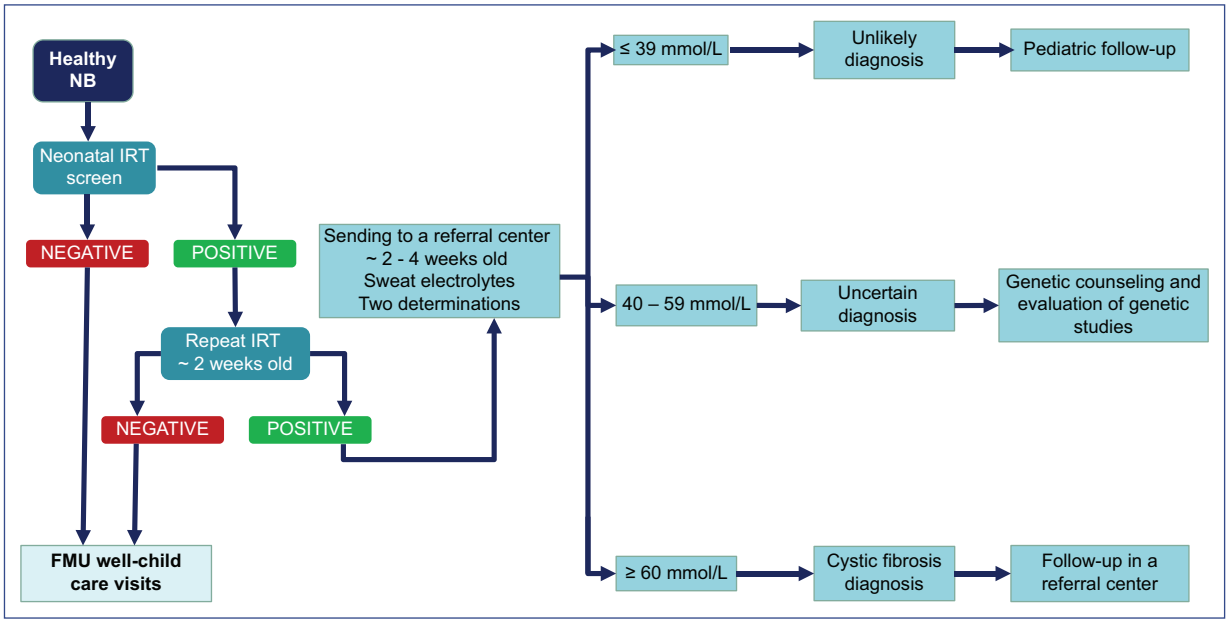


Figure 4. Cystic fibrosis diagnosis algorithm.
NB, newborn; FMU, family medicine unit; IRT, immunoreactive trypsin.

demonstrated a significant change in lung clearance index compared to isotonic saline[49]. Similar results were observed in another randomized trial in children aged 36-72 months[50].

Keep the airway free from infections

Respiratory tract infections are persistent. The administration of antibiotics, together with physical therapy and pharmacological agents that allow the elimination of secretions, will facilitate the control of the CF patient. The following is a description of the antibiotics recommended for the four main etiologic agents in respiratory tract infections:

a) *S. aureus* is the predominant pathogen in the first years of life and the first to infect the respiratory tract. Treatment is based on oral dicloxacillin or flucloxacillin, or intravenous dicloxacillin in exacerbations.
b) *P. aeruginosa* causes the most severe chronic pulmonary infection and is associated with progressive deterioration of respiratory function. Treatment consists of oral ciprofloxacin or ceftazidime, intravenous aminoglycosides or antipseudomonal penicillin, and intravenous aminoglycoside in severe cases for 21 days.
c) *B. cepacia* is associated with more significant pulmonary deterioration in adolescents and adults. The incidence in Latin America is low, and treatment is based on temocillin with an aminoglycoside.
d) *H. influenzae* can cause chronic colonization. The indicated treatment is amoxicillin-clavulanic acid or second or third-generation cephalosporin[51].

Currently, intravenous therapy has been replaced by inhaled treatments, which allow prolonged treatments with high doses and minimal toxicity. The recommended drugs are tobramycin, colistin, and aztreonam-lysine, which should subsequently be inhaled beta-blockers such as salbutamol to prevent bronchoconstriction[37].

Maintain an optimal nutritional state

There is a close and bidirectional correlation between body mass index (BMI) and lung function (FEV1). The goal of nutritional therapy is to maintain a BMI above the 50th percentile[37].

Evidence has shown that CFTR dysfunction impairs β-cells, leading to a decrease in insulin levels. Since insulin from β-cells can also exert an inhibitory effect on glucagon release from α-cells, this suggests a dual role of CFTR in regulating glucagon secretion and may contribute to glucose intolerance in CF, leading to some conditions. In the plasma of CF patients, elevated levels of peroxidized lipids and oxysterols are observed, indicating abnormal lipid metabolism and increased

susceptibility to lipoprotein lipid oxidation. In addition, pancreatic insufficiency and decreased bile acids lead to malabsorption of critical lipid-soluble antioxidants, such as carotenoids, tocopherols, and coenzyme Q-10[30].

The elements for adequate management of nutritional status in the patient with CF are the following: a) evaluation of BMI or the weight/height ratio in all patients; b) enzyme replacement therapy in pancreatic insufficiency; c) replacement therapy of lipid-soluble vitamins (A, D, E, K); d) hypercaloric and hyperproteic regimen to maintain metabolic goals; e) maintenance of bone health; f) replacement of bile salts in case of liver disease; g) treatment of diabetes mellitus.

Management in a specialized multidisciplinary center

It is recommended that CF patients be managed in a specialized center with the following characteristics and staff: CF specialists, a team of support specialists, a coordinating nurse, infrastructure, laboratories, and integrated outpatient care.

Children with CF regularly require hospitalization, either electively or due to acute pulmonary exacerbations or deterioration of their health status. Criteria for hospitalization are increased frequency of productive cough, increased amount or changes in the presence of sputum, increased respiratory rate, dyspnea at rest, hypoxia, marked decrease in a vesicular murmur, new changes in chest X-ray, deterioration of pulmonary function tests, weight loss or inadequate weight gain, hemoptysis[52]. As the patient progresses to advanced lung disease, options for care and prognosis should be discussed. Among these options is lung transplantation, which should be of both lungs to avoid foci of infection that could damage the transplanted lung.

The following are the referral thresholds recommended by the Cystic Fibrosis Foundation:

- In patients > 18 years:
  a. FEV1 < 50% of the predicted value and rapidly declining
  b. FEV1 < 40% of the predicted value and any of the following markers of shortened survival: > 2 exacerbations per year requiring intravenous antibiotics, massive hemoptysis > 240 mL requiring intensive care unit admission or bronchial artery embolization, pneumothorax, BMI < 18
  c. FEV1 < 30% of the predicted value
- In patients < 18 years:
  a. FEV1 < 50% of the predicted value and rapidly declining
  b. FEV1 < 50% of the predicted value with any of the above markers of shortened survival or malnutrition
  c. FEV1 < 40% of the predicted value
- In all patients, any of the following, regardless of FEV1:
  a. 6-minute walk test < 400 m
  b. Hypoxemia (SpO2 < 88% or PaO2 < 55 mmHg) at rest or with exertion
  c. Hypercarbia (PaCO2 > 50 mmHg) confirmed on arterial blood gases
  d. Pulmonary artery systolic pressure > 50 mmHg on echocardiogram or evidence of right ventricular dysfunction in the absence of tricuspid regurgitant jet
  e. Any exacerbation requiring positive pressure ventilation
- Other factors to be considered for the possibility of earlier transplantation, even when other thresholds are not met, are as follows:
  a. Female sex, especially younger females
  b. Short stature (height < 162 cm)
  c. Liver cirrhosis or chronic kidney disease may require consideration of multiple-organ transplantation and may affect the timing or choice of transplant center[53].

Current therapies

At present, therapies to correct changes in the *CFTR* gene are focused on preventing a specific pathogenic variant from restoring messenger RNA levels (class I variants), correcting the folding and trafficking of CFTR to the apical plasma membrane (correctors for class II variants), or increasing CFTR channel function (enhancement therapy for class III variants and any variants with residual function at the apical plasma membrane). Other therapies in preclinical development are directed toward non-specific variants and include the following: gene therapy with viral and non-viral vectors (nanocarriers such as liposomes, dendrimers, exosomes); genome editing using zinc finger nuclease (ZFN) systems, effector nucleases such as transcription activators (TALENs) or CRISPR/Cas9; antisense oligonucleotides or small interfering RNAs to selectively inhibit ENaC expression; or stem cell therapy to repair airway tissue. Based on these options, personalized and more effective therapy for the CF patient can be determined[14,54,55].

Personalized treatment strategies include:

a. Agents that act through reading target premature stop codon changes, such as aminoglycosides, although

they are limited due to their ototoxicity and nephrotoxicity. NB124 restored 7% of CFTR function in respiratory cell lines with G542X, R553X, R1162X, and W1282X variants; PTC124 (Atularen®), for the G442X variant, showed mixed results and no improvement, and RCT101 used nanoparticle-transported suppressor transfer RNA[56].

b. Calcium-activated chloride channel agents (CaCCs) increase intracellular calcium release. These agents include duramycin and denufosol[14].
c. ENaC inhibitors block sodium channels used in combination with modulators. First-generation inhibitors include amiloride; second-generation inhibitors include benzamil and phenamil; third-generation inhibitors include GS-9411 and SPX-101. Camostat also indirectly inhibits ENaC by reducing Na+ transport through pulmonary epithelial cells[14].
d. CFTR modulators are drugs that correct protein folding, trafficking to the plasma membrane, or CFTR protein function caused by specific pathogenic variants in the *CFTR* gene. They are divided into the following groups:
   - Enhancers. They increase the probability of channel opening and enhance CFTR function, such as ATP analogs, IBMX (3-isobutyl-1-methylxanthine), genistein, PT1-808, GLPG1837, QBW251, and VX-770. VX-770 or ivacaftor prolongs the duration of channel opening, improves ion transport through protein channels making secreted mucus more fluid, decreases respiratory symptoms and the number of severe respiratory infections, increases FEV1 and weight, and decreases sweat chloride. It is authorized to treat CF caused only by specific pathogenic variants[44,54,57,58].
   - Correctors. They improve the folding defect, cellular processing, and trafficking of CFTR through the endoplasmic reticulum to the apical plasma membrane and increase CFTR expression on the cell surface, such as the chaperones 4-phenylbutyrate, curcumin, miglustat, and FDL169. VX-809 or lumacaftor increases chloride secretion by 14-25% for p.F508del homozygotes, but without clear clinical improvement, so some studies combine it with VX-770 (Orkambi®), although without adequate efficacy. VX-661 (tezacaftor) is also used for the p.F508del variant in homo or heterozygous state with variants with residual function, and combined with VX-770 (Symdeko®), a mean absolute improvement of 6.8% was obtained. Other correctors are currently being investigated, such as elexacaftor either alone or in double or triple combination (Trikafta®), apparently with better results in CFTR function[44,54,59].
   - Amplifiers. These agents stimulate CFR protein expression and are applied in class V variants. They can be used in combination with enhancers and correctors such as PTI-428[54].
   - Stabilizers. These molecules rectify protein instability, increase CFTR time at the plasma membrane, and decrease its degradation in the endoplasmic reticulum, such as hepatocyte growth factor, S-nitrosoglutathione (GSNO), and cavosonstat (N91115, an inhibitor of S-nitrosoglutathione reductase for p.F508del homozygotes)[54,60,61].

In conclusion, the measurement of IRT in the neonatal screen has allowed early diagnosis of patients with CF. However, these efforts imply challenges to homogenize diagnostic criteria and achieve more timely management, including the three pillars of treatment, to improve the quality and survival of CF patients. Research also offers new challenges and ethical issues due to its scope, but above all, a cure through precision medicine, a dream whose achievement we believe is not far off.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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ARTÍCULO DE REVISIÓN

Síndrome de disfunción de órganos y adaptación mitocondrial en el paciente séptico

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Resumen

Piedra angular para la sobrevida y la evolución de los organismos es su capacidad de mantener un adecuado balance energético, así como también que las células respondan y se adapten al estrés ambiental. Por ello, ante la presencia de diversos factores se origina una respuesta de protección celular mediante la activación de señalización dependiente de la función mitocondrial. Sin embargo, esta reacción, esencial para la supervivencia individual de las células, puede ser perjudicial para la función orgánica (adaptación inadecuada), transformando el estrecho equilibrio entre ambas en el eje patogénico de la disfunción orgánica y su eventual recuperación en el paciente séptico. Las alteraciones macrocirculatorias y microcirculatorias contribuyen, indudablemente, a la disfunción orgánica en la etapa precoz del choque séptico, mientras que la falla metabólica-bioenergética intrínseca (hipoxia citopática) perpetúa una función celular inadecuada. Por lo tanto, la disfunción mitocondrial es un proceso clave en la inducción del síndrome de disfunción multiorgánica en el paciente séptico. Este síndrome puede considerarse como un complejo fenómeno adaptativo hipometabólico ante un estímulo inflamatorio excesivo y prolongado, para lograr la regulación de la homeostasis energética y la preservación de la función de los órganos. En el futuro, debería producirse una transición entre las opciones terapéuticas actuales consensuadas, que se limitan al control del foco infeccioso y el soporte hemodinámico y vital, hacia una reanimación metabólica basada en las alteraciones moleculares y genéticas desencadenadas por la infección.

Palabras clave: *Mitocondria. Sepsis. Síndrome de disfunción multiorgánica. Adaptación metabólica. Estrés oxidativo.*

Organ dysfunction syndrome and mitochondrial adaptation in the septic patient

Abstract

The ability to maintain an adequate energy balance and to respond and adapt to environmental stress at the cellular level are cornerstones for the survival and evolution of organisms. Therefore, in the presence of various factors, a cellular protection response is triggered by activation of mitochondrial function-dependent signaling. However, this essential reaction for individual cell survival can be detrimental to organ function (maladaptation), transforming the close balance between the two into the pathogenetic axis of organ dysfunction and eventual recovery in septic patients. Macrocirculatory and microcirculatory disruption undoubtedly contributes to organ dysfunction in the early stage of septic shock, while intrinsic metabolic-bioenergetic failure (cytopathic hypoxia) perpetuates inadequate cellular function. Therefore, mitochondrial dysfunction is a key process in the induction of multiple organ dysfunction syndrome in the septic patient. This syndrome can be considered as

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a complex hypometabolic adaptive phenomenon in the face of excessive and prolonged inflammatory stimulus to achieve regulation of energy homeostasis and preservation of organ function. In the future, there should be a transition from the current consensus therapeutic options, which are limited to control of the infectious focus, hemodynamic and life support, to metabolic resuscitation based on the molecular and genetic alterations triggered by the infection.

Keywords: *Mitochondria. Sepsis. Multiple organ failure. Metabolic adaption. Oxidative stress.*

Introducción

Existe consenso en que la resucitación hemodinámica en el niño con choque séptico debe ser precoz y protocolizada[1]. Asimismo, la correcta y oportuna reanimación macrocirculatoria y microcirculatoria es de vital importancia para el pronóstico[2-4].

El síndrome de disfunción multiorgánica (SDMO) se caracteriza por la falla simultánea de dos o más órganos o sistemas[5]. El desarrollo de SDMO es común en los pacientes ingresados en la unidad de cuidados intensivos (UCI). Dependiendo de la población estudiada, los criterios diagnósticos empleados y el fenotipo analizado en los pacientes con sepsis, la incidencia y la mortalidad son variables. El estudio SPROUT[6] reportó un 25% de mortalidad hospitalaria por sepsis grave; de esta cohorte, el 58% presentó SDMO en el día de su reconocimiento, y el 40% falleció durante la hospitalización o desarrolló un nuevo o progresivo SDMO dentro de la semana siguiente. Villeneuve, et al.[7] monitorizaron prospectivamente la ocurrencia diaria de SDMO en 842 pacientes de UCI. Según los criterios diagnósticos de Proulx y los de Goldstein, estos autores reportaron la existencia de SDMO en el 21.4% y el 37.3%, respectivamente. Sin embargo, la proporción de pacientes con SDMO al momento de su admisión y que fallecieron dentro de los 90 días siguientes fue mayor en los diagnosticados con los criterios de Proulx. En fecha más reciente, un estudio nepalés encontró SDMO en el 51% de los pacientes admitidos en la UCI[8].

En ocasiones, a pesar de obtener adecuadas metas de resucitación (hemodinámicas y metabólicas) y de un oportuno soporte vital, muchos pacientes con sepsis desarrollan SDMO y fallecen[9-13]. Esto sugiere la participación de otros mecanismos fisiopatológicos[14,15], como la hipoxia citopática o, más precisamente, la disoxia citopática, que se origina por un desacoplamiento del sistema de producción energética celular (fosforilación oxidativa)[16,17]. Se ha propuesto, a modo de hipótesis, que la disfunción mitocondrial es una alteración relevante en el desarrollo de la falla orgánica inducida por sepsis, aunque no se encuentra totalmente caracterizada y su presencia no es necesariamente evidencia de causalidad[14]. No obstante, los trastornos metabólicos descritos sugieren que la disfunción mitocondrial podría ser un mecanismo involucrado[18]. Asimismo, la determinación de su papel (patogénico o adaptativo) —es decir, la supresión de actividades dependientes de energía en favor de otras esenciales para la sobrevida celular— es controversial[19,20]. Actualmente existe evidencia clínica de una mayor deficiencia bioenergética[21,22] en los pacientes con sepsis que fallecen, lo que sugiere que la disfunción mitocondrial es un mecanismo fisiopatológico trascendente que, además, explicaría la presencia de fallas orgánicas en el paciente con choque séptico.

La terapia orientada a la disfunción mitocondrial («resucitación metabólica») parece una opción razonable, posible y promisoria para la prevención y el tratamiento del SDMO[23-25].

El objetivo de la presente revisión es actualizar los conocimientos respecto a las alteraciones mitocondriales, el papel de su adaptación y, finalmente, realizar algunas breves consideraciones referentes a la resucitación mitocondrial en el paciente séptico con SDMO.

Mitocondrias y respiración celular

Las mitocondrias, presentes en todas las células eucariotas, son vestigios de un proceso ancestral endosimbiótico eubacteriano (α-proteobacterias) ocurrido hace más de un billón de años[26,27]. Su número, tamaño y forma pueden variar según el tipo de célula, tejido u órgano. Poseen dos tipos de ácido desoxirribonucleico (ADN): uno nuclear, que codifica la mayoría de las proteínas necesarias para los procesos metabólicos propios de la mitocondria, y otro independiente del genoma, denominado ADN mitocondrial (ADN_{mt}), que contiene un total de 37 genes que codifican para el ácido ribonucleico (ARN) de transferencia (22 tARN), ARN ribosómicos (2 rARN) y ARN mensajeros (13 proteínas componentes del sistema de fosforilación oxidativa). Esta última característica es única y diferencia a la mitocondria de cualquier otro tipo de organelo. Además, el ADN_{mt} contiene dinucleótidos CpG (islas CpG) hipometilados que se asemejan al CpG del ADN

bacteriano y son fundamentales en la activación de las vías de señalización y propagación de la inflamación[28].

La estructura de la mitocondria está formada por dos membranas: una externa, lisa y que pertenece a la célula, y otra interna, que se encuentra plegada formando crestas mitocondriales, lo que le permite incrementar su superficie (estimada en 14,000 m^2 de membrana interna en el ser humano)[27]. Esta capa interna pertenece al organelo y es impermeable (carece de poros). En ella se ubican las proteínas de la cadena transportadora de electrones (CTE), las proteínas transportadoras ubiquinona (coenzima Q) y citocromo C (cit C), y los oxisomas o partículas F (complejo enzimático adenosín trifosfato [ATP] sintasa). A su vez, la presencia de una doble membrana permite definir dos espacios, el espacio intermembrana y la matriz mitocondrial, rodeada por la membrana interna, que contiene, entre otras enzimas, las del ciclo de Krebs, el ADN_{mt} y los ribosomas.

La función principal de las mitocondrias es la respiración celular, cuyo fin es producir energía. En la glucólisis, la rotura de una molécula de glucosa origina dos moléculas de ácido pirúvico, que se convierten en acetil-CoA por oxidación y descarboxilación (a través del sistema enzimático piruvato-deshidrogenasa). A su vez, esta se convierte en el principal precursor del ciclo de Krebs. La acetil-CoA dona electrones a la CTE, principalmente al complejo I.

La CTE consiste en un grupo de proteínas y moléculas organizadas en cuatro grandes complejos (I-IV), que se reducen y oxidan al transferirse entre ellas electrones procedentes de las formas reducidas de la nicotinamida adenina dinucleótido (NADH) y del flavín adenín dinucleótido ($FADH_2$), ambas moléculas originadas en las fases más tempranas de la respiración celular.

Como resultado, la energía liberada en la oxidación de estas moléculas, al ser mayor que la consumida en la reducción, se utiliza para bombear protones desde los complejos I, III y IV al espacio intermembrana, generando así un gradiente electroquímico (potencial de membrana de aproximadamente –180 mV). El complejo IV, o citocromo C oxidasa, capta los electrones y los transfiere al oxígeno molecular, el cual es su aceptor final. Esta enzima es la encargada de la mayor parte del consumo de oxígeno del organismo (respiración).

La energía almacenada en este gradiente electroquímico, denominada fuerza protón-motriz, se debe a la diferencia de concentración de protones entre la matriz mitocondrial y el espacio intermembrana, denominada quimiosmosis, permitiendo la traslocación de protones desde el espacio intermembrana hacia la matriz a través de la proteína transmembrana ATP sintasa. La ATP sintasa cataliza la adición de un fosfato al adenosín difosfato (ADP) para finalmente sintetizar ATP. En conjunto, tanto el transporte de electrones como la quimiosmosis constituyen la fosforilación oxidativa (Figura 1).

En condiciones aeróbicas, la eficiente producción energética durante la fosforilación oxidativa representa un riesgo para la célula a consecuencia de la capacidad oxidante del oxígeno y de la formación de pequeñas cantidades de radicales libres (secundaria a la inevitable fuga de electrones) que dañan a las biomoléculas, ocasionando un efecto nocivo en la función y la sobrevida celular[29]. No obstante, en el paciente crítico con sepsis se ha descrito una importante reprogramación transcriptómica de genes mitocondriales[30] y la activación de diversos mecanismos homeostáticos redox con el objetivo final de lograr una «autoprotección celular»[31-33].

Homeostasis mitocondrial en el sujeto sano

Con excepción de los glóbulos rojos, todas las células del cuerpo poseen mitocondrias que desempeñan un papel clave en el metabolismo celular. Estas participan en más del 90% de la producción energética mediante la fosforilación oxidativa[34], que es un proceso por el cual las enzimas de la CTE transforman el potencial eléctrico transmembrana ($\Delta\Psi m$) en energía bioquímica. Junto con la fosforilación oxidativa basal, existe una capacidad respiratoria disponible que es la reserva de fosforilación mitocondrial destinada a responder al incremento de las demandas metabólicas (índice de reserva bioenergética).

La función mitocondrial varía en respuesta a factores intracelulares y extracelulares que regulan la homeostasis bioenergética celular. En condiciones de normalidad, el consumo de oxígeno a través de la CTE se encuentra estrechamente ligado a la producción de ATP (sustrato energético de los procesos metabólicos celulares) y regulado por la demanda metabólica (respiración acoplada).

Por otra parte, el oxígeno no empleado en la fosforilación oxidativa (1% del consumo de oxígeno mitocondrial) se destina a la producción de especies reactivas de oxígeno. Esta producción está estrictamente controlada por varias enzimas antioxidantes, como la

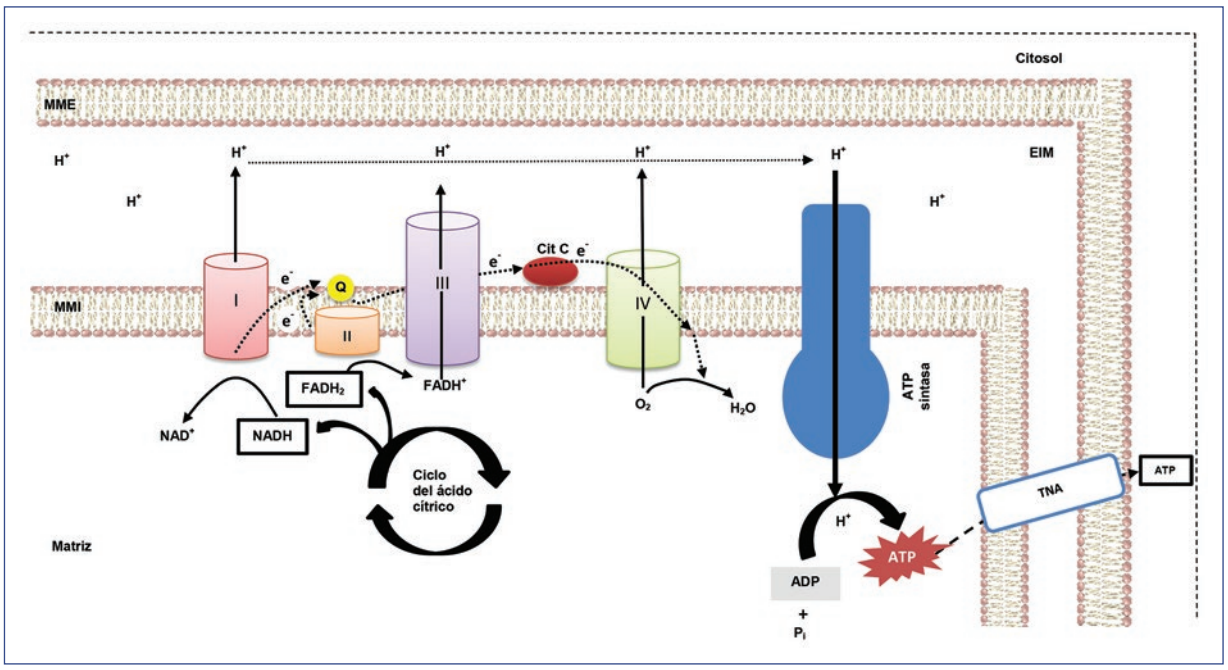

Figura 1. Representación esquemática de la fosforilación oxidativa y su interacción con el ciclo de Krebs. La cadena transportadora de electrones y la ATP sintasa se localizan insertadas en la membrana interna de la mitocondria. Los números romanos indican cada uno de los complejos de la cadena respiratoria. ADP: adenosín difosfato; ATP: adenosín trifosfato; Cit C: citocromo C; $FADH^+$: flavín adenín dinucleótido forma oxidada; $FADH_2$: flavín adenín dinucleótido forma reducida; H^+: protón; H_2O: agua; MME: membrana mitocondrial externa; MMI: membrana mitocondrial interna; NAD^+: nicotinamida adenina dinucleótido forma oxidada; $NADH^+$: nicotinamida adenina dinucleótido forma reducida; O_2: oxígeno; Pi: fosfato inorgánico; Q: coenzima Q; TNA: translocador de nucleótidos de adenina.

superóxido dismutasa manganeso o la glutatión oxidasa. Estas enzimas pueden desempeñar una función protectora o nociva en la señalización mitocondrial, dependiendo de la magnitud y la duración de su producción[35,36].

Finalmente, la homeostasis mitocondrial requiere un perfecto equilibrio entre la mitofagia y la biogénesis (incremento de la masa mitocondrial celular).

