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REVIEW ARTICLE

Unveiling the mystery of the female heart's rhythm: a look into gender inequalities in electrophysiology

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Abstract

This review explores gender disparities in cardiac electrophysiology, highlighting differences in the electrical activity of the heart between men and women. It emphasizes the importance of understanding these variances for correct diagnosis and effective treatment of cardiac arrhythmias. Women show distinct cardiac characteristics influenced by sex hormones, affecting their susceptibility to various arrhythmias. The manuscript covers the classification, mechanisms, and management of arrhythmias in women, considering factors such as pregnancy and menopause. By addressing these gender-specific nuances, it aims to improve healthcare practices and outcomes for female patients with cardiac rhythm disorders.

Keywords: *Women. Sudden cardiac death. Channelopathy. Cardiac electrophysiology. Arrhythmias. Female hormones.*

Revelando el misterio del ritmo cardiaco femenino: una mirada a las desigualdades de género en electrofisiología

Resumen

Esta revisión explora las disparidades de género en la electrofisiología cardiaca, destacando las diferencias en la actividad eléctrica del corazón entre hombres y mujeres. Se enfatiza la importancia de comprender estas variaciones para un diagnóstico correcto y un tratamiento efectivo de las arritmias cardiacas. Las mujeres muestran características cardiacas distintas influenciadas por las hormonas sexuales, lo que afecta su susceptibilidad a diversas arritmias. La revisión abarca la clasificación, los mecanismos y el manejo de las arritmias en las mujeres, considerando factores como el embarazo y la menopausia. Al abordar estos matices específicos de género, el objetivo es mejorar las prácticas de atención médica y los resultados para las pacientes de sexo femenino con trastornos del ritmo cardiaco.

Palabras clave: *Mujeres. Muerte súbita cardiaca. Canalopatías. Electrofisiología cardiaca. Arritmias. Hormonas femeninas.*

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Introduction

Women own unique cardiac characteristics, encompassing differences in signal intervals, refractory periods, wave amplitudes, and QT intervals compared to men. These disparities extend to the cellular level, influenced by sex hormones such as estrogen and progesterone, which modulate the heart's electrical activity[1-4]. Consequently, women show varying susceptibilities to different arrhythmias, with certain conditions disproportionately affecting them. Gender disparities in cardiac electrophysiology have appeared as a critical area of study, unveiling nuanced differences in the electrical activity of the heart between men and women[5,6]. Understanding these variations is paramount as they hold implications for the diagnosis, treatment, and management of cardiac rhythm disorders. While historically, research in cardiology has focused on male subjects, recent advancements have shed light on the distinct electrocardiographic and electrophysiological profiles shown by women[7-9]. This manuscript aims to comprehensively review the gender-specific differences in cardiac rhythm, unraveling the intricacies of the female heart's rhythm and its implications for clinical practice. In Fig. 1, a visual summary of the main differences is presented.

Electrocardiographic and electrophysiological differences in women

Electrocardiographic and electrophysiological variances in women display distinctive characteristics in comparison to men. Women typically present with shorter heart signal intervals (PR, AH, and HV), a diminished refractory period of the AV node, and smaller heart wave amplitudes (P, T) and QRS width. Despite adjustments for ventricular mass and body weight, women often show lower voltage in the QRS complex. In addition, the ST segment displays a slower slope, and the ascent of the T wave is less steep in women[10-12]. Notably, women's hearts show differences in the timing and strength of electrical signals, particularly at rest, where they display a longer QT interval, reflecting the heart's electrical recovery time. Although this discrepancy diminishes with increased heart rate, women present with a higher resting heart rate and show greater variability in RR intervals due to the influence of vagal tone on the sinus node. These gender-specific variations potentially contribute to women's susceptibility to certain heart rhythm disorders, such as atrioventricular nodal reentrant tachycardia (AVNRT) and long QT syndrome (LQTS), while showing reduced predisposition to arrhythmias associated with heart muscle damage[13]. At the level of individual cells, women's heart cells are smaller, contract more slowly, and have longer action periods, which increase their likelihood of experiencing irregular heartbeats. Hormonal influences, notably estrogen and progesterone, further modulate heart rate and electrical activity, with estrogen exerting protective effects against some rhythm disturbances by modulating potassium flux, while testosterone shows distinct impacts. Hormonal fluctuations throughout the menstrual cycle alter the heart's electrical dynamics, notably affecting the duration of the QT interval[14]. These insights underscore the critical importance of considering gender in the diagnosis and treatment of electrical heart conditions, emphasizing the significant impact of sex hormones on the heart's electrical system and its responsiveness to stress[15-19].

Main arrhythmias in women

Arrhythmias in women encompass a wide range of conditions, from benign irregular heartbeats to severe disorders potentially leading to sudden cardiac death (SCD)[20,21].

Supraventricular arrhythmias

Supraventricular premature beats (SVPBs)

Particularly prevalent in women, SVPBs increase the risk of severe cardiac events, such as stroke and death, by up to 60%, potentially due to a heightened risk of atrial fibrillation (AF)[22,23]. Women often experience a more significant impact on their quality of life. Treatment goals include preventing other supraventricular arrhythmias, reducing cardiovascular event morbidity, preventing stroke, and avoiding death. Individual management strategies involve assessing the need for medical intervention to control underlying conditions, anticoagulation therapy, and considering catheter ablation. Diagnosis in women presenting with palpitations and a normal electrocardiogram can be challenging, often leading to misdiagnosis associated with anxiety.

AVNRT

As the most common type of paroxysmal supraventricular tachycardia, AVNRT accounts for 50% of all

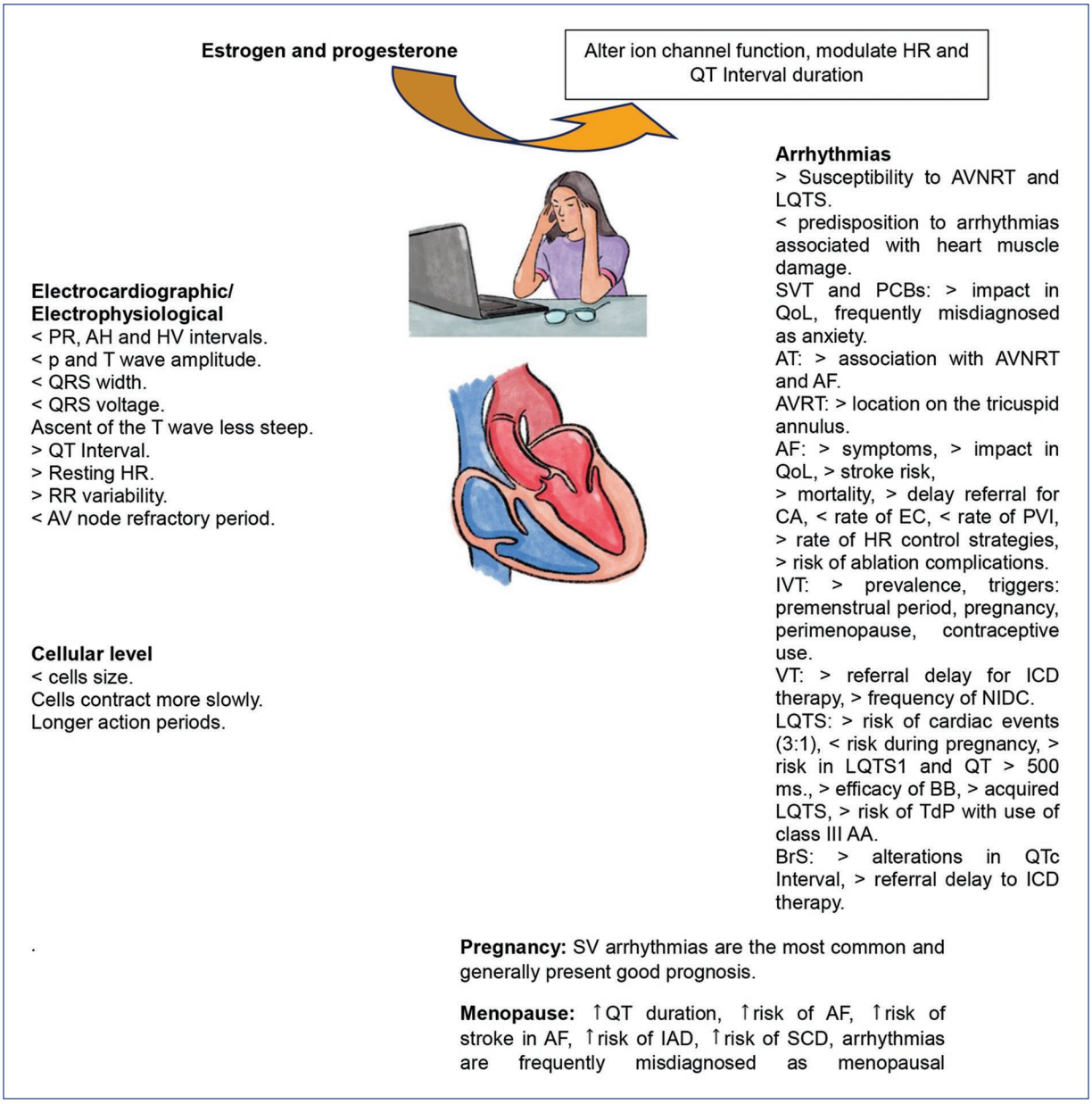

Figure 1. Most prominent electrophysiological differences in women compared to men. HR: heart rate; AVNRT: atrioventricular nodal reentrant tachycardia; LQTS: long QT síndrome; SVT: supraventricular tachycardia; PCBs: premature contraction beats; QoL: quality of life; AT: atrial tachycardia; AVRT: atrioventricular reentrant tachycardia; AF: atrial fibrillation; CA: catheter ablation; EC: electric cardioversión; PVI: pulmonary vein isolation; IVT: idiopathic ventricular tachycardia; VT: ventricular tachycardia; ICD: implantable cardioverter defibrillator; NIDC: nonischemic dilated cardiomyopathy; BB: beta-blocker; TdP: torsades de pointes; AA: antiarrhythmics; BrS: brugada síndrome; SV: supraventricular; IAD: ischemic arterial disease; SCD: sudden cardiac death.

tachycardia cases in both sexes, with a higher incidence in young women. Diagnosing AVNRT, especially in non-documented cases of short-duration paroxysmal tachycardia, can be challenging, leading to misdiagnosis associated with anxiety events. There are no observed sex differences in the acute success rate, complications, and recurrences in catheter ablation[24].

Atrial tachycardia (AT)

Common in women, AT has a similar anatomical origin and success rates in both sexes. Women diagnosed with focal AT may have associations with other arrhythmias such as AVNRT. In elderly women and those with AF risk factors, the origin site

may be the pulmonary veins, needing a thorough assessment for AF risk at diagnosis and during follow-up[25,26].

Atrioventricular reentrant tachycardia (AVRT)

More commonly found in men, AVRT is associated with a higher occurrence of accessory pathways. In women, these accessory pathways are often found in the tricuspid annulus, while in men, they tend to be on the left side. Catheter ablation is equally effective as a definitive treatment for both women and men[27].

AF

Although more prevalent in men, AF presents differently in women, often being more symptomatic and associated with higher stroke risk, needing a gender-tailored treatment approach. Women with AF experience worse quality of life and higher mortality rates[22]. Multinational registries show delayed referral for catheter ablation[28], lower likelihood of receiving electrical cardioversion and/or pulmonary vein isolation, and a greater tendency toward rate control strategies in women. In addition, women face a heightened risk of ablation-related complications[29,30].

Ventricular arrhythmias, channelopathies, and SCD

Ventricular arrhythmias

Ventricular arrhythmias are commonly associated with structural heart disease, ranging from frequent ventricular premature beats to ventricular tachycardia (VT) and even VT-induced cardiomyopathy.

VT without structural heart disease

While being a minority (10%) of ventricular arrhythmias, idiopathic VTs (IVTs) rarely lead to sudden death and are benign. More prevalent in women, IVTs often trigger during specific periods such as the premenstrual period, pregnancy, perimenopause, and contraceptive use. Catheter ablation, the definitive treatment, shows no gender-based differences in effectiveness or safety.

VT with structural heart disease

Scar tissue from earlier infarction is the typical substrate, yet women suffer more from non-ischemic dilated cardiomyopathy (NIDCM). Women with NIDCM experience referral delays and are less likely to receive proper implantable cardioverter-defibrillator (ICD) therapy. Although post-ablation recurrence is higher in women with ischemic cardiomyopathy, success rates, and complications stay consistent across genders.

Channelopathies

Cardiac channelopathies are heritable disorders caused by pathogenic variants in genes encoding cardiac ion channel subunits and ancillary proteins essential for human cardiomyocyte electromechanical function. This group includes congenital LQTS, Brugada syndrome (BrS), catecholaminergic polymorphic VT, and short-QT syndrome, each characterized by unique genetic and clinical features, electrocardiogram signatures, and typical presentation modes[14].

LQTS

Presents gender-specific considerations in risk assessment for ventricular arrhythmias, with a heightened risk seen in pre-pubertal children and women post-puberty. Following puberty, women with LQTS face a threefold increased risk of cardiac events, although their risk during pregnancy is lower, escalating postpartum[31,32]. High-risk women typically show the LQTS2 phenotype and a QTc > 500 ms, calling for primary prevention strategies such as ICD therapy to mitigate SCD risk.

LQTS1 arises from mutations in the *KCNQ1* gene, predisposing boys to a greater risk of ventricular arrhythmias and fatal events compared to girls. Risk patterns during puberty show a decline in boys but an escalation in girls.

LQTS2, associated with mutations in the *KCNH2* gene, poses a persistent risk of lethal arrhythmic events in women, even post-menopause. Beta-blockers show greater efficacy in women and remain a cornerstone of treatment.

LQTS3, linked to mutations in the *SCN5A* sodium channel gene, shows a lower risk in childhood but escalates significantly in adulthood, with reports suggesting a higher risk in men for severe events.

Acquired LQTS, more prevalent in women, often stems from factors, such as electrolyte imbalances and QT-prolonging medications[33]. These factors, combined with female sex and underlying conditions, such as renal dysfunction, heighten the risk of *torsades de pointes* (TdP) with class IIA and III antiarrhythmics.

BrS

Prevalent in adult males, particularly post-pubertal individuals, tends to manifest with more severe events in males, due to androgen modulation of Ito channel dysfunction. Female patients may show pronounced QTc interval alterations in response to certain medications, needing careful monitoring. The *SCN5A* gene mutation underlies BrS, with post-pubertal males showing a higher incidence of severe or lethal events compared to women[34,35].

SCD

Accounting for approximately 20% of all fatalities, with a higher incidence seen in men, SCD can be up to 35% of total cardiac deaths in women. Risk factors include smoking, hypertension, and diabetes. Women show specific electrophysiological traits associated with SCD, including a longer QT interval post-puberty, lower QRS voltage compared to men, and potential hormonal effects altering ion channel function. Increased vagal tone, manifested as bradycardia, and heightened heart rate variability are also prevalent[36].

The presentation and mechanism of SCD in women show distinct features, with only one-third of cases attributed to ischemic heart disease. Symptoms preceding sudden death are often absent, with shortness of breath being the primary reported symptom. Mechanistically, arrhythmias play a pivotal role, with VT/ventricular fibrillation being predominant in men, while pulseless electrical activity appears as the primary rhythm in women, influencing survival outcomes.

Women diagnosed with heart failure (HF) show a more favorable prognosis compared to men, attributed to factors such as sex hormones, differences in intracellular calcium handling, and myocardial remodeling.

In women, SCD is often associated with non-ischemic causes, as found in post-mortem analysis. Left ventricular ejection fraction serves as an independent predictor of mortality in men but lacks similar prognostic significance in women.

Regarding sports related to SCD, channelopathies may have a lesser impact on women compared to men. Diagnostic measures such as resting and exercise electrocardiograms, along with molecular genetic screening, play a pivotal role in showing underlying mutations and assessing disease severity[37].

Implantable cardioverter defibrillator

ICDs have proven efficacy in preventing SCD from arrhythmias, yet their use still is suboptimal, particularly among women. Despite both genders receiving proper therapies at similar rates, women are less often offered ICD therapy, underscoring disparities in access and treatment.

Cardiac resynchronization therapy (CRT)

CRT, a pivotal innovation in HF management, proves significant benefits, particularly for patients with severe systolic dysfunction and electrical dyssynchrony. Despite evidence suggesting a favorable response to CRT in women, there exists a notable underutilization of this therapy among female patients. Factors contributing to this disparity include delayed recognition of symptoms, diagnostic delays, and concerns on implantation-related complications in women.

Gender-specific ventricular remodeling

Gender-specific differences in ventricular remodeling are clear, as women show a slower reduction in ventricular mass over time due to lower rates of apoptosis. Women also show greater left ventricular hypertrophy, smaller ventricular diameters, and preserved ventricular function, albeit with more pronounced relaxation disorders.

Arrhythmias in pregnancy

Arrhythmias during pregnancy can arise de novo or worsen preexisting conditions, with risk factors including structural heart disease, channelopathies, and advanced maternal age. While the majority of cases follow a benign course and respond well to treatment, factors, such as labor and delivery can elevate risk levels[38]. Physiological changes in pregnancy, such as increased heart rate and cardiac axis deviation due to uterine expansion, contribute to the development of rhythm disturbances, along with hormonal fluctuations, autonomic tone variations, and hemodynamic shifts. Supraventricular arrhythmias, such as AF/flutter and supraventricular tachycardia are common, while ventricular arrhythmias occur less often. Women with underlying heart conditions require careful management due to heightened risk[39].