Mortalidad por choque séptico en pediatría

A pesar del conocimiento adquirido en las últimas décadas, la mortalidad hospitalaria de los niños con sepsis se mantiene elevada: del 19% en los países desarrollados y del 32% en aquellos en vías de desarrollo[37]. Las razones por las cuales los niños fallecen son variables y, por lo tanto, los mecanismos por los que se puede esperar que una determinada intervención afecte la mortalidad requieren especial consideración. A modo de ejemplo, la mortalidad temprana debería ser menos frecuente debido a la precocidad en el reconocimiento y el inicio de la terapia de reanimación en el paciente séptico[38]. En contraparte, la mortalidad tardía (> 3 días) es atribuible, principalmente, a la persistencia del SDMO[39]. Así, las nuevas terapias dirigidas a la disfunción orgánica deberían reducir la mortalidad en aquellos niños que logran una estabilización inicial, pero que posteriormente no mejoran.

Síndrome de distrés microcirculatorio y mitocondrial

El paciente con sepsis que presenta una pobre respuesta terapéutica habitualmente tiene unas variables macrocirculatorias relativamente normales, pero con signos microcirculatorios asociados a un mal pronóstico, condición que se ha denominado síndrome de distrés microcirculatorio y mitocondrial (SDMM)[40,41]. Lo fundamental de esta propuesta es la presencia de hipoxia tisular que persiste tras la normalización de las variables de la macrocirculación[42].

La hipoxia citopática se refiere a la alteración en la producción de ATP a pesar de la existencia de unos

valores normales o supranormales de oxígeno tisular[43,44]. Esta condición puede deberse a factores tales como la disminución de la entrega de sustratos clave o la inhibición de etapas dentro del ciclo de Krebs, la alteración de las enzimas de la CTE o el desacoplamiento de la fosforilación oxidativa resultando en la producción de calor más que en la formación de ATP[16,45].

Dos mecanismos se han propuesto para explicar el desarrollo del SDMM. El primero es una alteración de la microcirculación que se caracteriza por la disminución de la densidad de los capilares funcionales. De este modo, se incrementan tanto la distancia de difusión del oxígeno[46] como la heterogeneidad capilar, generando un *shunt* microcirculatorio[47], lo que implica una reprogramación metabólica: el cambio en la generación de ATP desde la fosforilación oxidativa a la glucólisis aerobia (efecto Warburg) y la inhibición de la CTE[48]; este segundo mecanismo es el que se ha planteado para el desarrollo del SDMM.

Dicha propuesta conceptual permitiría la identificación específica del compartimento donde ocurre la falla, y posibilitaría la instauración de estrategias terapéuticas adecuadas; las actuales están dirigidas casi en forma exclusiva a la corrección de la macrohemodinamia. Por consiguiente, el choque séptico, en parte, podría describirse fisiopatológicamente como un SDMM.

Respuesta inmunitaria celular y respiración mitocondrial

La respuesta protectora celular se desencadena por la activación de señales de «peligro» ante diferentes estímulos[49]. Existe evidencia de que los patrones moleculares asociados a patógenos microbianos (PAMP, *pathogen-associated molecular patterns*) y los patrones moleculares asociados al daño (DAMP, *damage-associated molecular patterns*), al ser identificados por los receptores de reconocimiento de patrones (PRR, *pattern-recognition receptors*), como los tipo Toll (TLR, *Toll-like receptors*), presentes en las células que participan en el sistema inmunitario innato, inician una respuesta sistémica por medio de las vías MyD88/TRADD/NF-κB y JAK1/STAT3 (*Janus kinase 1-signal transducer and activator of transcription 3*)[50]. La activación de los TLR facilita la activación de la vía dependiente y de la vía independiente de MyD88. En la vía independiente (MyD88/TRADD/NF-κB) se forma un complejo de señalización con TRADD (*TNF-receptor asocciated via death domain*) y otras proteínas acopladoras que conduce a la producción del interferón tipo I (IFN-I) y a la expresión de genes inducibles por IFN, y también involucra una fase tardía de activación de NF-κB[51]. De igual manera, diferentes citocinas utilizan la vía de señalización de JAK1/STAT3 para la transducción de señales desde la membrana celular al núcleo. Una vez que la citocina se une a su receptor, la JAK se activa, lo que estimula al factor de transcripción STAT, que a su vez induce a nivel nuclear los genes implicados en la producción de citocinas, las cuales son indispensables para la inmunidad innata y adaptativa[52,53]. Probablemente esta respuesta celular es modulada por la mitocondria[54].

La activación de las células inmunitarias vía TLR aumenta la transcripción de citocinas proinflamatorias y antiinflamatorias, del factor de necrosis tumoral (TNF, *tumor necrosis factor*), de interleucinas (IL), de especies reactivas de oxígeno (como peróxido de hidrógeno o radical hidroxilo) y de especies reactivas de nitrógeno, incrementando el estrés oxidativo y nitrosativo. En este último ocurre un aumento de la producción de óxido nítrico que determina su reacción con el anión superóxido, originando peroxinitrito, especie altamente reactiva capaz de oxidar y nitrar componentes celulares y tisulares[55]. Este mecanismo, junto con el estrés oxidativo, ocasiona daño proteico y del ADN, como el bloqueo de la respiración mitocondrial, originando la disfunción mitocondrial inducida por sepsis (Figura 2)[42,56,57].

Por otra parte, los tratamientos empleados sistemáticamente en el paciente séptico, como antibióticos bactericidas[58] y catecolaminas[59], también pueden inhibir la respiración mitocondrial. Las catecolaminas, además de su acción hemodinámica, presentan propiedades que afectan a la inmunidad y al metabolismo del paciente grave[60]. En modelos animales clínicamente relevantes se ha observado una alteración de la respiración mitocondrial relacionada directamente con la dosis requerida de epinefrina[61,62]. A futuro, esta observación permitiría otra perspectiva sobre su utilización (descatecolaminización)[59,63].

Propagación de la inflamación y mitocondrias

Las mitocondrias desempeñan un papel trascendental tanto en la propagación sistémica de la inflamación como en la disfunción de órganos distantes. El ADN_{mt} es particularmente vulnerable al daño ocasionado por el estrés oxidativo y los mediadores proinflamatorios,

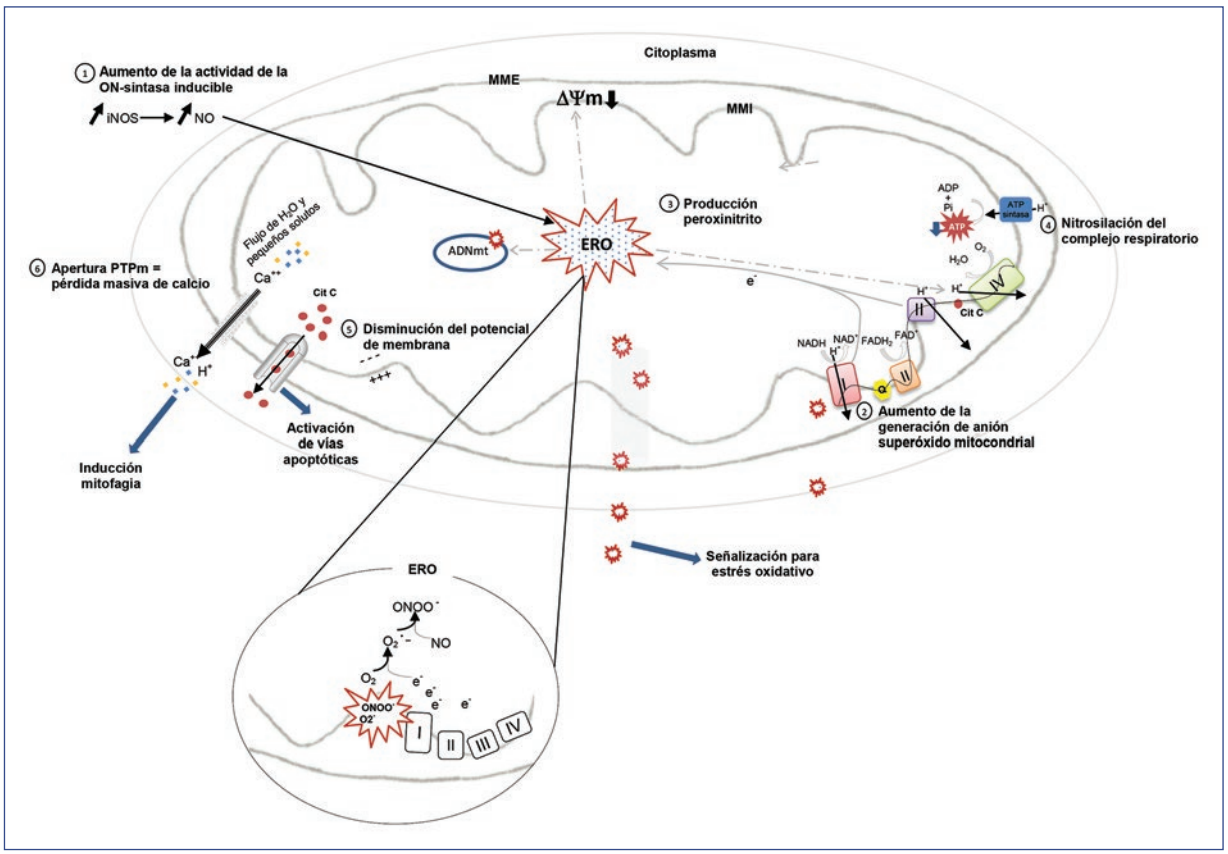

Figura 2. Sucesión de eventos causantes de disfunción mitocondrial en el paciente con sepsis. Los números romanos indican los complejos de la cadena respiratoria (I-IV). 1) Aumento de la actividad de la enzima óxido nítrico sintasa inducible. 2) Incremento de la producción de anión superóxido mitocondrial. 3) Producción de peroxinitrito. 4) Nitrosilación del complejo respiratorio. 5) Disminución del potencial de membrana. 6) Apertura de poro de transición mitocondrial. La disfunción de la cadena transportadora de electrones (CTE) da como resultado una producción intramitocondrial extrema de especies reactivas de oxígeno (ERO), lo que puede conducir a un daño oxidativo en la membrana, en la actividad de la CTE y el ADN mitocondrial. El incremento de permeabilidad de la membrana mitocondrial produce la liberación de citocromo C en el citosol; lo que conduce a apoptosis. El aumento de la permeabilidad de la membrana también hace que exista reflujo de Ca^{++} hacia el citoplasma. Las ERO mitocondriales también pueden transportarse al citoplasma e inducir estrés oxidativo, seguido de la activación de vías de señalización de estrés oxidativo que modulan diversas funciones celulares. Finalmente, las ERO liberadas en el espacio extracelular dañarán a otras células y órganos (DAMP, *damage-associated molecular patterns*). ADN_{mt}: ácido desoxirribonucleico mitocondrial; ADP: adenosín difosfato; ATP: adenosín trifosfato; Ca^{++}: calcio ionizado; e^{-}: electrón; ERO: especies reactivas de oxígeno; FAD^{+}: flavín adenín dinucleótido forma oxidada; $FADH_2$: flavín adenín dinucleótido forma reducida; H^{+}: protón; H_2O: agua; iNOS: óxido nítrico sintasa inducible; MME: membrana mitocondrial externa; MMI: membrana mitocondrial interna; NAD^{+}: nicotinamida adenina dinucleótido forma oxidada; $NADH^{+}$: nicotinamida adenina dinucleótido forma reducida; NO: óxido nítrico; O_2: oxígeno; O_2^{-}: anión superóxido; $ONOO^{-}$: peroxinitrito; Pi: fosfato inorgánico; PTPm: poro de transición de permeabilidad mitocondrial; $\Delta\psi m$: potencial eléctrico transmembrana.

dada su proximidad con la CTE, la carencia de histonas protectoras, la limitada eficiencia de sus mecanismos de reparación y contener exclusivamente regiones codificadoras[64,65]. De este modo, el ADN_{mt} que se ha fragmentado es transportado a la matriz mitocondrial o al espacio extracelular (ADN_{mt} extracelular), activando diversas vías inflamatorias debido a su similitud con el ADN bacteriano[66-69].

Una vez que el ADN_{mt} ha alcanzado el citosol, se promueve la formación del inflamasoma NLRP3 *(nod-like receptor-P3 inflammasome),* un complejo multimérico intracelular que desencadena la activación de caspasas inflamatorias, que a su vez generan la maduración proteolítica de la IL-1β y la IL-18, además de promover la expresión de IL-6 y TNF-α, ambos procesos clave en la respuesta inmunitaria innata[70].

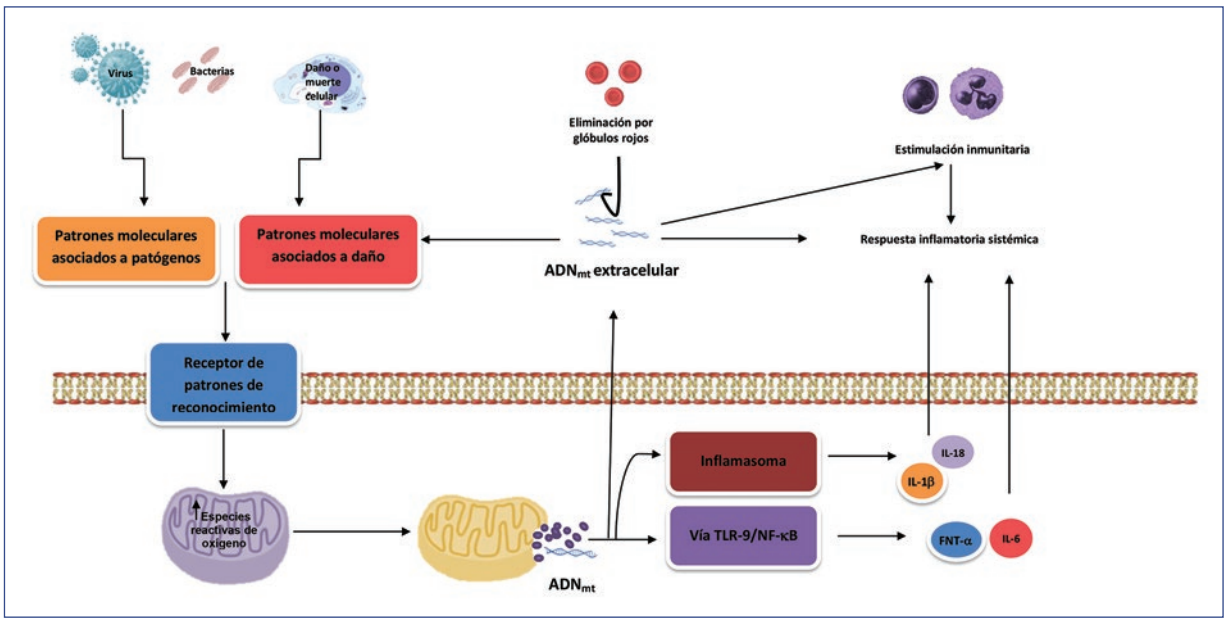

Figura 3. Representación de la producción y liberación del ácido desoxirribonucleico mitocondrial (ADN_{mt}) extracelular. Los patrones moleculares asociados a patógenos (PAMP, *pathogen-associated molecular patterns*) y los patrones moleculares asociados al daño (DAMP, *damage-associated molecular patterns*), los cuales han sido liberados ante una infección o daño celular, respectivamente, ocasionan la estimulación de receptores de reconocimiento de patrones (PRR, *pattern recognition receptors*). Posteriormente se origina la producción de especies reactivas de oxígeno (ERO) mitocondrial, que dañan y fragmentan el ADN_{mt} permitiendo su descompartimentalización y llegada al citosol. Este ADN_{mt} actúa como un potente DAMP, estimulando el inflamasoma o la vía dependiente de los receptores Toll (TLR, *Toll-like receptor*), TLR-9/factor nuclear-κβ, ocasionando la producción de citocinas proinflamatorias. El ADN_{mt} puede alcanzar el medio extracelular, donde propaga la respuesta inflamatoria inicial al ser reconocido como DAMP por células inmunitarias y no inmunitarias. Se representa la eliminación del ADN_{mt} circulante (*cell-free* ADN_{mt}) por los glóbulos rojos (vía TLR-9). IL-6: interleucina 6; IL-18: interleucina 8; IL-1β: interleucina 1β; FNT-α: factor de necrosis tumoral-α. (Modificada de Harrington, et al.[75].)

En la circulación, el ADN_{mt} es reconocido como un potente DAMP[71], desencadenando una respuesta inflamatoria sistémica (Figura 3)[67,72,73]. Los estudios clínicos han demostrado la existencia de una asociación estadística entre sus niveles circulantes y la mortalidad, aunque la mayoría de los reportes son de series relativamente pequeñas y carecen de un protocolo estandarizado para su medición, aspectos que deben considerarse antes de establecer su real utilidad clínica como posible biomarcador[74,75]. En fecha más reciente se ha evaluado su valor pronóstico[76] y también su correlación con el desarrollo de SDMO en niños con sepsis[77].

Disfunción mitocondrial en el paciente con sepsis

La relación entre la función mitocondrial y el SDMO aún no se ha esclarecido por completo; sin embargo, existe conocimiento de diversos papeles de las mitocondrias durante la sepsis (Tabla 1).

Las células del paciente con SDMO son incapaces de consumir el oxígeno disponible, ocasionando un daño en la CTE que genera un «apagón mitocondrial» y, como consecuencia, se produce deterioro de la bioenergética celular, exacerbación del estrés oxidativo y nitrosativo, incremento de la apoptosis y alteración de vías metabólicas esenciales[78-81]. Estos hallazgos han sido confirmados tanto en modelos animales[21,82] como en humanos[83], lo cual ratifica el papel de la disfunción mitocondrial en la patogenia del SDMO[54]. Brealey, et al.[21] comunicaron menores cantidades de ATP en las biopsias muscular de pacientes fallecidos en comparación con los sobrevivientes. En la misma línea, la demostración de una mayor concentración tisular de oxígeno apoya el papel de la hipoxia citopática en la falla orgánica en el choque séptico[16].

Tabla 1. Funciones mitocondriales en el sujeto sano y durante el desarrollo de sepsis

Metabolismo y señalización celular	
Fosforilación oxidativa	Fuente primaria de VO_2 y VCO_2 Prioridades en el uso de energía: transporte de Na^+ y Ca^{+2}, síntesis proteica, replicación de ADN y ARN
Homeostasis Ca^{+2} intracelular Generación de especies reactivas de oxígeno y nitrógeno	Esencial para el normal funcionamiento celular Riesgo potencial ante su exceso
Daño mitocondrial y reparación	
Apoptosis vía intrínseca: citocromo C	Requiere energía, efecto antiinflamatorio
Necrosis por rotura de membrana	Liberación de ADN_{mt} (efecto proinflamatorio, DAMP) Ocasiona mecanismo de mitofagia
Fusión, fisión y biogénesis mitocondrial	Con el objetivo de mantener la salud mitocondrial

ADN: ácido desoxirribonucleico; ADN_{mt}: ácido desoxirribonucleico mitocondrial; ARN: ácido ribonucleico; DAMP: *damage-associated molecular patterns* (patrones moleculares asociados al daño); VCO_2: producción de dióxido de carbono; VO_2: consumo de oxígeno.

Finalmente, la restauración espontánea o farmacológica de la disfunción mitocondrial se asocia con recuperación del SDMO y con una mayor sobrevida. En concreto, en animales y en humanos[22] se ha evidenciado que se logra la recuperación de la función orgánica y una mayor sobrevida[54] cuando mejoran tanto la biogénesis mitocondrial como la mitofagia[84-87]. No obstante, esto podría tratarse solo de un epifenómeno, pues faltan estudios intervencionales que lo demuestren fehacientemente.

Hibernación celular como causa de disfunción orgánica múltiple

El suministro insuficiente de oxígeno ocasiona hipoxia tisular, mientras que la utilización alterada de este lleva a disoxia. Ambos mecanismos generan una reducción en la producción de ATP, provocando no solo disfunción celular en órganos específicos, sino también pérdida de la integridad celular, ya que mantener su estructura depende de la energía. Así, se podría suponer que, debido a las importantes alteraciones bioquímicas y metabólicas existentes en los pacientes que fallecen, la falla orgánica es consecuencia de una extensa muerte celular[88]. Sin embargo, los estudios *post mortem* han revelado una discordancia entre los hallazgos histológicos y la magnitud de la disfunción orgánica en los pacientes sépticos[89,90].

Lo previamente mencionado, en concomitancia con un flujo sanguíneo preservado y la existencia de una tensión tisular de oxígeno adecuada[91] asociada a un bajo consumo de este, han llevado a cuestionar el papel de la hipoxia tisular como principal mecanismo fisiopatológico en el paciente con SDMO.

Por ello, se necesita un paradigma que pueda explicar la existencia de la disfunción orgánica en ausencia de un daño estructural significativo y, aún más, ante un aporte adecuado de oxígeno[92].

Una consecuencia notable de la activación de las vías de respuesta celular ante la presencia de señales de peligro es la supresión de las actividades dependientes de energía en favor de aquellas que son esenciales para la sobrevida celular, lo que se ha corroborado en cardiomiocitos (hibernación miocárdica)[93,94], hepatocitos[95] y neumocitos (conformidad hipóxica)[96].

En esta misma línea, quizás el fenómeno de parálisis inmunitaria *(vide infra),* descrito en el paciente séptico[97], refleje una hibernación leucocitaria en vista de que la respiración mitocondrial de las células mononucleares periféricas circulantes no puede responder ante un incremento de la demanda metabólica[98-101]. Asimismo, la escasa cantidad de células epiteliales tubulares necróticas observadas en el paciente con falla renal aguda es consistente con el concepto de hibernación epitelial renal[102]. Esta idea no es nueva, pues hace más de cuatro décadas ya se señaló que la falla renal aguda era, más bien, un «éxito» renal agudo, pues esta respuesta adaptativa permitía al riñón «ahorrar» en tareas altamente dependientes de energía (reabsorción tubular), configurando así un mecanismo de protección[103].

El paradigma de la inflamación exacerbada no logra explicar por completo los eventos observados en los pacientes con sepsis. De hecho, durante este proceso también se liberan citocinas antiinflamatorias que buscan regular la respuesta inmunitaria, llegando a desarrollar, en ocasiones, un síndrome de respuesta antiinflamatoria compensatoria (CARS, *compensatory anti-inflammatory response syndrome*). La inmunoparálisis o CARS consiste en una hiperactividad de esta respuesta antiinflamatoria caracterizada por la alteración en la expresión del HLA-DR monocitario (mHLA-DR, *monocytic human leukocyte antigen-DR*), apoptosis linfocitaria y aumento de citocinas reguladoras[104], mecanismos que parecen influir en el desarrollo de infecciones secundarias y la muerte del paciente[105].

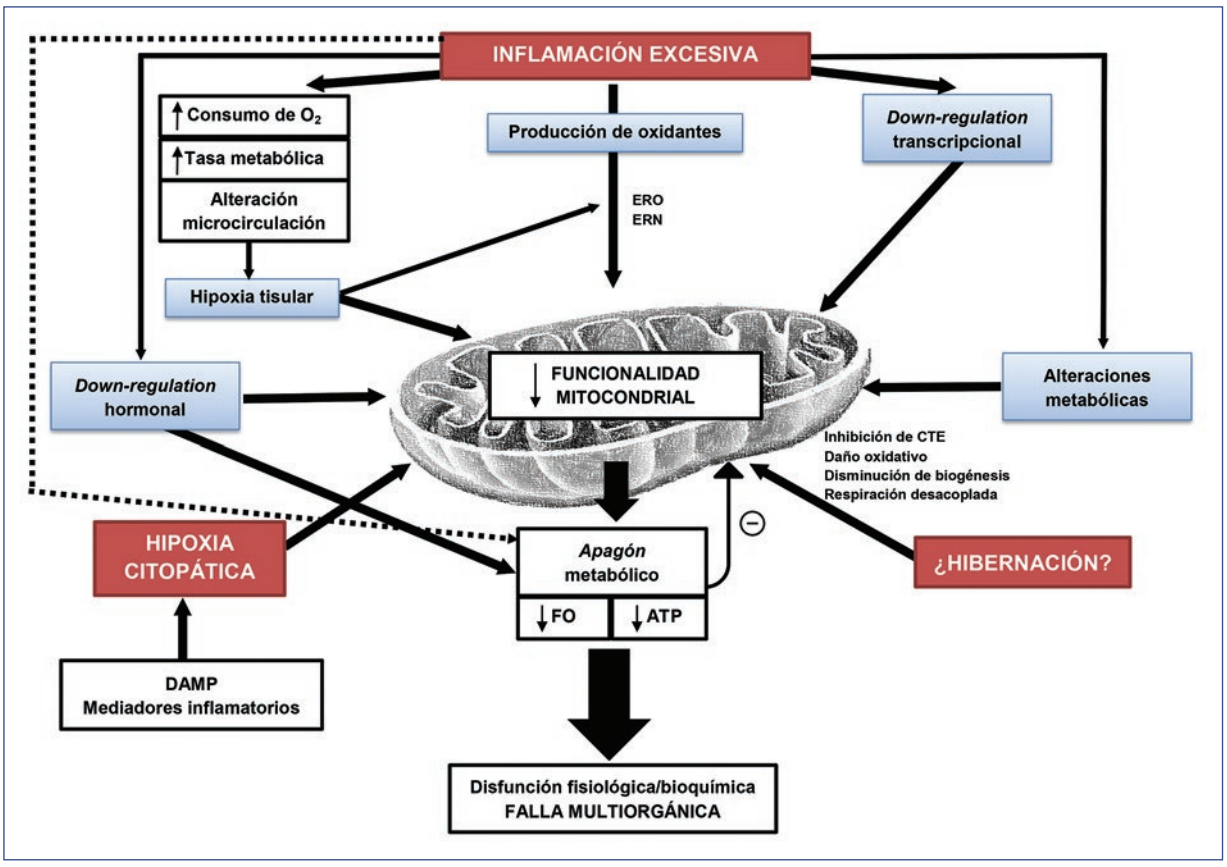

Figura 4. Mecanismos involucrados en la disfunción metabólica y apagón mitocondrial. ATP: adenosín trifosfato; CTE: cadena transportadora de electrones; ERO: especies reactivas de oxígeno; ERN: especies reactivas de nitrógeno; DAMP: *damage-associated molecular patterns;* FO: fosforilación oxidativa; O_2: oxígeno.

Lo previamente señalado sugeriría que el SDMO es un fenómeno más bien de carácter funcional que estructural, basado en una reducción primaria temporal del metabolismo celular[79,106]. Así, la falla multiorgánica puede verse como una respuesta adaptativa y protectora que ayudaría a prevenir la muerte celular (Figura 4).

Carcillo, et al.[107] han señalado que el término «disfunción mitocondrial» sería una denominación errónea, ya que la regulación a la baja o la reducción temporal de la actividad metabólica observada en modelos experimentales probablemente representa una respuesta adaptativa (estado hipometabólico), hallazgo que con frecuencia se observa en los pacientes muy graves[80,108].

Al parecer, esta idea estaría avalada por la observación de que la función orgánica usualmente se restaura (en días a semanas) en los pacientes sobrevivientes de SDMO, incluso en órganos con una pobre respuesta regenerativa, lo que indica que la disminución de la actividad mitocondrial es adaptativa e inicialmente reversible[49,79,106].

El cambio desde el estado de apagón mitocondrial[109] al de activación de la biogénesis[22] se encuentra finamente regulado por diversos factores, los cuales dependerán de la gravedad de la sepsis, de factores genéticos[110], de las características del individuo (edad, enfermedades asociadas) y de la terapia empleada[111].

En suma, el SDMO refleja una respuesta funcional adaptativa, transitoria, protectora y potencialmente reversible, más que una lesión estructural, en el paciente con sepsis[42].

Monitorización de la función mitocondrial

En la actualidad, la evaluación de la función mitocondrial se encuentra limitada al ámbito experimental y preclínico, principalmente mediante métodos *ex vivo,* lo que podría no ser representativo de una situación *in vivo*. Esto se debe a que la mitocondria es un organelo subcelular, y también a la comprensión inexacta y cabal de los procesos bioquímicos complejos que involucran a las reacciones redox, así como a la

Tabla 2. Agentes farmacológicos propuestos para la prevención o la disminución de la disfunción mitocondrial séptica

Relacionados con la matriz mitocondrial y la cadena transportadora de electrones	Antioxidantes mitocondriales y depuradores de radicales libres	Estabilizadores de la membrana mitocondrial	Terapia hormonal y otros
Succinato	Mitoquinona[c, d]	CsA/NIM 811	Glucocorticoides
Glutamina	Mito-Vit-E[c, d]	Tetrametilpirazina	Insulina
ATP-$MgCl^2$	Péptidos SS[c]	Metformina	Melatonina
L-carnitina	Mito-TEMPO[c, d]	Imeglimina	Estrógenos
Coenzima Q (ubiquinona)	Tetrametilpiperidina (tempol)[c]	Ciclosporina	Leptina
Citocromo C	Inhibidores NOS		CeO_2NPs
Cafeína	N-acetilcisteína		
Ácido tióctico (ácido α-lipoico)	Etilpiruvato		
rhTFAM[a]	Inductor HO		
H_2S[b]	Fenol (resveratrol)		
NO[b]	GSH		
CO[b]			

[a]Promotor de la biogénesis.
[b]Gasotransmisor.
[c]Antioxidante sintético exógeno con diana en la mitocondria.
[d]Catión lipófilo.
ATP-$MgCl_2$: adenosín trifosfato-cloruro de magnesio; CeO_2NPs: nanopartículas de óxido de cerio; CO: monóxido de carbono; CsA: ciclosporina A; GSH: glutatión; HO: hemo oxigenasa; H_2S: sulfuro de hidrógeno; NIM 811: N-metil-4-isoleucina; NO: óxido nítrico; NOS: óxido nítrico sintetasa; SS: péptidos Szeto-Schiller; rhTFAM: factor A de transcripción mitocondrial recombinante humano.

incapacidad de realizar mediciones confiables en tiempo real en medios biológicos[112].

Se dispone de técnicas *in vivo*, como la fluorometría para NADH, la espectroscopía por resonancia magnética y la espectroscopía cercana al infrarrojo (NIRS, *near infrared spectroscopy*) para medir el estado redox de la enzima citocromo C oxidasa[113]. Por otra parte, la tensión de oxígeno mitocondrial se puede evaluar en la epidermis mediante la fluorescencia de protoporfirina IX[114].

Aunque la magnitud de la disfunción mitocondrial inducida por la sepsis es variable en los diversos sistemas orgánicos comprometidos[115], existe evidencia experimental en un modelo de choque hemorrágico de que la reducción de la respiración mitocondrial en células mononucleares periféricas se correlaciona con cambios similares en las mitocondrias del riñón y del corazón[116]. Por otro lado, en células mononucleares periféricas de niños sépticos se correlacionó el $\Delta\Psi m$ durante las primeras 48 horas con la magnitud del daño orgánico a la semana. Se evidenció un mayor $\Delta\Psi m$ en aquellos pacientes con función orgánica normal al séptimo día en comparación con los que mostraron persistencia del SDMO posteriormente[83]. Weiss, et al.[117] demostraron que la permanencia de una respiración mitocondrial disminuida en células mononucleares periféricas se asocia con una lenta recuperación de la función orgánica. Sin embargo, en esta misma línea, se requieren mayores estudios para la obtención de resultados concluyentes.

Terapia farmacológica para la disfunción mitocondrial

El listado de los agentes farmacológicos destinados a prevenir o tratar la disfunción mitocondrial en el paciente con sepsis es extenso (Figura 5). Estos pueden ser clasificados de una manera esquemática en las siguientes categorías: entrega de sustratos, cofactores y donantes de electrones favorecedores de la fosforilación oxidativa; aporte de antioxidantes exógenos y depuradores de radicales libres; estabilizadores de la membrana mitocondrial; y terapia hormonal (Tabla 2)[118,119].

Además, es relevante conocer el momento adecuado de su aplicación o uso para una correcta evaluación

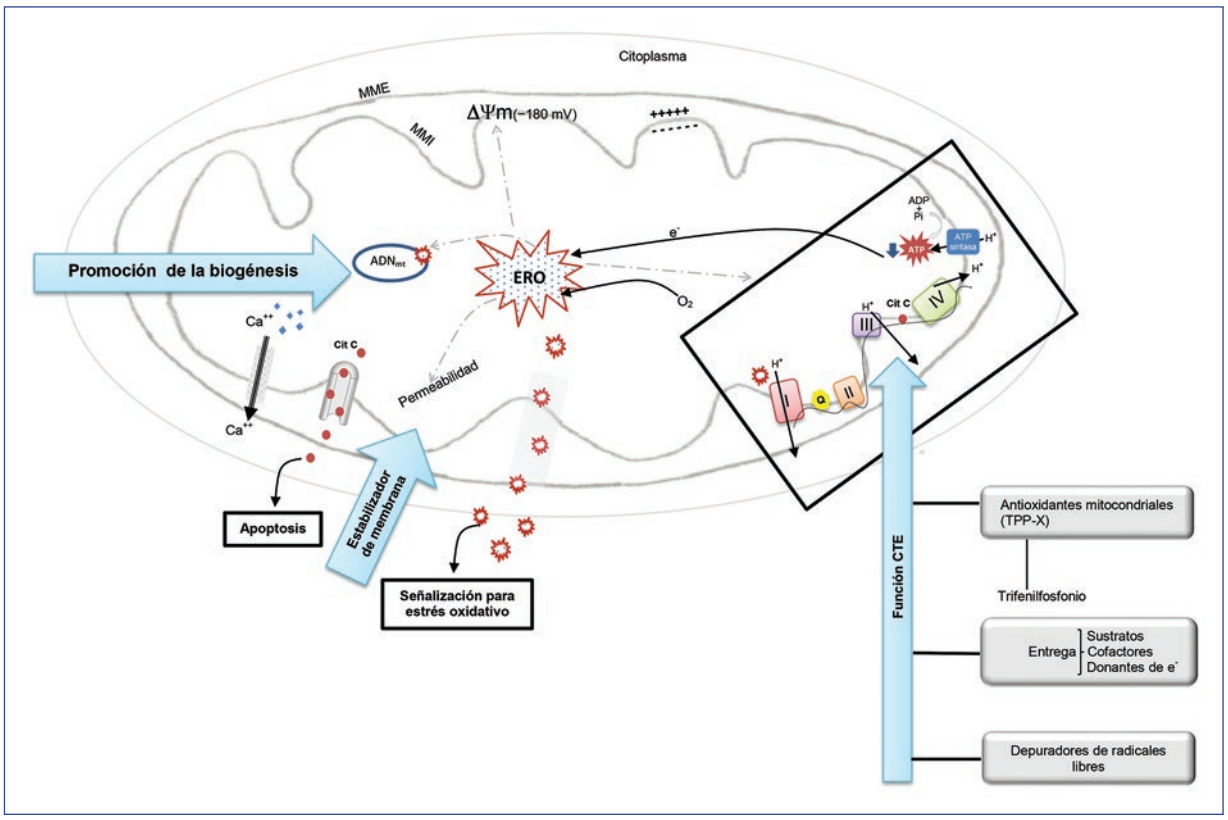

Figura 5. Estrategias terapéuticas con diana en la mitocondria. Los números romanos indican cada complejo de la cadena respiratoria. La terapia más promisoria son los antioxidantes conjugados con cationes (trifenilfosfonio, TPP^+), los cuales se acumulan específicamente en las mitocondrias y mejoran la función de la cadena transportadora de electrones. La estabilización de la membrana inhibe que las especies reactivas de oxígeno provoquen más lesiones y protege a las mitocondrias de la inflamación y la rotura, reduciendo así la fuga de moléculas que causan apoptosis y alteración del calcio en el citoplasma. La promoción de la biogénesis mitocondrial reactiva las expresiones del ADN_{mt}, mejorando así la expresión de proteínas mitocondriales. ADN_{mt}: ácido desoxirribonucleico mitocondrial; ADP: adenosín difosfato; ATP: adenosín trifosfato; Ca^{++}: calcio ionizado; Cit C: citocromo C; e^-: electrón; ERO: especies reactivas de oxígeno; H^+: protón; MME: membrana mitocondrial externa; MMI: membrana mitocondrial interna; O_2: oxígeno; Pi: fosfato inorgánico; Q: coenzima Q; $\Delta\psi m$: potencial eléctrico transmembrana. (Modificada de Zhang, et al.[24].)

de su eficacia: a) prevención y restitución precoz de la disfunción mitocondrial; b) una vez establecida, prevención del colapso energético celular; c) en el periodo de biogénesis mitocondrial; y d) en el periodo de reparación o sustitución de aquellas mitocondrias que se encuentran dañadas.

Experimentalmente, estas terapias han demostrado una disminución del estrés oxidativo y de las citocinas inflamatorias circulantes, junto con una restauración de la generación de ATP. Se han reportado los hallazgos de estudios preclínicos en modelos animales que han evaluado el efecto de diversos tipos de agentes sobre la función orgánica (Tabla 3)[120-124]. No obstante, aún queda pendiente la valoración de su eficacia clínica[125-127].

A futuro

Un desafío en el manejo de los pacientes con sepsis muy graves es reconocer el momento en que los esfuerzos terapéuticos, muchos de ellos orientados a la búsqueda de la normalidad fisiológica, pueden inducir modificaciones dañinas para la adecuada puesta en marcha del intento alostático adaptativo[128,129].

La pronta identificación y el conocimiento del subgrupo de pacientes sépticos que se beneficiarían de una resucitación metabólica es esperable que se obtengan a través de la medicina de precisión mediante transcriptómica, metabolómica y farmacogenómica[31,130]. Como la mayoría de las intervenciones terapéuticas en el paciente séptico, el momento en que

Tabla 3. Trabajos experimentales en animales que evalúan el uso de diversas terapias farmacológicas antioxidantes mitocondriales y no antioxidantes

Autor, año[ref]	Sepsis	Animal/ modelo	Agente utilizado	Efectos orgánicos	Efectos clínicos observados	Mortalidad
Lowes, et al., 2008[120]	Sí	Ratones LPS-PG	Antioxidante mitocondrial (MitoQ)	Disminución de marcadores bioquímicos de disfunción hepática Disminución de marcadores bioquímicos de disfunción renal	—	—
Patil, et al., 2014[121]	Sí	Ratones LCP	Antioxidante mitocondrial (Mito-TEMPO)	Mejoría de la microcirculación renal Mejoría de la tasa de filtración glomerular	—	Incremento a las 96 h en la sobrevida del 40% al 80%
Selvaraj, et al., 2015[122]	Sí	Ratones LPS	No antioxidante (CeO_2NP)	Disminución del daño hepático	Normalización de temperatura, frecuencia respiratoria y presión arterial	Disminución de la mortalidad del 70% al 10%
Xu, et al., 2020[123]	Sí	Ratones LPS	Mixto (estrógeno/ Mito-TEMPO)	Mitigación del daño hepático con disminución de AST y ALT Menor grado de infiltración hepática por células inflamatorias	—	—
Xu, et al., 2020[124]	Sí	Ratones LCP	Nutrientes-antioxidantes (ascorbato, taurina, glutatión)	Mitigación del daño hepático con disminución de ALT Menor grado de infiltración hepática por células inflamatorias Menor grado de necrosis hepatocelular Disminución de creatinina plasmática	—	—

ALT: alanina aminotransferasa; AST: aspartato aminotransferasa; CeO_2NP: nanopartículas de óxido de cerio; LCP: ligazón cecal y punción; LPS: lipopolisacárido; PG: peptidoglicano

estas se efectúen es de suma relevancia, ya que el organismo puede defenderse ante el incremento prematuro de su metabolismo.

La capacidad de identificar y seguir los cambios de la función mitocondrial (evaluación bioenergética) en el niño en riesgo de prolongación de la disfunción orgánica y que podría beneficiarse de una terapia mitocondrial será, entonces, un paso clave.

Finalmente, una atractiva e interesante área de desarrollo es la inducción farmacológica de un estado hipometabólico bajo demanda, ya sea global u orgánico, proceso denominado «animación suspendida»[131,132].

El papel de la hipoxia citopática y la reanimación metabólica son campos de investigación activa. No obstante, los mecanismos precisos que están involucrados en la falla multiorgánica permanecen desconocidos.

Existe suficiente certeza para apoyar que la disfunción mitocondrial es clave en la fisiopatología del SDMO y que se caracteriza por una producción reducida de ATP con un incremento del estrés oxidativo. La evidencia orienta a la existencia de un apagón metabólico adaptativo originado por una reducción del metabolismo celular, en particular de la fosforilación oxidativa, priorizando la utilización de la energía para mantener la homeostasis del ATP.

El ADN_{mt} liberado es reconocido como un importante desencadenante de la inflamación sistémica, que daña múltiples órganos y se asocia a mortalidad en los pacientes gravemente enfermos.

Existe controversia al analizar la disfunción mitocondrial en enfermedades graves, especialmente en modelos animales de sepsis, ya que no siempre se consideran las diferencias entre especies y entre

órganos, o el momento en que se realiza su evaluación. Por esto, es necesario buscar modelos más representativos y que permitan su extrapolación al entorno clínico.

Los agentes farmacológicos para la prevención y el tratamiento de la disfunción mitocondrial, como aquellos para la inducción terapéutica de la biogénesis, son opciones atractivas y se constituyen en una promisoria línea de investigación para la resucitación metabólica. Sin embargo, ninguna se ha reflejado en la práctica clínica actual.

La monitorización de la oxigenación tisular y la función mitocondrial confiere un periodo ventana para determinar la suficiencia de la perfusión orgánica y del bienestar celular en el paciente séptico muy grave. Por lo tanto, queda pendiente definir quiénes son los pacientes candidatos a recibir terapia orientada a la mitocondria.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que en este artículo no aparecen datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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ARTÍCULO DE REVISIÓN

Fórmulas metabólicas disponibles en México para pacientes con fenilcetonuria

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Resumen

La fenilcetonuria y otras hiperfenilalaninemias son enfermedades genéticas cuya detección actualmente es obligatoria en México, tanto en el sector público como en el privado. La detección y el tratamiento oportunos han demostrado prevenir las manifestaciones neurológicas y la discapacidad que caracterizan esta enfermedad. Por ello, es de suma importancia que el pediatra y el personal de salud involucrados en la atención de estos pacientes conozcan, comprendan e implementen el manejo nutricional de manera correcta. Aunque existen varios tratamientos, el más utilizado es la restricción dietética de fenilalanina. El tratamiento nutricio incluye el uso de la llamada «fórmula médica» o «fórmula metabólica sin fenilalanina», la cual fue concebida desde el primer tercio del siglo XX. Posteriormente, se han realizado múltiples estudios y modificaciones con el fin de mejorar el pronóstico de los pacientes. El presente trabajo describe las principales características y diferencias entre las fórmulas libres de fenilalanina de seguimiento disponibles en México, para que el personal de salud cuente con elementos para su correcta prescripción.

Palabras clave: *Fenilcetonuria. Alimentos especializados. Proteína. Micronutrimentos.*

Metabolic formulas for phenylketonuric patients available in Mexico

Abstract

Hyperphenylalaninemias such as phenylketonuria are rare genetic diseases whose detection is currently mandated nationwide in both the public and private sectors in Mexico. Timely detection, diagnosis and treatment have been shown to prevent the neurological manifestations and disability that characterize this disease. Therefore, the importance of health personnel in charge of these patients to know, understand, and be able to implement an adequate nutritional management. Currently, although there are several treatments approaches, the most common has been dietary restriction of phenylalanine. Nutritional treatment includes the use of the so-called "medical formula" or "phenylalanine-free metabolic formula", which was conceived from the first third of the 20th century. Subsequently, many studies and modifications have been performed to improve patient outcomes. This review aimed to describe the main characteristics and the differences between the metabolic follow-up formulas available in Mexico, so that health personnel have elements for their correct prescription.

Keywords: *Phenylketonuria. Specialized foods. Proteins. Micronutrients.*

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Introducción

Las hiperfenilalaninemias, cuya forma más grave es la fenilcetonuria clásica (PKU, OMIM ID 261600), constituyen el grupo de errores innatos del metabolismo más común. Se caracterizan por la deficiencia de la enzima fenilalanina hidroxilasa, cuya función consiste en transformar al aminoácido esencial fenilalanina (PHE) a tirosina por hidroxilación.

La acumulación de PHE y sus metabolitos tóxicos causa daño principalmente en el sistema nervioso central[1]. Por ello, actualmente se incluye la detección de la PKU en el Programa de Tamiz Neonatal de la Secretaría de Salud en México. La instauración de un tratamiento temprano ayuda a prevenir la discapacidad intelectual, por lo que resulta de especial importancia para el pediatra conocer esta enfermedad y su adecuado manejo. El éxito del tratamiento depende de numerosos factores, como la edad de inicio del tratamiento, la continuidad de este y que el equipo multidisciplinario proporcione el tratamiento adecuado e individualizado, entre otros[1].

Dentro de las opciones terapéuticas existen diversos fármacos, como la tetrahidrobiopterina, que es cofactor de la enzima fenilalanina hidroxilasa. Se utiliza principalmente en pacientes con actividad enzimática residual y en aquellos que presentan una mejoría tanto neurológica como bioquímica. Otra opción de tratamiento es la fenilalanina amonio liasa, enzima que metaboliza la PHE en ácido trans-cinámico y una pequeña cantidad de amonio, disminuyendo así los niveles dañinos de PHE en sangre[2]. Sin embargo, hoy en día, el manejo dietético con restricción de PHE continúa siendo el tratamiento más utilizado para la PKU debido a su bajo costo y su accesibilidad, y porque es un tratamiento permanente para los pacientes[3,4].

Para evitar que aumente la PHE en sangre, y por ende las complicaciones neurológicas asociadas con la enfermedad, es necesario limitar la cantidad de este aminoácido en la dieta diaria. Por ser un aminoácido esencial, no puede ser eliminado en su totalidad, pero debe restringirse su consumo. Los alimentos que contienen proteínas contienen PHE, y los grupos de alimentos con mayores cantidades de PHE son los productos de origen animal, las leguminosas y las oleaginosas, los cuales deben ser eliminados de la dieta del paciente[5]. Los grupos de los cereales, frutas y verduras pueden ser ingeridos, y por lo general se contabiliza el contenido de proteína y de PHE para cubrir las recomendaciones diarias por edad y mantener los valores de PHE en sangre por debajo de 6 mg/dL o 360 μmol/L[4].

Sin embargo, al restringir la PHE se limita también la cantidad de proteína total de la dieta. En general, esta cantidad no es suficiente para el aporte diario recomendado de proteína por edad y sexo que se necesita para crecer y desarrollarse de forma adecuada[4]. Para proporcionar la cantidad suficiente de proteína sin exceso de PHE se han creado fórmulas de aminoácidos libres sin PHE, cuyo objetivo principal es aportar la proteína que el paciente requiere. De acuerdo con la Food and Drug Administration de los Estados Unidos, estas fórmulas se denominan «alimentos médicos» y constituyen una piedra angular en el tratamiento de la PKU[6]. Dependiendo de la presentación y la marca, las fórmulas metabólicas pueden contener hidratos de carbono, lípidos, vitaminas, nutrimentos inorgánicos adicionales a la proteína o suplementos de ácidos grasos esenciales, como los omega 3[5,7]. Por lo general, una misma marca maneja diferentes versiones: las denominadas de inicio o etapa 1, enfocadas en el recién nacido o hasta el primer año de vida, y las diseñadas para etapas posteriores, como la niñez y la adolescencia, llamadas de seguimiento o etapa 2.

Debido a que existen variaciones en cuanto a la cantidad de proteína y energía entre las fórmulas de inicio y seguimiento, en esta revisión solo se incluyen las fórmulas de seguimiento libres de PHE que se encuentran disponibles en México. El objetivo de esta revisión es que el pediatra y los profesionales especialistas en nutrición conozcan las principales características y diferencias de las fórmulas de seguimiento libres de PHE que existen en México para el tratamiento de la PKU.

Historia de las fórmulas

La idea de tratar la PKU con una dieta baja en PHE fue sugerida por primera vez por L. Penrose a mediados de los años 1930. Sin embargo, dicha dieta estaba compuesta solo por fruta, azúcar, aceite de oliva y vitaminas[8,9]. Alrededor de 1949, el químico L.I. Woolf, del Great Ormond Street Hospital de Londres, desarrolló un método para eliminar la PHE y otros aminoácidos aromáticos (triptófano y tirosina). El método consistía en pasar hidrolizados de caseína por columnas de carbón activado y después adicionar aminoácidos esenciales, vitaminas y minerales[9,10]. Entre 1951 y 1953, H. Bickel y E. Hickmans, del Birmingham University Children's Hospital, utilizaron por primera

vez con éxito la formulación de Woolf[9,11]. A partir de entonces, esta formulación ha demostrado ser altamente eficiente y sigue siendo la opción más utilizada en todo el mundo. Otra importante aportación de Woolf al tratamiento de la PKU fue enfatizar la necesidad de una estrecha vigilancia nutricional de los pacientes alimentados con fórmulas libres de PHE y de la permanencia del tratamiento[9].

Con el paso del tiempo, los efectos benéficos de una dieta restringida en PHE suplementada con fórmula han sido ampliamente demostrados[12,13].

Panorama de la fenilcetonuria en México

Desde hace poco más de 50 años, la detección de PKU mediante el tamiz neonatal se realiza de forma sistemática en los países desarrollados para, en general, iniciar el tratamiento en etapas tempranas de la vida[14]. En México, la detección y el tratamiento de la PKU comenzaron en la década de 1970[15]. Sin embargo, el tamiz neonatal para esta enfermedad se suspendió, a pesar de los buenos resultados, y se reinició gradualmente en los años 1990 en diversas instituciones[16]. En la actualidad, el tamiz neonatal se realiza de manera obligatoria en todo el sector salud (NOM-034)[17] y se han descrito prevalencias de 1 en cada 27,546 recién nacidos vivos en México[18].

Tratamiento de la fenilcetonuria en México

Por varios años, la única fórmula metabólica para PKU disponible en México fue la de los laboratorios Abbott, llamada Phenex®, para las etapas 1 y 2. Actualmente existen otras dos fórmulas sin PHE que se distribuyen en diferentes sectores de la población mexicana: Enastamine®, de laboratorios Nucitec®, recomendada para mayores de 8 años, y Beu 2 Intoleranz®, de laboratorios Fraca®. En la Tabla 1 se muestran las tres opciones de fórmulas de seguimiento o de etapa 2 disponibles en el mercado mexicano. Se realizó una comparación en términos de 100 g de polvo (Tabla 1) y otra por 30 g de proteína (Tabla 2), que es la cantidad promedio que un niño de 4-10 años ingeriría al día de acuerdo con las recomendaciones establecidas[19]. Si bien se utiliza comúnmente la comparación por 100 kcal cuando se trata de fórmulas, en este caso es más relevante comparar en gramos de polvo y gramos de proteína, debido a que la fórmula sin PHE se utiliza sobre todo para proporcionar proteína en la dieta de los pacientes. Al ser el principal nutrimento que contiene, el aporte energético se puede completar con otras fuentes, como alimentos hipoproteicos, cereales, frutas y verduras. En México, las fórmulas libres de PHE de inicio y de seguimiento se encuentran catalogadas en el Cuadro Básico y Catálogo de Medicamentos del Sector Salud con los números 010.000.5400.00 y 010.000.5401.00, respectivamente[20].

Energía y cantidad de proteína en las fórmulas

Con respecto al aporte energético, existen diferencias entre las tres fórmulas en la misma cantidad de polvo (Tabla 1). Al comparar la cantidad de energía por 30 g de proteína, Enastamine® es la fórmula con el mayor aporte energético, con 164 kcal más que la Phenex-2® y 78 kcal más que la Beu 2 Intoleranz® (Tabla 2). Por otro lado, la cantidad de proteína total en 100 g es mayor en la Phenex-2®, con una diferencia importante de 9 g en comparación a las otras dos fórmulas. Esto resulta relevante, ya que el cálculo de la fórmula se realiza en relación a la proteína, por lo que cuanto menor es el contenido de proteína, mayor cantidad de polvo se tendrá que utilizar al día. Si se considera un paciente de sexo masculino de 8 años, de aproximadamente 25 kg de peso, el requerimiento diario de proteína recomendado para su edad, enfermedad y requerimiento de fórmulas a base de aminoácidos libres sería de 35 g al día. El 80% de este aporte total de proteína normalmente proviene de la fórmula metabólica (28 g). Es decir, para cubrir esta cantidad de proteína, este niño tendría que ingerir 93 g de Phenex-2® o 133 g de Enastamine® o de Beu 2 Intoleranz®.

Considerando que las tres fórmulas se presentan en latas de 400 g, una lata de Phenex-2® alcanzaría para 4.3 días de tratamiento, mientras que una lata de cualquiera de las otras dos fórmulas rendiría 3 días. El costo por lata varía entre las tres fórmulas: la Phenex-2® es la de menor costo y la Beu 2 Intoleranz® la de más elevado costo (Tabla 1). Además, si se toma en cuenta que se utiliza menos producto con la Phenex-2®, se puede concluir que el impacto económico con esta fórmula es menor, ya que el costo total del tratamiento disminuye de manera importante.

En cuanto a los aminoácidos, las tres fórmulas incluyen todos los aminoácidos esenciales; sin embargo, existe una diferencia con los no esenciales. La fórmula Phenex-2® contiene solo tres y la Enastamine® y la Beu 2 Intoleranz® contienen diez.