Cardiac arrhythmias during labor have been associated with negative outcomes, such as higher rates of

cesarean section, preterm delivery, neonatal care admission, and extended hospital stays. Among these arrhythmias, ventricular ones pose the greatest risk to both the mother and the fetus[40]. Management typically involves standard protocols to ensure maternal and fetal well-being, including telemetry during labor and maintenance of normal electrolyte levels and euvolemia. Device placement, like pacemakers or defibrillators, is safest during the second trimester, and breastfeeding is safe due to compatible medications. Supraventricular tachycardias are common and often benign, but ventricular arrhythmias and channelopathies like LQTS require specialized treatment to prevent complications, including SCD.

A collaborative approach that integrates maternal-fetal medicine, obstetrics, and arrhythmia specialists is crucial. Tailored strategies, such as using antiarrhythmic drugs, performing catheter ablation, and considering device placement, should be carefully weighed to balance risks and benefits. In high-risk cases, the recommendation is to consider ICD during pregnancy. However, it requires careful consideration of potential complications, as well as optimization of device programming and medication regimens. Alternative options like subcutaneous and wearable defibrillators require further investigation about their utility in pregnancy. Close monitoring and collaboration among specialists are crucial for ensuring the best outcomes for both mother and baby.

Arrhythmias in menopause

During menopause, disruptions in the delicate balance of estrogen and progesterone receptors in the myocardium contribute to increased susceptibility to AF[41]. Postmenopausal women also experience heightened periatrial adipose tissue, impairing ionic and voltage transport function[42]. Fluctuations in sex hormone levels correlate with tachycardia paroxysms, with estrogen deficiency linked to more frequent events and a higher likelihood of requiring catheter ablation. Despite a lower prevalence of AF in women compared to men, the risk becomes comparable or higher after age 75, particularly among postmenopausal women with comorbidities, such as hypertension and obesity. While studies like the Framingham Heart Study have not linked menopause onset with AF incidence[43], female sex combined with advanced age and comorbidities elevates the risk of cerebral embolism. Postmenopausal women face increased risks of ischemic heart disease and SCD due to the loss of estrogen's cardioprotective effects. Hormone replacement therapy's effects on arrhythmia induction remain controversial since it has been suggested an increase in QT interval post-replacement. Palpitations, accompanied by vasomotor symptoms, are common manifestations of arrhythmias in perimenopausal and postmenopausal women, often overlooked as menopausal symptoms. Sex hormones significantly contribute to arrhythmogenesis during menopause, underscoring the importance of prompt evaluation and referral for specialized treatments like ablation procedures or cardiac stimulation device implantation.

Antiarrhythmics in women

Antiarrhythmic therapy presents distinctive challenges in women due to their heightened risk of TdP and susceptibility to adverse drug effects. It is imperative for patients to be vigilant in recognizing symptoms indicative of TdP, such as dizziness or palpitations differing from their usual ones. Extensive research has uncovered gender-specific differences, with up to 70% of women facing an elevated TdP risk when prescribed class IA and III antiarrhythmics[15,44]. Higher doses of sotalol, exceeding 320 mg/day, have been associated with a 4.1% risk in women, compared to 1.9% in men. Similarly, dofetilide administration in women, particularly those with risk factors, such as HF and prolonged QTc, carries a heightened proarrhythmic risk, reaching 47% versus 28% in men, especially in patients with functional class III/IV or recent infarction and ventricular dysfunction. Ibutilide usage in women entails a proarrhythmic risk of 5.6% versus 3% in men, while quinidine, known for its proarrhythmic potential, poses a 4.8% risk in women, contrasting with no clear risk in men. Given women's longer QT duration due to reduced repolarization reserve, they are particularly vulnerable to developing malignant arrhythmias when exposed to medications prolonging the QT interval, with 65-75% of drug-induced TdP cases occurring in women.

Gender disparities in pediatric arrhythmias

Some differences in arrhythmias based on gender have been observed in pediatric populations. In a study involving 3556 patients aged 12-21 years, significant disparities were noted in the gender distribution of AVRT and AVNRT, with females exhibiting a higher likelihood of AVNRT than AVRT ($p < 0.0001$). Conversely, no significant gender discrepancies were identified in

younger age groups[45]. In another study comprising 233 cases of SVT in individuals aged 0-18 years, male predominance was observed across all SVT subtypes, except for AVNRT[46]. Regarding hereditary arrhythmogenic diseases, differences in gender have also been noted. In prepubescent children, boys with LQT1 exhibit an elevated risk of arrhythmias compared to girls, while the risk is similar between genders in LQT2 or LQT3[47]. However, after puberty, the risk pattern reverses, with post-pubertal females with LQT1 facing a higher risk of arrhythmias[47], and those with LQT2 show a greater risk for ventricular arrhythmias compared to males. In addition, a study of 967 consecutive cases of sudden arrhythmic death syndrome (SADS) demonstrated a male predominance, particularly in younger age groups[48]. Notably, in BrS, an exception to the male-predominant arrhythmic risk exists in the pediatric age group, where spontaneous BrS ECG was associated with earlier onset of arrhythmic events, particularly related to fever, in girls compared to boys[49].

Conclusion

This study emphasizes the significance of recognizing and addressing gender disparities in cardiac electrophysiology and arrhythmias. Variations in electrocardiographic and electrophysiological profiles between men and women have significant implications in clinical practice, affecting correct diagnosis and tailored treatment approaches. Unique hormonal and physiological factors contribute to differences in women's heart electrical activity, influencing the prevalence and manifestation of certain arrhythmias. Considering these gender-specific factors is essential for managing arrhythmias during pregnancy and menopause and selecting proper antiarrhythmic therapies. We need a combined approach that mixes basic and clinical research to better understand the underlying causes of health issues and create better treatment plans tailored specifically to each gender. By acknowledging and addressing these disparities, we can strive for more inclusive and effective cardiological care for individuals of all genders.

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

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RESEARCH ARTICLE

Clinical and epidemiological characteristics of pilomatricomas in a Mexican pediatric population

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Abstract

Background: *Pilomatricoma is a common benign adnexal neoplasm in children. There are few epidemiological studies on this subject, with most relying solely on descriptive statistics.* **Methods:** *A cross-sectional study conducted in two tertiary hospitals in Mexico City from January 2017 to December 2023. Clinical and electronic records of patients with histopathological diagnosis of pilomatricoma, both sexes, under 18 years old, with any type of present comorbidity were selected. Records of patients with diagnosis not confirmed by histopathology or incomplete records were not included in the study.* **Results:** *Fifty-two cases with pilomatrixoma were included in the study, showing a total of 74 lesions. About 23.1% of the cases had multiple pilomatrixomas. 40.4% of the cases experienced pain; this symptom was associated with lesions > 15 mm in diameter and with multiple pilomatrixomas. Risk factors for lesions > 15 mm included age under 8 years, positive tent sign, tumor evolution longer than a year, and a non-classical clinical variety. The head and neck were the most commonly affected areas. The left upper extremity presented larger pilomatrixomas (median 18.5 mm) and occurred more frequently in adolescent patients (mean age 12.1 years) compared to other body areas.* **Conclusions:** *Pilomatrixoma in children shows clinical diversity, with specific findings based on size, number, and anatomical location.*

Keywords: *Pilomatricoma. Pilomatrixoma. Multiple pilomatrixomas. Epithelioma of Malherbe. Pediatric pilomatrixoma.*

Características clínicas y epidemiológicas de los pilomatricomas en una población pediátrica mexicana

Resumen

Introducción: *El pilomatricoma es una neoplasia anexial benigna frecuente en la infancia. Hay muy pocos estudios epidemiológicos al respecto y la mayoría solo han utilizado estadística descriptiva.* **Métodos:** *Estudio transversal realizado en dos hospitales de concentración de la Ciudad de México de enero de 2017 a diciembre de 2023. Se seleccionaron expedientes clínicos y electrónicos de pacientes con diagnóstico histopatológico de pilomatricoma, ambos sexos, menores de 18 años, con cualquier tipo de comorbilidad presente. No se incluyeron los expedientes de pacientes con diagnóstico no confirmado por histopatología o expediente incompleto.* **Resultados:** *Se incluyeron 52 casos con diagnóstico de pilomatricoma que mostraron un total de 74 lesiones. El 23.1% de los pacientes tuvieron pilomatricomas múltiples. El 40.4% experimentaron dolor; este signo se asoció con lesiones de diámetro superior a 15 mm y pilomatricomas múltiples. La edad menor de 8 años,*

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el signo de la tienda de campaña positivo, un tiempo de evolución mayor de 1 año y una variedad clínica no clásica son factores de riesgo asociados con las lesiones mayores de 15 mm. La cabeza y el cuello fueron las áreas más comúnmente afectadas por estos tumores. La extremidad superior izquierda presento pilomatricomas de mayor tamaño (mediana 18.5 mm), y ocurrieron más en pacientes adolescentes (media 12.1 años), en comparación con otras áreas del cuerpo. **Conclusiones:** *El pilomatricoma en niños muestra diversidad clínica. Presenta hallazgos y asociaciones específicas según el tamaño, el número y la ubicación anatómica.*

Palabras clave: *Pilomatricoma. Pilomatrixoma. Pilomatricomas múltiples. Epitelioma de Malherbe. Pilomatricoma pediátrico.*

Introduction

Adnexal skin tumors are rare and usually benign neoplasms that originate from the epithelial adnexal of the skin, such as the pilosebaceous unit, and the eccrine or apocrine sweat glands. These tumors often have morphological similarities, making histopathological examination necessary for diagnostic confirmation[1].

Pilomatrixoma, also known as calcifying epithelioma of Malherbe, is a benign adnexal neoplasm that originates from the matrix cells of hair follicles. It accounts for 1-1.59% of benign skin tumors, and its incidence in dermato-histopathological materials ranges from 0.001% to 0.0031%. Pilomatrixomas are more frequent before the age of 20, with a mean age of 16 years and 7 months. Their size varies from 0.4 to 20 cm, with a mean of 0.8 cm[2-4].

At the clinical level, classic pilomatrixoma presents as a mobile, firm nodule with a hard or stony consistency when calcified, featuring irregular yet well-defined borders, and it is typically asymptomatic with slow growth. Variants include the perforating type, where the lesion is superficial and calcific material erodes the epidermis, forming a crust over a small ulcer; the anetodermic or pseudoampullar type, where the tumor skin may be thinned, atrophic, with telangiectasias, and herniation of the underlying mass; and the giant type, when the lesion measures over 4 cm[4]. Some patients may experience pain (50%), sensitivity, and itching at the site[3,5]. They are often misdiagnosed as other skin conditions, with only 16% of lesions correctly diagnosed on clinical examination[3].

Pilomatrixomas can occur throughout the body, with a predominance in the head and neck region among the Mexican population (39.6-55.2%). Other affected areas include the upper extremities (26.3-42.4%), trunk (15.7-16.4%), and lower extremities (51.3-2.6%)[5]. Laterality is reported in 15% of cases, with 72% occurring on the right side[3].

Diagnosis is confirmed through histological examination, revealing a neoplasm composed of three cellular populations: basaloid cells, transition cells with picnotic nuclei, and eosinophilic anucleate cells ("ghost cells"). Definitive treatment involves complete excision with clear margins, with recurrence rates ranging from 0.48% to 1.4%[3,5].

Epidemiological studies in pediatric populations are scarce, particularly among Latino children, and most research has been limited to descriptive analysis of findings. We sought to describe the clinical-epidemiological characteristics of pilomatricomas in a Mexican pediatric population and determine their potential clinical associations.

Methods

Study type and location

This is a cross-sectional, descriptive, retrospective, and observational study conducted at two tertiary hospitals in Mexico City (General Hospital "Dr. Gaudencio González Garza" CMN La Raza and General Hospital of Mexico "Dr. Eduardo Liceaga") from January 1, 2017, to December 31, 2023. This study adhered to the guidelines outlined in the Helsinki Declaration, the Belmont Report, and the General Health Law regarding health research, including information on internal ethics committees in healthcare institutions (articles 100, 103, and 105) and the Official Mexican Standard NOM012-SSA3-2012, with internal registration number R-2023-3502-107[6,7].

Protocol

Clinical and electronic records of patients with the histopathological diagnosis of pilomatricoma were selected for inclusion in the study. Both sexes under the age of 18 with any type of present comorbidity were included in the study. Records of patients with a diagnosis not confirmed by histopathology and incomplete clinical records were excluded from the study. Epidemiological and clinical information was collected from the records. The study variables analyzed were sex, age, nutritional status, underlying diseases or comorbidities, number of lesions, duration, size, signs and symptoms present,

diagnostic suspicion, variety, topography, and treatment. Data collection was performed by three pediatric dermatologists.

Statistical analysis

The sample size was calculated using the statistical software Open Epi version 3, based on a population proportion with a hypothetical disease frequency of 1.5%, derived from prevalence information described in the literature[2,3]. A sample of 52 cases was obtained. The sample was selected using a non-probabilistic and non-random method.

Kolmogorov-Smirnov tests were conducted to assess normality. Variables that met this criterion were summarized as means and standard deviations as a measure of dispersion. Variables with non-normal distribution were summarized as medians and interquartile range as a measure of dispersion. Nominal variables were summarized with frequencies and percentages. Inferential statistics were applied, and the Student's t-test was used to compare means, Mann–Whitney U test for medians, and Pearson's R2 test or Fisher's exact test to evaluate categorical variables. Multivariate logistic regression analyses were performed and stratified by lesion size and number. Variable selection was carried out using the backward regression method. The IBM SPSS version 26 software was used, and a bilateral $p < 0.05$ was considered statistically significant.

Table 1. Baseline demographic characteristics of pediatric patients with pilomatricomas

Variable	n = 52
Sex, No. (%)	
Male	29 (59.8)
Female	23 (44.2)
Age, mean (SD), years	
At diagnosis	9.8 (± 3.5)
Onset of dermatosis	8.3 (± 3.9)
Nutritional status, No. (%)	
Underweight	1 (1.9)
Normal	22 (42.3)
Overweight	16 (30.8)
Obesity	13 (25.0)
Comorbidity, No. (%)	
Absent	36 (69.2)
Present	16 (30.8)
Lesion, No. (%)	
Single	40 (76.9)
Multiple	12 (23.1)
Time of evolution, months, median (IQR)	10.0 (6.0, 24.0)
Clinical size in mm, median (IQR)	15.0 (10.0, 20.0)
Referral diagnostic suspicion, No. (%)	
Pilomatricoma	27 (51.9)
Lesion description	7 (13.5)
Tumor of cutaneous adnexa	11 (21.2)
Other cutaneous tumors	7 (13.5)
Pilomatricoma variety, No. (%)	
Classic	64 (86.5)
Perforating	2 (2.7)
Anetodermic	7 (9.5)
Giant	1 (1.4)

IQR: interquartile range; SD: standard deviation.

Results

A total of 52 cases of pilomatricomas were included in the study, with 40 cases (76.9%) presenting a single lesion and 12 cases (23.1%) multiple lesions. Among cases with multiple lesions, six cases had two lesions, three cases had three lesions, two cases had four lesions, and one case had five lesions. In total, 74 pilomatricomas were documented. The baseline epidemiological characteristics of the studied population are summarized in table 1. Underlying medical conditions were found in 15 patients (28.8%): 6 with atopy, 3 with attention deficit hyperactivity disorder, and only one case each of alopecia areata, autism, Hodgkin lymphoma, Turner syndrome, hyperlaxity syndrome, metabolic syndrome, and short stature, respectively. The patient with Turner syndrome had multiple pilomatricomas (2 lesions).

Table 2 presents the results of pilomatricomas according to lesion size. It was observed that the presence of the tent sign (Fig. 1) and pain is associated with lesions > 15 mm in diameter, while the rest of the clinical variables showed no significant associations. Table 3 shows an unadjusted logistic regression model that also demonstrates the association of pain and the tent sign with larger lesions. Table 4 presents the adjusted logistic regression model, which found that age under 8 years, a positive tent sign, a tumor evolution time of more than one year, and the presence of another clinical variety of pilomatricoma (different from the classic type) are risk factors associated with lesions > 15 mm in diameter.

Table 5 summarizes the results of pilomatricoma cases according to the number of lesions. Multiple pilomatricomas were associated with the presence of pain and a longer duration of evolution, with single lesions having a median duration of 7 months compared to

Table 2. Baseline characteristics of pilomatrixomas stratified by lesion size

Variable	Less than 15 mm (n = 30)	Greater than 15 mm (n = 22)	p-value
Sex, No. (%)			
Male (n = 29)	16 (53.3)	13 (59.1)	0.78*
Female (n = 23)	14 (46.7)	9 (40.0)	
Age, mean (SD), years			
At diagnosis	10.3 (± 3.4)	9.3 (± 3.7)	0.34**
Onset of dermatosis	8.8 (± 4.0)	7.8 (± 3.0)	0.38**
Nutritional status, No. (%)			
Low/normal (n = 23)	11 (36.7)	12 (54.5)	0.26*
Overweight/obesity (n = 29)	19 (63.3)	10 (45.5)	
Comorbility, No. (%)			
Absent (n = 37)	20 (66.7)	17 (73.3)	0.76*
Present (n = 15)	10 (33.3)	6 (22.7)	
Lesion, No. (%)			
Single (n = 40)	24 (80.0)	16 (72.6)	0.53*
Multiple (n = 12)	6 (20.0)	6 (27.3)	
Time of evolution, months, median (IQR)	6.5 (3.7, 15.0)	12 (8.0, 24.0)	0.28***
Signs and symptoms, No. (%)			
Positive tent sign (n = 19)	6 (20.0)	13 (59.1)	< 0.01*
Pain present (n = 21)	8 (26.7)	13 (59.1)	0.02*
Calcification (n = 24)	11 (36.7)	13 (22.0)	0.16*
Pilomatricoma variety, No. (%)			
Classic (n = 42)	26 (86.7)	16 (72.7)	0.50****
Perforating (n = 2)	1 (3.3)	1 (4.5)	
Anetodermic (n = 7)	3 (10.0)	4 (18.2)	
Giant (n = 1)	0	1 (4.5)	
Referral diagnosis suspicion, No. (%)			
Pilomatricoma (n = 27)	17 (56.7)	10 (45.5)	0.57*
Other tumors (n = 25)	13 (43.3)	12 (54.5)	

*Pearson's R2.
**Student's t-test.
***Mann-Whitney U test.
****Fisher's X2.
IQR: interquartile range; SD: standard deviation.