La tirosina es un aminoácido muy importante, ya que se convierte en un aminoácido esencial en los pacientes con PKU[7]. Al comparar por cada 30 g de proteína,

Tabla 1. Comparación de las fórmulas libres de fenilalanina por 100 g de polvo disponibles en el mercado mexicano

Nutrimentos	Phenex-2®	Beu 2 Intoleranz®	Enastamine®
Laboratorio	Abbott	Fraca	Nucitec
Indicación de la fórmula metabólica	Soporte en la nutrición de niños y adultos con fenilcetonuria	Seguimiento para niños mayores de 8 años y adultos con fenilcetonuria	Seguimiento para niños mayores de 8 años y adultos con fenilcetonuria
Costo por lata de 400 g (MXN)	$551.16	$1150	$600
Energía (kcal)	410	360	404.45
Equivalentes de proteína (g)	30	21.8	21.13
Nitrógeno (g)	4.8	SD	SD
Aminoácidos (g)	31.58	SD	22.18
Alanina (mg)	2020	1500	1000
Arginina (mg)	2120	1500	1000
Ácido aspártico (mg)	250	2000	1800
Acido glutámico (mg)	430	SD	SD
Carnitina (mg)	40	30	30
Cistina (mg)	300	500	700
Glutamina (mg)	SD	500	350
Glicina (mg)	2000	1200	1800
Histidina (mg)	840	400	700
Isoleucina (mg)	2160	1600	1800
Leucina (mg)	3360	2700	3200
Lisina (mg)	2000	1800	1900
Metionina (mg)	600	400	500
Fenilalanina (mg)	Trazas	0	0
Prolina (mg)	2870	1000	1800
Serina (mg)	1520	600	1200
Taurina (mg)	50	80	100
Treonina (mg)	1400	1000	1300
Triptófano (mg)	340	300	500
Tirosina (mg)	3000	2500	2800
Valina (mg)	2440	1800	2200
Lípidos (g)	14	7.5	14
Linoleico-linolénico (g)	1.5-0.17	SD	SD
Hidratos de carbono (g)	35	59.1	48.48
Calcio (mg)	880	805	800
Cloruro (mg/mEq)	940	700	850
Cromo (µg)	27	35	35
Cobre (mg)	1	1.25	1.3

(*Continúa*)

Tabla 1. Comparación de las fórmulas libres de fenilalanina por 100 g de polvo disponibles en el mercado mexicano (*continuación*)

Nutrimentos	Phenex-2®	Beu 2 Intoleranz®	Enastamine®
Yodo (µg)	100	75	80
Hierro (mg)	13	12.5	12.5
Magnesio (mg)	225	200	200
Manganeso (mg)	0.8	1.03	1
Molibdeno (µg)	30	65	60
Fósforo (mg)	760	775	820
Potasio (mg/mEq)	1370	1150	1422.76
Selenio (µg)	35	35	35
Sodio (mg/mEq)	880	725	750
Zinc (mg)	13	12.5	12.5
Biotina (µg)	100	85	100
Colina (mg)	100	105	100
Ácido fólico (µg)	450	370	350
Inositol (mg)	70	60	70
Niacina (mg)	21.7	17.5	20
Ácido pantoténico (mg)	8	6	6.5
Riboflavina (mg)	1.8	2.05	1.5
Tiamina (mg)	3.25	2.44	2
Vitamina A (µg) (retinol)	660	480	480
Vitamina B 6 (mg)	1.3	1.7	1.5
Vitamina B 12 (µg)	5	4	4
Vitamina C (mg) (ácido ascórbico)	60	92.5	120
Vitamina D (µg)	8	8.75	11
Vitamina E (mg) (alfa-tocoferoles)	12.10	8.25	6.6
Vitamina K (µg)	60	45	50

SD: sin dato. Información nutricional recabada en 2020.

Enastamine® aporta una mayor cantidad, con una diferencia del 32% con respecto a Phenex-2® y del 15% con respecto a Beu 2 Intoleranz®.

Lípidos en las fórmulas

La fórmula Beu 2 Intoleranz® proporciona 6.5 g menos de lípidos en 100 g de polvo en comparación con Phenex-2® y Enastamine®. La Phenex-2® proporciona 5.32 g de grasas saturadas, 4.61 g de monoinsaturadas y 2.93 g de poliinsaturadas. El caso de Enastamine® es diferente, ya que únicamente declara un aporte de grasa saturada de 2.79 g, valor inferior a la otra formulación; la Beu 2 Intoleranz® no reporta estos datos.

Al comparar el contenido de lípidos con la misma cantidad de proteína (Tabla 2), Enastamine® proporciona el 42% más de grasas que Phenex-2®. Este dato resulta relevante en los pacientes cuya dieta contenga un porcentaje alto de lípidos. En tal caso, se debe recalcular el aporte de lípidos al usar esta formulación para no tener un exceso de este macronutriente. Por el contrario, la Beu 2 Intoleranz® contiene el 28% menos de lípidos que Phenex-2®, por lo que si se utiliza

Tabla 2. Comparación de las fórmulas de seguimiento por 30 g de proteína para pacientes con fenilcetonuria

Nutrimentos	Phenex-2®	Beu 2 Intoleranz®	Enastamine®
Laboratorio	Abbott	Fraca	Nucitec
Energía (kcal)	410	495	574.23
Equivalentes de proteína (g)	30	30	30
Nitrógeno (g)	4.8	SD	SD
Aminoácidos (g)	31.58	SD	31.49
Alanina (mg)	2020	2064	1419.78
Arginina (mg)	2120	2064	1419.78
Ácido aspártico (mg)	250	2752	2555.60
Ácido glutámico (mg)	430	SD	SD
Carnitina (mg)	40	41	42.59
Cistina (mg)	300	688	993.84
Glutamina (mg)	SD	688	496.92
Glicina (mg)	2000	1651	2555.60
Histidina (mg)	840	550	993.84
Isoleucina (mg)	2160	2202	2555.60
Leucina (mg)	3360	3716	4543.30
Lisina (mg)	2000	2477	2697.58
Metionina (mg)	600	550	709.89
Fenilalanina (mg)	Trazas	0	0
Prolina (mg)	2870	1376	2555.60
Serina (mg)	1520	826	1703.73
Taurina (mg)	50	110	141.97
Treonina (mg)	1400	1376	1845.71
Triptófano (mg)	340	413	709.89
Tirosina (mg)	3000	3440	3975.39
Valina (mg)	2440	2477	3123.52
Lípidos (g)	14	10	19.87
Hidratos de carbono (g)	35	81	68.83
Calcio (mg)	880	1108	1135.82
Cloruro (mg/mEq)	940	963	1206.81
Cromo (µg)	27	48	49.69
Cobre (mg)	1	2	1.84
Yodo (µg)	100	103	113.58
Hierro (mg)	13	17	17.74
Magnesio (mg)	225	275	283.95
Manganeso (mg)	0.8	1	1.419

(Continúa)

Tabla 2. Comparación de las fórmulas de seguimiento por 30 g de proteína para pacientes con fenilcetonuria (*continuación*)

Nutrimentos	Phenex-2®	Beu 2 Intoleranz®	Enastamine®
Molibdeno (µg)	30	89	85.18
Fósforo (mg)	760	1067	1164.22
Potasio (mg/mEq)	1370	1583	2020
Selenio (µg)	35	48	49.69
Sodio (mg/mEq)	880	998	1064.83
Zinc (mg)	13	17	17.74
Biotina (µg)	100	117	141.97
Colina (mg)	100	144	141.97
Ácido fólico (µg)	450	509	496.92
Inositol (mg)	70	83	99.38
Niacina (mg)	16	24	28.39
Ácido pantoténico (mg)	8	8	9.22
Riboflavina (mg)	1.8	3	2.12
Tiamina (mg)	3.3	3	2.83
Vitamina A (µg) (retinol)	660	681.4	681.49
Vitamina B 6 (mg)	1.3	2	2.12
Vitamina B 12 (µg)	5	6	5.67
Vitamina C (mg) (ácido ascórbico)	60	127	170.37
Vitamina D (µg)	8	12	15.61
Vitamina E (mg) (alfa-tocoferoles)	12.10	11	9.37
Vitamina K (µg)	60	62	70.98

SD: sin dato. Información nutricional recabada en 2020.

esta fórmula se recomienda aportar otras fuentes externas de grasas.

Cabe mencionar que la fórmula Phenex-2® contiene 1.5 g de ácido linoleico y 0.17 g de ácido linolénico. Aunque estos ácidos grasos son precursores del ácido docosahexaenoico (DHA), este no se encuentra suplementado en ninguna de las fórmulas. Existe evidencia con respecto a la deficiencia de DHA en pacientes PKU[21], por lo que, actualmente, muchas fórmulas disponibles en otros países ya se encuentran suplementadas con este nutrimento, y los pacientes con PKU que se apegan al tratamiento no presentan deficiencia de ácidos grasos[22]. Sin embargo, al no existir esta suplementación en las fórmulas disponibles en México, resulta importante vigilar los niveles de ácidos grasos esenciales y, en caso necesario, suplementarlos, ya que tampoco existen fuentes significativas de este tipo de lípidos en la dieta para pacientes con PKU.

Hidratos de carbono en las fórmulas

Con respecto a los hidratos de carbono, se puede encontrar una diferencia considerable entre las tres fórmulas: Beu 2 Intoleranz® aporta una mayor cantidad por 100 g de fórmula y por 30 g de proteína. La comparación por 30 g de proteína reporta 46 g más de hidratos de carbono en Beu 2 Intoleranz® que en Phenex-2® y 12 g más que en Enastamine®. En cuanto a las fuentes de este macronutriente, Enastamine® reporta que el 2.2% corresponde a azúcares como almidón modificado, y el restante, a maltodextrina. En el caso de Phenex-2®, el aporte de hidratos de carbono es proporcionado con sólidos de jarabe de maíz o

maltodextrina en su totalidad (no contiene azúcar). La Beu 2 Intoleranz® no reporta este dato.

Moretti, et al.[23] describieron un alto índice glucémico y carga glucémica en las dietas de 21 pacientes con PKU en comparación con dietas de niños sin PKU. En este mismo estudio se encontró una asociación positiva entre la carga glucémica y el índice de triglicéridos con glucosa, sugiriendo una posible relación entre la calidad de los hidratos de carbono y la resistencia a la insulina periférica.

Vitaminas y micronutrientes en las fórmulas

Al comparar con respecto a la misma cantidad de proteína, Enastamine® es la fórmula que aporta más vitaminas y micronutrientes (Tabla 2). Algunos micronutrientes descritos como deficientes en los pacientes con PKU son hierro, calcio, zinc, cobre y selenio[24]. A pesar de que las tres fórmulas contienen estos micronutrientes, Enastamine® los presenta en mayor cantidad.

Se sabe que pueden existir deficiencias vitamínicas en los pacientes con PKU, especialmente de vitaminas D y B12, y de ácido fólico. Sin embargo, debido a que las fórmulas metabólicas están suplementadas, se ha observado que la ingesta de cantidades adecuadas de fórmula disminuye el riesgo de presentar dichas deficiencias para los pacientes. Incluso, algunos estudios sugieren que las fórmulas contienen cantidades adecuadas o excesivas de ácido fólico, por lo que ya no representa un riesgo nutricional, siempre y cuando se ingiera la fórmula médica[25,26]. Recientemente, la evidencia ha demostrado que los niveles de vitamina B12 pueden encontrarse disminuidos en los pacientes[27,28], incluso en aquellos con terapia de tetrahidrobiopterina[26]. Enastamine® contiene el 13% más de vitamina B12 que Phenex-2® y el 2% más que Beu 2 Intoleranz® por cada 30 g de proteína. Solo para la tiamina y la vitamina E, las cantidades son inferiores en Enastamine® en comparación con las otras fórmulas. En el caso específico de la tiamina, Phenex-2® y Beu 2 Intoleranz® aportan una cantidad similar en la misma cantidad de proteína, y Enastamine® contiene el 15% menos. Este dato es relevante porque las fuentes principales de este nutrimento son la levadura, la carne magra de cerdo y las leguminosas, y ninguno de estos alimentos son ingeridos por los pacientes con PKU. Por lo tanto, es necesario vigilar que las cantidades que se administran en aquellos que toman Enastamine® sean adecuadas. El estado nutricio de la tiamina depende de factores como la biodisponibilidad, la presencia de folatos y el aporte adecuado de proteína. Su deficiencia puede confundirse con datos clínicos de la PKU, como trastornos neurológicos (apatía, pérdida de memoria a corto plazo, confusión e irritabilidad, entre otros)[29]. En el caso de la vitamina E, si bien la diferencia es marcada entre las fórmulas (Phenex-2® contiene una mayor cantidad y Beu 2 Intoleranz® proporciona un menor aporte), es más fácil que los pacientes con PKU puedan ingerir fuentes que la contengan, ya que principalmente se encuentra en algunas frutas y verduras, y en aceites vegetales. Estos últimos son los que contribuyen de manera más importante al aporte de esta vitamina en la dieta mexicana (1.3 mg/día)[29]. Se debe realizar un análisis detallado de la dieta de cada paciente e investigar posibles deficiencias o excesos derivados de las restricciones en los grupos de alimentos que se realizan en este padecimiento.

De acuerdo con los datos de esta revisión, se concluye que existen diferencias importantes en las características y la composición de las fórmulas metabólicas para PKU disponibles en México. La más relevante es el porcentaje de proteína con respecto al valor energético total: el 29% en Phenex-2®, el 20.7% en Enastamine® y el 24.2% en Beu 2 Intoleranz®. Las necesidades nutricionales de cada individuo, al ser diferentes, deben ser cubiertas con el fin de no perjudicar su estado de nutrición. Por ello, no se recomienda utilizar el mismo gramaje de manera indistinta para las tres fórmulas aquí descritas, ya que no contienen las mismas cantidades de ningún nutrimento. Es importante que la cantidad de fórmula la indique un profesional de la nutrición especialista en esta área.

Por otro lado, debido a que cada vez son mejores la detección y el tratamiento oportuno de esta enfermedad, los pacientes están llegando a la edad adulta y sus necesidades nutricionales son distintas, por lo que se necesitarán otras opciones de fórmulas metabólicas o alimentos con mayor cantidad de proteína que las que existen en el mercado actual.

A futuro, será necesario hacer modificaciones en las cantidades de proteína, energía y micronutrientes que se adapten a nuestra población, por lo que se requiere que se lleven a cabo más estudios sobre el estado nutricional de los pacientes con PKU con respecto al aporte de diferentes micronutrientes y vitaminas con las distintas marcas de fórmulas.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han

realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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CLINICAL CASE

Hyperpigmented lesions with acquired atrophy following Blaschko lines in a patient diagnosed with localized scleroderma

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Abstract

Background: *Linear atrophoderma of Moulin (LAM) is a dermatosis that affects children and adolescents characterized by hyperpigmented and atrophic linear lesions following Blaschko lines. So far, less than 50 cases have been published. Therefore, it is a rare entity with unknown etiology and a chronic and self-limited course. Histologically, it is described as hyperpigmentation of the basal layer without the involvement of the dermis and subcutaneous tissue. No specific treatment exists currently. Localized scleroderma is a chronic and progressive autoimmune connective tissue disorder that affects the skin and adjacent tissues, characterized by abnormal collagen deposition and alteration in elastic fibers, blood vessels, and annexes. No reports have been published on the coexistence of localized scleroderma and LAM.* **Case report:** *We describe the case of an 11-year-old male with a clinical diagnosis of linear scleroderma since 5 years of age. Four years later, the patient developed atrophic and hyperpigmented lesions following Blaschko lines in the posterior trunk. A biopsy of both dermatoses was performed: the trunk showed epidermis with hyperpigmentation of the basal layer, and within the dermis, no alteration in the collagen bundles; the forearm biopsy corroborated scleroderma. Based on the clinical-pathological correlation, LAM coinciding with localized linear scleroderma was diagnosed.* **Conclusions:** *LAM is an infrequent entity by itself. Moreover, its coexistence with sclerodermiform syndrome has not been reported in the indexed literature.*

Keywords: *Atrophoderma of Moulin. Scleroderma. Linear. Blaschko.*

Lesiones hiperpigmentadas con atrofia adquiridas siguiendo las líneas de Blaschko en un paciente con diagnóstico de esclerodermia localizada

Resumen

Introducción: *La atrofodermia lineal de Moulin (ALM) es una dermatosis que afecta a niños y adolescentes, caracterizada por lesiones lineales hiperpigmentadas y atróficas que siguen las líneas de Blaschko. Al día de hoy, se conocen menos de 50 casos en la literatura, por lo que se considera una enfermedad rara, de etología aún desconocida, que presenta un curso crónico y autolimitado. Histológicamente se describe hiperpigmentación de la capa basal sin afección de las dermis ni*

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del tejido subcutáneo. No existe tratamiento específico. La esclerodermia localizada es un trastorno autoinmunitario del tejido conectivo, de curso crónico y progresivo, que afecta la piel y los tejidos adyacentes, caracterizada por un depósito anómalo de colágeno y una alteración en las fibras elásticas, los vasos sanguíneos y los anexos. No existen informes sobre la coexistencia de esclerodermia localizada y ALM. **Caso clínico:** *Se describe el caso de un paciente de sexo masculino de 11 años con diagnóstico clínico de esclerodermia lineal desde los 5 años. Cuatro años después desarrolló lesiones atróficas e hiperpigmentadas que siguen las líneas de Blaschko en la parte posterior del tronco. Se realizó una biopsia de ambas dermatosis: la de tronco mostró epidermis con hiperpigmentación de la capa basal; la de dermis, sin alteración en los haces de colágeno; y la de antebrazo corroboró la esclerodermia. Basándose en la correlación clínico-patológica, se concluyó el diagnóstico de ALM en coexistencia con esclerodermia localizada lineal.* **Conclusiones:** *La ALM es una afección infrecuente por sí misma. La coexistencia con procesos esclerodermiformes no ha sido reportada en la literatura indexada.*

Palabras clave: *Atrofodermia de Moulin. Esclerodermia. Lineal. Blaschko.*

Introduction

Localized scleroderma or morphea is a chronic, slowly progressive, autoimmune connective tissue disorder that affects the skin and adjacent tissues[1]. The etiopathogenesis is not yet fully understood, but multiple factors that increase pro-inflammatory cytokines are most likely involved, leading to increased collagen production and extracellular matrix deposition.

Furthermore, in the first two decades of life, hyperpigmented lesions and skin atrophy following Blaschko lines are distinctive features of linear atrophoderma of Moulin (LAM)[2]. LAM is a rare condition of unknown etiology and chronic and self-limited course, with no specific treatment to date.

We report the case of a male patient with a diagnosis of linear scleroderma, who subsequently developed atrophic and hyperpigmented lesions following Blaschko lines.

Clinical case

We report the case of an 11-year-old male with no relevant clinical history. At 5 years of age, dermatosis appeared in the extremities of the right hemibody, with hyperpigmented plaque-type lesions and sclerosis. Local rheumatology and dermatology services evaluated the patient and diagnosed clinical linear scleroderma. Subsequently, topical and systemic steroid treatment was given with partial improvement. Then, the patient was referred to the pediatric rheumatology of our unit. Laboratory studies, including rheumatoid factor, complement C3, C4, and antinuclear antibodies, were made, which were negative. Treatment with methotrexate and colchicine was started.

In 2017, the patient was evaluated for the first time in the pediatric dermatology department, clinically confirming the diagnosis of linear scleroderma. Antibodies for *Borrelia* were requested but reported negative. Due to limited mobility secondary to scleroderma, he was referred to physical medicine and rehabilitation. At 9 years of age, during the clinical follow-up, dermatosis localized to the trunk affecting the posterior and right lateral part of the patient was observed, characterized by discretely atrophic, hyperpigmented linear plaques that followed Blaschko lines, with an absence of induration or evidence of sclerosis (Fig. 1). These lesions were asymptomatic, without inflammation. A biopsy of both dermatoses was taken with the diagnostic proposal of linear atrophoderma of Moulin in a patient with localized scleroderma (Fig. 2). The diagnosis was confirmed. To date, the trunk lesions have remained without progression, clinically without inflammation or sclerosis.

Concerning scleroderma, no more lesions have appeared. Immunosuppressive-based treatment was suspended in December 2019. Finally, the patient continues with rehabilitation therapy, obtaining a functional improvement in the elbow joint and right foot mobility.

Discussion

LAM is a rare disease first described by Moulin in 1992, who published a series of five cases describing hyperpigmented and atrophic lesions[3]. It is a rare, self-limited dermatological disorder that manifests in childhood and adolescence, with no family history of involvement. The exact etiology is currently unknown, but it is theorized to be a mosaic resulting from a post-zygotic somatic mutational event during early embryogenesis[3]. This predisposition, together with external factors not yet well established, is responsible for this dermatosis. Clinically, LAM is characterized by a unilateral band-like or linear dermatosis of variable size following the Blaschko lines, hyperpigmented and atrophic[4]. The lesion does not present induration or sclerosis, it is unilateral, and its usual topography is the

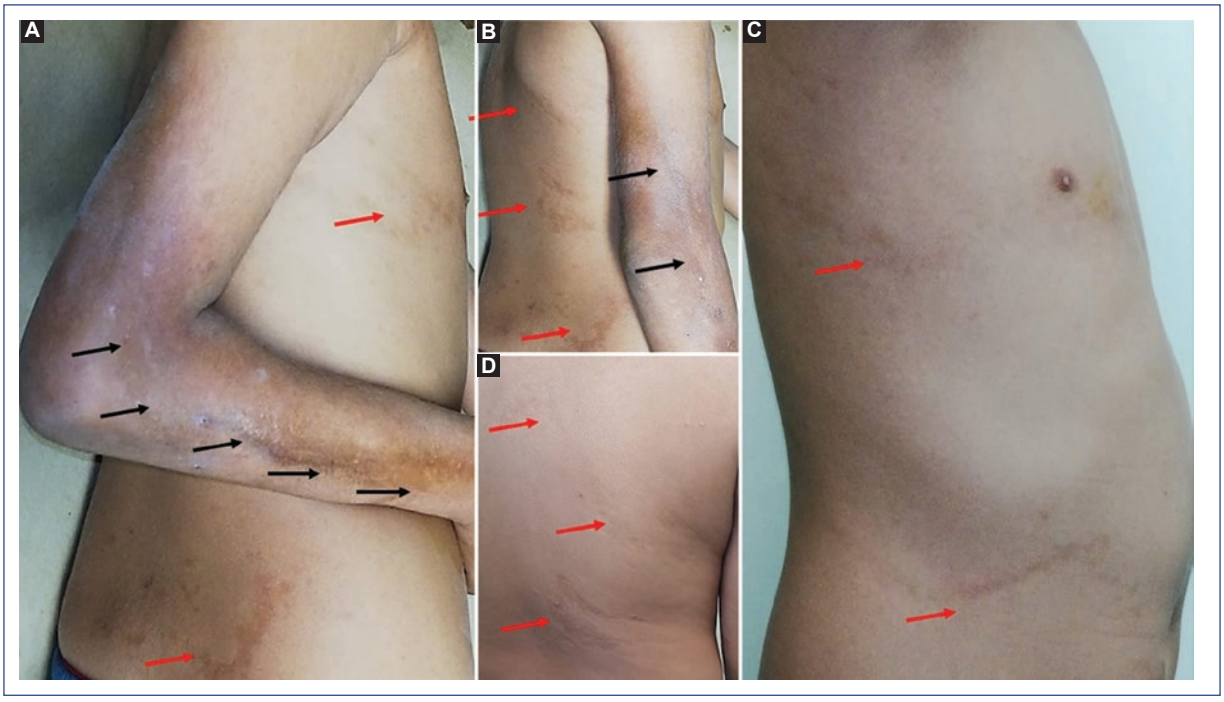

Figure 1. A. Indurated, hyperpigmented plaque with sclerosis and atrophy on right arm and forearm, following a linear trajectory (Black arrows) **B.** Limitation of full elbow extension is observed. **C and D.** Hyperpigmented linear plaques, slightly atrophic following Blaschko lines in the posterior and lateral trunk in the right hemibody (red arrows).

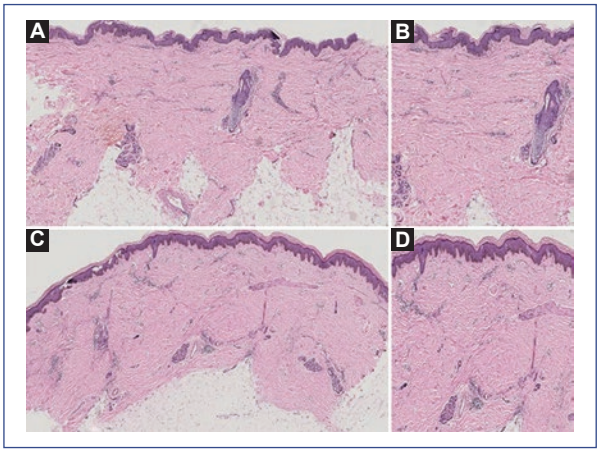

Figure 2. A and B. Epidermis with hyperpigmentation of the basal layer; dermis with moderate perivascular inflammatory infiltrate, no alteration in the collagen bundles. **C and D.** Epidermis with hyperpigmentation of the basal layer dermis with lymphocytic and neutrophilic inflammatory infiltrate at the perivascular level, irregular dense collagen foci with atrophy, and scarcity of adjacent tissue. The changes extend to the subcutaneous cellular tissue.

trunk and extremities[3,5]. Its course is asymptomatic with an absence of systemic involvement or progression[6]. Histopathological findings are controversial. Originally it was described in five cases; only three had a biopsy, where hyperpigmentation was identified without other changes in the epidermis or dermis[7]. Later reports described hyperpigmentation in the lower epidermis, with perivascular lymphocytic infiltrate in the dermis, slightly thickened collagen bundles, or compact dermis[5]. The recommendation is to perform a skin biopsy of both healthy skin and the lesion to establish the histopathological diagnosis since, in some cases, the histopathological findings are very subtle[8].

In 2008, López et al.[9] conducted a review of reported cases up to that date, proposing the following diagnostic criteria:

1. Onset from infancy to adolescence
2. Development of hyperpigmented, slightly atrophic, unilateral lesions following Blaschko lines on the trunk or extremities
3. Lack of previous inflammation and subsequent absence of scleroderma
4. Stable and non-progressive clinical course with no pattern of remission
5. Histologic findings showing hyperpigmentation of the epidermis' basal layer and normal dermis with unaffected connective tissue and elastic fibers

López et al. reviewed 23 cases, of which ten had collagenization of the dermis, and four had no biopsy, meaning that less than 50% of the cases described were those expressing changes at the epidermal level[9].

In the literature, we found 46 cases. Only five patients (10.6%) strictly met the criteria proposed in 2008. We identified reports that showed an atypical clinical expression due to the presence of erythematous plaques, telangiectasias, dissemination to trunk and extremities, and histopathological changes in 34 cases (72%). In these cases, findings in the dermis were described, such as thickening and compacted collagen bundles (Table 1)[2-4,6-37].

In different reports of LAM, we identified a diversity of manifestations that do not fall under the criteria for the disease. For example, Yan et al., in 2016, described a patient with different alterations, including positive antinuclear antibodies, ribonucleoprotein, and anti-SM antibodies[36]. In 2012, Afshar et al.[32] reported that the clinical presentation progressed over 46 years. Other patients were adults[3,7,32] presenting with inflammatory-type[11,18,34], bilateral[17,20,26] lesions associated with lentiginosis[26,33], which is atypical for the clinical picture in LAM. From the histopathological point of view, collagen alterations have been identified in a large percentage of cases. This information raises the question of whether the reports were LAM cases or other conditions.

The case described here presented localized linear scleroderma with subsequent appearance of hyperpigmented and atrophic lesions, asymptomatic, with histology supporting the diagnosis of LAM. This coexistence is exceptional, with no other previous report to date.

Regarding treatment, various drugs have been used, ranging from topical steroids, platelet-rich plasma, PUVA therapy [psoralen (P) and long-wavelength ultraviolet radiation (UVA)], oral potassium, and high-dose penicillin, without optimal results[1,6]. A case treated with methotrexate at a dose of 20 mg per week was reported, where improvement in skin color and texture was clinically demonstrated after 6 months of treatment[1]. However, further studies are required for its recommendation.

The prognosis of this disease is excellent for life and self-limited. There is no evidence of long-term progression[3].

Differential diagnoses of LAM include conditions affecting Blaschko's lines such as linear and whorled nevoid hypermelanosis, *incontinentia pigmenti*, lichen striatus, epidermal nevi, and atrophoderma of Pasini and Pierini (APP)[5,6,37]. A review of the transcendent conditions to establish the diagnosis of LAM is made.