38 months for multiple lesions ($p \leq 0.01$). No other variables showed significant associations. Table 6 presents an unadjusted model confirming the association of multiple pilomatricomas with pain and a longer evolution time. These two variables were the only ones included in the adjusted logistic regression model (Table 7).

In addition, the only significant finding from comparing different clinical types of pilomatrixoma was age: (a) the classic type appeared at an average age of 7.9 ± 3.9 years, compared to other clinical varieties that emerged at 10.4 ± 3.5 years ($p = 0.05$), and (b) the anetodermic type appeared at 10.8 ± 1.4 years, significantly later than other varieties, which presented at 8.0 ± 4.1 years ($p < 0.01$).

Table 8 describes the global and specific topography of pilomatricomas. The tumors predominantly appeared on the right side of the body (51.4%). The most common location was the head and neck (36.5%), followed by the trunk (21.6%), with the fewest lesions appearing on the lower extremities (6.8%). Table 9 compares the variables of age and pilomatricoma size with respect to topography. The results show that the left upper extremity exhibited two distinct characteristics compared to other regions: (a) pilomatricomas had a larger diameter in this location compared to others (18.5 mm vs. 10.0 mm, $p = 0.01$, Mann–Whitney U test), and (b) the age of presentation in this site was during adolescence (12.1 ± 2.8 years), compared to other locations where it appeared in childhood (9.5 ± 3.2 years, $p < 0.01$, Student's t-test).

In 14 cases (26.9%), ultrasound was considered necessary to guide the clinical diagnosis. All lesions were surgically excised, and their diagnosis was confirmed by histopathology. No lesion showed signs of malignancy.

Table 3. Unadjusted model of clinical factors and dermatological findings of pilomatricomas associated with lesion size

Variable	OR	CI 95% inferior	CI 95% superior	p-value	R squared
Sex, male	1.26	0.41	3.84	0.68	<0.01
Age: < 8 years	2.27	0.68	7.54	0.17	0.04
Nutritional status, overweight/obesity	2.07	0.67	6.35	0.20	0.04
Comorbility, present	1.70	0.48	5.95	0.40	0.01
Multiple lesions	1.50	0.41	5.48	0.54	0.01
Time of evolution: > 1 year	2.27	0.68	7.54	0.17	0.04
Signs and symptoms, No. (%)					
Positive tent sign	5.77	1.68	19.84	< 0.01	0.20
Pain present	3.97	1.22	12.84	0.02	0.13
Calcification	2.49	0.80	7.71	0.11	0.06
Pilomatricoma variety, classic	2.43	0.59	9.98	0.21	0.04

CI: confidence interval; OR: odds ratio.

Table 4. Adjusted logistic regression model of clinical factors associated with pilomatricoma size >15 mm

Variable	OR	CI 95% inferior	CI 95% superior	p-value	R squared
Age: < 8 years	7.17	1.33	38.74	0.02	0.41
Positive tent sign	9.89	2.15	45.36	<0.01	
Time of evolution: > 1 year	5.73	1.12	29.22	0.03	
Other types of pilomatricoma (non-classic)	7.38	1.17	46.33	0.03	

CI: confidence interval; OR: odds ratio.

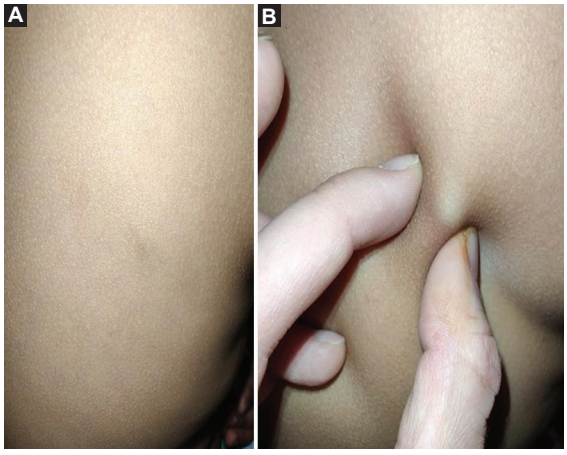

Figure 1. A: in the case of pilomatricoma, a blue grayish discoloration is observed on the skin surface. **B:** the tent sign facilitates a better appreciation of the lesion by stretching the overlying skin, allowing for a clearer definition of the tumor margins and its characteristic faceted nature.

The median time for surgery was 1 month (0, 2.0). In no case was recurrence of the lesion reported.

Discussion

There are few studies on pilomatricomas focused exclusively on the pediatric population, despite this being the age group where these adnexal tumors are most common. The reasons for their higher incidence in childhood and the main risk factors in children remain unknown. The mean age of lesion appearance in this study was 8.3 ± 3.9 years, similar to what has been reported in studies with Canadian (8.7 years), Turkish (9.5 years), Argentine (9.5 years), and Korean (7.7 years) children[8-11]. Regarding sex, our study observed a slight male predominance at a ratio of 1.2:1, contrasting with findings in American and Italian children where females predominated at ratios of 1.75:1 and 2:1, respectively[12,13]. However, other studies have reported similar

Table 5. Baseline characteristics of pilomatricomas contrasted by number of lesions

Variable/lesion	Single (n = 40)	Multiple (n = 12)	p-value
Sex, No. (%) Male (n = 29) Female (n = 23)	 21 (52.5) 19 (47.5)	 8 (66.7) 4 (33.3)	 0.51*
Age, mean (SD), years At diagnosis Onset of dermatosis	 9.8 (+ 3.8) 8.8 (+ 4.0)	 10.1 (+ 2.6) 7.0 (+ 3.7)	 0.82** 0.18**
Nutritional status, No. (%) Low/normal (n = 23) Overweight/obesity (n = 29)	 20 (50.0) 20 (50.0)	 3 (25.0) 9 (75.0)	 0.18*
Comorbility, No. (%) Absent (n = 37) Present (n = 15)	 28 (70.0) 12 (30.0)	 9 (75.0) 3 (25.0)	 0.99***
Size, No. (%)	15 (9.0, 20.0)	17.5 (10.0, 28.5)	0.24****
Time of evolution, months, median (IQR)	7.0 (5.0, 12.0)	38.5 (10.5, 57.0)	< 0.01****
Signs and symptoms, No. (%) Positive tent sign (n = 19) Pain present (n = 21) Calcification (n = 24)	 14 (35.0) 12 (30.0) 17 (42.5)	 5 (41.7) 9 (75.0) 7 (58.3)	 0.73*** < 0.01*** 0.51*
Pilomatricoma variety, No. (%) Classic (n = 42) Other varieties (n = 10)	 32 (80.0) 8 (20.0)	 10 (83.3) 2 (16.7)	 1.00***
Referral diagnosis suspicion, No. (%) Pilomatricoma (n = 27) Other tumors (n = 25)	 22 (55.0) 18 (45.5)	 5 (41.7) 7 (58.3)	 0.51*

*Pearson's R2.
**Student's t-test.
***Fisher's X2.
****Mann-Whitney U test.
IQR: interquartile range; SD: standard deviation.

Table 6. Unadjusted model of clinical factors and dermatological findings associated with multiple pilomatricomas

Variable	OR	CI 95% inferior	CI 95% superior	p-value	R squared
Sex, male	1.81	0.46	6.98	0.39	0.02
Age: < 8 years	1.44	0.33	6.24	0.62	< 0.01
Nutritional status, overweight/obesity	3.00	0.70	12.74	0.13	0.07
Comorbility, Present	1.28	0.29	5.59	0.73	< 0.01
Size > 15 mm	1.50	0.41	5.48	0.54	0.01
Time of evolution: > 1 year	4.82	1.22	18.91	0.02	0.14
Signs and symptoms, No. (%) Positive tent sign Pain present Calcification Pilomatricoma variety, classic	 1.37 7.00 1.89 1.25	 0.35 1.60 0.51 0.22	 4.96 30.4 7.00 6.87	 0.67 0.01 0.33 0.79	 < 0.01 0.21 0.02 < 0.01

CI: confidence interval; OR: odds ratio.

frequencies in both sexes[8,10,11,14]. To date, no significant differences or associations have been identified when contrasting different clinical findings with sex.

Clinically, several studies have reported that pilomatricomas are usually asymptomatic and slow-growing tumors[8,13,15]. However, Figueroa-Basurto et al., in a study

Table 7. Adjusted model of clinical factors associated with multiple pilomatricomas

Variable	OR	CI 95% inferior	CI 95% superior	p-value	R squared
Pain present	5.00	1.06	23.63	0.04	0.25
Time of evolution: > 1 year	2.86	0.64	12.67	0.16	

CI: confidence interval; OR: odds ratio.

Table 8. Topography of pilomatricomas

Hemibody side	No. (%)	General topography	No. (%)	Specific topography	No. (%)
Right	38 (51.4)	Head		Scalp	
Left	27 (36.5)	Scalp	4 (5.4)	Temporal	4 (5.4)
Near the midline	9 (12.2)	Face	16 (21.6)	Face	
Total	74 (100)	Neck	7 (9.5)	Forehead	2 (2.7)
		Trunk	16 (21.6)	Eyebrow	2 (2.7)
		Right upper extremity	14 (18.9)	Eyelid	1 (1.4)
		Left upper extremity	12 (16.2)	Preauricular	3 (4.1)
		Right lower extremity	3 (4.1)	Ear	1 (1.4)
		Left lower extremity	2 (2.7)	Cheek	6 (8.1)
		Total	74 (100)	Jaw	1 (1.4)
				Neck	
				Anterior	2 (2.7)
				Posterior	4 (5.4)
				Lateral	1 (1.4)
				Trunk	
				Posterior thorax	7 (9.5)
				Scapula	7 (9.5)
				Clavicle	1 (1.4)
				Armpit	1 (1.4)
				Upper extremity	
				Shoulder	5 (6.8)
				Arm	11 (14.9)
				Elbow	3 (4.1)
				Forearm	6 (8.1)
				Wrist	1 (1.4)
				Lower extremity	
				Thigh	2 (2.7)
				Leg	3 (4.1)
				Total	74 (100)

on a Mexican population, described that 49% of patients with pilomatricomas presented with pain, a finding similar to our results[5]. In our study, the presence of pain was significantly higher in lesions with a diameter > 15 mm and in patients with multiple pilomatricomas, an association not previously reported in other studies.

Another distinctive sign of the disease is the "tent sign," (Fig. 1) first described in 1978 by Graham and Merwin. This sign allows visualization of the lesion's margins and the faceted nature of the tumor by stretching the overlying skin[4,16]. Few studies describe the frequency of this sign and its association with clinical presentation. In our study, the "tent sign" was present in 19 patients (36.5%) and was associated with larger lesions. This clinical sign can assist physicians in identifying the tumor.

Through this study, we have identified several risk factors associated with the presence of larger pilomatricomas (> 15 mm). These factors include early onset of lesions (< 8 years), the presence of the tent sign, a tumor evolution time of over 1 year, and the presence of clinical variants different from the classical form. These findings have not been previously described in the literature due to the descriptive nature of earlier studies. We consider this information relevant as it enables physicians to identify these risk factors early, which could facilitate the timely removal of tumors and thus prevent the formation of larger residual scars.

Regarding the location of lesions, our study identified the head and neck as the most common areas for pilomatricomas, consistent with other studies[11-13,17]. Descriptive

Table 9. Comparison of age and size of pilomatricomas according to their topography

Variable/topography	Age, mean (SD), years	p-value	Clinical size in mm, median (IQR)	p-value
Topography 1 Head and neck (n = 27) Other locations (n = 47)	 9.2 ± 3.2 10.4 ± 3.3	0.12*	 13.0 (9.0, 20.0) 12.0 (6.0, 20.0)	0.96**
Topography 2 Trunk (n = 16) Other locations (n = 58)	 9.3 ± 2.6 10.1 ± 3.5	0.35*	 10.0 (5.0, 15.0) 13.5 (8.5, 20.0)	0.19**
Topography 3 Right upper limb (n = 14) Other locations (n = 60)	 10.6 ± 3.7 9.8 ± 3.2	0.41*	 11.0 (6.0, 18.5) 12.5 (7.5, 20.0)	0.82**
Topography 4 Left upper limb (n = 12) Other locations (n = 62)	 12.1 ± 2.8 9.5 ± 3.2	0.01*	 18.5 (10.0, 49.5) 10.0 (5.7, 18.5)	0.01**
Topography 5 Lower extremities (n = 5) Other locations (n = 69)	 9.4 ± 4.1 10.0 ± 3.3	0.69*	 5.0 (3.0, 25.0) 12.0 (8.0, 20.0)	0.36**
Total number of pilomatricomas	74			

*T student.
**Mann-Whitney U test.
IQR: interquartile range; SD: standard deviation.

studies have reported that 15% of pilomatricomas exhibit laterality, with 72% located on the right side[3]. Our inferential analysis revealed two significant findings in the left upper extremity compared to other locations: pilomatricomas were larger and more frequently appeared in adolescents. At present, there is no medical literature explaining the biological cause of this predominance, highlighting the need for further studies on this issue. Unfortunately, this study did not investigate the predominant laterality in each case.

Some studies in pediatric populations have indicated that multiple pilomatricomas occur in 7-14% of cases[9,11,15,17]. In our study, 23.1% of cases presented with multiple pilomatricomas, constituting the highest frequency reported in pediatric research. In addition, our results indicate that multiple pilomatricomas were associated with the presence of pain and a longer evolution time. The presence of multiple pilomatricomas can be sporadic, familial, or associated with other diseases[18,19]. The existence of six or more pilomatricomas is highly suggestive of an underlying syndrome (95.52% specificity and 80.65% positive predictive value)[18], warranting referral to genetics and pediatrics services for a multidisciplinary approach to identify more clinical indicators of syndromic pathology. When fewer than five tumors are present, they are considered sporadic and only require a thorough medical evaluation. Close follow-up is recommended, as in many associated syndromes, the lesions appear before the syndrome is detected[18]. The main syndromes associated with multiple pilomatricomas include myotonic dystrophy, syndromes related to Adenomatous Polyposis FAP (including Gardner syndrome), Turner syndrome, Kabuki syndrome, Rubenstein-Taybi syndrome, and Sotos syndrome[18,19]. In our study, only one patient with Turner syndrome was identified, presenting with two pilomatricomas.

The main strengths of this study were: (1) the use of both descriptive and inferential statistics for data analysis, (2) the inclusion of two referral hospitals in Mexico City, which increased the representativeness of the sample and the reliability of the results, (3) highlighting the high frequency of multiple pilomatricomas and their possible clinical associations, contributing to the existing knowledge about this pathology, (4) the study was conducted exclusively in a pediatric and Latin population, (5) some findings are consistent with previous studies in other populations, such as topography and clinical variation, and (6) this research provides a foundation for future prospective studies.

The main limitations of our study were: (1) as a cross-sectional and retrospective study, there is a possibility of selection and information biases, (2) although the sample size was determined, the number of cases analyzed may limit the applicability of the results to a broader population, (3) the lack of follow-up limits the ability to assess the recurrence of pilomatricomas,

and (4) although possible clinical associations are described, a cross-sectional study does not allow for definitive causal relationships to be established between the variables analyzed and pilomatricomas.

Conclusion

The main findings of our study are as follows: (a) 23.1% of the cases presented with multiple pilomatrixomas, the highest frequency reported in pediatric studies to date; (b) the presence of pain was associated with larger lesions and multiple pilomatrixomas; (c) age under 8 years, a positive tent sign, a tumor evolution time > 1 year, and the presence of a clinical variant different from the classic type are risk factors for lesions > 15 mm in diameter; (d) anetodermic pilomatrixomas appeared at the onset of adolescence (10.8 ± 1.4 years); (e) multiple pilomatrixomas had a longer evolution time; (f) the head and neck were the most commonly affected areas, confirming previous findings; and (g) the left upper extremity presented with larger pilomatrixomas (median 18.5 mm) and was more frequent in adolescents (mean 12.1 years) compared to other body areas.

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Conflicts of interest

The authors declare no conflicts of interest.

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.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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RESEARCH ARTICLE

Exploring atypical manifestations and multisystem involvement of Epstein-Barr virus infection in hospitalized pediatric patients from Mexico: insights from a tertiary hospital (2012-2022)

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Abstract

Introduction: *Epstein-Barr virus (EBV) infection, with a global prevalence exceeding 95%, typically manifests in children as infectious mononucleosis. However, clinical practice frequently encounters diverse atypical presentations characterized by multisystem involvement, often resulting in an unfavorable clinical course. Our objective is to describe the clinical manifestations and results of EBV infection in a tertiary pediatric hospital in Mexico.* **Method:** *An observational, transversal, retrospective, and descriptive study that included a systematic review of medical records (2012-2022) of patients under 18 years of age with detectable EBV particles in peripheral blood.* **Results:** *The study included 26 patients with a median age of 5 years and a male predominance of 53.8%. Predominant symptoms were fever (85%) and lymphadenopathy (35%). Sixty-five percent had severe and atypical manifestations, including pneumonia and hepatic, hematologic-oncologic, and autoimmune diseases. Anemia, thrombocytopenia and leukopenia were common, with lymphocytosis in 19% of cases. The median EBV viral load was 2816 copies/mL (range: 555-355,500 copies/mL). Four deaths related to EBV infection were reported. Viral load in these cases also varied widely from 594 to 121,000 copies/mL. Supportive care was administered to 85% of patients, while others received antiviral treatment, steroids, and rituximab.* **Conclusion:** *Atypical manifestations were common, especially in children with multisystem involvement. EBV should be considered as a potential contributor to a diverse spectrum of clinical presentations, emphasizing the need for comprehensive evaluation and awareness in clinical diagnosis.*

Keywords: *Epstein-Barr virus. Infectious mononucleosis. Hemophagocytic lymphohistiocytosis. Tertiary-level hospital. Multisystem disease. Atypical manifestations.*

Explorando las manifestaciones atípicas y el compromiso multisistémico de la infección por el virus de Epstein-Barr en pacientes pediátricos hospitalizados de México: perspectivas de un hospital de tercer nivel (2012-2022)

Resumen

Introducción: *La infección por el virus de Epstein-Barr (VEB) tiene una prevalencia mundial superior al 95%. Se considera que en los niños se manifiesta principalmente como mononucleosis infecciosa; sin embargo, en la práctica clínica, a menudo*

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encontramos numerosas manifestaciones atípicas con compromiso multisistémico que llevan a un curso desfavorable. Nuestro objetivo es describir las manifestaciones clínicas y los resultados de la infección por VEB en un hospital pediátrico de tercer nivel en México. **Método:** *Estudio observacional, transversal, retrospectivo y descriptivo, en el cual se revisaron sistemáticamente los expedientes médicos de pacientes menores de 18 años con una detección positiva de partículas de VEB en sangre periférica en el periodo 2012-2022.* **Resultados:** *Se incluyeron 26 pacientes con una mediana de edad de 5 años y predominio de varones (53.8%). El 65% presentaron manifestaciones graves y atípicas, incluyendo enfermedades respiratorias, hepáticas, hematooncológicas y autoinmunitarias. Los síntomas más frecuentes fueron fiebre (85%) y linfadenopatía (35%). El 54% presentaron manifestaciones atípicas, incluyendo linfohistiocitosis hemofagocítica, neumonía y neoplasia. La anemia, la trombocitopenia y la leucocitopenia fueron comunes, mientras que el 19% presentaron linfocitosis. La media de la carga viral fue de 2816 copias/ml (555-355,500). Se informaron cuatro muertes atribuidas a la infección por VEB, con valores de carga viral de 594 a 121,000 copias/ml. El 85% de los pacientes recibieron solo tratamiento sintomático, mientras que otros recibieron antivirales, esteroides y rituximab.* **Conclusión:** *Las manifestaciones atípicas se observaron comúnmente, en especial en niños con compromiso multisistémico. El VEB debe considerarse como un potencial factor contribuyente en el diagnóstico de una amplia gama de manifestaciones clínicas.*

Palabras clave: *VEB. Mononucleosis infecciosa. Hemofagocitosis linfohistiocítica. Hospital de tercer nivel. Enfermedad multisistémica. Manifestaciones atípicas.*

Introduction

Primary infection with the Epstein-Barr virus (EBV), also known as human herpesvirus 4, typically occurs in early childhood after exposure to the oral secretions of seropositive individuals following intimate contact. The virus spreads mainly through saliva and infects B cells and epithelial cells, persisting in the former for a lifetime. Infection activates both humoral and cellular immunity. CD8+ lymphocytes and NK cells play a crucial role in controlling infection[1], as massive, atypical lymphocytosis can be seen in infectious mononucleosis[2]. Infectious mononucleosis has been considered the most common disease associated with EBV infection in adolescents and young adults. Mononucleosis is characterized by the production of heterophile antibodies, which are predominantly immunoglobulin (Ig) M. The detection of these antibodies in patients' serum is indicative of acute EBV infection[3].

Although most EBV infected children are asymptomatic, some develop symptomatic disease. Clinical manifestations include typical and atypical presentations. Typical manifestations include infectious mononucleosis-like symptoms, such as pharyngitis, fever, fatigue, severe headache, general malaise, lymphadenopathy, and splenomegaly[3-5]. However, these manifestations can vary, ranging from mild to more severe cases with various complications. Atypical manifestations encompass a wide range of conditions, including acute dacryocystitis[6], airway obstruction[7], pneumonia[8], acute myocarditis[9], atherosclerosis[10], thrombocytopenia, hemolytic anemia, agranulocytosis, hemophagocytic lymphohistiocytosis (HLH)[11,12], neurological disorders[13-18], hepatic involvement[19], renal manifestations[20], acute acalculous cholecystitis[21], splenic rupture[22], Kawasaki disease[23], Henoch-Schönlein purpura[24], velvety oral leukoplakia[25], neoplasms[26], psychiatric symptoms[27], and more complex inflammatory and/or autoimmune diseases[28]. The prognosis varies depending on the clinical presentation, with most patients recovering within a few weeks. However, severe and chronic complications can occur, especially in cases of HLH, neurological involvement or neoplasia.

Reported laboratory findings in acute or chronic EBV infection often include leukocytosis, relative lymphocytosis, mild thrombocytopenia, and elevated levels of aspartate transaminase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and ferritin[29]. Diagnosis can be confirmed through the detection of heterophile antibodies, specific EBV antibodies (IgM and IgG), and viral load measurement. Treatment is primarily supportive, as EBV infections are usually self-limiting. However, antiviral treatment may be considered in cases with atypical symptoms or complications[30-32], and steroids can be used to manage autoimmune and inflammatory symptoms. Rituximab, a monoclonal antibody targeting CD20, may be beneficial in lymphoproliferative disorders.

In the realm of pediatric virology in the hospital setting, symptomatic EBV infections are common; however, there is a notable gap in research regarding atypical manifestations. This study aims to describe the clinical manifestations and results of EBV infection in a tertiary pediatric hospital in Mexico. We identified the most common clinical manifestations delineating the differences between atypical manifestations of EBV infection and their typical counterparts in a hospitalized

pediatric population. The results of this study will enrich our understanding of EBV infection in pediatric patients, especially within the Mexican population, thereby facilitating early recognition and competent management of atypical presentations.

Methods

Patients

An observational, transversal, retrospective, and descriptive study was conducted at the Hospital de Pediatría of Centro Médico Nacional Siglo XXI (CMNSXXI) of the Instituto Mexicano del Seguro Social. The study was approved by the local Health Research Committee (Institutional registration number R-2022-3603-048). Records of pediatric patients with positive EBV viral load results from January 2012 to December 2022 were collected. Patients without complete medical records were excluded from the study.

Quantification of EBV load

EBV loads were quantified by a reverse – polymerase chain reaction (RT-PCR) –based method using 400 µL of whole blood and using a commercial kit according to the hospital's routine protocol. Results are reported as the number of viral copies per mL.

Statistical analysis

Correlation analysis was performed using Spearman rank-based testing. In the correlation analysis between the hepatic enzymes and viral load, a $p < 0.05$ between a marker and any of the viral load measurements was the threshold to include that marker in the reported results. Logistic regression and other statistical analyses were performed using GraphPad Prism 6.

Results

A total of 68 patients exhibited positive viral load results indicative of EBV infection. Following strict inclusion criteria, 26 hospitalized patients were found to be eligible for our study, with the remainder excluded due to incomplete medical records. Age at diagnosis ranged from 1 to 14 years, with a notable concentration in the preschool and school-age demographic groups (Table 1). Males were predominant, representing 62% (n = 16) of the final cohort, with the majority from Mexico City. A diverse distribution across different regions of the country is also shown in table 1. Initial pediatric medical care accounted for 38.4% of patients, while the remainder sought care under different services such as hematology, oncology, immunology, surgery, and gastroenterology, consistent with the diverse symptomatic presentations observed at the time of diagnosis.

Table 1. General characteristics of patients with Epstein-Barr virus infection (n = 26)

Variable	Medium	Min-Max
Age (years)	5	1-14
	n	%
Sex		
Male	14	53.8
Female	12	46.2
Age group		
Infants	5	19.2
Preschoolers	8	30.7
School-age	8	30.7
Adolescents	5	19.2
Place of origin		
Mexico city	16	61.5
Chiapas	3	11.5
Guanajuato	2	7.7
Guerrero	2	7.7
Estado de México	1	3.8
Sinaloa	1	3.8
Tabasco	1	3.8
Comorbidities		
Without comorbidities	6	2
With comorbidities*		
Hepatic	9	34.6
Transplant	7	26.9
Aplastic anemia	7	26.9
Oncologic	5	19.2
Juvenile idiopathic arthritis	2	7.7
Chronic kidney disease	2	7.7
Severe combined immunodeficiency	1	3.8

*Some patients had multiple comorbidities.

Among the patient cohort, 6 individuals (23%) were previously healthy, with no identified comorbidities before the EBV infection diagnosis. The remaining subjects presented with a spectrum of comorbidities, including oncological conditions such as four cases of leukemia and one of lymphoma, one of juvenile idiopathic arthritis, one severe combined immunodeficiency, and two cases of chronic kidney disease. Liver-related comorbidities were evident, with 8 individuals (31%) having acute hepatitis and 1 patient (4%) experiencing intrahepatic cholestasis. In addition, 6 patients (23%) had aplastic anemia. A history of transplantation was noted in 7 cases (27%). Regarding to other infections, 4 individuals (15%) were

HIV-positive, 3 (11.5%) were diagnosed with cytomegalovirus (CMV) infection, and 1 patient (4%) had concurrent SARS-CoV-2 infection (Table 1 summarizes all these data).

Fever was the predominant symptom in 23 patients (85%), followed by lymphadenopathy in 9 cases (35%). Of note, only 2 patients (8%) presented with the classic triad of sore throat, lymphadenopathy, and fever, characteristic of infectious mononucleosis. Therefore, atypical symptoms were prevalent, including gastrointestinal abnormalities in 14 patients (54%), hepatic abnormalities in 11 patients (42%), splenomegaly in 6 patients (23%), HLH in 6 patients (23%), pneumonia in 3 patients (11.5%), and airway obstruction, renal abnormalities, and post-transplant lymphoproliferative disorder all in 1 patient each (4%). Leukopenia was observed in 5 patients (19%) and five patients had lymphocytosis (Table 1).

Analysis of viral load data revealed a range of 555 to 355,500 copies/mL, with a median of 2,826 copies/mL (Table 2 and Fig. 1). The most common biochemical abnormalities included liver function test abnormalities and elevated LDH levels. Specifically, 27% of individuals had elevated LDH, while 61.5% had elevated liver function test results. Six patients had missing LDH measurements and four had missing AST and/or ALT measurements (Table 2). We did not observe a significant correlation between the levels of LDH, AST and ALT and the EBV loads (Supplementary Fig. 1).

The treatments given to patients are shown in table 3, the most common therapeutic approach was supportive management, given to 22 (85%) of the patients, 5 patients (19%) required specific antiviral treatment (acyclovir or a related drug), and 3 (11.5%) were treated with Rituximab. Regarding the total length of hospital stays for the studied patients, the median duration was 17.5 days, ranging from 7 to 32 days. Twenty-two (85%) patients were discharged home, while the remaining patients died during their course of illness due to the direct manifestations of EBV infection. Table 3 describes six patients who developed HLH secondary to EBV infection, with two of these unfortunate cases resulting in death. Additional details on the deceased patients, including comorbidities, atypical manifestations, and the direct cause of death, are summarized in table 4. While the EBV load in deceased patients ranged from a minimum of 500 copies/mL to a maximum of 120,000 copies/mL, we did not find a significant difference between the deceased patients and those who survived (Fig. 2). This lack of significance may be attributed to the small number of deceased patients in our sample.

Table 2. Biochemical alterations in patients with Epstein-Barr virus infection

Variable	Medium	Min-Max
DHL	467.5	39.4-1083
AST	57.5	9.6-151.5
ALT	64.1	2.5-240.9

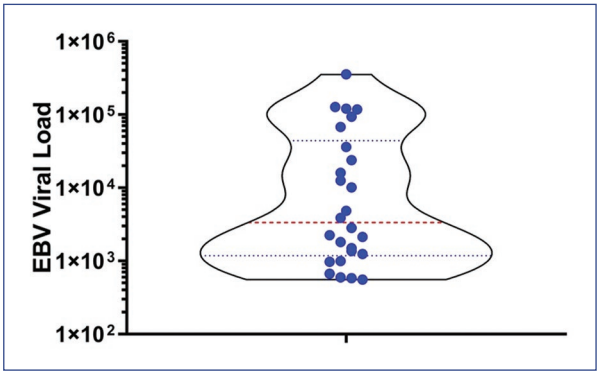

Figure 1. Distribution of Epstein-Barr virus viral load among the 26 patients included in the analysis. Viral load values are presented on a logarithmic scale to accentuate the variability observed between individuals. Each data point on the graph corresponds to the viral load of a specific patient.

Discussion

While the majority of patients in this study presented with a self-limiting clinical course and were discharged home in good condition, we observed four fatalities (15%) directly linked to EBV infection. It is noteworthy that all four of these patients had severe comorbidities coexisting with the positive EBV load, such as HLH, lymphoma, pneumonia, and renal disease. This suggests that patients with compromised immunity have a more severe disease course. Three of the deceased patients had higher than 2000 copies/mL. We found eight patients coinfected with other agents at the time of EBV diagnosis, including four with HIV, three with CMV, and one with SARS-CoV-2. This latter patient was one of those who died due to this coinfection. Singh et al. found that among viral infections associated with SARS-CoV-2, EBV had the highest incidence, without knowing the exact cause of this association[33]. Moreover, SARS-CoV-2 has the ability to reactivate EBV[34].

Our study revealed a diverse spectrum of both typical and atypical clinical manifestations in pediatric patients with EBV load detection. Notably, these manifestations

Table 3. Characteristics of patients with HLH secondary to Epstein-Barr virus infection (n = 6)

Patient	Year of diagnosis	Age (years)	Sex	Comorbidity	Viral load (copies/mL)	Therapy*	Outcome
1	2019	12	Male	Acute lymphoblastic leukemia	36,270	Antiviral	Discharge
2	2020	1	Male	Juvenile idiopathic arthritis/chronic kidney disease	594	Steroids	Deceased
3	2019	8	Male	None	584	None	Discharge
4	2021	6	Female	None	973	None	Discharge
5	2020	1	Female	SARS-CoV2 infection and aplastic anemia	2,826	Rituximab	Deceased
6	2020	10	Male	Severe combined immunodeficiency	117,900	Antiviral/ Rituximab	Discharge

*Refers to any treatment besides the supportive care.

Table 4. Characteristics of patients who died with complications secondary to EBV infection (n = 4)

Patient	Age (years)	Sex	Comorbidity	Atypical Manifestations	Viral Load (copies/mL)	Treatment	Cause of death
1	1	Male	Juvenile idiopathic arthritis/chronic kidney disease	HLH	594	Steroids	Septic Shock
2	1	Female	Sars-Cov2 coinfection/ aplastic anemia	HLH/Acute Renal Lesion	2,826	Rituximab	EBV
3	13	Male	Chronic hepatitis	Pneumonia	12,510	Steroids/ Antiviral	Septic and hypovolemic Shock
4	3	Male	Limphoma/CMV coinfection/transplant	LPD	121,000	None	Septic and Hypovolemic Shock

HLH: hemophagocytic lymphohistiocytosis; LPD: lymphoproliferative disease; CMV: cytomegalovirus; EBV: Epstein-Barr virus.

frequently correlated with underlying comorbidities within our study cohort, underscoring the imperative role of contextual clinical assessment when faced with EBV infection in children. Surprisingly, the classic triad of symptoms conventionally associated with infectious mononucleosis -pharyngitis, adenomegaly, and fever- was present in only a minority of cases. This observation underscores the critical need to consider EBV infection in individuals with complex underlying pathologies or compromised immune status, even when the presentation deviates from the typical infectious mononucleosis pattern. In our study, a variety of atypical manifestations of EBV infection was observed, so diverse that they are difficult to distinguish from other pathologies[35]. The atypical manifestation ranges from renal abnormalities, airway obstruction, bicytopenias, pancytopenias, and the development of HLH. HLH is a syndrome that usually occurs in patients with severe systemic hyperinflammation, which includes persistent fever, cytopenias, hepatosplenomegaly, coagulopathies, and elevated ferritin[36]. A study conducted in Japan in 2007 reported 277 cases of HLH, of which 130 (46%) had EBV as the causative agent[37]. We can observe that out of the six patients who developed HLH in our study, two died, with one receiving treatment with steroids and the other with rituximab. Chellapandian et al., conducted a study to evaluate the treatment with rituximab in pediatric patients with EBV-positive HLH, in which an immediate improvement in the signs and symptoms of HLH was observed[38]. In our study, rituximab was used in only three patients, of whom two were diagnosed with EBV-induced HLH. Unfortunately, one of these patients died despite the treatment.