Scleroderma is a fibrosing dermatosis limited to the skin and subcutaneous tissue. Two subtypes are distinguished: systemic scleroderma with associated visceral involvement and sclerodactyly with Raynaud's phenomenon or localized scleroderma or morphea limited to the skin and underlying tissues[38]. It occurs predominantly in females and affects children and adults similarly. The peak incidence is between 2 and 14 years of age in children; in adults, between 40 and 50 years of age. Patients with scleroderma usually have a family history of this pathology or other autoimmune disorders[39]. The etiology is not yet well established, but several elements involved in the fibrosis pathway are recognized. Among these elements are vascular damage or anomalous activation of T lymphocytes with abnormal tissue production by fibroblasts, which could interact with external triggering factors, such as trauma, insect bites, vaccinations, and exposure to X-rays, resulting in the development of sclerosis[7,40].

The clinical classification depends on the consulted literature, but it is usually divided into circumscribed morphea with linear expression (including trunk and extremities, *en coup de sabre*, and Parry-Romberg syndrome), generalized, pansclerotic, and the mixed variant[38].

In the early stages of the disease, differentiation of scleroderma and systemic sclerosis is impossible, as both present perivascular lymphocytic infiltration in the reticular dermis and endothelial inflammation. They also share standard features such as thickening of collagen bundles extending into the subcutaneous tissue, loss of eccrine glands, and involvement of blood vessels in later stages[38].

When there is head and neck involvement, a periodic ophthalmologic examination is indicated to rule out third cranial nerve damage since it may be irreversible[38].

The clinical picture consists of an indurated plaque of insidious onset, with an active border of violaceous or erythematous coloration and a slightly whitish center that progresses to sclerotic tissue[41]. Later, the plaque becomes pigmented with loss of adjacent tissue. Extracutaneous involvement is exceptional. However, it may be associated with myalgias, arthralgias, fatigue, and central nervous system fibrosis, present in up to 22% of cases[38]. The evolution is variable and tends to progress, especially in childhood-onset cases, although it usually becomes inactive after 3-5 years[42].

Multiple treatment options include phototherapy, topical or systemic steroids, topical calcipotriol, oral

Table 1. Characteristics of linear atrophoderma of Moulin cases reported in the literature

Patient	Author (year)	Sex	Age of onset (years)	Clinical picture	Topography	Histology	DXC (X/5) and OC
1	Moulin et al. (1992)[7]	M	8		Left trunk	Basal hyperpigmentation	5/5
2		F	7		Right trunk	Basal hyperpigmentation	5/5
3		M	15		Right trunk	Basal hyperpigmentation	5/5
4		M	20		Left trunk	No biopsy	4/5
5		M	6		Trunk and left arm	No biopsy	4/5
6	Baumann et al. (1994)[10]	M	22		Trunk and right arm	Epidermis: basal ballonization Dermis: perivascular lymphocytic infiltrate, increased collagen	3/5
7	Larregue et al. (1995)[11]	M	15		Left trunk	Dermis: collagenization	4/5
8	Wollenberg et al. (1996)[12]	F	5		Right trunk and arm	Epidermis: atrophy Dermis: perivascular lymphocytic infiltrate and increased collagen	4/5
9	Artola-Igarza et al. (1996)[13]	F	16		Left trunk	Epidermis: acanthosis and basal hyperpigmentation Dermis: perivascular lymphocytic infiltrate and increased collagen	4/5
10	Braun and Saurat (1996)[14]	M	16		Trunk and left abdomen	Increased collagen fibers	4/5
11	Cecchi and Giomi (1997)[15]	F	12	*Classic	Trunk and right arm	Basal hyperpigmentation	5/5
12	Rompel et al. (2000)[16]	F	17		Trunk and right gluteal region	Epidermis: vacuolar degeneration of the basal area Dermis: increased collagen	4/5
13	Browne and Fisher (2000)[17]	M	10	Classic, also erythematous patches with papules with linear distribution	Trunk and extremities, bilateral	Epidermis: thinned Dermis: prominent vessels and increased collagen	3/5
14	Martin et al. (2002)[18]	M	9		Left trunk	Increased collagen	4/5
15	Miteva and Obreshkova (2002)[19]	F	16	Classic + telangiectasia	Arm, gluteal region, and right leg	Increased collagen	4/5

(Continues)

Table 1. Characteristics of linear atrophoderma of Moulin cases reported in the literature *(continued)*

Patient	Author (year)	Sex	Age of onset (years)	Clinical picture	Topography	Histology	DXC (X/5) and OC
16	Utikal et al. (2003)[20]	M	23	Classic + telangiectasia	Trunk and extremities, bilateral	Perivascular lymphocytic infiltrate and edema	2/5
17		F	13	Erythematous lesions with atrophy and telangiectasia following Blaschko lines	Trunk and extremities, bilateral	Dermis: edema, perivascular infiltrate	3/5
18	Danarti et al. (2003)[21]	F	14		Left hemibody	Perivascular lymphocytic infiltrate	4/5
19		F	24		Left arm, trunk, and abdomen	No biopsy	3/5
20		F	38		Left thigh	Epidermis and dermis without relevant findings	4/5
21	Miteva et al. (2005)[22]	F	15		Gluteal region and left iliac crest	No biopsy	4/5
22	Atasoy et al. (2006)[23]	M	9		Trunk and left arm	Increased collagen	4/5
23	Peching et al. (2005)[4]	F	19	Classic	Trunk and left thigh	Epidermis: hyperkeratosis, orthokeratosis, basal hyperpigmentation. Dermis: disorganized collagen with loss of configuration.	4/5
24	Atasoy et al. (2006)[23]	M	16	Classic + telangiectasia	Arm and right trunk	Epidermis: atrophy Dermis: destruction of collagen fibers, vascular ectasia, perivascular lymphocytic infiltrate.	3/5
25	Zampetti et al. (2008)[24]	F	37		Arm and left trunk	Basal hyperpigmentation, thickening of collagen bundles	3/5
26	Cecchi et al. (2008)[25]	M	9		Neck	Basal hyperpigmentation, perivascular lymphocytic infiltrate	4/5
27	López et al. (2008)[9]	M	16	Classic	Right arm	Basal hyperpigmentation	5/5
28	Özkaya et al. (2010)[26]	F	18	Classic + lentiginosis	Bilateral	Epidermis: acanthosis, basal hyperpigmentation, decrease of elastic fibers.	3/5
29	Ripert and Vabres (2010)[27]	F	14		Left trunk	Basal hyperpigmentation, perivascular lymphocytic infiltrate	4/5

(Continues)

Table 1. Characteristics of linear atrophoderma of Moulin cases reported in the literature *(continued)*

Patient	Author (year)	Sex	Age of onset (years)	Clinical picture	Topography	Histology	DXC (X/5) and OC
30	Schepis et al. (2010)[28]	M	14	Classic	Left trunk	Basal hyperpigmentation, dilated vessels, edema, perivascular lymphocytic infiltrate	4/5
31	Tukenmez Demirci et al. (2011)[29]	F	39		Left side of the neck	Basal hyperpigmentation, proliferation of vessels, macrophages, and inflammatory infiltrate	3/5
32	Norisugi et al. (2011)[30]	M	26	Classic	Trunk and right leg	Basal hyperpigmentation, thickening of collagen bundles, perivascular inflammatory infiltrate	3/5
33	Patsatsi et al. (2013)[31]	F	17	Classic	Left trunk	Epidermis: thinned, basal hyperpigmentation, increased collagen fibers	3/5
34	Zaouak et al. (2014)[2]	F	11	Classic	Arm, trunk, and right leg	Basal hyperpigmentation, perivascular lymphocytic infiltrate	4/5 Treated with methotrexate with clinical improvement
35	Afshar et al. (2012)[32]	M	20	Pruritic pink areas that later become hyperpigmented and atrophic while remaining asymptomatic	Trunk and left arm	Epidermal atrophy, Thinned collagen bundles and fragmented elastic fibers	3/5 Lesions progressed over 46 years
36	Yücel et al. (2013)[33]	F	23	Classic + lentiginosis	Right leg	Melanophages and perivascular lymphocytic infiltrate	3/5
37	Villani et al. (2013)[3]	M	8	Classic	Thigh and right gluteal area	Basal hyperpigmentation, perivascular inflammatory infiltrate, thickened collagen bundles	4/5
38		F	6	Classic	Abdomen and right leg	No biopsy	4/5
39		F	9	Classic	Left back	No biopsy	4/5
40		M	20	Classic	Left arm	Pigmentation of the basal layer, perivascular inflammatory infiltrate, thickened collagen bundles	3/5

(Continues)

Table 1. Characteristics of linear atrophoderma of Moulin cases reported in the literature *(continued)*

Patient	Author (year)	Sex	Age of onset (years)	Clinical picture	Topography	Histology	DXC (X/5) and OC
41	De Golian et al. (2014)[34]	M	10	Classic	Left side	Normal epidermis Thickening of collagen bundles, Plasma cells, perivascular lymphocytic infiltrate	4/5
42	Zahedi et al. (2015)[35]	F	10	Classic	Right arm	Basal hyperpigmentation, perivascular inflammation	4/5
43	Yan et al. (2016)[36]	M	15	Classic	Arm and trunk, ipsilateral	Epidermis: acanthosis, basal hyperpigmentation, perivascular lymphocytic infiltrate, and increased collagen	4/5 Antibodies (+)
44	Tan and Tay (2016)[8]	F	11	Classic	Arm, trunk, and right leg	Perivascular lymphocytic infiltrate, collagen bundle compaction	4/5
45	Zhang et al. (2020)[6]	F	10	Classic	Trunk and leg	Basal hyperpigmentation, perivascular inflammatory infiltrate	4/5
46	Present case (2020)	M	9	Classic	Trunk	Basal hyperpigmentation, perivascular lymphocytic infiltrate	5/5

*Classic: hyperpigmented, atrophic skin areas following the Blaschko lines.
DXC, diagnostic criteria; F, female; M, male; OC, other characteristics.

calcitriol, tacrolimus, topical pimecrolimus, methotrexate, mycophenolate mofetil, intralesional interferon-gamma, cyclosporine, D-penicillamine, imiquimod, and penicillin. In pediatric patients, the therapies with the highest degree of evidence are phototherapy and pulse regimen with corticosteroids and methotrexate[42].

Moreover, APP is a rare dermatosis characterized by mild dermal atrophy affecting adolescent and young adult women[43,44]. It was first reported in 1923 by Pasini as "progressive idiopathic atrophoderma" and was described later in 1936[45]. It predominates in young women in the second or third decade of life, has a predilection for the trunk, and clinically presents as a plaque, single or multiple, atrophic with well-defined borders, hyperpigmented, non-indurated, which can vary in size and tone, and tends to be bilateral. APP may be accompanied by pruritus, pain, or paresthesias[45]. About 100 cases of APP have been described in the literature. Although the cause is still unknown and no genetic factors have been identified, Pasini and Pierini reported familial atrophoderma[43,45]. Some authors have related it to *Borrelia* infection[44].

Regarding histology, the most characteristic finding is a decrease in dermal thickness and collagen changes, including atrophy, sclerosis, fragmentation, and hyalinization. The elastic fibers show reduction and fragmentation. The adjacent tissues do not show alterations[32]. To date, no definitive treatment is available. However, when positive antibodies for *Borrelia* are present, it can be managed with tetracyclines, although the response is partial[43,45].

The coexistence of different sclerodermiform conditions is recognized. Most reports describe the association of morphea with lichen sclerosus and atrophic lichen[42,46-48] and of morphea with APP[26]. However, in the latter case, several authors share the theory that

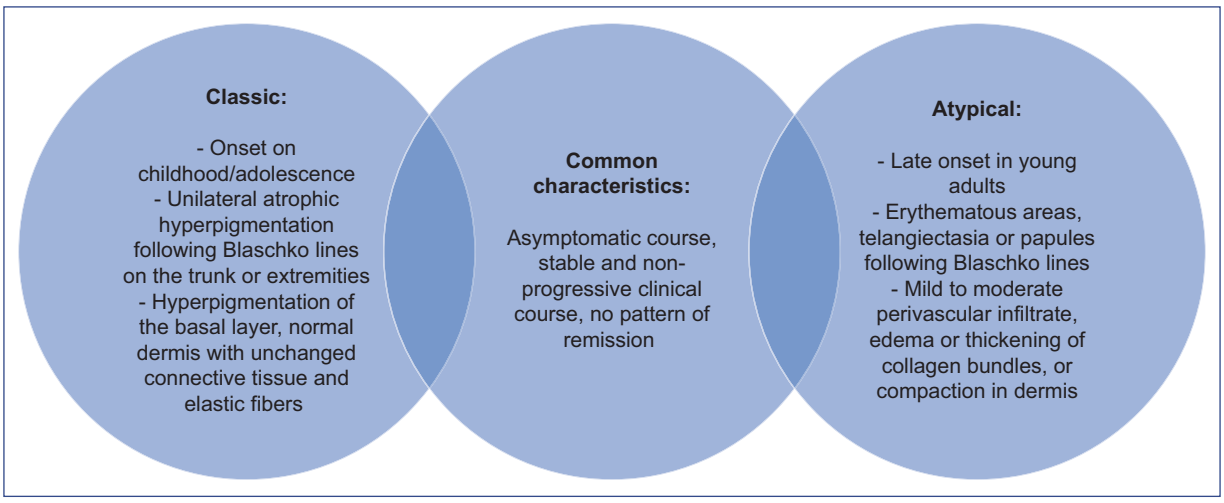

Figure 3. Interaction of features obtained from literature reports.

both conditions are part of the same spectrum or that APP is an abortive variant of morphea[37,49].

Currently, the possibility has been raised that LAM, APP, and linear scleroderma are part of the same spectrum, as they all share some clinical and histological manifestations[34,49].

Finally, from the reported cases, we compiled and analyzed the following common features: (a) dermatosis characterized by hyperpigmented patches and mild atrophy following Blaschko lines; (b) children and adolescents; (c) on trunk and extremities, unilateral; d) epidermis with hyperpigmentation, scarce perivascular lymphohistiocytic inflammatory infiltrate, dermis unchanged, or the slight thickening of collagen or compaction without alteration of elastic fibers; e) asymptomatic course, without clinical progression to induration or involution. This information represents an opportunity to expand the previously proposed diagnostic criteria for LAM, adding a subdivision according to the findings (Fig. 3).

LAM is a controversial entity. Of the 46 published cases, only five fully meet the diagnostic criteria already established. Furthermore, these criteria are exceeded, as they are not strictly met, mainly due to histopathological findings. In the literature, LAM is a dermatosis without changes in the dermis. However, more than 70% of the reports show alterations in the dermis: collagenization, thickening of bundles, edema, compacting of collagen bundles, or decrease of elastic fibers. Therefore, we face a dermatosis that shows the importance of the clinical-pathology-evolutionary correlation. Overall, the above provides a guideline to reconsider LAM, linear scleroderma, and APP as part of a clinical and histopathological spectrum, concurring in the manifestations of hyperpigmentation, the Blaschko lines pattern, the presence of thickening of the collagen bundles, or the compacting of the dermis, where LAM would be the mildest form, APP an intermediate form, and scleroderma as the significant clinical expression due to tissue damage.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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CLINICAL CASE

Primary meningococcal arthritis of the hip due to serogroup W in a pediatric patient

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Abstract

Background: *Primary meningococcal arthritis (PMA) is defined as the presence of acute septic arthritis with the identification of Neisseria meningitidis in synovial fluid or blood cultures but no clinical evidence of sepsis or meningitis. This report aimed to describe a clinical case of PMA caused by serogroup W, an uncommon etiology of this disease in Uruguay, and review the available literature.* **Case report:** *We report the case of a 5-year-old female, with no past medical history, admitted to the emergency department with a 12-hour history of fever of 39 °C and a limp. The patient was hemodynamically stable and had no clinical evidence of meningitis. Hip ultrasound showed an increase in synovial fluid. Arthrocentesis showed purulent exudate and synovial fluid culture showed no growth after five days. The blood culture showed isolates of N. meningitidis, serogroup W. The patient received treatment with ceftriaxone, and drainage of the affected joint was performed with excellent clinical response.* **Conclusions:** *Primary meningococcal arthritis is a rare presentation of meningococcal disease. Systematic arthrocentesis and the adequacy of antibiotic therapy when septic arthritis is clinically suspected are essential for confirming the diagnosis and decompressive drainage of the involved joint. This report is the first of PMA caused by serogroup W in Uruguay. Although the most common serogroup involved in meningococcal arthritis is serogroup B in Uruguay, an increase in serogroup W-related diseases has been reported in Chile and Argentina, emphasizing the need for epidemiological surveillance.*

Keywords: *Infectious arthritis. Meningococcal infections. Neisseria meningitidis.*

Artritis meningocócica primaria de cadera por serogrupo W en un paciente pediátrico

Resumen

Introducción: *La artritis meningocócica primaria (AMP) se define como la presencia de artritis séptica aguda sin meningitis ni sepsis meningocócica y con aislamiento de Neisseria meningitidis en líquido articular o sangre. El objetivo de este reporte es presentar un caso clínico de AMP causada por el serogrupo W, una etiología poco frecuente de esta enfermedad en Uruguay, y revisar la literatura disponible.* **Caso clínico:** *Se reporta el caso de una paciente de 5 años, sana, que ingresó por cojera dolorosa y fiebre de 39 °C de 12 horas de evolución. La paciente se encontró hemodinámicamente estable y sin evidencia de meningitis. La ecografía de cadera mostró un aumento del líquido sinovial; la artrocentesis, material purulento . No se observó desarrollo en el cultivo del líquido articular y en el hemocultivo se reportó N. meningitidis del serogrupo W. Se realizó drenaje articular y se administró ceftriaxona intravenosa. La paciente presentó buena evolución.* **Conclusiones:** *La presentación de la enfermedad meningocócica como artritis séptica aguda es extremadamente infrecuente. La*

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punción articular sistemática y la adecuación del tratamiento antibiótico frente a la sospecha de artritis séptica son fundamentales para la confirmación del diagnóstico, además del drenaje descompresivo de la articulación. Este es el primer caso clínico reportado en Uruguay de AMP causada por el serogrupo W. Si bien en nuestro país la mayoría de los casos se deben al serogrupo B, en Chile y Argentina se ha comunicado un aumento del número de casos por el serogrupo W, lo que enfatiza la importancia de la vigilancia epidemiológica.

Palabras clave: *Artritis infecciosa. Infecciones meningocócicas. Neisseria meningitidis.*

Introduction

Acute septic arthritis is a frequent and potentially severe disease with a risk of sequelae at joints. In Uruguay, the most frequent etiology is *Staphylococcus aureus*, with the prevalence of *Kingella kingae* in the group of children under 5 years of age[1].

Primary meningococcal arthritis (PMA) is defined as the presence of acute septic arthritis with no association with meningitis or meningococcal sepsis and with isolation of *Neisseria meningitidis* in synovial fluid or blood[2,3].

From a clinical and pathogenic point of view, four forms of joint involvement by meningococcus are described[3]:

- *Early septic arthritis*. It is produced by direct invasion of the microorganism in the context of acute meningococcemia. It generally occurs between the first and second day of evolution. The microorganism grows in joint cultures.
- *Arthritis associated with chronic meningococcemia*. It is also produced by direct invasion during chronic meningococcemia. There may be mono or oligoarticular involvement.
- *Primary meningococcal arthritis*. It is produced by direct invasion of the microorganism without sepsis or meningitis. It constitutes 1.5% of septic arthritis in the pediatric age[4]. In general, it is monoarticular with a preference for large joints as the knee, which is the most common.
- *Allergic arthritis*. It is one of the post-infection inflammatory manifestations of meningococcal disease, including arthritis, vasculitis, pericarditis, and uveitis. It has an immune mechanism due to the deposit of immune complexes at the joint level. It occurs between days 4 and 8 from the beginning of the disease[5].

Within the spectrum of meningococcal disease that ranges from asymptomatic carrier to meningococcal septic shock, joint involvement is frequent, occurring in approximately 10% of patients[2,4,6]. However, most cases of joint involvement occur as a part of systemic disease. PMA is the least common form of joint involvement[3].

In Uruguay, meningococcal disease is low endemic, with an average of 34 cases per year and an incidence of 0.4/100,000 inhabitants[7]. It usually presents as meningitis or septic shock.

N. meningitidis is a Gram-negative coccus bacterium. Meningococci associated with the invasive form of the disease generally have a polysaccharide envelope that characterizes their serogroup. Twelve capsular serogroups have been identified (A, B, C, X, Y, Z, 29E, W135, H, I, J, and L). Serogroups A, B, C, Y, W, and recently X are the most frequently associated with the disease. The others are related to asymptomatic carriers and could very occasionally cause disease[5].

Considering all forms of meningococcal disease, serogroup B is responsible for most of the cases of endemic disease in Uruguay[7]. Of the serogroups that have been involved in epidemic outbreaks, the most frequent is serogroup C, which caused the outbreaks of the 90s. These outbreaks were controlled with the massive application of the A + C polysaccharide vaccine to the group between 2 and 19 years of age. Serogroup B was implicated in an outbreak in 2001 in the town of Santa Lucía, Canelones[8]. The other serogroups have a less frequent incidence. Of the 21 cases reported in 2017, one corresponded to serogroup Y and another to serogroup W[7].

Before 2000, serogroup W was responsible for a small number of cases[9]. Since the outbreak reported in the Arabian Peninsula, an increase in cases attributable to this serogroup has been reported worldwide[9,10]. There are substantial epidemiological differences between the different countries of the region. In Chile, since the epidemic by serogroup W in 2012 and despite vaccination with the conjugate vaccine for serogroups A, C, W, and Y (Men ACWY), serogroup W continues to be the most frequent[11,12]. In Argentina, the most frequent serogroups are B and W, with an increasing trend of the latter since 2008[11]. In Brazil, serogroup C is the most frequent, except in the southern region where, as in Uruguay, serogroup B

predominates[11,13]. The incidence of serogroup C has decreased since the start of vaccination with the conjugate vaccine in 2010. Similar to Chile and Argentina, cases due to serogroup W[13] increased in the southern region of Brazil since 2008.

The exact incidence of PMA in our country is unknown. One case report of PMA caused by serogroup B has been published[14]. In a series of nine cases of PMA published in Argentina, five cases were caused by serogroup W[3].

This study aimed to report a case of PMA caused by serotype W and review the available literature on the matter.

Clinical case

We describe the case of a 5-year-old female patient with no relevant past medical history who did not travel abroad. The patient lives with both parents, adequate housing without overcrowding. According to the national vaccination plan, she received one dose of BCG tuberculosis vaccine, four doses of pentavalent vaccine (diphtheria, cellular pertussis, tetanus, *Haemophilus influenzae* type B, hepatitis B), three doses of 13-valent pneumococcal conjugate vaccine, four doses of the inactivated polio vaccine, two doses of hepatitis A vaccine, two doses of varicella vaccine, and two doses of measles, rubella, and mumps (MMR) vaccine. Twelve hours before admission, she presented a fever of up to 39°C and a painful limp that restricted standing and walking. In the days before the consultation, she reported a runny nose and catarrhal cough. On physical examination, the patient was found to be in good general condition. Glasgow Coma Scale (GCS) 15; immediate capillary refill time; warm limbs, full pulses, skin without lesions. The hip presented with antalgic posture in abduction and external rotation and pain on mobilization with minimal movements. No other joints were involved, neither stiff neck nor meningeal signs. The rest of the physical examination was found with no alterations. She was hospitalized with probable septic arthritis of the hip.

Hip ultrasound reported an increase in synovial fluid with simple characteristics, measured 5 mm at the level of the anterior recess. Synovial membrane thickening and capsule protrusion were associated. The hip X-ray showed no alterations. Blood test results showed leukocytes 7300/mm^3, neutrophils 32%, lymphocytes 48%, hemoglobin 12.1 g/dL, platelets 217,000/mm^3. C-reactive protein (CRP) levels were 70 mg/L, and procalcitonin (PCT), 0.5 mg/L. A sample was collected for blood culture.

Arthrocentesis was performed 5 hours after hospital admission before the start of antibiotic treatment. Purulent material was obtained and sent for culture. Surgical cleaning was performed, maintaining drainage. According to local epidemiology, empirical antibiotic treatment with intravenous clindamycin and cefuroxime was started targeting a possible staphylococcal etiology and less likely *K. kingae*.

The patient presented a good evolution. Twenty-four hours after admission, she was apyretic, with progressive improvement in pain and joint functionality *N. meningitidis* serogroup W no producer of beta-lactamase was found in blood culture 48 hours later. Antibiotic therapy was modified to ceftriaxone, which the patient received for up to 10 days. Subsequently, she completed 21 days of oral amoxicillin. No bacterial growth was reported in the joint fluid culture.

After hospital discharge, complement components C3 and C4 were evaluated due to the infrequent clinical presentation and serogroup and found within normal values.

Discussion

The patient presented PMA given the joint involvement and isolation of *N. meningitidis* in blood culture but no meningeal involvement or sepsis.

The presentation of meningococcal disease as acute septic arthritis is extremely rare[3]. Among the most frequent causes of septic arthritis in our country, *S. aureus* is included in all age ranges, and *K. kingae* in children[1,15]. The empirical treatment, in this case, was directed to these etiologies.

The serogroup of *N. meningitidis* involved in this clinical case is rare. Although most cases are due to serogroup B in our country, an increase in the number of cases caused by serogroup W[11] has been reported in Chile and Argentina. Also, cases of serogroup W have increased in Europe, which has led to adjustments in vaccination programs[16]. We found only two previous reports of PMA caused by this serogroup in PubMed; however, this was the most frequent serogroup in a series of nine cases in Argentina[3,16,17].

Regarding the site, the involvement is generally monoarticular, and the knee is the most frequently involved joint, followed by the hip, as in this case[3,18].

Several factors predispose to invasive meningococcal disease. Age is one of the fundamental risk factors, with children under one year of age being the highest

risk group. However, approximately 40% of cases occur in children under 5 years of age[5,6,19]. The cases caused by serogroup B tend to occur in younger children, while the other less frequent serogroups usually cause disease in older patients[5].

In the present case, the lab study was indicated to rule out complement alterations due to disease caused by other serogroups rather than A, B, and C[5,6]. The deficiency of specific antibodies or terminal complement components (C5-C8) is mainly associated with an increased risk of meningococcal disease, up to 600 times higher[5,6]. The complement deficiency studies performed on this patient were incomplete. The screening method to identify complement alterations is the CH50 test that is altered in the case of any of these factors[20].

The initial selection of antibiotics (clindamycin and cefuroxime) was decided based on national guidelines and directed to the etiological agents of septic arthritis in our country, the most frequent being *S. aureus* and considering *K. kingae* because of its prevalence in this age group. For convenience, the antibiotic plan with ceftriaxone was continued, although penicillin could have been used since the microorganism was sensitive to this antibiotic. *N. meningitidis* generally remains susceptible to penicillin; however, strains with resistance to penicillin but not to cephalosporins have been reported, which has caused therapeutic failures. The mechanism involved in resistance to penicillin is structural changes at the level of penicillin-binding proteins (PBP)[5,6]. The empirical treatment in the patient showed activity against *N. meningitidis*, even against the possible strains with resistance to penicillin. Regarding duration, there are no specific guidelines for the treatment of PMA. Following the national guidelines for treating septic arthritis, a duration of 21 days of antibiotic therapy was chosen[15].