While the majority of patients received primarily supportive care, a variety of treatment modalities was implemented on a case-by-case basis. Supportive care was aimed at alleviating symptoms, while some patients

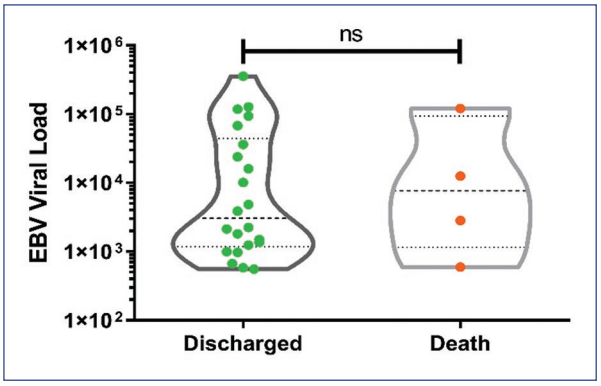

Figure 2. Comparison of Epstein-Barr virus load in patients who succumbed to the infection with those who were discharged. The viral load values were logarithmically scaled, with each data point representing an individual patient. Mann–Whitney U test for non-parametric data, without normal distribution, statistical significance was determined with a $p = 0.05$.

underwent more targeted therapies, including the administration of rituximab. In addition, three patients were treated with steroids. Corticosteroids, known to alleviate symptoms such as fever, lymphadenopathy, and oropharyngeal manifestations, are beneficial in atypical presentations or when associated with severe atypical symptoms such as airway obstruction, acute hemolytic anemia, and significant cardiac or neurologic involvement[30]. However, the specific reasons for prescribing steroids and rituximab, as well as the discernible benefits of their use, were not explicitly documented in the patients' medical records.

A notable finding was the lack of a clear association between EBV viral load and patient outcomes. Although some patients had elevated viral loads, the majority experienced favorable clinical outcomes, while others with lower viral loads succumbed to more severe disease. This underscores the critical role of factors beyond viral load, such as a patient's immune status and underlying comorbidities. This finding is consistent with previous research highlighting the multifaceted nature of EBV and its direct capacity to cause damage or complicate other underlying conditions.

EBV infection in pediatric populations has been the subject of various studies worldwide, shedding light on its diverse clinical presentations and outcomes. García-Peris et al., conducted a study in Madrid, Spain, involving 103 children[39]. They reported that 63% of the children exhibited typical mononucleosis symptoms, while the remaining 37% presented with atypical manifestations, all with favorable outcomes. These findings also underscore the diverse clinical spectrum of EBV infection, although the frequency of typical mononucleosis symptoms was higher than in our population. Examined 61 pediatric patients in Shanghai and found typical symptoms in the majority, but a significant portion exhibited atypical symptoms, including respiratory (in 31% of cases), urinary (14.8%) and hematological (14.8%) manifestations[5]. Similarly, Jeon et al. found typical symptoms as the most frequent, reporting fever, lymphadenopathy, liver involvement and various cytopenias in their study of 38 EBV-infected children in Korea[40]. In the Mexican context there is a lack of comprehensive studies addressing the atypical manifestations of EBV infection in pediatric patients. Napoleón et al. conducted a study spanning four decades and reported lymphadenopathy as the most common symptom. Although they documented some atypical manifestations, no fatalities were reported[41]. Lozano et al. described clinical manifestations in seven patients with EBV infection, primarily presenting typical symptoms (faringitis, esplenomegalia, hepatomegalia, and linfoadenopatias y fiebre)[42].

The present study underscores the need to recognize the diverse clinical presentations of EBV infection in pediatric cohorts. Our findings are consistent with the global literature and reinforce the concept that EBV infection should be considered in children presenting with a broad spectrum of symptoms. In particular, our research reveals an increased prevalence of atypical manifestations beyond the typical symptoms associated with infectious mononucleosis. Examples include juvenile idiopathic arthritis or aplastic anemia, each observed in 23% of patients. Thus, EBV should be considered as a potential contributor to a variety of diseases, particularly in patients with underlying comorbidities or immunosuppression. Furthermore, the lack of a discernible correlation between viral load and outcome underscores the multifaceted nature of EBV-related disease and emphasizes the need for thorough patient evaluation and a comprehensive management approach.

In conclusion, this study adds to the evolving body of knowledge regarding EBV infection in pediatric patients and highlights the ongoing need for research in this area. Future investigations should address novel treatment modalities, especially in complicated cases with comorbidities or severe multisystemic involvement. Our study, conducted in a tertiary hospital specializing in severe pediatric pathologies, provides valuable insights into the peculiar clinical characteristics of EBV infection in this specific population.

Study limitations

Our study, while providing insights into EBV infection in pediatric patients, has several limitations. Firstly, its observational nature precludes establishing causality between EBV infection and clinical outcomes, given the associative study design. Although viral load measurement is informative, it alone does not fully predict clinical outcomes, which are likely influenced by multiple factors such as underlying diseases or coinfections besides EBV activity. The heterogeneity of the patient population, drawn from various hospital services without standardized treatment guidelines, introduces variability in clinical presentation, interpretation, and management. Moreover, incomplete patient records may have biased our findings, potentially underestimating certain parameters. Despite these limitations, our study underscores the need for further research to better understand EBV infection in pediatric cohorts.

Acknowledgment

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Conflicts of interest

We declare that there is no conflict of interest regarding the publication of this manuscript.

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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 approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

Supplementary data

Supplementary data are 10.24875/BMHIM.24000027. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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RESEARCH ARTICLE

Intramuscular vascular malformations in pediatric patients: a retrospective study in a vascular anomalies clinic

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Abstract

Background: *Intramuscular vascular malformations (IVMs) are rare developmental congenital structural abnormalities. Their clinical diagnosis is difficult, and imaging studies are essential to determine the type and extent of vessels involved. Treatment can be challenging and must be managed by a multidisciplinary team.* **Methods:** *A descriptive, observational, retrospective, longitudinal study of clinical records of patients diagnosed with IVMs who were evaluated at the vascular anomalies clinic from January 2011 to December 2021 was performed. Demographic, clinical, imaging, diagnosis, treatment, and response data were collected.* **Results:** *Seven patients (five females and two males) with a mean age of 13.66 years (standard deviation 5.82 years) were included in the study. In all cases, the clinical diagnosis was venous and lymphatic malformation. The radiological findings were dilated and tortuous vascular structures or multilobulated lesions with septa inside, with or without vascular flow; these findings allowed diagnosis in all cases. Treatment modalities included sclerotherapy in five patients, surgical resection in two, medical treatment with sirolimus in three, and surveillance in one. Subsequent clinical evolution was favorable in all patients, with decreased pain in six (partial in four and total in two) and size reduction in one patient.* **Conclusion:** *IVMs in our pediatric population most frequently affect the lower extremities. The main symptoms and signs were pain on exertion and volume increase. Treatment can be challenging given the extension and depth of the malformations, so a combination of therapeutic modalities may be necessary to obtain the best outcome.*

Keywords: *Vascular malformation. Sclerotherapy. Sirolimus.*

Malformaciones vasculares intramusculares en pacientes pediátricos: un estudio retrospectivo de una clínica de anomalías vasculares

Resumen

Introducción: *Las malformaciones vasculares intramusculares (MVI) son anomalías estructurales congénitas del desarrollo raras. Su diagnóstico clínico es difícil y los estudios de imagen son fundamentales para determinar su tipo y extensión. Su tratamiento puede ser un desafío y debe ser dirigido por un equipo multidisciplinario.* **Métodos:** *Se realizó un estudio descriptivo, observacional, retrospectivo y longitudinal de los expedientes clínicos de pacientes con diagnóstico de MVI que fueron valorados en la Clínica de Anomalías Vasculares desde enero 2011 a diciembre 2021. Se recolectaron datos demográficos, clínicos, imagenológicos, diagnóstico, tratamiento y respuesta al mismo.* **Resultados:** *Se incluyeron 7 pacientes*

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(5 mujeres y 2 hombres) con una edad media de 13.66 años (DE 5.82 años). En todos, el diagnóstico clínico fue malformación venosa y/o linfática. Los hallazgos radiológicos mediante ultrasonido y/o resonancia magnética nuclear fueron estructuras vasculares dilatadas y tortuosas o lesiones multilobuladas con septos en su interior, con o sin flujo vascular; y en todos los casos permitieron hacer el diagnóstico. El tratamiento fue escleroterapia en 5 pacientes, resección quirúrgica en 2, tratamiento con Sirolimus en 3 y vigilancia en 1. La evolución clínica posterior fue favorable en todos, con disminución del dolor en 6 (parcial en 4 y total en 2) y reducción del tamaño en 1 paciente. **Conclusión:** *Las MVI en nuestra población pediátrica, afectan con mayor frecuencia las extremidades inferiores. Los principales síntomas fueron dolor de esfuerzo y aumento de volumen. Su tratamiento puede ser un reto dada su extensión y profundidad, por lo que la combinación de modalidades terapéuticas puede ser necesarias para obtener el mejor desenlace.*

Palabras clave: *Malformación vascular. Escleroterapia. Sirolimus.*

Introduction

Vascular malformations are congenital structural anomalies of development. They commonly affect the dermis and subcutaneous tissue (superficial) or infiltrate muscle and bone tissue (deep)[1]. The latter are characterized by greater symptomatology, difficult diagnosis, and poor response to conventional therapy compared to their superficial counterparts[2,3].

Intramuscular vascular malformations (IVMs) have for many years been erroneously termed "intramuscular hemangiomas," "cavernous hemangiomas," or "angiomas," terms which due to their suffix "oma" incorrectly suggest a true neoplasm. This inadequate nomenclature can lead to erroneous study, diagnosis, and treatment. Since 1996, the International Society for the Study of Vascular Anomalies has classified IVMs as true malformations, distinct from hemangiomas, and tumors with undetermined proliferative potential[4,5].

IVMs are quite rare; the true incidence and prevalence are unknown, but they are believed to be < 1% of all vascular malformations. Females are more affected, with a ratio of up to 2:1[6-8]. Clinically, only 8%-15% can be diagnosed[9], which is why imaging studies are fundamental in determining the type and extent of the malformation. Treatment can be challenging and should be directed by a multidisciplinary team[1].

This study aims to describe pediatric patients with IVMs, including clinical manifestations, radiological characteristics, evolution, treatment, and therapeutic response.

Methods

A descriptive, observational, retrospective, and longitudinal clinical study was conducted on all clinical records of patients diagnosed with IVMs who were evaluated and registered in our hospital's vascular anomalies clinic (VAC) database from January 2011 to December 2021. Demographic, clinical, and imaging data, as well as diagnosis, treatment, and response to treatment, were collected. Patient records lacking the clinical variables to be studied were excluded/eliminated.

Descriptive statistics were used with frequency distribution and measures of central tendency.

Results

Seven patients (five females and two males) with a mean age of 13.66 years (standard deviation ± 5.82) were included in the study. The reason for consultation was the presence of swelling or a palpable mass (Figs. 1-3) following trauma (three patients) and associated with limb pain (four patients). The clinical diagnosis was venous or lymphatic malformation (LMs) in all cases. Radiological findings in all cases allowed the diagnosis of IVM and were described as dilated and tortuous vascular structures (in four patients) or multilobulated/multi-compartmentalized lesions (Figs. 4-6) with internal septa (in three patients), with or without vascular flow. The affected muscles were the triceps (Fig. 4), quadriceps (Fig. 5), and gluteus maximus. Treatment consisted of sclerotherapy in five patients, surgical resection in two, medical treatment with Sirolimus in three, and surveillance in one patient. The clinical evolution after treatment was favorable in all cases, with pain reduction (partial in four and total in two) and size reduction in one patient. One patient was lost during follow-up. The individual characteristics of each patient are shown in table 1.

Discussion

IVMs are benign lesions[8] secondary to congenital errors in vascular morphogenesis[10] that infiltrate the muscle thickness[11]. There are few reports on the epidemiology of vascular malformations in general, but

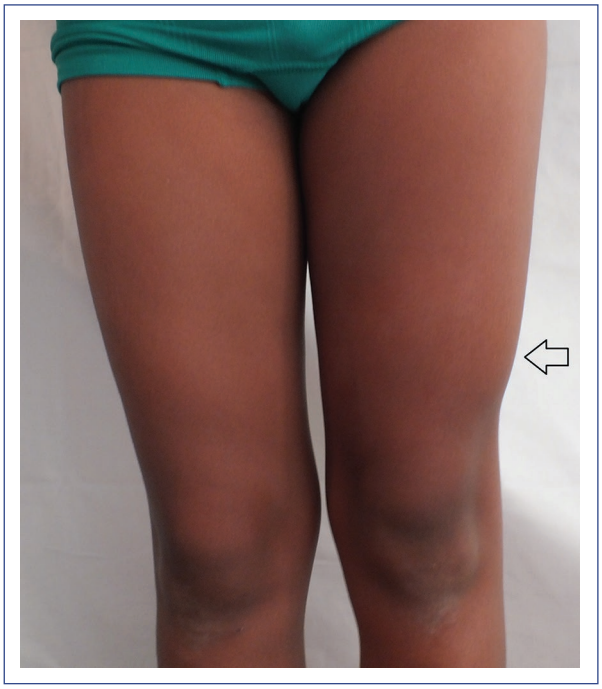

Figure 1. Discrete increase in volume in the distal third of the left thigh.

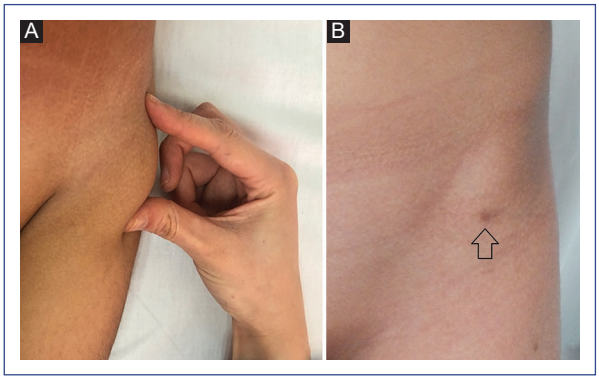

Figure 2. A: increase in volume observed on the lateral aspect of the left hip before sclerotherapy. **B:** after treatment with sclerotherapy, only a post-inflammatory hyperpigmented spot is observed at the puncture site.

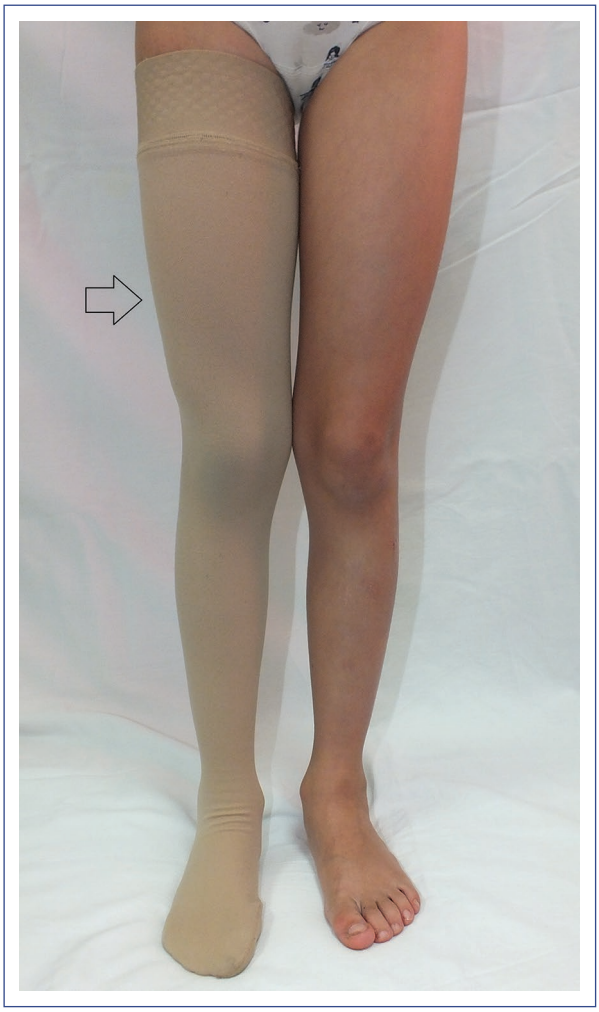

Figure 3. Discrete increase in volume in the distal third of the right thigh. A custom compression stocking is visible as part of the home treatment.

they are estimated to have an incidence of 1.2%[12]; IVMs are estimated to comprise 0.8%- < 1% of all vascular malformations[13,14]. In our institute, they accounted for 1.43% of all cases of vascular malformations during the study period, likely attributed to our status as a referral center with a specialized clinic in vascular malformations, which facilitated their diagnosis.

The most frequent sex was female (71.4%), as described in the literature[4,7,8]. Although vascular anomalies are present at birth, only 25% are evident at that time[15,16]; in our series, only 1 (14.3%) case is presented at birth. The remaining 75% manifest between the first and third decades of life[15,16]; however, in our study, the mean age of disease onset was 5.28 years. It is reported in the literature that clinical presentation starts during adolescence or early adulthood[6,17] due to increase in volume secondary to the effect of hormonal factors on blood vessels[10]. However, IVMs can also appear after trauma, as in three of the patients in our series, or after an infection[10].

IVMs typically present with pain as the initial or distinctive symptom or with swelling; they can be significant enough to limit physical activity[17,18]. In all our patients, the reason for consultation was swelling, which can be secondary to vascular congestion due to

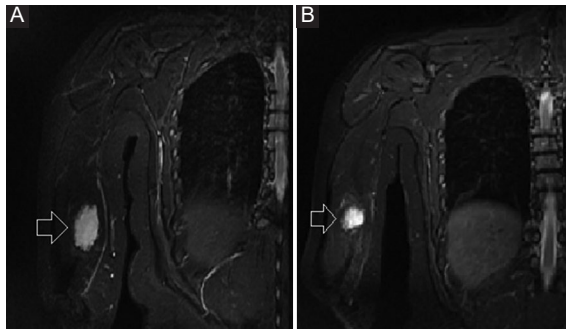

Figure 4. Magnetic resonance images in short-TI inversion recovery sequence. **A:** coronal view of the right arm showing an ovoid image with lobulated edges and hyperintense signal on T2 at the level of the triceps muscle. **B:** comparative study after sclerotherapy showing a significant decrease in size.

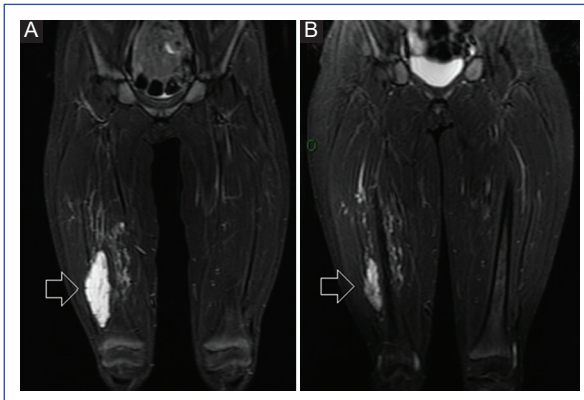

Figure 5. Magnetic resonance images in short-TI inversion recovery sequence. **A:** coronal view of the left thigh showing a fusiform image with lobulated edges and hyperintense signal at the level of the vastus lateralis and intermedius muscles. **B:** comparative study after sclerotherapy showing a significant decrease in size.

movement[3,13]. About 57.1% presented with pain, a symptom that has been reported in the literature in up to 50-80% of patients[8,17], as a consequence of microthrombus formation at rest[4,19] and due to the diffuse and infiltrative growth of IVMs along the longitudinal axis of the muscle that follows and compresses neurovascular bundles[17]. Moreover, the pain can be even more intense if found in long and narrow muscles, as in all our patients, and even if they are relatively small, they can cause intense pain[13].

The most frequent type of malformation in the presented patients was venous, representing 42.8% of

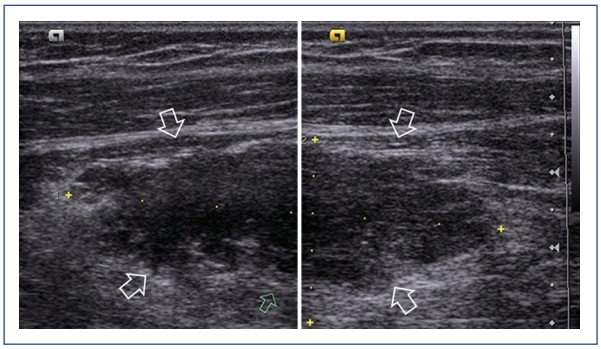

Figure 6. Gray scale ultrasound image of the muscular plane of the right arm showing an ovoid image with markedly lobulated edges and hypoechoic appearance.

cases, similar to the 40% reported in the literature[15,17]. The most frequently affected topography was the lower extremities, of which the thigh was the most common region, as in the case series reported by Scorletti et al.[7], and differs from what was reported by Wieck et al., where the lower portion of the leg was the most affected[17].

In 71.4% of patients, the initial suspicion coincided with the final diagnosis, while in other reports, only 8-15% coincided[14]. This higher concordance may be due to the fact that in our institute, we have the multidisciplinary VAC composed of Dermatology, Interventional Radiology, and Oncological Surgery services (among others), with whom doctors from different subspecialties have contact, increasing their knowledge, and improving their diagnostic skills.

The first study requested in 71.4% of cases was ultrasound, which is recommended to identify the location (superficial or deep), nature (cystic or solid), and flow (null, low, or high) of IVMs[4,8], and it should always be complemented with a contrast-enhanced magnetic resonance imaging (MRI) for precise characterization of its extension and relationship with other adjacent vital structures, such as the neurovascular bundle[4,18,20].

The characteristic radiological findings on ultrasound are well-defined, fusiform or oval masses, lobulated or septated, of variable echogenicity, arranged along the muscle fibers, thus having a hypoechoic appearance, and whose flow in Doppler mode depends on their etiology[4]. Regarding MRI, they are described as well-defined intramuscular masses, oval-shaped, multiseptated, as they are composed of vascular channels oriented longitudinally to the muscle fibers, markedly hyperintense on T2, and with Gadolinium administration, in the late phases, the enhancement becomes more intense and

Table 1. Main demographic, clinical, radiological characteristics and response to treatment of reported cases

Case no.	Age (years, months)	Sex	Reason for consultation (age at onset)	Topography	Symptoms	Diagnosis		Imaging study	Radiological finding	Affected muscle(s)	Affected vessel	Treatment (quantity of procedure)	Response to treatment
						Initial (Service that made the diagnosis)	Final at VAC (age at diagnosis)						
1	9y 1m	M	Increased volume (7d)	Right thigh distal third	Asymptomatic	Intramuscular hemangioma (Oncologic Surgery)	VM (4 m)	US, contrast MRI	Dilated and tortuous vascular structures	Rectus anterior and vastus lateralis of quadriceps	Vein	Surveillance	No progression[a]
2	16y 10	M	Increased volume (9y 3m)	Right thigh distal third	Pain when walking	Prob. Synovioma vs VM (Orthopedics)	VM (11y 2 m)	Contrast CT	Multiple dilated tortuous veins with abnormal paths that cause a significant increase in volume	Vastus lateralis of quadriceps	Vein	Sclerotherapies with polidocanol 3% (6)	Partial pain reduction
3	18 y	F	Increased volume post-trauma (11y)	Right arm, distal third	Pain, paresthesias	Lipoma vs Myositis ossificans (Orthopedics)	VM (15y 3m)	US, contrast MRI	Multilobulated lesion of 43 × 11 mm, hyperintense on T2	Triceps (N/S)	Vein	Surgical resection (2) Sclerotherapy with polidocanol 3% (1), aspirin and rehabilitation	Total pain reduction
4	15y 3m	M	Increased volume, post-trauma (6y)	Left thigh distal third	Pain	Prob. VM (Dermatology)	VLM (8y 8m)	US, contrast MRI	Anechoic areas with tortuous appearance showing vascular flow	Vastus internus of quadriceps	Vein and lymphatic	Sclerotherapies with polidocanol 3% (6), aspirin, rehabilitation	Size reduction (100%), partial pain improvement
5	8y 8 m	F	Palpable tumor (1y 11m)	Right thigh, distal third	Asymptomatic	Prob. LM (Oncology)	VLM (3y)	US	Fusiform image of 3.8 × 1.2 cm, with fine and coarse echoes inside suggesting the presence of septa and without vascular flow	Vastus medialis of quadriceps	Vein and lymphatic	Sclerotherapy with polidocanol (4), Sirolimus[b], Sclerotherapy with bleomycin (4)	Partial improvement of pain, resolution of CIL
6	17 y 9m	M	Increased volume (0y 0m)	Left buttock and thigh	Asymptomatic	LM in gluteus (Oncological Surgery)	LM (14y 4m)	Contrast MRI	Heterogeneous multicompartmental lesion, with cystic areas and reticular component of soft tissues, with intense and heterogeneous enhancement with Gadolinium	Gluteus maximus and vastus lateralis of quadriceps	Lymphatic	Surgical resection[c], Sirolimus	100% pain reduction
7	15 y 2 m	M	Increased volume, post-trauma (12y)	Left thigh, distal third	Intermittent pain	Prob. LM (Dermatology)	LM (13y 8m)	US, contrast MRI	Serpiginous hypoechoic lesion that does not affect bone	Vastus intermedius and lateralis of quadriceps	Lymphatic	Sclerotherapy with bleomycin (3), Sirolimus	Partial improvement of pain

[a]Lost to follow-up.
[b]Sirolimus was suspended due to adverse effects.
[c]Performed before being known in the Vascular Anomalies Clinic.
y: years; m: months; d: days; M: male; F: female; Prob: probable; LM: lymphatic malformation; VM: venous malformation; VLM: venolymphatic malformation; VAC: vascular anomalies clinic; US: ultrasonography; MRI: magnetic resonance imaging; CT: computed tomography; N/S: not specified.

homogeneous[4]. This is an important clue for diagnosis, as this phenomenon is explained by the relative isolation from systemic venous circulation, which limits the passage of contrast to these low-flow lesions[4]. All our patients presented some or several of the findings described above.

There is no precise algorithm for choosing the treatment of IVMs[17]; it depends on the location, size, extent, and associated symptomatology[17,21]. Treating vascular malformations, in general, can be challenging and should be approached by a multidisciplinary team[20,22]. Regarding the treatment of our patients, two had an initial surgical resection with partial clinical improvement. Some authors report that these patients with IVM frequently undergo multiple surgical procedures that generally result in little improvement or even worsening of symptoms by damaging functional muscles[20,23]. However, it has also been reported that surgery can be effective in combination with medical treatment or sclerotherapy[17]. In well-defined malformations that measure < 5 cm or that only affect a single muscle, surgery, even as monotherapy, can improve movement, quality of life, and radiological image more effectively than isolated sclerotherapy[21,24].

The rest of the patients were referred to the VAC to offer them the best therapeutic option agreed upon by an experienced team, thus reducing morbidity and improving quality of life. Sclerotherapy is considered the first-line treatment, and an average of 2-6 sessions may be required[7,15,17]. However, in our series, only one patient required up to 8 sessions due to the appearance of an IVM in the same affected segment. 82-94% success rate has been reported[14], especially in reducing pain. In our study, 57.1% had partial improvement, and 28.6% had total pain resolution, similar to those found by Crawford et al. (57.9% and 21.1%, respectively)[21,25]. However, in other studies, such as Bianchini et al., pain improvement of up to 88.9% was reported, although most were large venous malformations, which generally have a better response[15].

Regarding medical treatment[26], it has been reported that sirolimus directly inhibits mTOR (mammalian target of Rapamycin), a serine/threonine protein kinase, part of the PI3K/Akt/mTOR pathway, which acts as a master switch in numerous cellular processes, such as cell proliferation and growth, as well as angiogenesis and lymphangiogenesis[27,28]. Up to 92% of patients treated with sirolimus show a decrease in size, especially in LMs, and improvement in pain, particularly in mixed malformations, as well as a decrease in bleeding and improvement in their quality of life[28,29]. In general, the response is evident after 2 months of treatment, and as such, the optimal duration of treatment has not been established[29]. The suggested dose is 0.8 mg/m²/dose twice daily[30]. In our case series, four of our patients were treated with sirolimus, either because they were not candidates for initial surgical treatment or sclerotherapy (patient 6) or because they persisted with pain or swelling despite having had surgical treatment or sclerotherapy (patients 4, 5 and 7). All patients showed improvement in pain and continued treatment for up to 2 years, except for patient 5, whose treatment was suspended due to hypertriglyceridemia and recurrent infections, which have been described as the most frequent adverse effects[26].

Possible limitations of this study include referral bias, as ours is the only clinic of its kind in the country, and those limitations inherent to a retrospective study. However, studying the clinical manifestations, radiological characteristics, evolution, treatment, and therapeutic response of this group of seven patients with such a rare condition allows for the generation of valuable knowledge for the medical community caring for the pediatric population.

Conclusion

In our pediatric population with IVM, lower limb involvement was found more frequently, and the main symptoms were exertional pain and swelling. Diagnosis can be difficult; it is important not only to suspect them but also to identify and characterize them with the support of imaging studies. Treatment is challenging given the extent and depth of the lesions; a multidisciplinary team should carry out their care and follow-up, and the combination of therapeutic modalities (surgery and sclerotherapy) may be necessary to obtain the best outcome for patients.

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.

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Conflicts of interest

The authors declare no conflicts of interest.

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ARTÍCULO DE INVESTIGACIÓN

Epidemiología de la intoxicación aguda infantil en urgencias de pediatría del occidente de México

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Resumen

Introducción: *El aumento en la producción de sustancias para mejorar la calidad de vida, la biodiversidad de los diferentes ecosistemas en México, así como las características propias de los pacientes pediátricos, contribuyen a la intoxicación dentro de esta población.* **Método:** *Estudio retrospectivo analítico de los ingresos por envenenamiento en niños menores de 16 años en urgencias pediátricas (2016 a 2020). Se analizaron la edad, el sexo, el tipo de xenobiótico, las características de exposición y la estación del año. Se obtuvieron frecuencias, porcentajes, rango, promedio y desviación estándar. En el análisis bivariado se utilizó la prueba chi al cuadrado, considerando estadísticamente significativo un valor p < 0.05.* **Resultados:** *En el periodo de 5 años se atendieron 459 casos, con una prevalencia del 3.16%. No se observó predominio de sexo. La intoxicación más frecuente fue por animales venenosos (28.5%), seguida de la ingesta de medicamentos (27.6%). El 95% de los casos fueron accidentales y el 5% por intento de suicidio. En los menores de 5 años, lo más frecuente fue la ingesta de medicamentos, hidrocarburos o productos de uso doméstico (p = 0.03, p = 0.0001), mientras que en los mayores de 6 años fue por contacto con animales venenosos e ingesta de drogas estimulantes (alcohol, anfetaminas, cannabis, cocaína) (p = 0.0001, p = 0.006). El 100% de los intoxicados por herbicida cuaternario de amonio fallecieron.* **Conclusiones:** *Los menores de 5 años son más propensos a la intoxicación con productos que se utilizan en sus propios domicilios. En los mayores de 6 años es más frecuente la combinación de drogas estimulantes.*

Palabras clave: *Intoxicación. Envenenamiento. Pediátrico. Infancia.*

Epidemiology of acute childhood poisoning in pediatric emergencies in Western Mexico

Abstract

Introduction: *The increase in the production of substances to enhance the quality of life, the biodiversity of the different ecosystems in Mexico, and the unique characteristics of pediatric patients, contribute to intoxications within this population.* **Method:** *Analytical retrospective study of admissions to pediatric emergency care due to poisoning in < 16-year-old (2016 to 2020). Included variables were age, gender, type of toxic substance, exposure characteristics, and the season of the year. Frequencies, percentages, range, average and standard deviation were obteined. In the bivariate análisis, the Chi square test was used. A p-value < 0.05 was considered statistically significant.* **Results:** *Over 5 years, there were 459 cases, with a*

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prevalence of 3.16%. No gender predominance was observed. The most common was caused by venomous animals (28.5%), followed by medication ingestion (27.6%). Only 5% of cases were suicide attempts, the rest were accidental (95%). Children up to 5 years old were more commonly by medication ingestion, hydrocarbons, or household products (p = 0.03, p = 0.0001), while the causes in older children were contact with venomous animals and ingestion of stimulants drugs (alcohol, amphetamines, cannabis, cocaine) (p = 0.0001, p = 0.006). Intoxication with quaternary ammonium herbicides was lethal in all cases.
Conclusions: *Children under the age of 5 are more susceptible to intoxication from common household products. Older kids tend to be more frequently a combination of stimulants drugs.*

Keywords: *Intoxication. Poisoning. Pediatric. Childhood.*

Introducción

Cada año se producen más de 2000 sustancias químicas nuevas que ingresan al medio ambiente y aumentan el riesgo de intoxicación[1]. Los envenenamientos son una causa frecuente de morbimortalidad en todo el mundo, que representa el 15% de los ingresos a las áreas de urgencias[2]. En el año 2005, un estudio global de intoxicaciones reportó que en México cada año se envenenan 136,000 personas[3]. La incidencia en la edad pediátrica tiene dos picos: el primero en los menores de 5 años y segundo en los adolescentes[1]. El pico de incidencia en los menores de 5 años se ha vinculado a la fase oral del desarrollo psicoemocional del niño[1] y el alto índice de curiosidad del menor[4], junto con el almacenamiento inadecuado o descuidado de los agentes xenobióticos por parte de los cuidadores[1]. Incluso se ha reportado la ingesta de plantas de ornato o de tipo medicinal por los infantes, sin considerar, tanto el cuidador como la comunidad médica, el alto grado de toxicidad que pueden tener las hojas de los vegetales[5].

En el otro pico de incidencia, que es en la adolescencia, se han asociado dos causas: una como medio para el suicidio[1] y la otra por el incremento del consumo de sustancias recreativas, como el alcohol y el cannabis, en la población general, que ha provocado un mayor consumo también en los adolescentes[6-9]. Existen diferencias entre la forma del consumo de estas sustancias entre adultos y adolescentes; mientras que los adultos consumen con mayor frecuencia, los adolescentes, por su inmadurez social, lo hacen con menor frecuencia, pero con mayor cantidad del producto, provocando un mayor riesgo y por lo tanto más ingresos en las unidades de urgencias[10].

Se ha reportado que, en la misma área, la etiología y la demografía de los diferentes tipos de envenenamientos pueden cambiar con el tiempo[11], y por esto se recomienda realizar estudios epidemiológicos por regiones, que podrían ayudar a comprender, prevenir y tratar este problema sanitario[1]. El objetivo de esta investigación es describir y analizar los xenobióticos en la población pediátrica que ingresa a la unidad de urgencias en un hospital del Occidente de México.

Método

Estudio transversal retrospectivo analítico de los pacientes de 0 a 16 años atendidos en el área de urgencias de pediatría de un hospital en el Occidente de México por algún tipo de contacto con un xenobiótico, de enero de 2016 a diciembre de 2020. Esta unidad hospitalaria atiende a la población de Guadalajara y su zona metropolitana, compuesta por otros cinco municipios (Zapopan, El Salto, Tlaquepaque, Tonalá y Tlajomulco) de Jalisco. Se incluyeron en el análisis todos los menores de 16 años que acudieron por algún tipo de envenenamiento. Para obtener la información se revisaron las hojas de registro de todos los pacientes y se obtuvieron los datos del expediente electrónico de cada paciente: sexo, edad, fecha de ingreso, motivo de consulta, agente xenobiótico (animal, sustancia química, planta) característica del contacto con el agente (accidental, intencional, recreativa o intento de suicidio), zona de exposición (oral, cutánea, inhalado), diagnóstico y calidad de egreso (vivo o defunción). Los xenobióticos se dividieron en ocho categorías: ingesta de medicamentos, picadura o mordedura de animal venenoso, contacto con plaguicidas o herbicidas, ingesta de hidrocarburos, ingesta de productos de uso doméstico, contacto con plantas, uso de drogas adictivas o estimulantes, e ingesta de metales.