Arthrocentesis was performed early and before the start of antibiotic treatment. Systematic joint puncture in the event of suspected septic arthritis is essential for the study of synovial fluid, confirmation of the diagnosis, and the adjustment of antibiotic treatment, additionally to decompressive drainage of the joint[5]. The need for drainage and debridement of the joint should be decided with a pediatric orthopedic surgeon. At the hip joint, the standard open approach is indicated.

PMA is a potentially vaccine-preventable disease. There are two meningococcal vaccines available: Men ACYW is composed of polysaccharides for serogroups A, C, Y, and W135 conjugated to diphtheria toxoid; Men B-4C is formed by three recombinant proteins, NHBA, NadA, FHbp, and by outer membrane vesicles that contain the PorA membrane protein of the P1.4 serosubtype[21]. According to data from the United Kingdom, where this vaccine is used routinely, its effectiveness in preventing invasive meningococcal disease caused by serogroup B is 92.4%[7].

In Uruguay, these vaccines are not part of the national vaccination scheme, and their indication is considered free of charge for risk groups and in the context of outbreak control.

The universal incorporation of meningococcal vaccines is under constant review. As PMA is a disease with high lethality despite treatment, vaccination is a fundamental strategy[9]. However, in developing countries with limited financial resources, vaccination costs against meningococcal diseases limit their universal inclusion. In Uruguay, under the current low endemic epidemiological situation, it has been decided to maintain the vaccination strategy in outbreaks and risk groups[7].

In Uruguay, the current recommendations for these vaccines are the following[22]:

- In cases of outbreaks or epidemics
- High risk of invasive meningococcal disease
- People with C5-C9 complement deficiency (properdin, factor H, or factor D)
- People with functional or anatomical asplenia
- Hematoncological diseases
- Hematopoietic stem and solid organ transplant recipients
- People traveling to endemic or outbreak areas
- Health or laboratory personnel who handle bacteriological samples
- Previous episode of invasive multiple sclerosis
- Leakage of cerebrospinal fluid (due to congenital malformations, skull fracture, or neurosurgical procedure)
- Carriers of human immunodeficiency virus regardless of immune status

The present report is the second PMA case documented in Uruguay. No cases of children with arthritis caused by *N. meningitidis* serogroup W have been reported in our country. Considering the current situation in the region, we must be attentive to epidemiological surveillance and possible changes in serogroups. With appropriate treatment, PMA is a disease that evolves adequately with no sequelae. However, the diagnostic delay is associated with a higher risk of complications. Therefore, high diagnostic suspicion, systematic joint puncture, and timely initiation of antibiotic treatment are fundamental[3,4].

Although the incidence of invasive meningococcal disease is low, its high lethality aims to vaccination as an attractive measure for controlling this disease in the future.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on patient data publication.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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CLINICAL CASE

Cerebral aneurysms in pediatrics: a case report and review of the literature

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Abstract

Background: *Cerebral aneurysms in pediatrics represent < 4% of the total of this condition, and their rupture represents 10-23% mortality. Aneurysms have been associated with infections, head injuries, sickle cell anemia, cardiovascular diseases, autoimmune diseases, immunodeficiencies, and connective tissue diseases. Their clinical presentation includes severe headache, seizures, motor-sensory deficits, and death due to subarachnoid and intraparenchymal hemorrhage.* **Case report:** *We describe the case of a 12-year-old female patient who presented with a sudden intense headache; after 72 hours, generalized tonic-clonic seizures were observed. At the hospital, she was stabilized with antiepileptic drugs and analgesics. A simple head computed tomography scan showed intraparenchymal hemorrhage in the right frontal lobe and subarachnoid hemorrhage. The study was complemented with a cerebral angiotomography, which revealed an aneurysm of the anterior communicating artery. The pediatric neurosurgeon evaluated the case, and management in the pediatric intensive care unit was decided. Two weeks after the stroke, the aneurysm was clipped and excluded. The patient developed adequate clinical evolution and resolution of initial symptoms, resuming her daily activities.* **Conclusions:** *Pediatric cerebral aneurysms differ from their adult counterparts, mainly in their etiology and evolution. In addition, pediatric patients have a longer life expectancy. Aneurysm clipping and neurological endovascular therapy have shown similar results.*

Keywords: *Cerebral aneurysm. Pediatrics. Aneurysm clipping. Endovascular therapy.*

Aneurismas cerebrales en pediatría: reporte de un caso y revisión de la literatura

Resumen

Introducción: *Los aneurismas cerebrales en pediatría representan menos del 4% del total de estos padecimientos, aunque su rotura tiene una mortalidad del 10-23%. Se han asociado con infecciones, traumatismos craneoencefálicos, anemia de células falciformes, enfermedades cardiovasculares, enfermedades autoinmunitarias, inmunodeficiencias y enfermedades del tejido conectivo. Su presentación clínica se manifiesta con cefalea intensa, crisis convulsivas, déficit motor-sensitivo y muerte debida a la hemorragia subaracnoidea e intraparenquimatosa.* **Caso clínico:** *Se describe el caso de una paciente de 12 años que presentó cefalea súbita intensa; a las 72 horas se agregaron crisis convulsivas tónico-clónicas generalizadas. En el hospital se estabilizó con fármacos antiepilépticos y analgésicos. Se le realizó una tomografía de cráneo simple que evidenció hemorragia intraparenquimatosa en el lóbulo frontal derecho y hemorragia subaracnoidea. El estudio se complementó con una angiotomografía cerebral, la cual reveló un aneurisma de la arteria comunicante anterior. Fue valorada por*

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el neurocirujano pediatra y se decidió su manejo en la unidad de terapia intensiva pediátrica. A las 2 semanas de iniciado el evento se realizó clipaje y exclusión del aneurisma. La paciente tuvo una adecuada evolución clínica y resolución de los síntomas iniciales, retomando sus actividades de la vida diaria. **Conclusiones:** *Los aneurismas cerebrales en pediatría difieren de su contraparte en los adultos, principalmente en su etiología y evolución, ya que los pacientes pediátricos tienen mayor expectativa de vida. El clipaje del aneurisma y la terapia endovascular neurológica han mostrado resultados similares.*

Palabras clave: *Aneurisma cerebral. Pediatría. Clipaje de aneurisma. Terapia endovascular.*

Introduction

Internationally, cerebral aneurysms in pediatrics represent < 4% of all aneurysms[1,2], and their rupture has a mortality rate of 10-23%. They have been associated with infections, traumatic brain injury (TBI), sickle cell anemia, cardiovascular diseases, autoimmune diseases, immunodeficiencies, connective tissue diseases, dysmorphic syndromes, and family history of aneurysms. The clinical presentation is due to subarachnoid and intraparenchymal hemorrhage and the mass effect caused by the size of the aneurysm, which can produce severe headaches, seizures, disorientation, motor-sensory deficit, and even death. Diagnosis is made by cranial computed tomography angiography (CTA), cerebral magnetic resonance angiography (MRA), and, ideally, with four-vessel cerebral digital subtraction angiography (DSA)[3,4].

Aneurysms should be considered as one of the differential diagnoses in patients with the described clinical manifestations and associated pathologies for prompt diagnosis and treatment.

Clinical case

We describe the case of a 12-year-old female patient who presented with a sudden intense headache while at home and without exertion. She was initially managed with oral paracetamol at home, and after 72 hours, she developed generalized tonic-clonic seizures and was transferred to the hospital, where she was stabilized with antiepileptics and analgesics. She immediately underwent a simple cranial tomography, which showed an intraparenchymal hemorrhage within the right frontal lobe and a subarachnoid hemorrhage in the interhemispheric fissure. The study was complemented with a CTA, showing a 12 mm bilobed saccular aneurysm in the anterior communicating artery, so she was evaluated by the pediatric neurosurgeon (Figure 1).

The patient was awake, with a tendency to somnolence, reactive isochoric pupils (3 mm), without cranial nerve involvement, left body hemiparesis with strength 4/5. She presented the following scores: on the Glasgow Coma Scale, 12 points (O3, V4, M5); on the World Federation of Neurologic Surgeons scale (WFNS), grade IV; on the Hunt and Hess scale, grade 3, and on the Fisher scale, grade 4 (by tomography). Management was decided in the Pediatric Intensive Care Unit (PICU) to ensure stability, and clipping of the aneurysm was performed by right pterional craniotomy two weeks after the event (Figure 2). The patient was extubated 72 hours after the procedure and subsequently returned to the ward for continued management.

On day 7, a postoperative CTA was performed, which showed adequate clipping and exclusion of the aneurysm (Figure 3). The patient was evaluated by Rheumatology, Cardiology, Neurology, Infectology, and Genetics, performing whole body CTA, echocardiography, bilateral renal ultrasound, and immunological tests. However, it was not possible to identify the etiology of the aneurysm. She was discharged on postoperative day 8 with an antiepileptic drug and resolution of symptoms. She is currently asymptomatic with outpatient follow-up.

Discussion

Aneurysms are classified according to their size and morphology and can be single or multiple in 10% of cases. By size, they are small (< 5 mm), large (6-24 mm), or giant (> 25 mm). Morphologically, they are saccular and fusiform or dissecting. Their location has a predilection for the anterior circulation in 75% of cases, with the internal carotid artery, middle cerebral artery, and anterior cerebral artery being the most frequent locations, and the posterior circulation in 25%, most commonly in the basilar artery. The location and size are similar in pediatric and adult patients[1,5].

In pediatric patients, aneurysm etiology is identified in < 50% of the cases; 5-10% are associated with TBI, 15% with infections, and 50% with vascular dissection. TBI-associated aneurysms cause a lesion of the three vascular layers, producing pseudoaneurysms and true aneurysms. Those related to infections (generally by *Staphylococcus aureus*, *Streptococcus viridans*, and

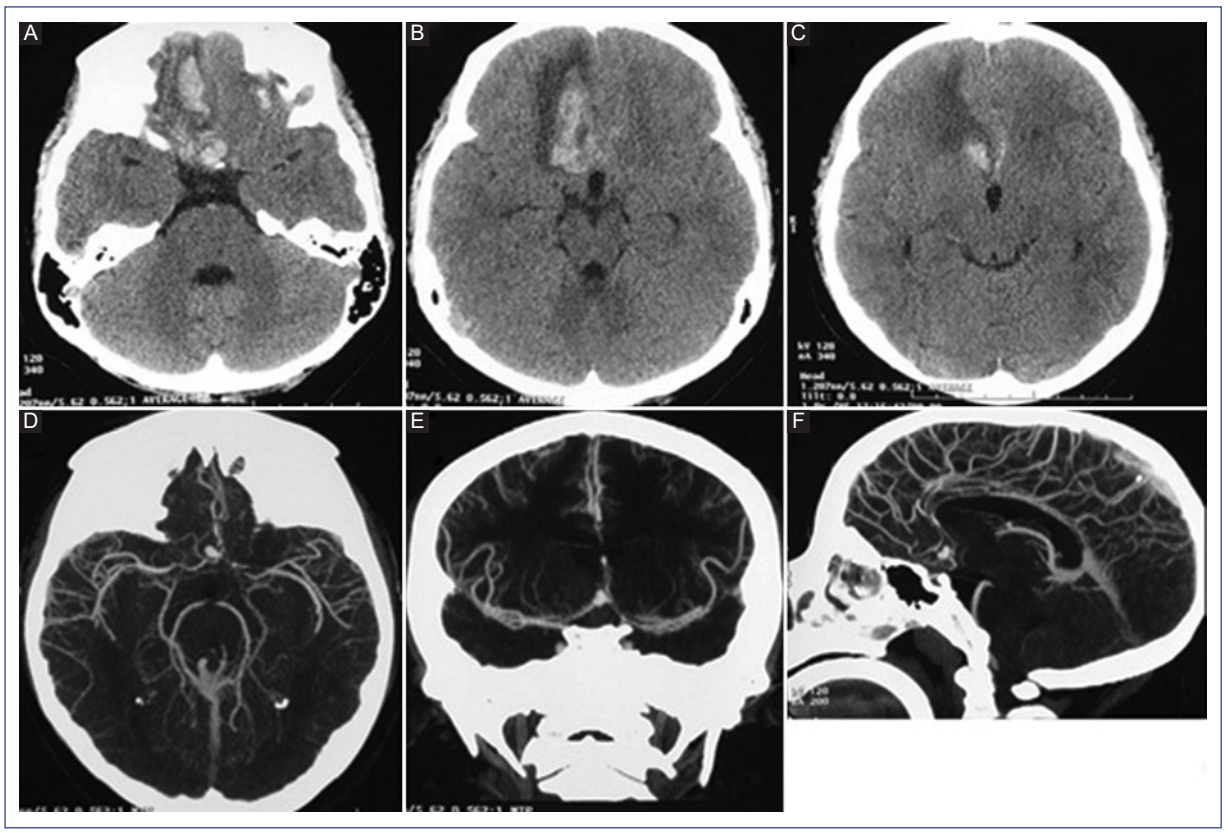

Figure 1. A-C: Axial section of the simple cranial tomography showing a hemorrhage in the medial side of the right frontal lobe. **D-F:** Axial, coronal, and sagittal tomography-angiography showing bilobed aneurysm of the anterior communicating artery.

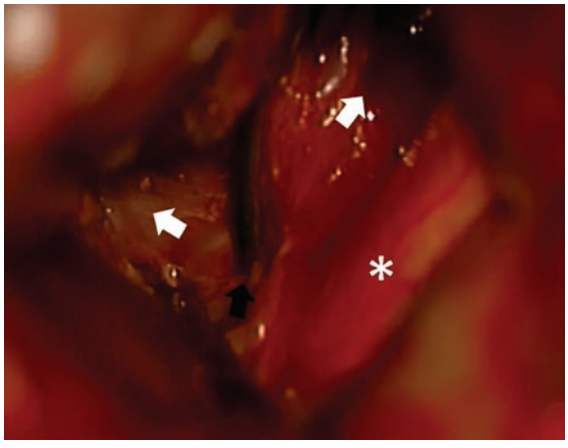

Figure 2. Intraoperative image showing the bilobed suprachiasmatic aneurysm. The optic chiasm (asterisk), the transient clip (black arrow), and the lobes of the aneurysm with anterior and superior projection (white arrows) are observed.

other Gram-negative microorganisms) show vasculitis and consequent weakening of the vascular wall.

Dissecting aneurysms are caused by endothelial injury and transmural vascular dissection that weakens the muscular and adventitial layer. They are associated with medical-genetic diseases (polycystic kidney disease, aortic coarctation, aortic valve stenosis, moyamoya disease, sickle cell anemia, Kawasaki syndrome, Takayasu disease, human immunodeficiency virus (HIV), tuberous sclerosis, neurofibromatosis type 1, Ehler-Danlos syndrome, and Marfan syndrome)[3,5].

In adults, aneurysms develop near a vascular bifurcation point, where the endothelium is damaged, there is a thinning or absence of the muscular layer, and, frequently, there is fibrinoid material in the adventitial layer. These lesions are favored by alcohol abuse, smoking, aging, systemic arterial hypertension, and several medical (aortic aneurysm, aortic valve stenosis, aortic coarctation, Ehler-Danlos syndrome, fibromuscular dysplasia, among others) and genetic (hereditary hemorrhagic telangiectasia, intracranial arteriovenous malformation, Klinefelter syndrome, Marfan syndrome, neurofibromatosis, Noonan syndrome, pheochromocytoma, polycystic kidney disease,

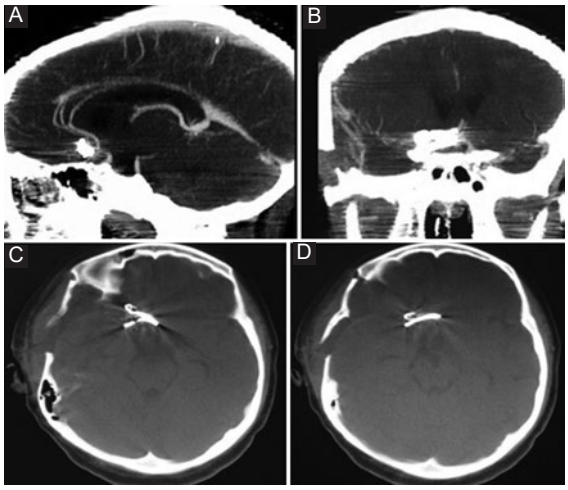

Figure 3. A, B: Sagittal and coronal sections of tomography-angiography show adequate exclusion of the aneurysm and permeability of the anterior cerebral arteries and their branches. **C, D:** Simple axial skull tomography (bone window) shows the position of vascular clips in the aneurysm.

tuberous sclerosis, alpha-1 antitrypsin deficiency, and alpha-glucosidase deficiency) conditions. Alcoholism, smoking, and hypertension are rare conditions in the pediatric population[2,6].

DSA is the gold standard for diagnosing aneurysms; however, it is increasingly common to use CTA and MRA, which have detected aneurysms larger than 3 mm in size[1,2,7-9]. DSA was not used in this study, as neurological endovascular therapy (NET) was not considered the first treatment line.

Ruptured cerebral aneurysms present high morbidity and mortality. Management by surgical clipping or NET should be performed once diagnosed. However, vasospasm and cerebral edema may limit such management. Therefore, the recommendations are to operate in the first 72 hours of the event or wait until cerebral edema decreases to favor microsurgical management and also in cases with poor neurological status. These recommendations are based on the adult population. In the case of multiple aneurysms, Burkhardt et al. proposed clipping the ruptured aneurysm first and then waiting up to 30 days to treat the rest, with no impact on the patient[10]. There is no consensus on the timing of surgery in the pediatric population. Unlike adults, in whom vasospasm is the leading cause of death, vasospasm is tolerated in children due to leptomeningeal circulation and higher cerebral blood flow, allowing more time to reduce cerebral edema and facilitate exposure of the aneurysm for clipping[2,3,6,11].

Aryan et al. conducted a study of 50 patients with aneurysms, in which clipping was performed in 78.8%, all in the anterior circulation, and NET was used in 21.2% located in the posterior circulation[12]. Additionally, Sanai et al. reported similar results with both techniques in 32 patients: clipping was performed in 40% and NET in 60%, but they found residual aneurysm or recurrence in 19% of the NET group and no recurrence in the clipping group[13].

Lasjaunias et al. conducted a study in 59 patients with aneurysms, in which they embolized (68.8%), clipped (21.9%), or used combined treatment in 9.3% of cases. These authors observed complete exclusion of the aneurysm in patients who underwent clipping and recurrence of 8.3% in those who underwent embolization[14]. Furthermore, in a study of 22 patients, Proust et al. performed clipping in 77.3%, NET in 18.2%, and combined therapy in 4.5%; in the patients in whom clipping was performed, the aneurysms were located in the anterior circulation[15]. In a series of 22 patients with aneurysms, 77% located in the anterior circulation and 23% in the posterior circulation, Slator et al. embolized 80% and performed clipping in 20%, without finding statistically significant differences between the treatments used[16]. In another case series of 6 patients < 1 year of age with giant aneurysms, Ren Y et al. recommended clipping since it allows draining the intraparenchymal hematoma, excluding the aneurysm and removing the mass effect, a situation not offered by NET. However, they recognize that NET produces less bleeding than clipping[17].

Garg et al. treated 62 patients with aneurysms: 51.6% underwent clipping, 30.6% underwent NET, 6.4% underwent another type of treatment (bypass or ligation of the main aneurysm artery), and 9.6% underwent conservative management; 1.6% died before surgery. Of the aneurysms, 3.2% were of infectious origin, and another 3.2% were post-traumatic. The authors found no differences between the clipping group and the NET group, and patients did not have recurrence either; they mentioned that the treatment decision was influenced by its cost since clipping is less expensive than NET[18]. Requejo et al. treated 17 patients with aneurysms: 23.5% underwent clipping, 64.7% underwent NET, 5.8% were managed conservatively, and the other 5.8% died before surgical management. The authors reported similar results with NET and clipping[19]. Of 10 patients with aneurysms, Thioub et al. performed

clipping in 7 and NET in one. One of the patients died during anesthetic induction, and another did not accept surgical management. Also, one aneurysm was of traumatic origin and four with possible infectious origin. The authors recommend clipping when socioeconomic conditions are unfavorable[20]. Ilovar et al. treated eight patients with cerebral aneurysms: one underwent clipping, four underwent NET, and three were managed conservatively (two incidental and one symptomatic), concluding that endovascular and microsurgical management are similar[21].

In two international trials, Molyneux et al.[22,23] demonstrated that clipping offers more prolonged survival and a lower risk of rebleeding than NET in managing cerebral aneurysms.

Four cases of aneurysms in pediatric patients have been reported in Mexico: Mercado et al. reported the case of a 14-year-old male patient with a posterior communicating artery aneurysm and aortic coarctation resolved with NET[24]. Martinez-Longoria et al. reported the second case: a 12-year-old female patient with HIV and a fusiform aneurysm of the right internal carotid artery associated with vasculitis. The patient was managed conservatively and presented remission of the aneurysm at 6 months[25]. Palomera Gómez et al. reported the case of a 10-year-old female patient with a large aneurysm of the right carotid apex[26]. Finally, Escobar-de la Garma et al. reported the case of an 11-year-old male patient with a small aneurysm of the left internal carotid artery bifurcation[27]. These last two cases were resolved with clipping of the aneurysm.

In conclusion, pediatric cerebral aneurysms differ from their adult counterparts mainly in their etiology and evolution. Although aneurysm clipping and NET have shown similar results, more recommendations are still needed to choose the best option in children. Due to a longer life expectancy, pediatric patients should be offered the best therapeutic option.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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CLINICAL CASE

Systemic lupus erythematosus complicated with macrophage activation syndrome mimicking COVID-19 multisystemic inflammatory syndrome in children

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Abstract

Background: *Macrophage activation syndrome (MAS) is characterized by excessive activation of macrophages and lymphocytes, leading to multiorgan dysfunction. As the initial manifestation of systemic lupus erythematosus (SLE), MAS is rare in children. Due to the COVID-19 pandemic, it is vital to identify the MAS as it shares similar characteristics with the multisystem inflammatory syndrome in children (MIS-C).* **Case report:** *We report the case of an 11-year-old male adolescent with symptoms of MIS-C. Although with negative results of RT-PCR (reverse transcription-polymerase chain reaction) and serology for SARS-CoV-2, contact with a positive COVID-19 relative was reported. When admitted to a referral hospital center, the patient received standard treatment for MIS-C. Although the same scheme was given on three occasions, the patient showed no response to initial therapy. Thus, the patient was classified as a refractory case. When the study was extended to other differential diagnoses, we found MAS associated with SLE. Therefore, the patient was treated with etoposide, cyclosporine, dexamethasone, and methotrexate and showed a good clinical response.* **Conclusions:** *MAS associated with SLE is rare in the pediatric population. MAS shares inflammatory markers with the MIS-C and is often confused with rheumatologic, infectious, and neoplastic entities. Reporting this case is important to identify differential diagnoses in patients presenting as MIS-C and decide on timely treatment, as it could be harmful or even fatal if a definitive diagnosis is not obtained on time.*

Keywords: *Macrophage activation syndrome. Systemic lupus erythematosus. Child. SARS-CoV-2.*

Lupus eritematoso sistémico complicado con síndrome de activación macrofágica mimetizando el síndrome multisistémico inflamatorio secundario a la COVID-19 en pediatría

Resumen

Introducción: *El síndrome de activación de macrófagos (SAM) se caracteriza por una activación excesiva de los macrófagos y de los linfocitos que conduce a una disfunción multiorgánica. Como manifestación inicial del lupus eritematoso sistémico (LES), el SAM es poco común en la infancia. Debido a la pandemia de COVID-19, es importante identificar el SAM, ya que*

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comparte características similares con el síndrome inflamatorio multisistémico en niños (MIS-C, por sus siglas en inglés). **Caso clínico:** *Presentamos el caso de un varón de 11 años con síntomas de MIS-C. Resultó negativo en la prueba de reacción en cadena de la polimerasa con retrotranscriptasa y en la serología para SARS-CoV-2, aunque reportó contacto con un familiar positivo para COVID-19. Ingresó en un centro hospitalario de referencia y recibió tratamiento estandarizado para MIS-C. A pesar de recibir el mismo esquema en tres ocasiones, no mostró respuesta a la terapia inicial, por lo que fue clasificado como caso refractario. Al ampliar el estudio para otros diferenciales, se encontró SAM asociado con LES, por lo que el paciente recibió tratamiento con etopósido, ciclosporina, dexametasona y metotrexato, y mostró buena respuesta clínica.* **Conclusiones:** *La asociación entre el SAM y el LES es rara en la población pediátrica. El SAM comparte marcadores inflamatorios con el MIS-C y suele confundirse con enfermedades reumatológicas, infecciosas y neoplásicas. La importancia de reportar este caso es identificar los diagnósticos diferenciales en los pacientes que se presentan como MIS-C, y decidir el tratamiento con prontitud, pues podría ser dañino o incluso fatal si no se obtiene un diagnóstico definitivo a tiempo.*

Palabras clave: *Síndrome de activación macrofágica. Lupus eritematoso sistémico. Niño. SARS-CoV-2.*

Introduction

Macrophage activation syndrome (MAS) is characterized by an immune dysregulation secondary to macrophage and lymphocyte proliferation leading to systemic hyperinflammation[1]. MAS associated with systemic lupus erythematosus (SLE) is rare. Fukaya et al. reported 18 patients with hemophagocytic syndrome and SLE among 350 patients admitted with SLE to a hospital in Japan between 1997 to 2007 (a study population-specific frequency of 5%)[2].

Multisystemic inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 is a recently described entity[3]. Rigorous use of clinical criteria for MIS-C without considering it a dynamic, evolving entity with imprecise limits could lead to diagnostic errors. Regardless of a consensus international definition, it is necessary to apply medical reasoning in managing these patients. Given that MIS-C presents with specific signs and symptoms and different clinical presentations[4], we report this case to describe the association between MAS and SLE in a male pediatric patient initially diagnosed with MIS-C due to overlapping clinical features.

Clinical case

We describe the case of a previously healthy 11-year-old Hispanic male from Lima, Peru, who was admitted to the pediatric emergency department with a history of skin erythema, general discomfort, headache, and arthralgias with a duration of one week. One day before admission, he presented with nausea, vomiting, abdominal pain, and fever. RT-PCR (reverse transcription-polymerase chain reaction) for SARS-CoV-2 was negative; however, two months earlier, the mother was positive for COVID-19.

Oxygen saturation was 98%, heart rate 110 bpm, temperature 37.6°C, respiratory rate 20 rpm, blood pressure 106/70 mmHg, weight 57 kg, and he showed a facial expression consistent with pain. On physical examination, he had an erythematous rash on the anterior region of the right chest and the palms of the hands, hip arthralgia, and chest pain over the ribs on palpation. Bilateral cutaneous findings are shown in Figure 1. The patient presented with diffuse abdomen tender to palpation, McBurney (+), fever, and decreased joint mobility ranges in arms and legs due to pain. Laboratory test results showed inflammatory markers including leukocytosis, lymphopenia, and elevated C-reactive protein levels, d-dimer, elevated pro-B natriuretic peptide, ferritin, and fibrinogen.