Para un mejor análisis se dividieron las edades en dos grupos: menores de 5 años y mayores de 6 años. A su vez, los menores de 5 años se subdividieron en ≤ 2 años y 3-5 años, y los mayores de 6 años se dividieron en 6-12 años y ≥ 13 años. Según la fecha del ingreso, se clasificaron en primavera (marzo a mayo), verano (junio a agosto), otoño (septiembre a noviembre) o invierno (diciembre a febrero) en los diferentes años.

Para el análisis estadístico se obtuvieron las frecuencia y los porcentajes en las variables cualitativas, y la media, el rango y la desviación estándar (DE) en las variables cuantitativas. Se utilizaron la prueba de chi al cuadrado y la prueba exacta de Fisher para evaluar diferencias entre las variables nominales, considerando estadísticamente significativo un valor de $p < 0.05$. Se obtuvo la prevalencia de una población desconocida, con un origen de los datos de una muestra perfecta (total de pacientes atendidos en la unidad de urgencias en el mismo lapso de tiempo), con un intervalo de confianza del 95% (IC95%).

El estudio fue aprobado por el comité de ética e investigación del hospital (registro 17C114 039 116 COFEPRIS), y cumple con la Ley General de Salud en Materia de Investigación para la Salud en México y con la Declaración de Helsinki en su última actualización de 2016.

Resultados

En un periodo de 5 años, de enero de 2016 a diciembre de 2020, se ingresaron al servicio de urgencias 459 menores de 16 años por algún tipo de intoxicación, lo que supone una prevalencia del 3.16% en un total de 14,539 pacientes ingresados en el área de urgencias en ese mismo periodo. Se realizó un cálculo de prevalencia real en la población entre el 2.87% y el 3.44% (IC95%). En la figura 1 se presentan la distribución de los casos según el tipo de xenobiótico en cada año y su porcentaje. Se observa un promedio del 3% en la prevalencia por año, con excepción de 2020, cuando hubo un descenso tanto en los casos (29 niños) como en los ingresos generales al área de urgencias pediatría (n = 1372 pacientes), debido a que el hospital se convirtió en «hospital COVID» para la atención en la pandemia.

En la tabla 1 se muestra la distribución del total de los envenenamientos según la estación del año, comparando las más calientes (primavera y verano) con las más frías (otoño e invierno). Se observa una diferencia estadísticamente significativa en la ingesta de plaguicidas o herbicida en las estaciones frías en comparación con las cálidas ($p = 0.03$), en asociación con el suicidio y el ciclo agrícola local.

Con respecto a los medicamentos, todas las intoxicaciones fueron por ingesta del producto, no por inhalación ni por contacto con la piel. La mayoría fueron de forma accidental (75%), principalmente por imitación de los menores de 5 años a sus padres o abuelos, con un solo medicamento. Los más utilizados fueron benzodiacepinas (32 casos), carbamacepina (12 casos), metoclopramida (22 casos), risperidona (7 casos), paracetamol (7 casos), aspirina (1 caso), hipoglucemiantes (6 casos), antihistamínicos (6 casos) y antibióticos (2 casos, uno con ceftriaxona y el otro con clindamicina). El resto de los casos fueron por intento de suicidio, siendo el agente más usado las benzodiacepinas o la ingesta de poli fármacos (combinación de benzodiacepinas, carbamacepina, melatonina, omeprazol, sildenafilo, diuréticos, antihipertensivos e incluso anticonceptivos orales). No se reportaron defunciones por ingesta de medicamentos.

Los casos por animales venenosos fueron 131, todos por contacto accidental. La mayoría fueron por picaduras de alacrán (95 casos), 12 fueron por mordedura de araña *Loxosceles* (araña violinista) y 11 por mordedura de araña *Latrodectus* (viuda negra). La mordedura de serpiente *Crotalus* (cascabel) se reportó en 2 casos, hubo otros 2 casos por mordida de oruga *Megalopyge* (oruga peluche), 2 más por picadura de abeja y 7 por insecto desconocido. No se reportaron defunciones por contacto con animales venenosos, ya que no solo se utilizaron medidas de soporte, sino también faboterápicos específicos (antiviperino, antialacrán, antiloxosceles y antiarácnido).

Con respecto a los plaguicidas y herbicidas, el 95% fueron ingestas accidentales y el 5% por intento de suicidio. El incremento del riesgo de estos productos fue por la combinación de sustancias adulteradas, como por ejemplo los raticidas, que indican en su etiqueta de contenido ser un anticoagulante, pero en realidad son una mezcla de organofosforados, carbamatos o fosfuro de zinc. Los menores de 5 años ingirieron accidentalmente el xenobiótico en un cebo de pan distribuido por toda la casa. Los cumarínicos (warfarina) se reportaron en 19 casos, los organofosforados o carbamatos en 17 casos, las piretrinas o piretroides en 11 casos, el fluoroacetato de sodio en 3 casos, el fosfuro de zinc en 5 casos y un herbicida cuaternario de amonio (paraquat) en 3 casos. Este último fue utilizado con fines suicidas y todos los casos resultaron en fallecimiento.

Los hidrocarburos fueron por ingesta accidental de Thinner, Disel, gasolina y varios tipos de desengrasantes. De los productos de uso doméstico, el 71% fueron sosa cáustica (59 casos) y el resto cloro, enjuague bucal, alcanfor y sustancias para limpiar los pisos, todos por ingesta y en forma accidental. Dos casos fueron por inhalación de monóxido de carbono producto de la combustión de hidrocarburos. Con los

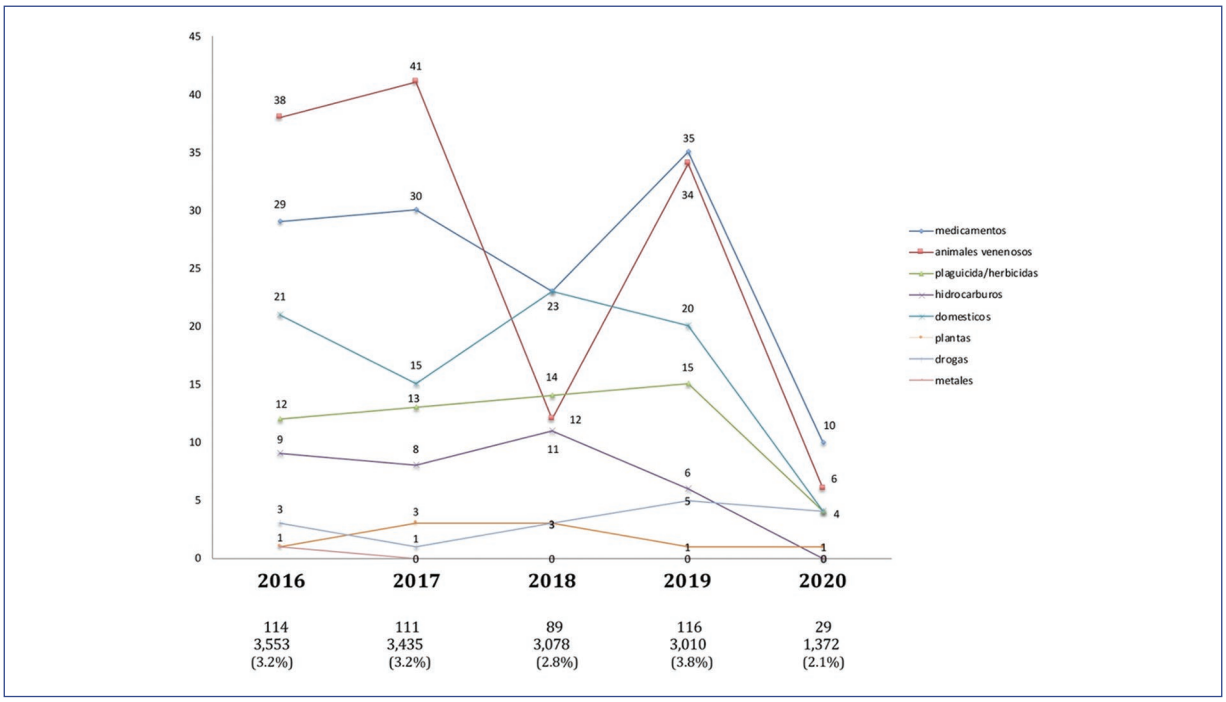

Figura 1. Distribución de los casos por año y su respectiva prevalencia de los xenobióticos.

Tabla 1. Distribución de los tipos de envenenamiento según la estación del año

Xenobiótico	Primavera	Verano	Otoño	Invierno	Total	p*
Medicamentos	27 (23.9)	39 (32.5)	36 (31.3)	25 (22.5)	127	0.74
Animales venenosos	44 (38.9)	29 (24.2)	26 (22.6)	32 (28.8)	131	0.17
Plaguicidas/herbicidas	5 (4.4)	17 (14.2)	25 (21.7)	11 (9.9)	58	0.03†
Hidrocarburos	6 (5.2)	10 (8.3)	6 (5.2)	12 (10.8)	34	0.65
Uso doméstico	26 (23.2)	19 (15.8)	16 (13.9)	22 (19.8)	83	0.40
Plantas	1 (0.9)	4 (3.3)	2 (1.7)	2 (1.8)	9	0.77
Drogas adictivas	4 (3.5)	2 (1.7)	4 (3.5)	6 (5.4)	16	0.28
Metales	-	-	-	1 (0.9)	1	0.54
Total	113 (24.6)	120 (26.3)	115 (25)	111 (24.1)	459	

*Chi al cuadrado o exacta de Fisher: diferencia de envenenamiento entre primavera-verano y otoño-invierno.
†Valor de p significativo (< 0.05).

hidrocarburos, los productos de uso doméstico y la inhalación de gases no hubo defunciones.

Hubo 9 casos de envenenamiento por plantas, por ingesta intencional de sus hojas, y todos los casos fueron dentro de la casa del menor. Siete niños mordieron una hoja de la planta *Xanthosomas robustum* (hoja elegante), que es tóxica por contener oxalatos de calcio y puede provocar desde escozor local hasta daño renal. En los otros 2 casos no se identificó la planta.

Con respecto a las drogas adictivas, la mayoría del consumo fue por más de dos sustancias (alcohol con cannabis, anfetaminas junto con cocaína). Y en cuanto a los metales, solo se reportó un caso de ingesta de mercurio como tratamiento para el malestar estomacal. Todos estos pacientes se egresaron vivos.

La edad mínima de los niños envenenados fue de 10 meses, siendo la máxima de 16 años y el promedio de 4.9 años ± 4 meses (DE). No se observó un

Tabla 2. Distribución de los envenenamientos por grupo etario y sexo

Xenobióticos	≤ 2 años	3-5 años	6-12 años	≥ 13 años	p*
	M/F	M/F	M/F	M/F	
Medicamentos	26/28	23/4	10/10	7/19	0.03†
Animales venenosos	17/18	18/12	24/23	10/9	0.0001‡
Plaguicidas/herbicidas	19/15	9/3	6/3	1/2	0.06
Hidrocarburos	15/10	5/2	0/1	1/0	0.0001†
Uso doméstico	28/26	17/7	2/2	0/1	0.0001†
Plantas	2/3	1/1	0/2	-	0.55
Drogas adictivas	3/2	1/0	1/1	1/7	0.006‡
Metales	-	-	0/1	-	0.23
Total	110/102	74/29	43/43	20/38	

F: femenino; M: masculino.
*Chi al cuadrado o exacta de Fisher: diferencia de tipos de xenobióticos según la edad en ambos sexos.
†Valor de p significativo (< 0.05) en < 5 años.
‡Valor de p significativo (< 0.05) en > 6 años.

predominio de sexo. La ingesta de medicamentos, productos domésticos e hidrocarburos fue más frecuente en los menores de 5 años (p = 0.03 y p = 0.0001), mientras que las intoxicaciones por animales venenosos (p = 0.0001) y drogas adictivas (cocaína, cannabis, alcohol y metanfetaminas) fueron más frecuentes en los niños mayores de 6 años (p = 0.006). La distribución del xenobiótico por grupo etario y sexo se describe en la tabla 2.

Discusión

Se reporta que los envenenamientos en edades pediátricas en los países desarrollados (0.5 por 100,000 habitantes) tienen una prevalencia menor que en los países en vías de desarrollo (2 por cada 100,000 habitantes)[2]. En nuestra población, por año, se reportó un promedio de un 3%, un poco más elevado de lo esperado; incluso en 2013, Fernández y Sánchez[3], en su estudio realizado en el Hospital La Raza, reportaron una prevalencia más baja, del 0.5% de sus ingresos en el área de pediatría[3], probablemente porque es un hospital de alta concentración y las intoxicaciones son procesos agudos que necesitan ser atendidos rápidamente en las unidades de primer contacto, como nuestro hospital, o porque Jalisco es un Estado con una gran variedad de animales venenosos, como los alacranes.

Con respecto a la época del año, la literatura no reporta un predominio relacionado con el clima, como ocurre con las enfermedades infecciosas o los accidentes en periodos vacacionales en la población pediátrica. Sin embargo, sí se reporta que más del 75% de los envenenamientos ocurren en el hogar[1,2,9,12]. Cuando se analiza por agentes xenobióticos, se observa que, por ejemplo, las ingestas por plaguicidas en Taiwán son más frecuentes en verano por el ciclo de cultivos[11], similar a lo que nosotros encontramos en otoño-invierno, que corresponde al ciclo agrícola de nuestra zona, mientras que en invierno se reportan mayores envenenamientos por inhalación de monóxido de carbono en todo el mundo[3,11]. Los dos casos que nosotros reportamos se presentaron en esta temporada.

Kang et al.[13] reportan, en los Estados Unidos de América, que el 30% de los ingresos son por picadura o mordedura de animales venenosos, principalmente por alacranes, en temporada de temperaturas más calientes (primavera y verano) y en menores de 10 años. Los envenenamientos por picadura de alacrán fueron los más frecuentes en nuestra población, por la gran diversidad de esta fauna, y no encontramos un predominio según la estación del año. Una característica de nuestra región es que no contamos con temperaturas extremas, y esta puede ser la causa de una frecuencia muy similar durante todo el año.

En la población pediátrica se ha observado, en relación con el contacto con xenobióticos, que los menores de 5 años se envenenan en forma accidental, a diferencia de los adolescentes, que lo hacen en forma intencional, ya sea por actividad recreativa o por intento

de suicidio[2,9,11,12]. Además, en los menores de 5 años es por productos de uso doméstico, medicamentos y plaguicidas[2,4,11], mientras que en los adolescentes es por ingesta de medicamentos como intento de suicidio[1,3,9] y por el uso de sustancias adictivas (alcohol y cannabis) como actividad recreativa[6,10,14,15]. Llama la atención que la mayoría de los investigadores reportan que, de los intentos de suicido con medicamentos, ninguno resultó en fallecimiento[1,3,11]. En nuestra comunidad, al igual que lo reportado en la literatura, la mayoría de los intentos de suicidio fueron con fármacos, principalmente benzodiacepinas o una combinación de varios medicamentos, sin reportar defunciones. Sin embargo, los adolescentes que utilizaron el herbicida cuaternario (paraquat) con este fin, fallecieron todos.

Baraniecki et al.[7], en Canadá, en su estudio realizado en 2018, compararon la ingesta de cannabis antes y después de su despenalización como uso recreativo. Observaron que el consumo del producto aumentó, pero no así los ingresos a las áreas de urgencias por este xenobiótico en adolescentes y niños. Por el contrario, Claudet et al.[14], en Francia, reportaron que no solo los adolescentes, sino también los menores de 18 meses, ingresaron más como victimas colaterales del consumo de cannabis. La Organización Mundial de la Salud reporta que la mitad de la población europea de 15 a 19 años ha consumido sustancias adictivas, como el alcohol[9,10]. Hay varios factores que favorecen el consumo de cannabis y alcohol en los niños, incluye a los padres, ya que son el modelo social para el menor y sus supervisores[6]. Los niños que viven en hogares donde se consumen sustancias adictivas tienen mayor riesgo de sufrir envenenamiento en forma accidental[12]. En nuestra población, el porcentaje de niños con ingesta de estas sustancias fue bajo en comparación con otros xenobióticos. Por mucho tiempo México se ha considerado un país que produce y trafica sustancias ilícitas, pero la realidad es que actualmente no solo somos productores, sino también consumidores. Mintegi et al.[9] dividieron la frecuencia de intoxicaciones por zonas (Europa, Norteamérica, Suramérica, Pacífico occidental y Mediterráneo oriental), y hallaron que en Europa y América del Norte hubo un incremento de intoxicaciones por actividades recreativas. La última encuesta de adicciones en México, que fue en 2017, reportó que el 43% de los adolescentes habían consumido alcohol[16]. Hay que recordar que la interacción positiva entre los padres y los hijos es importante para el desarrollo mental y la conducta del menor[12]; sin embargo, la prevención del consumo de estas sustancias requiere un enfoque integral de políticas, comercialización y educación a la población[10].