With the diagnosis of MIS-C, the patient was treated with intravenous immunoglobulin (2 g/kg/dose), acetylsalicylic acid (50 mg/kg/day), and methylprednisolone acetate (2 mg/kg/day). Upon clinical and inflammatory marker improvement, he was discharged. However, on the ninth day since the initial presentation, he was readmitted with a similar clinical picture, fever, and elevated inflammatory markers. Therefore, the admission diagnosis was refractory MIS-C associated with suspected sepsis. Extensive empirical treatment of antibiotic coverage and a second dose of immunoglobulin and corticosteroids was started. An echocardiography study showed normal coronary arteries, a patent foramen ovale (1.6 mm), mild left ventricular diastolic dysfunction, no signs of pulmonary hypertension, and no pericardial effusion. An abdominal CT scan showed hepatosplenomegaly, and a chest X-ray demonstrated bilateral pulmonary consolidation. Forty-eight hours after initiating treatment, fever persisted, and a diffuse exanthema was observed. Inflammatory markers were elevated, including interleukin-6 (Table 1). The third cycle of immunoglobulin with corticosteroid pulse was administered, and prophylactic anticoagulation was ordered. The list of differential diagnoses was reviewed,

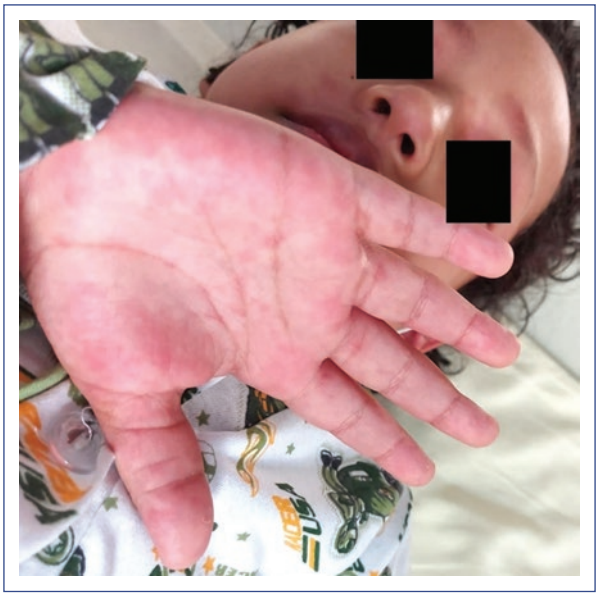

Figure 1. Maculopapular eruptions on hands.

and it was decided to extend the study to infectious, hemato-oncologic, and rheumatologic causes.

On day 22 of admission, the patient remained febrile; laboratory results revealed a quantitative increase of inflammatory markers, worsening anemia, worsening thrombocytopenia, severe hyperferritinemia, severe transaminitis, hypertriglyceridemia, and hypocomplementemia (C3 and C4) (Table 1). We performed a bone marrow aspirate, which showed granulocytes and platelet hemophagocytosis with the presence of histiocytes. A positive antinuclear antibody with a speckled nucleated pattern was obtained in titer 1/320: autoantibodies against positive Ro52 recombinant antigens and positive lupus anticoagulant. The infectious study revealed positive serology for *Bartonella henselae*. Given the diagnosis of MAS due to SLE, a chemotherapy treatment protocol was initiated, including etoposide, cyclosporine, dexamethasone, and methotrexate. The patient presented complications secondary to chemotherapy (febrile neutropenia, severe pancytopenia) and received broad-spectrum antibiotic coverage, including *Bartonella* therapy and antifungal treatment. As we observed a good clinical response to treatment and normal paraclinical tests, home discharge and outpatient follow-up was indicated.

Discussion

The new presenting condition secondary to SARS-CoV-2 infection in children is MIS-C[3]. Its early recognition for pediatricians could be challenging, and the appropriate indication of therapeutic options is still under debate. There may be a high bias in MIS-C diagnosis during the pandemic, also considering that diagnostic definitions are broad.

Here, we report a case with a problematic diagnostic pathway due to a presentation similar to MIS-C, hemophagocytic lymphohistiocytosis (HLH), and macrophage activation syndrome (MAS). Several diseases may present with similar clinical manifestations, so we may currently overestimate the diagnosis of MIS-C in the pediatric population. Similarly, the use of empiric therapy without a definitive diagnosis and the cost-benefit should be evaluated. MIS-C is a syndrome and a new pathologic entity with a solid epidemiologic correlation. It is a primary diagnosis in any patient with clinical presentation, as in this case, but it is not always the presenting disease.

The sequelae and mortality of pediatric SLE are associated with several risk factors: age at early diagnosis, male sex, and non-Caucasian race (African American, Asian, and Hispanic). Most children present with fever, arthralgia, arthritis, rash, myalgia, fatigue, and weight loss. These symptoms are quite nonspecific, so the patient must meet the diagnostic criteria determined by the American College of Rheumatology, as described in this case[5]. Gracia-Ramos presented a review of cases linking lupus erythematosus and SARS-CoV-2. However, the presentation of MAS mimicking MIS-C in a pediatric patient has not been described, thus presenting different challenges[6]. A difference of presentation between MIS-C and MAS can be observed in Figure 2.

MAS falls within the “cytokine storm syndrome” spectrum and is characterized by low blood cell count (cytopenia) and multiorgan failure, involving the lung, liver, kidney, and heart[1]. In addition to elevated serum cytokines, elevated ferritin concentrations are characteristic of this syndrome. Macrophages expressing CD163 are the source of ferritin; in this sense, elevated serum ferritin is also a biomarker of poor prognosis[1].

In the case of negative RT-PCR and serology for SARS-CoV-2 and high clinical suspicion of MIS-C, repeat serology is recommended 3-4 weeks after admission. It has been described that 26-55% of patients with MIS-C have positive RT-PCR and up to 90% positive IgG serology[7,8]. The broad diagnosis that mentions a positive contact as a diagnostic criterion can be misleading.

MAS-associated SLE is rare. Children with rheumatologic conditions such as SLE and Kawasaki disease

Table 1. Evolution of paraclinical results during hospitalization

Laboratory	Reference range	Days of hospitalization										
		0	4	9	11	12	15	22	37	39	48	59
Leukocytes (x10^3/µL)	5.0-14.5	20.26	11.30	25.76	21.63	16.28	11.45	9.07	2.45	5.29	11.01	8.61
Neutrophils (x10^3/µL)	1.8-8.0	17.91	8.60	24.12	19.65	14.11	9.02	6.4	0.78	2.70	6.09	4.04
Lymphocytes (x10^3/µL)	0.9-5.2	1.10	1.69	1.05	1.29	0.98	1.55	1.98	1.05	1.38	3.73	4.13
Hemoglobin (g/dL)	11.5-15.5	12.7	12	11.3	11.2	10.9	11.1	10.2	12	11.1	9.9	9.9
Platelets (x10^3/µL)	150-400	318	309	382	405	309	229	79	195	132	393	517
Urea (mg/dL)	22-55	30	32.1	21.4	27.8	21.4	15	25.7	—	19.3	21.4	44.9
Creatinine (mg/dL)	0.3-0.7	0.45	0.29	0.44	0.48	0.34	0.34	0.36	—	0.38	0.32	0.58
Albumin (g/dL)	3.2-4.8	4.38	3.66	3.42	3.23	2.78	2.86	3.09	4.17	3.44	3.42	4.95
LDH (U/L)	120-246	297	304	—	—	368	723	2760	671	665	582	291
Cholesterol (mg/dL)	<200	—	—	109	—	76	102	104	—	—	164	254
Triglycerides (mg/dL)	<250	—	—	117	—	93	102	313	—	—	316	275
Ferritin (ng/mL)	28-365	1409	—	5985	8592	—	32473	75706	—	—	5776	1949
C-reactive protein (mg/dL)	0-1.0	23.7	12.7	10.8	13.4	17.3	11.4	8.4	—	10.8	3.7	—
GOT (U/L)	10-35	29	43	43	40	62	76	651	153	141	125	64
GPT (U/L)	10-49	34	30	48	37	44	37	424	189	191	159	148
CPK (U/L)	34-145	23	—	18	—	—	23	—	—	—	—	—
CPK-MB (ng/mL)	0-6	—	0.3	—	< 0.3	—	—	—	—	—	—	—
Pro-BNP (pg/mL)	0-125	9.3	278.1	—	—	—	—	158	—	—	—	—
Troponins (ng/mL)	0-0.01	< 0.003	< 0.003	—	0.005	—	—	< 0.003	—	—	—	—
Fibrinogen (mg/dL)	200-400	632.04	468.9	521.02	420.49	371.4	342.07	201.62	—	422.69	453.45	561.2
D-dimer (ug/mL)	0-0.54	5.23	—	1.7	4.3	22.95	16.41	29.37	—	6.45	—	—
IL-6 (pg/mL)	0-2.0	—	—	—	77.2	—	—	—	—	—	—	—

BNP, B-natriuretic peptide; CPK, creatine phosphokinase; CPK-MB, creatine phosphokinase myocardial band; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; IL-6, interleukin 6; LDH, lactate dehydrogenase.

are also at risk for MAS[1]. Borgia et al. reported 9% of patients with SLE and MAS in a cohort of children in Canada[9]. In this study, most patients with MAS were female, and the mean age at diagnosis of SLE was 13 years[9]. MAS is primarily described in patients with juvenile idiopathic arthritis (JIA) but can occur in different rheumatologic diseases. Bennett et al. described 121 patients with MAS; only 19 pediatric patients had MAS secondary to SLE[10]. The case described here falls into this reduced group of patients. In the previously mentioned study, patients with SLE presented similar mortality but required more ICU care, more mechanical ventilation, and higher vasopressor support[10].

Our patient was diagnosed with MAS secondary to SLE. Delayed treatment of this condition could have been life-threatening and could have progressed into multiorgan failure. Treatment of secondary MAS is directed at the underlying condition[1]. Gupta et al. reported a case of a 15-year-old female patient with MAS secondary to SLE who received methylprednisolone pulses and oral cyclosporine with a good response to treatment[11]. This report was similar to another case in a 22-year-old male treated with methylprednisolone pulses and azathioprine[12]. Similar to previous reports,

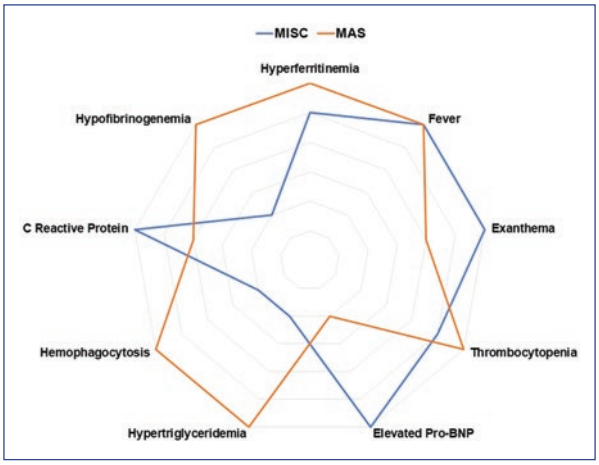

Figure 2. Differential diagnosis of multisystem inflammatory syndrome in children (MIS-C) and macrophage activation syndrome (MAS).
BNP, B-natriuretic peptide.

our patient had an adequate evolution with the proposed treatment for this disease[13]. In addition, the patient was managed by a multidisciplinary group including oncology and rheumatology, with a hybrid therapy scheme for HLH and MAS.

The coexistence of SLE and MAS has overlapping clinical features, so a high level of suspicion is necessary for diagnosis. Rapid initiation of treatment of MAS is of extreme importance, as it is a potentially fatal and rapidly progressive condition, even with adequate treatment.

In conclusion, MAS-associated SLE is rare. Identification of differential etiologic diagnoses that share MIS-C criteria is critical to avoid delays in therapies. MIS-C refractory to treatment should raise suspicion of other etiologies such as MAS, which can be fatal if a definitive diagnosis is not reached.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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CASO CLÍNICO

Sarcoma hepático embrionario indiferenciado: reporte de caso y revisión de la literatura

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Resumen

Introducción: *El sarcoma hepático embrionario indiferenciado representa el 9-13% de los tumores hepáticos malignos en la edad pediátrica y es la tercera neoplasia maligna primaria de hígado en la infancia. Sin embargo, son pocos los casos reportados en la literatura. Se puede manifestar con fiebre, pérdida de peso, dolor y sensación de tumor abdominal. Los estudios de imagen, además de los estudios anatomopatológico e inmunohistoquímico, son las herramientas adecuadas para el diagnóstico.* **Caso clínico:** *Se presenta el caso de una paciente de 6 años de edad con diagnóstico de sarcoma hepático embrionario indiferenciado mediante cirugía y posterior resultado de la biopsia.* **Conclusiones:** *Al revisar la literatura se encontró que este tipo de neoplasia maligna no es frecuente en la infancia. Sin embargo, es importante considerar este tipo de tumor como causa en aquellos casos de hepatomegalia en la edad pediátrica.*

Palabras clave: *Sarcoma hepático embrionario indiferenciado. Neoplasia maligna. Inmunohistoquímica.*

Undifferentiated embryonal liver sarcoma: case report and review of the literature

Abstract

Background: *Undifferentiated embryonal sarcoma of the liver accounts for 9-13% of malignant tumors in the pediatric age group, and is the third primary malignant neoplasm of the liver in children. However, few cases are reported in the literature. It may manifest with fever, weight loss, pain, and abdominal tumor sensation. In addition to pathology and immunohistochemistry, imaging studies are the appropriate tools for diagnosis.* **Case report:** *We present the case of a 6-year-old female patient diagnosed with undifferentiated embryonal sarcoma of the liver by surgery and subsequent biopsy results.* **Conclusions:** *When reviewing the literature, we found that this type of malignant neoplasm is not frequent in children. However, it is important to consider this type of tumor as a cause in those cases of hepatomegaly in the pediatric age.*

Keywords: *Undifferentiated embryonal sarcoma of the liver. Malignant neoplasm. Immunohistochemistry.*

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Introducción

Las neoplasias primarias de hígado representan aproximadamente el 0.5-2% de los tumores en la edad pediátrica[1]. En 1978, Stocker e Ishak[2] describieron el sarcoma hepático embrionario indiferenciado como una condición clínico-patológica que se subdivide en rabdomiosarcoma biliar, angiosarcoma, rabdoide e indiferenciado (Tabla 1)[3,4].

Esta enfermedad se manifiesta principalmente en niños entre los 5 y 12 años de edad, con una distribución similar en ambos sexos. Después del hepatoblastoma y del carcinoma hepatocelular, el sarcoma hepático ocupa el tercer lugar de frecuencia, con un 9-13%. Se puede presentar con las siguientes manifestaciones clínicas: disnea, pérdida de peso, mal estado general, dolor epigástrico y tumor hepático palpable de grandes dimensiones, predominantemente en el lóbulo hepático derecho[5]. Las pruebas de función hepática tienden a resultar normales o ligeramente elevadas, y pocas veces los marcadores tumorales, como la alfa-fetoproteína y la fracción beta de la gonadotropina coriónica humana, se encuentran incrementados[6].

El ultrasonido, la tomografía computada (TC) y la resonancia magnética son relativamente inespecíficas. En general muestran una lesión sólida, heterogénea, que puede presentar áreas quísticas (necrosis) o hemorragia, y algunas veces la lesión se observa avascular. El diagnóstico definitivo se confirma mediante histopatología con tinción de hematoxilina-eosina y análisis inmunohistoquímico, que es positivo para CD56, CD68, vimentina y desmina[7].

Histopatológicamente se observan elementos mesenquimatosos malignos sin ninguna evidencia de diferenciación específica. Dicha variabilidad histológica dificulta el diagnóstico y origina diferentes nombres: mesenquimoma maligno, rabdomiosarcoma del hígado, fibromiosarcoma, sarcoma indiferenciado o sarcoma embrionario. La relación entre el hamartoma y el sarcoma, así como con el hepatoblastoma, es un factor predisponente[8,9]. Este tipo de tumores son típicamente grandes en el momento del diagnóstico y difíciles de resecar[10].

El comportamiento clínico de este tumor es agresivo, pero potencialmente tratable con terapia multimodal, incluyendo quimioterapia, cirugía, radioterapia y, en casos específicos, trasplante de hígado[11]. Los regímenes de quimioterapia incluyen doxorubicina, ifosfamida, ciclofosfamida, vincristina y etopósido[12].

Los resultados de los estudios prospectivos de grupos europeos publicados en la última década confirman la baja frecuencia de este diagnóstico dentro de los tumores hepáticos malignos en niños.

Si bien la supervivencia ha mejorado, la biología y el comportamiento agresivo del tumor condicionan aún una alta mortalidad.

En el año 2002 se reportaron los resultados de 17 pacientes con diagnóstico de sarcoma hepático indiferenciado tratados entre 1979 y 1995 por el grupo colaborativo italiano y alemán de sarcomas en tejidos blandos. Diez de los 17 pacientes (58%) se encontraban vivos con un seguimiento de entre 2.4 y 20 años. De los pacientes en que se documentó alguna recaída, uno de ellos aún vivía después de 4 años de la recurrencia y había respondido adecuadamente.

Tabla 1. Diagnóstico diferencial de neoplasias malignas hepáticas según sus marcadores inmunohistoquímicos

Neoplasia hepática maligna	Marcadores inmunohistoquímicos
Hepatoblastoma	Ki-67
Carcinoma hepatocelular	HepPar-1, glipican-3, arginasa, HSP70, CD34
Sarcoma Rabdomiosarcoma biliar Angiosarcoma Rabdoide Indiferenciado	 CK7, CK19, CD31, CD34, citoqueratina CD31, CD 34 Vimentina, desmina, CD56, CD68
Metástasis	CK8, CK18, CK20
Tumor de Wilms	CD99, CD56, actina, mioglobina, desmina
Neuroblastoma	Enolasa
Colorrectal	CK20
Tumor carcinoide	Cromogranina, sinaptofisina
Hemangioendotelioma kaposiforme	CD31, CD34
Linfohistiocitosis hemofagocítica	CD68
Histiocitosis de células de Langerhans	S-100, CD1-a
Leucemia megacarioblástica	CD61

Caso clínico

Se presenta el caso de una paciente de 6 años, previamente sana, con antecedente familiar de cáncer cervicouterino por rama materna. Inició su padecimiento actual 2 semanas antes de su ingreso, al

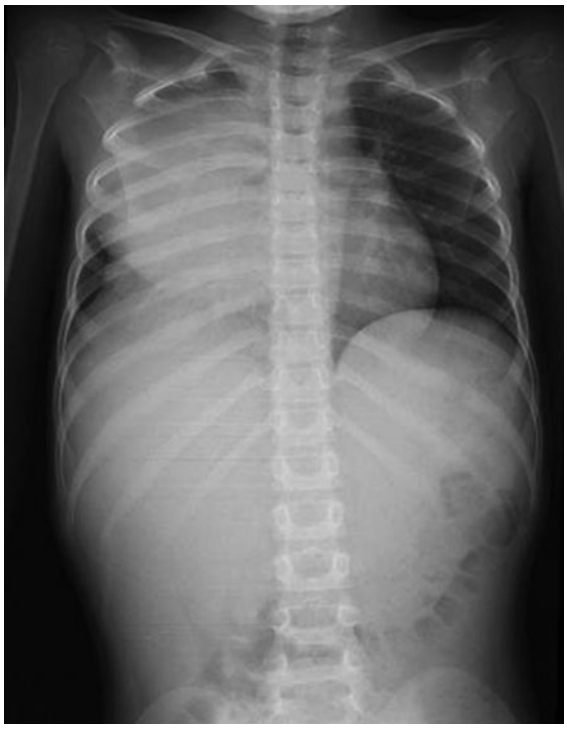

Figura 1. Radiografía de tórax con radioopacidad del hemitórax derecho, signo de silueta y atelectasia adyacente.

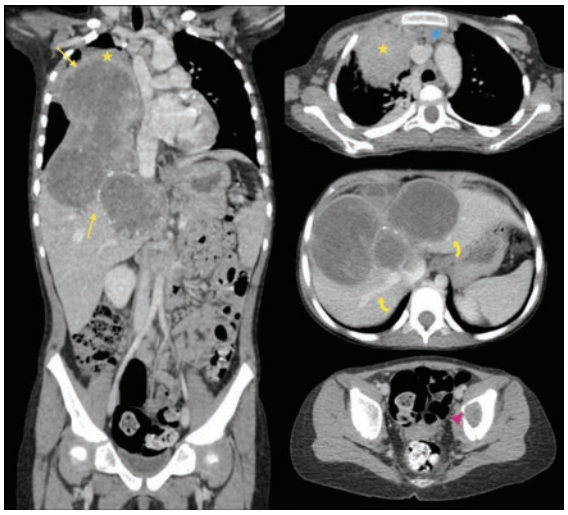

Figura 2. Tomografía computada toracoabdominal contrastada. Cortes sagital y axial que evidencian una tumoración hepática con extensión supradiafragmática derecha (⇨), atelectasia del lóbulo medio derecho (☆), íntimo contacto con las venas suprahepáticas derecha e izquierda con involucro de la media (◠), adenopatías mediastinales (★) y lesión lítica en el hueso ilíaco izquierdo (◥).

presentar fiebre intermitente de predominio nocturno. Al acudir a su médico particular, este solicitó una radiografía de tórax que evidenció una radioopacidad que ocupaba casi la totalidad del hemitórax derecho, con signo de silueta respecto a las estructuras cardiomediastínicas y atelectasia del pulmón adyacente (Figura 1), por lo que fue remitida a un hospital de tercer nivel.

A su ingreso en el hospital, la exploración física reveló hepatomegalia > 5 cm, no dolorosa, fija a planos profundos, sugerente de tumor hepático. Los estudios de laboratorio reportaron anemia microcítica hipocrómica, pruebas de función hepática normales, y fosfatasa alcalina y lactato deshidrogenasa elevadas. A continuación se realizó una TC toracoabdominal contrastada en la que se evidenció hepatomegalia condicionada por una tumoración de 14 × 12 × 7.8 cm que afectaba los segmentos VIII, V, IVa y el lóbulo caudado, predominantemente hipodensa, de aspecto sólido, asociada con áreas de necrosis y hemorragia. Con un borde lobulado y circunscrito, y presencia de calcificaciones periféricas, la lesión se extendía hacia la zona supradiafragmática con ocupación del hemitórax derecho, condicionando el desplazamiento del parénquima pulmonar y atelectasia del lóbulo medio derecho. Además, la lesión mostraba extensión anterior, posicionándose adyacente a la pared abdominal y en íntimo contacto con las venas suprahepáticas derecha e izquierda; también involucraba la vena suprahepática media, comprimiendo la vena cava inferior y la aurícula izquierda. Asimismo, se identificaron múltiples adenopatías mediastinales y una lesión lítica con componente de tejidos blandos en el hueso ilíaco izquierdo (Figura 2).

Por sospecha de neoplasia hepática maligna, se solicitó su valoración por los servicios de oncología y cirugía pediátrica. Debido a la fiebre persistente, se sospechó un absceso hepático, por lo que se realizó un ultrasonido abdominal en el que se reportaron múltiples lesiones hepáticas. Se solicitó una biopsia, que se realizó por radiointervencionismo guiado por ultrasonido con búsqueda intencionada de *Entamoeba*. Se reportó necrosis masiva de aspecto neoplásico, además de la prueba serológica negativa. Se evaluaron los marcadores tumorales indicados por parte de oncología pediátrica: alfa-fetoproteína de 1.74 ng/mL y fracción beta de la gonadotropina coriónica humana < 0.10 mUI/mL, ambos dentro de los valores normales.

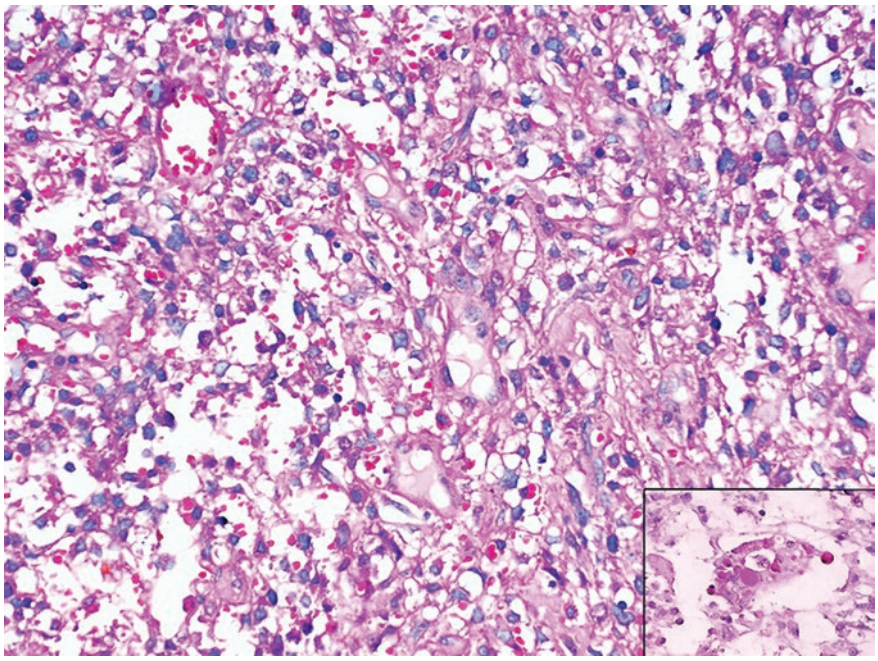

Figura 3. Neoplasia mesenquimatosa primitiva compuesta por células redondas a ovales indiferenciadas. Se identificaron glóbulos hialinos ocasionales (recuadro) (tinción con hematoxilina y eosina 40×).

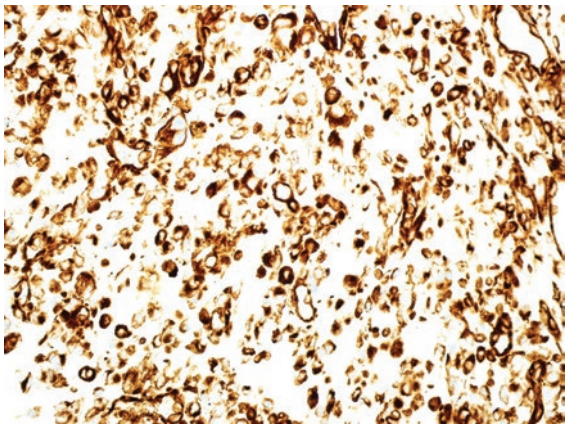

Figura 4. Células neoplásicas fuertemente positivas para vimentina (40×).

Con respecto a la evolución de la paciente, presentó compromiso neurológico a expensas de crisis convulsivas tónico-clónicas, aparentemente relacionadas con alteraciones electrolíticas. Se solicitó estudio de imagen que descartó la infiltración al sistema nervioso central. Se realizó una nueva biopsia a cielo abierto, en la que se observó un tumor con aspecto de racimo de uvas en el epiplón. El reporte de patología informó un diagnóstico de sarcoma hepático embrionario indiferenciado con inmunohistoquímica positiva para vimentina y negativa para desmina, CD56 y CD58 (Figuras 3 y 4). Posteriormente se inició tratamiento de quimioterapia con vincristina, ifosfamida y etopósido. La paciente cumplió nueve ciclos y presentó buena tolerancia y buena respuesta clínica, aunque pobre respuesta radiológica.

Se realizó una nueva TC toracoabdominal contrastada, en la que se observó la persistencia del tumor hepático (con respuesta a la quimioterapia), pero aún con involucro vascular de la vena suprahepática media y el efecto de masa de la vena cava inferior, además de la aurícula izquierda. La lesión lítica en la región ilíaca izquierda se encontró de menor tamaño.

A pesar de la pobre respuesta radiológica, la paciente se sometió a la resección del tumor primario y su extensión al tórax. Después de múltiples complicaciones transoperatorias, se logró la resección total de la tumoración. Sin embargo, la evolución fue desfavorable por complicaciones asociadas a un evento de choque hipovolémico hemorrágico, por lo que la paciente falleció 24 horas después del evento quirúrgico.

Discusión

El sarcoma indiferenciado hepático es un tumor raro, predominantemente de la edad pediátrica (aunque también puede presentarse en adultos), sin predominio por ningún sexo. En este reporte se describe el caso de una paciente de 6 años que inició con un cuadro febril de larga duración sin foco aparente. Al ser sometida a estudios de imagen se evidenció una masa que comprometía el hemitórax derecho, motivo por el cual fue referida a un hospital de segundo nivel. Se realizó una TC torácica y abdominal en la que se encontró una lesión sugestiva de hepatoblastoma que se correlacionaba con la presencia de una tumoración abdominal durante la exploración física, por lo que fue referida a un hospital de tercer nivel para su abordaje integral. En dicha institución se realizó el abordaje multidisciplinario hasta concluir con un diagnóstico histopatológico de sarcoma hepático indiferenciado, el cual correspondía, según el reporte patológico, con lo descrito en la literatura. Se encontró un tumor de aspecto heterogéneo, solitario y bien circunscrito, con predominio en el lóbulo hepático derecho. Sus características sugerían un origen mesenquimal indiferenciado. En el análisis inmunohistoquímico destacó la presencia del marcador vimentina, lo cual se describe en la literatura. El tratamiento de elección fue combinado, quimioterapia y cirugía, aunque con un pronóstico desfavorable. En esta paciente se descartó la posibilidad de un trasplante ya que, como se ha descrito en la literatura, el tratamiento ideal de estos tumores es la resección[13].

El sarcoma hepático es una neoplasia agresiva y poco frecuente en la infancia, con síntomas inespecíficos, diagnosticado mediante estudios de imagen y estudio histopatológico de una muestra obtenida por biopsia. El abordaje y el tratamiento deben ser multidisciplinarios, involucrando desde médicos de primer contacto hasta equipos de alta especialidad.

Cabe destacar que el abordaje de los tumores abdominales de probable origen hepático debe ser realizado de acuerdo con algoritmos establecidos en la literatura universal que permitan realizar el diagnóstico de manera oportuna y, por ende, el inicio temprano de un tratamiento. Este tipo de reportes de un tumor hepático de baja frecuencia en la infancia obliga al pediatra de atención primaria a considerar esta patología como una más de las causas de cuadros clínicos sugerentes de neoplasia hepática.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido el consentimiento informado de los pacientes y sujetos referidos en el artículo. Este documento obra en poder del autor de correspondencia.

Conflicto de intereses

Los autores declaran no tener ningun conflicto de intereses.

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CASO CLÍNICO

Dermatitis granulomatosa neutrofílica en empalizada como presentación inicial de lupus eritematoso sistémico

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Resumen

Introducción: *La dermatitis granulomatosa neutrofílica en empalizada es una manifestación cutánea poco frecuente en la infancia que se asocia con patologías autoinmunitarias. La patogénesis exacta de esta enfermedad aún se desconoce. Sin embargo, se ha sugerido que el depósito de complejos inmunitarios podría iniciarla.* **Caso clínico:** *Se describe el caso de una paciente de 11 años que presentó lesiones polimórficas en las extremidades asociadas a poliartralgias. Fue diagnosticada de lupus eritematoso sistémico y nefritis lúpica. Por las lesiones en la piel, se realizaron estudios histopatológico e inmunohistoquímico (CD68, CD163, mieloperoxidasa), que dieron como resultado dermatitis granulomatosa neutrofílica en empalizada. Debido al compromiso renal, se administró tratamiento con pulsos de metilprednisolona, además de hidroxicloroquina, micofenolato de mofetilo, antihipertensivos y antiinflamatorios no esteroideos. La respuesta clínica fue favorable durante el seguimiento.* **Conclusiones:** *La dermatitis granulomatosa neutrofílica en empalizada asociada a lupus eritematoso sistémico es inusual. Por ello, es importante su reconocimiento, ya que puede presentarse como manifestación inicial de la enfermedad autoinmunitaria.*

Palabras clave: *Dermatitis granulomatosa neutrofílica en empalizada. Dermatitis granulomatosa intersticial. Lupus eritematoso sistémico. Niños.*

Palisaded neutrophilic granulomatous dermatitis as the initial presentation of systemic lupus erythematosus

Abstract

Background: *Palisaded neutrophilic granulomatous dermatitis is a rare cutaneous manifestation in children associated with autoimmune pathologies. The exact pathogenesis of this disease is still unknown. However, it has been suggested that the deposition of immune complexes could initiate this pathology.* **Case report:** *We describe the case of an 11-year-old female patient who presented with polymorphic lesions in extremities associated with polyarthralgia. She was diagnosed with systemic lupus erythematosus and lupus nephritis. Because of the skin lesions, histopathological and immunohistochemical skin studies (CD68, CD163, myeloperoxidase) were performed, which resulted in palisaded neutrophilic granulomatous dermatitis. Due to renal involvement, treatment was administered with methylprednisolone pulses, hydroxychloroquine, mycophenolate mofetil, antihypertensives, and nonsteroidal anti-inflammatory drugs. The clinical response was favorable during follow-up.* **Conclusions:** *Palisaded neutrophilic granulomatous dermatitis associated with systemic*

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lupus erythematosus is unusual. Therefore, its recognition is important, as it may appear as the initial manifestation of this autoimmune disease.

Keywords: *Palisaded neutrophilic granulomatous dermatitis. Interstitial granulomatous dermatitis. Systemic lupus erythematosus. Child.*

Introducción

La dermatitis granulomatosa neutrofílica en empalizada (DGNP) es una rara erupción cutánea polimórfica y simétrica[1]. En 1951 fue descrita como granuloma de Churg-Strauss, y en 1996 Wilmoth y Perniciaro confirmaron su asociación con algunas enfermedades sistémicas en la población adulta, como artritis reumatoide y poliangeítis granulomatosa, entre otras[2]. Aunque los reportes de DGNP en pacientes pediátricos son raros, algunos han descrito su asociación con enfermedades sistémicas autoinmunitarias, como esclerosis sistémica y granulomatosis eosinofílica con poliangeítis[3].

La asociación entre DGNP y lupus eritematoso sistémico (LES) ha sido poco descrita. Terai et al.[4] reportaron una mayor frecuencia de esta asociación en adultos jóvenes (media de edad de: 36 años), con predominio del sexo femenino, acompañada de nefritis lúpica en la mayoría de los casos, mientras que Larson y Granter[5] estudiaron 14 pacientes (media de edad de: 41 años; 13 mujeres) con LES y dermatosis neutrofílica y solo encontraron un paciente con características de DGNP.

Debido a la diversidad de manifestaciones cutáneas, el diagnóstico resulta complicado, por lo que se requiere realizar un estudio histopatológico.

El objetivo de este artículo es reportar un caso de DGNP como manifestación inicial en una paciente de 11 años con debut de LES.

Caso clínico

Paciente de 11 años, de sexo femenino, que 4 meses antes de su ingreso a la institución presentó poliartralgias e hiporexia, 2 meses después aparecieron lesiones polimórficas en las zonas extensoras de los miembros superiores e inferiores, y 1 mes antes de su hospitalización presentó diariamente fiebre y debilidad generalizada que le dificultaba la deambulación.

Entre los antecedentes familiares se informaron psoriasis y fibromialgias. El esquema de vacunación estaba completo. No se reportaron hospitalizaciones previas, enfermedades ni intervenciones quirúrgicas.

En la exploración física se encontró: frecuencia cardiaca 105 latidos/min, frecuencia respiratoria 22 respiraciones/min, presión arterial 105/80 mmHg, temperatura 37.2 °C, peso 48 kg y talla 147 cm. Se observó palidez en piel y mucosas (++/+++), una úlcera no sangrante en la mucosa oral (Figura 1) y lesiones pápulo-eritematosas y vesículo-costrosas violáceas distribuidas de manera simétrica y bilateral en la zona extensora de los miembros superiores e inferiores (Figuras 2 y 3). En el examen neurológico, la puntuación en la escala de Glasgow fue 15/15, la fuerza muscular 4/5 en todas las extremidades y el tono muscular conservado, con reflejos rotulianos presentes. El resto del examen, sin alteraciones.

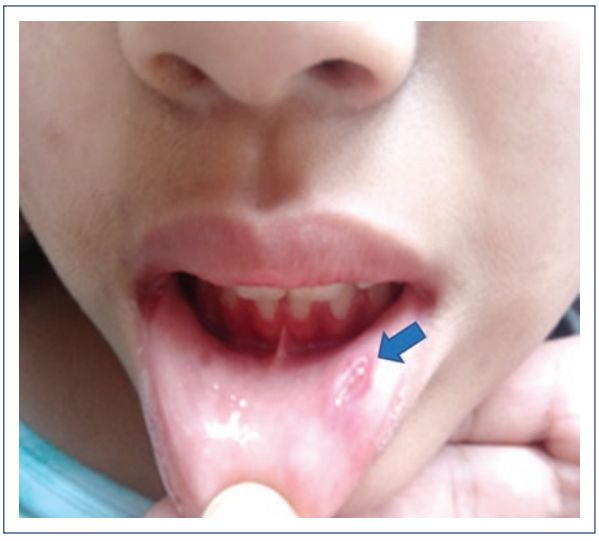

Figura 1. Úlcera de base eritematosa y bordes definidos en la mucosa yugal inferior (flecha).

En las pruebas de laboratorio se encontró: hemoglobina 8.6 g/dL, leucocitos 5170/mm^3, linfocitos 775 (valores normales [VN]:1500-6500), plaquetas 227,000/mm^3, proteína C reactiva 5.65 mg/dL y velocidad de sedimentación globular 60 mm/h. La prueba de Coombs directa fue positiva, y además se encontraron 291 mg/dL de haptoglobina (VN: 30-200), 806 U/L de lactato deshidrogenasa (VN: 230-460), 21 mg/dL de complemento C3 (VN: 90-180), 2 mg/dL de C4 (VN: 10-40), 7309 mg/mL de B2 microglobulina (VN: 699-1836), 54 mg/dl de urea (VN:10-38), 1.03 mg/dL de creatinina (VN: 0.3-0.7) y proteinuria de 2315 mg/24 h

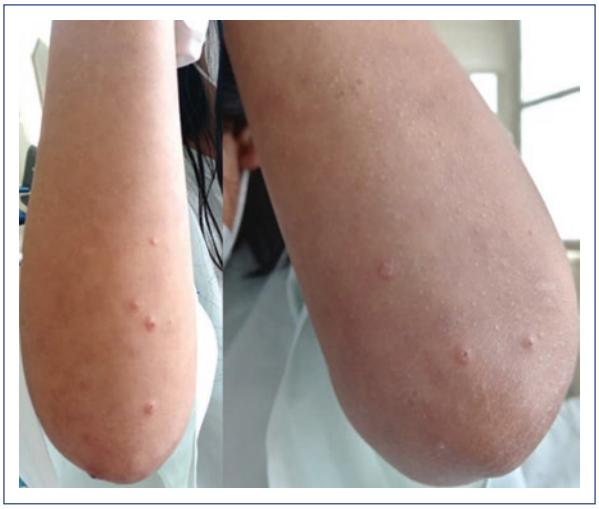

Figura 2. Pápulas con costras centrales, simétricas, en la superficie extensora de los miembros superiores.

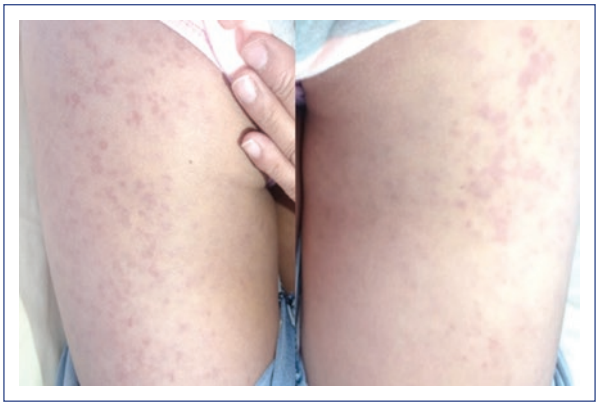

Figura 3. Placas eritemato-violáceas simétricas en la región posterior de los muslos.

(65.6 mg/m^2/h). Los electrolitos séricos estaban dentro de los valores normales y en el examen de orina se encontró hematuria. Las pruebas inmunológicas fueron positivas para anticuerpos antinucleares (título de 1:100), con patrón homogéneo y citoplasmático. El perfil de antígeno nuclear extraíble fue positivo para anticuerpos dsDNA, RNP/Sm, Sm, nucleosomas, histonas y proteína P-ribosomal.

Con respecto a las lesiones en la piel, en el estudio histopatológico se encontró una dermis reticular con abundantes neutrófilos, polvo nuclear y degeneración basófila del colágeno, vasos con edema intenso de células endoteliales con fibrina de la pared, ambos rodeados por histiocitos e infiltrado linfomononuclear leve que se extiende y sigue a los anexos (Figura 4).

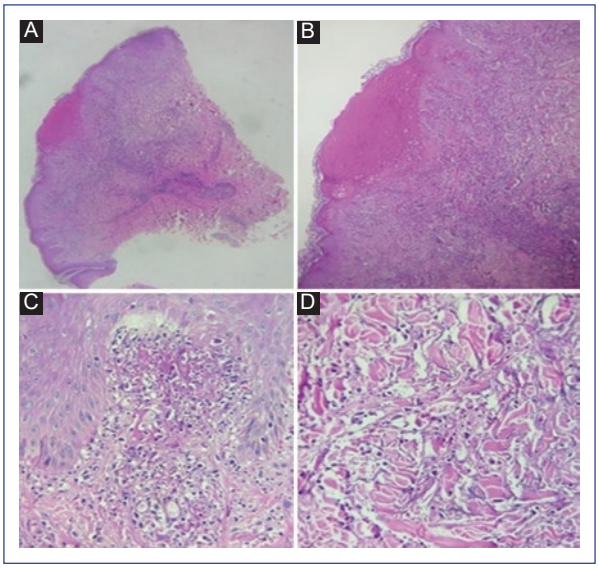

Figura 4. Imágenes macroscópica **(A)** y microscópica **(B)** en las que se observa un infiltrado linfomononuclear en la dermis y los anexos (tinción de hematoxilina-eosina, ×100). **C)** En la dermis reticular se observan abundantes neutrófilos y polvo nuclear (tinción de hematoxilina-eosina, ×200). **D)** Degeneración basófila de colágeno y vasos con edema intenso de células endoteliales con fibrina de la pared (tinción de hematoxilina-eosina, ×400).

El estudio mediante tinción HQ Alcian Blue fue positivo, mientras que la inmunohistoquímica detectó CD68 y CD163 positivos en histiocitos y mieloperoxidasa positiva en el infiltrado neutrofílico (Figura 5).

También se realizaron otros exámenes complementarios, como radiografía de tórax, prueba de tuberculina, baciloscopia directa en esputo y tinción con ácido peryódico de Schiff en la biopsia de piel, para descartar *Mycobacterium tuberculosis* y hongos como causa de los granulomas, los cuales fueron negativos.

Con los hallazgos clínicos, histopatológicos y de laboratorio, la paciente fue diagnosticada de DGNP asociada a debut de LES con afectación renal. Se realizó una biopsia renal que reveló nefritis lúpica membranoproliferativa difusa de clase IV A/C, puntaje de actividad 9 y cronicidad 2.

Como tratamiento, se le administraron pulsos de metilprednisolona (30 mg/kg/día por 3 días), para continuar con prednisona (1 mg/kg/día), micofenolato de mofetilo (1200 mg/m^2/día), hidroxicloroquina (4 mg/kg/día) y enalapril (0.5 mg/kg/día) de manera permanente, y se agregaron paracetamol (15 mg/kg/dosis) o naproxeno (10 mg/kg/dosis) según el dolor. La paciente respondió adecuadamente: las lesiones

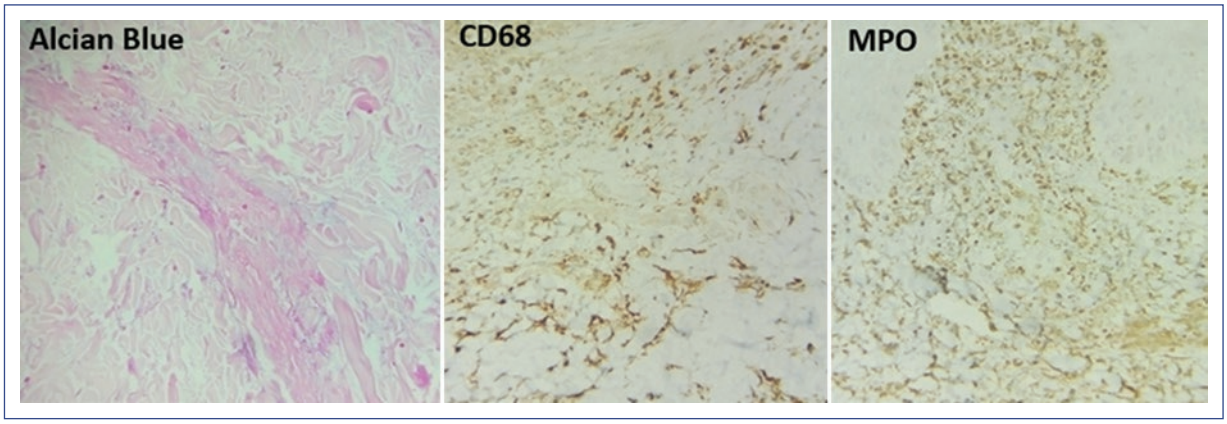

Figura 5. Estudio inmunohistoquímico: tinción HQ Alcian Blue positiva, marcador CD68 positivo en histiocitos y mieloperoxidasa positiva en infiltrado neutrofílico.

desaparecieron y se observó una mejoría de la función renal a las 2 semanas de iniciado el tratamiento. En el seguimiento, la paciente continúa sus controles por reumatología, nefrología y dermatología, con la misma medicación, sin presentar actividad del LES ni aparición de nuevas lesiones en la piel.

Discusión

Las dermatosis neutrofílicas son trastornos poco frecuentes en la infancia, que se caracterizan por la presencia de infiltrados neutrofílicos estériles en la piel y comparten aspectos clínicos similares[6-8]. El término general incluye dermatitis granulomatosa intersticial, granuloma de Churg-Strauss y reacción intersticial granulomatosa por fármacos[9].

Aunque la patogenia exacta de esta enfermedad aún se desconoce, se ha sugerido que, debido a una patología autoinmunitaria de base, ciertos inmunocomplejos se depositan en los vasos dérmicos, desencadenando una serie de eventos como liberación de quimiocinas y de factor de necrosis tumoral. A su vez, esto conllevaría procesos de inflamación, daño del colágeno e infiltrado granulomatoso en la dermis intersticial y perivascular[10]. Por lo tanto, el proceso comienza como una vasculitis leucocitoclástica que luego progresa a la degeneración del colágeno seguida de inflamación crónica y fibrosis. Todo esto causaría el espectro de características clínicas e histológicas. También se mencionan, como causas secundarias, fármacos como el adalimumab, inhibidores de la enzima convertidora de angiotensina, diuréticos, inhibidores del factor de necrosis tumoral y productos de soya[11,12]. En el presente caso, se puede suponer que la patología cutánea fue el resultado de un proceso inflamatorio que produjo el LES en los vasos sanguíneos de la dermis intersticial.

Dentro de los casos reportados de DGNP en adultos, se ha descrito la asociación con artritis reumatoidea en el 26.8% de los casos y con LES en el 11.3%[13]. Esta asociación puede estar mediada por inmunocomplejos y correlacionada con el empeoramiento de la enfermedad subyacente. Además, se han informado casos de DGNP como forma de presentación de debut o brote de LES[3], como ocurrió en esta paciente.

Clínicamente, la DGNP se caracteriza por lesiones polimórficas y heterogéneas, como máculas, placas (eritematosas de configuración anular) y nódulos de distribución simétrica en el tronco, las extremidades, los codos y la región proximal e interna de los brazos. Dentro de los síntomas asociados se describen artralgias y prurito, y en general el tiempo entre el diagnóstico de la patología de base y la presentación de las lesiones es menor de 1 año[10].

En la histopatología se describe un infiltrado intersticial inflamatorio difuso, perivascular, superficial y profundo, compuesto principalmente por neutrófilos e histiocitos CD68 positivos[10]. También puede observarse una zona central de colágeno degenerado, rodeada por histiocitos y linfocitos en empalizada (asemeja a un granuloma anular), además de eosinófilos, células plasmáticas o células gigantes multinucleadas. La histoquímica puede revelar la presencia de Alcian Blue de forma escasa[10]. En la paciente estudiada se observaron características similares a las descritas en la literatura, como el infiltrado inflamatorio compuesto por gran cantidad de neutrófilos, vasos rodeados por histiocitos y linfocitos con Alcian Blue positivo, que demostraría el depósito de mucina intersticial

observado en los pacientes con LES, además de CD68 positivo en histiocitos (por inmunohistoquímica).

Es importante distinguir las lesiones características de DGNP de otras afecciones con una apariencia clínica o histológica similar. Por ello, dentro de los diagnósticos diferenciales hay que considerar el lupus eritematoso túmido, el eritema nudoso, el síndrome de Sweet y el granuloma anular[14].

El tratamiento se basa en controlar la enfermedad subyacente y esteroides tópicos y sistémicos, inmunosupresores como la dapsona, la ciclofosfamida, el micofenolato de mofetilo, la ciclosporina, el metotrexato, la colchicina, la hidroxicloroquina y el infliximab, y antiinflamatorios no esteroideos (AINE). La respuesta al tratamiento es variable, pero en la mayoría de los casos es satisfactoria[15]. La paciente recibió tratamiento con corticoides sistémicos, AINE, micofenolato de mofetilo e hidroxicloroquina, con completa involución de las lesiones de la piel y control de la nefropatía lúpica. Con respecto al compromiso renal, Terai et al.[4] encontraron que la presencia de nefritis lúpica de clase II y V fue una característica frecuente en los pacientes con DGNP, como en nuestra paciente (clase IV). Este hallazgo demostraría una relación entre las lesiones en la piel y el compromiso renal en pacientes con debut de LES.

El presente caso se considera importante porque apoya la hipótesis de que las lesiones de la piel en la DGNP podrían adelantar el compromiso renal en el LES, por lo que son un probable e importante factor pronóstico. Sin embargo, debido a la escasa casuística, son necesarios estudios con mejor metodología para fortalecer esta posibilidad.

En conclusión, la DGNP es una manifestación cutánea asociada con patologías autoinmunitarias poco frecuente en la infancia. Es importante su reconocimiento, ya que puede presentarse como una manifestación inicial de LES. Aunque la DGNP en pacientes con LES se relaciona de manera incierta con la evolución de la enfermedad, la presencia de nefritis lúpica se ha descrito en reportes previos, lo que evidencia una relación que se debe considerar para futuros estudios.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido el consentimiento informado de los pacientes y sujetos referidos en el artículo. Este documento obra en poder del autor de correspondencia.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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LETTER TO THE EDITOR

Epidemiological differences in SARS-CoV-2 admissions in a Peruvian pediatric intensive care unit during one year of pandemic

Diferencias epidemiológicas de los ingresos por SARS-CoV-2 en una unidad de cuidados intensivos pediátricos peruana durante un año de pandemia

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Dear Editor,

It has been more than a year since the World Health Organization declared SARS-CoV-2 infection a pandemic[1]. Since then, more than 174 million people worldwide have been infected, and 3.7 million have died[2]. Cases have occurred in progressive increases termed waves, and many countries are currently in the second wave. It might be expected that the epidemiology and care requirements would be similar in both waves; however, it appears that this is not the case. Therefore, to understand these differences in critically ill children, SARS-CoV-2 admissions in the Pediatric Intensive Care Unit (PICU) of the Hospital Nacional Edgardo Rebagliati Martins (HNERM) during the first year of the pandemic in Peru were analyzed.

HNERM is a national reference center located in Lima, with more than 1,600 beds[3], nine of which correspond to PICU and two of which were assigned to the care of infected patients.

The end of March 2021 marked the first year of the pandemic in Peru. According to the Centro Nacional de Epidemiología, Prevención y Control de Enfermedades (National Center for Epidemiology, Disease Prevention, and Control), the first wave ended in December 2020, while the second wave started in January 2021 and is still ongoing during the writing of this letter[4]. Therefore, for the analysis of the first year, it is considered the first wave from April to December 2020 and the second wave from January to March 2021.

Digital medical records of PICU admissions for SARS-CoV-2 were reviewed. According to their diagnosis, cases were divided into pneumonia, multisystem inflammatory syndrome in children (MIS-C), and others. This last category included patients admitted for a cause unrelated to the virus, so its analysis was not further explored.

The following data were collected: diagnosis, admission date, admittance to the PICU area, age in years, sex, days of stay, and death or discharge. Qualitative variables were described as absolute or relative frequencies, while quantitative variables as medians and interquartile ranges.

In the first year of the pandemic, 53 patients with a critical condition associated with SARS-CoV-2 were admitted to the HNERM PICU, representing 19% of all admissions in the period considered. Of these, 45 were diagnosed by serological, molecular, or antigenic testing, seven by domiciliary contact with a positive case, and one by pulmonary tomography.

There were 33 admissions (62%) in the first wave and 20 (38%) in the second wave. Fifteen (28%) were admitted for pneumonia, six in the first and nine in the second wave; 24 (45%) for MIS-C, 15 in the first and nine in the second wave, and 14 (27%) for other causes, 12 in the first and two in the second wave.

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Notably, nine cases of pneumonia were admitted during three months in the second wave, while there were six cases in nine months of the first wave. This difference could be related to social restrictions decrease and not to an increase in the number of cases, since the incidence per 100 inhabitants was lower in the second wave compared to the first, both in the general (2.67 vs. 3.32) and the pediatric population (0.25 vs. 0.63)[4].

The cases of pneumonia in the second wave were older (12.3 years [8.8-12.9] vs. 9.5 years [0.7-12.3]), and MIS-C cases were younger (6.3 years [2.1-9.9] vs. 8 years [5.9-10.5]) compared to the cases in the first wave. Also, there was greater involvement of the male sex in both cases of pneumonia (78% vs. 50%) and MIS-C (78% vs. 53%) in the second wave.

All cases of pneumonia in both waves, 87% of MIS-C cases in the first wave, and 44% in the second wave were admitted to the PICU-COVID. The median length of stay for pneumonia was 8 days [6-10], and for MIS-C, 5 days [4.5-7]. Six of the 53 patients died (11.3%), four in the first wave and two in the second. This percentage was slightly lower than the 12.7% overall mortality in the PICU during the same period.

Although only three months have passed since the second wave, it can be concluded that there have been more cases of pneumonia in this wave. In general, males were more affected, and this difference has been more significant in the second wave. Those who developed pneumonia were older than those who developed MIS-C in both waves. The mortality of critically ill children due to SARS-CoV-2 was slightly lower than overall PICU mortality.

The present analysis has limitations. It only evaluates one PICU, with a small sample size that limits applying a more robust statistical analysis. Although what has been observed in our unit has likely occurred in other units, it is necessary to conduct adequate studies, learn about our reality, and prepare ourselves to navigate successfully in this wave and those to come.

Ethical disclosures

Protection of human and animal subjects. The author declares that no experiments were performed on humans or animals for this study.

Confidentiality of data. The author declares that he has followed the protocols of his work center on the publication of patient data.

Right to privacy and informed consent. The author has obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The author declares no conflict of interest.

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