En conclusión, ya sea por la curiosidad de la infancia o por la negligencia del cuidador, los menores de 5 años se envenenan más frecuentemente en forma accidental con productos que se usan en el hogar, en donde las sustancias cáusticas y los hidrocarburos ocupan los primeros lugares, junto con los medicamentos y los plaguicidas, mientras que los mayores de 6 años están más en contacto con sustancias adictivas, principalmente el alcohol, solo o combinado con cannabis, anfetaminas y cocaína, en un país con graves problemas de narcotráfico. No obstante, los animales venenosos fueron el principal motivo de ingreso al área de urgencias pediátricas, por la biodiversidad de la fauna en la zona.

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que los procedimientos seguidos se conformaron a las normas éticas del comité de experimentación humana responsable y de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki.

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 la aprobación del Comité de Ética para el análisis y publicación de datos clínicos obtenidos de forma rutinaria. El consentimiento informado de los pacientes no fue requerido por tratarse de un estudio observacional retrospectivo.

Uso de inteligencia artificial para generar textos. Los autores declaran que no han utilizado ningún tipo de inteligencia artificial generativa en la redacción de este manuscrito ni para la creación de figuras, gráficos, tablas o sus correspondientes pies o leyendas.

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RESEARCH ARTICLE

Exploring medical ethics: moral reasoning among new pediatric resident physicians in a tertiary hospital

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Abstract

Background: *Physicians are frequently faced with ethical dilemmas that require answers based in moral reasoning, which develops and evolves during their lives and their medical education. According to Kohlberg, there are three levels of moral reasoning development: pre-conventional (in which decisions are guided by oneself convenience), conventional (focused on obeying society's rules), and post-conventional (decisions are based in universal ethical principles). The aim of this study was to describe the level of moral reasoning among new pediatric resident physicians in a tertiary hospital.* **Method:** *This cross-sectional descriptive study was conducted from 2020 to 2023. The Defining Issues Test was used to assess the level of moral reasoning among 195 new pediatric resident physicians in a tertiary hospital.* **Results:** *Most resident physicians considered the fourth stage affirmations to be the most important. The median P-index (PI) was 40, and 49% of participants were on the post-conventional level of moral reasoning. The year with the lowest number of new resident physicians on the post-conventional level was 2021.* **Conclusion:** *The moral reasoning level among pediatric resident physicians was higher than the average found in general population. This suggests that the education received during the medical formation may influence the individuals' moral development.*

Keywords: *Ethical dilemmas. Moral development. Moral reasoning. Resident physicians.*

Explorando la ética médica: evaluación del razonamiento moral en nuevos residentes de pediatría en un hospital de tercer nivel

Resumen

Introducción: *Los médicos se enfrentan cotidianamente a dilemas éticos que exigen respuestas basadas en el razonamiento moral, el cual evoluciona a lo largo de la vida y con su formación médica. Kohlberg distingue tres niveles de desarrollo moral: preconvencional (decisiones guiadas por interés propio), convencional (enfocado a obedecer reglas de la sociedad) y posconvencional (decisiones basadas en principios éticos universales). El propósito de este estudio fue describir el nivel de razonamiento moral en residentes de pediatría recién ingresados en un hospital de tercer nivel.* **Método:** *Se realizó un estudio transversal descriptivo de 2020 a 2023. Se evaluó el nivel de razonamiento moral con el defining issues test (DIT) en 195 residentes de pediatría de primer año en un hospital pediátrico de tercer nivel.* **Resultados:** *Se encontró una mediana*

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de edad de 26 años, el 60% de los residentes fueron mujeres, el 74% refirieron profesar alguna religión, el 51% nacieron en Ciudad de México, en donde el 45% cohabitan en una vivienda compartida. El estadio con mayor puntuación del DIT fue el cuarto. Se observó una mediana de índice P (IP) de 40. Respecto al nivel de razonamiento moral, el 49% se encontraban en el nivel posconvencional. **Conclusión:** *Los residentes de pediatría mostraron un nivel de razonamiento moral más alto que lo reportado como promedio en la población general (nivel posconvencional vs. convencional, respectivamente), lo que sugiere que la enseñanza en la carrera de medicina pudiera influir en el desarrollo moral de los sujetos.*

Palabras clave: *Dilemas éticos. Desarrollo moral. Razonamiento moral. Médicos residentes.*

Introduction

Lawrence Kohlberg developed his "Moral development theory" in 1958 while investigating the ability to elaborate moral judgements[1,2]. He asked participants to reflect individually on several dilemmas that presented value-based conflicts, and to make decisions to solve the dilemmas[3,4].

Kohlberg concluded that moral reasoning develops in three levels: pre-conventional, conventional, and post-conventional[5]. Each level has two cognitively structured stages that determine the way an individual gathers and processes information[4]. To move from one stage to another, the development of intelligence and logical operations is fundamental, as well as the social perspective from which we decide what is right, and the motives to act in an appropriate way[2]. Intelligence is related to moral development, individuals with a lower intellectual level tend to have a lower moral reasoning level; however, individuals with higher intellectual levels do not necessarily have a higher moral reasoning level[1].

In the pre-conventional level, there is an individualistic perspective, focusing mainly on the self-interest. In the stage one, individuals have a punishment-obedience orientation; and in the stage two, the most crucial factor is to follow rules according to self-interests and individual needs[2].

In the conventional level, individuals manage moral problems from the perspective of being a member of a society, considering the expectations of the group or society for the individual as a member or as a role player. Individuals identify with the society, and the group rules are the defining point for their moral judgments. This level is usually reached during adolescence and keeps a predominant place in the moral reasoning of most adults in many societies[1,2].

In the post-conventional level, individuals generally comprehend and accept the society norms as they are based in universal moral principles, such as the respect for life and the dignity of each individual. If these principles are in conflict with the society norms, the post-conventional individual will judge and act accordingly to their principles over the social conventionalisms[1,4,6]. In the stage five, the values and rights preceding the social contract are considered, and in the stage six, individuals must be acknowledged by themselves by universal ethical principles[2].

One of the most often used instruments to evaluate moral reasoning is the defining issues test (DIT), designed by James Rest. It is the most comprehensive as it was developed using Kohlberg's moral development theory[4,7].

Through their training, medical professionals learn that values and human lives must be preserved, as well as to respect the illnesses that they find in every patient[8]. The main objective of medical education is to develop an appropriate interaction of social skills[9]. Some Mexican educational institutions, including the National Autonomous University of Mexico, the National Polytechnic Institute, the Autonomous University of the State of Mexico, the Autonomous University of Guadalajara, the Anáhuac University, and the La Salle University, contemplate in their academic programs the teaching of ethics and bioethics, promoting the comprehensive training[10-16]; however, most of the ethical training of undergraduate and postgraduate medical students happens during their clinical practice, by observing other physicians and students from a higher echelon, which is often referred to as a "hidden curricula"[17]. Medical ethics, moral reasoning, and complex medical decisions are not a recent subject of discussion. Ethical dilemmas that rise during the medical formation generate questions that many times are not solved or even discussed with students[8,9,18].

Pediatricians face many ethically challenging situations. Having to decide when to limit life prolonging treatments, disagreements with the child's family, and end of life discussions are frequent ethical dilemmas in pediatrics[18]. Ethical capacitation in this medical specialty may help to face ethical dilemmas in a better way[19].

Some studies have studied moral reasoning among medical students and physicians. One study found a

lightly lower P-index (PI) in medical interns compared with surgical residents (37.2 vs. 46)[6,20-25]. Another 2019 study found that most of 88 medical graduates were in 5[a] and 5b stages. This could suggest that as individuals have more medical practice experience, they reach a higher level of moral reasoning, which is beneficial to the patients' treatment and the quality of the medical attention provided[5].

The aim of this study was to describe the level of moral reasoning among physicians who are about to begin the pediatrics residency course in a tertiary hospital.

Methods

This is a descriptive cross-sectional study that took place between 2020 and 2023. The study population included 223 physicians who were about to begin their 1st year of the pediatrics residency course in a tertiary hospital. All physicians were invited to participate. All participants who were about to begin their 1st year of the pediatrics residency course and accepted to participate were included in the study. Participants from other hospitals who were in temporal rotations in the hospital were excluded from the study.

The study was explained to participants and an informed consent was obtained from all of them. Participants were asked to respond a socio-demographic questionnaire including general information about age, gender, and marital status, and to complete the DIT instrument[26], which has been validated in Mexico among other Latin-American countries. The test validation has shown an adequate internal consistency, with a Cronbach's $\alpha = 0.71$, and test-retest reliability of 0.65[7,26], similar to the original instrument designed by rest, which has a Cronbach's $\alpha = 0.70$ and a test-retest reliability of 0.70-0.80.

The DIT consists of six stories in the original version and three stories in the brief version. The brief version was used in this study. Each story stands for a moral dilemma, and each story has three answering sections. In the first section, participants are asked for their opinions about the decision that the story's main character must make, the possible answers being "Agree," "Disagree," and "Indecisive." In the second section, participants must assign a level of importance in a five-point Lickert scale from "Not important" to "Very important" to 12 affirmations regarding the stories. In the third section, participants have to select the four affirmations from the second section that they consider to be the most important from each story and assign them a descending level of importance from one to four. Each of the 12 affirmations corresponds to a moral reasoning stage. Some examples of the affirmations include: "Community rules must be respected," "The pharmacist deserved to be robed for being cruel and ambitious."

The PI is used to classify the individual's moral reasoning in one of the three levels corresponding to Kohlberg's theory. A < 30 PI score in classified as a pre-conventional level, a score between 30 and 40 is considered as a conventional level, and a > 40 PI score indicates a post-conventional level.

With the answers from the three sections, a raw and a percentage score is obtained. The percentage score has a 0-100 scale to define the frequency in which each 2-6 sub-stage of moral reasoning is used. A raw and percentage score PI is obtained by adding the scores from 5a, 5b to 6 stages. The PI reflects an individual's tendency to use universal ethical principles to solve ethical dilemmas, which suggest that the individual may be in a post-conventional level.

On the other hand, a M score reflects an individual's tendency to consider meaningless affirmations as especially important. When this score is high, the level of participant's moral reasoning cannot be determined, and a higher than 16 score invalidates the test.

Statistical analysis

Descriptive statistics were used to describe sociodemographic variables. Qualitative variables were reported as totals and percentages, and quantitative variables were expressed with medians and maximum and minimum ranges. The quantitative DIT results (scores from stage 2 to 6 and IP scores) were reported with medians and maximum and minimum ranges. Qualitative DIT results (moral reasoning level) were reported as totals and percentages.

An exploratory inferential analysis was performed to compare the IP scores between the participants from different generations and socio-demographic variables with a Mann–Whitney U-test, and a linear X^2 test was used to compare the levels of moral reasoning. Statistical analysis was performed using STATA v.24 software (STATA Corp, College Station, TX). The statistical significance level was defined with two-tailed $p < 0.05$. Confidence intervals were determined at the 95% confidence level.

Results

A total of 218 physicians agreed to participate in this study. Five tests were invalidated for having a high M

Table 1. Sociodemographic characteristics of resident physicians categorized by generation and as a group

Variable	2020 (n = 47)		2021 (n = 55)		2022 (n = 46)		2023 (n = 47)		2020-2023 (n = 195)	
	M	Min-max	M	Min-max	M	Min-max	M	Min-max	M	Min-max
Age	26	23-20	26	24-31	26	23-32	26	24-28	26	23-32
	TN	%	TN	%	TN	%	TN	%	TN	%
Gender										
Female	32	68.1	37	67.3	35	76.1	36	76.6	140	71.8
Male	15	31.9	18	32.7	11	23.9	11	26.4	55	28.2
Marital status										
Single	41	87.2	53	96.4	44	95.7	43	91.5	181	92.8
Common law	6	12.8	2	3.6	1	2.2	4	8.5	13	6.7
Separated	-	-	-	-	1	2.2	-	-	1	0.5
Practices a religion	29	61.7	37	67.3	39	84.8	39	83	144	73.8
Place of birth										
CDMX and MA	18	38.3	22	40	28	63	31	66	100	51.3
Other state	25	53.2	31	56.4	13	28.3	15	31.9	84	43.1
Other country	4	8.5	2	3.6	4	8.7	1	2.1	11	5.6
Living situation										
Parents	-	-	21	38.2	18	39.1	-	-	39	20
Other family	14	29.8	1	1.8	-	-	12	25.5	27	13.8
Alone	6	12.8	7	12.7	2	4.3	8	17	23	11.8
Roomates	25	53.2	25	45.5	15	32.6	22	46.8	87	44.6
Other	2	4.3	1	1.8	11	23.9	5	10.6	19	9.7
Monthly economical income										
0-2,699	-	-	-		5	10.9	-	-	5	2.6
2,700-6799	4	8.5	3	5.5	1	2.2	-	-	8	4.1
6,800-11,599	1	2.1	12	21.8	5	10.9	-	-	18	9.2
11,600-34,999	15	31.9	15	27.3	14	30.4	-	-	44	22.6
35,000-84,999	8	17	16	29.1	16	34.8	-	-	40	20.5
> 85,000	15	31.9	3	5.5	4	8.7	-	-	22	11.3
Doesn't know	4	8.5	6	10.9	1	2.2	47	100	58	29.7

M: median; Min-max: minimum-maximum; TN: total number; CDMX and MA: Mexico City and metropolitan area.

score, and 188 tests were eliminated for being incomplete. A total of 195 participants with valid tests and questionnaires were included in the study.

Socio-demographic characteristics from the 195 participants are resumed as a whole and sub-divided by participants' generations in table 1. The median age was 26 and ranged between 23 and 32 years. About 71.8% of participants were female, 92.8% were single, and 51.3% was born in Mexico City or nearby areas, while 5.6% came from another country to study, and 44.6% of participants lived with a roommate. About 73.8% of participants reported to profess a religion, 55.4% describing themselves as Catholics, 2% as Christians, and 0.5% as agnostics, Buddhist, and others. The percentage of participants who began their specialty course in 2022 and 2023 (Generations 2022 and 2023) who reported professing a religion was higher than the one from Generations 2020 and 2021 (84% vs. ≈65%). The most frequent monthly family income bracket was $11,600-$34,999, and it was similar among generations.

Moral reasoning analysis

The moral reasoning profile from the group was obtained for each stage (Fig. 1). The score medians were found to increase from stage 2 (0, 0-23.3) through 4 (36.6 0-70), and then decreased in stage 6 (10, 0-26.6). Statistically significant differences were found for stages 4, 5a, 5b, and 6 (Mann–Whitney U: $p < 0.05$). The median PI was 40, with a minimum-maximum range of 0-76.6. There were no statistically significant differences in the PI median across generations.

Moral reasoning development levels are shown in figure 2. Thirty-nine (20%) of the 195 participants were in a pre-conventional level, 61 (31%) were in a conventional

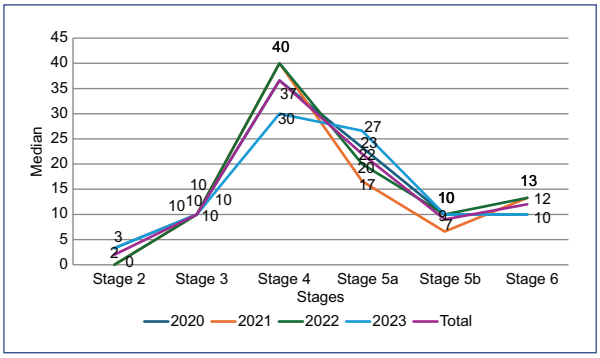

Figure 1. Medians of moral reasoning stages and P-index of resident physicians categorized by generation and as a group.

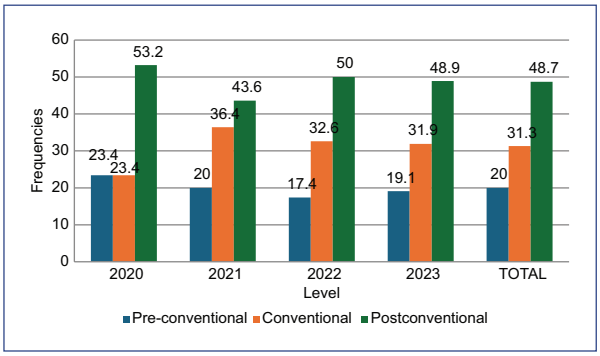

Figure 2. Percentages of moral reasoning levels of resident physicians categorized by generation and as a group.

level, and 95 (49%) were in a post-conventional level. The percentage of participants who were on a post-conventional level in Generation 2021 participants was lower than the one found in the other generations. This difference was not statistically significant.

As for gender differences, females had a PI median of 43 (0-76.6) while male participants had a median of 36 (16.6-66.6). The percentage of females who were on a pre-conventional, conventional, and post-conventional levels was 20.7%, 25%, and 54.3%, respectively, while the percentage distribution in males was 18.2%, 47.3%, and 34.5%, respectively. These differences were not statistically significant.

A PI median of 40 (0-76.6) and 43.3 (23.3-60) was found for single and married participants, respectively. About 47.8% of single participants and 62% of married participants were on a post-conventional level. This difference was not statistically significant.

There were no statistically significant differences between participants concerning religion or their monthly income.

Discussion

In this study, physicians who were about to begin their 1st year of pediatric residency training in a tertiary hospital had a moral reasoning PI median of 40, corresponding to a borderline place between a conventional and a post-conventional level according to Kohlberg's theory, where almost half of them were in the latter level. This finding differs from other studies where moral reasoning has been evaluated in other populations, such as non-medical bachelor's students and general population. In these studies, an average PI between 25 and 38 has been found, with most participants being in the conventional level[27,28]. On the other hand, the findings from this study are similar to those that evaluated moral reasoning among undergraduate medical students[5,6,21].

Although the research about this subject is scarce, a previous study found significant differences between pediatric residents and recent graduates from other careers, where a 33.3 and 26.6 PI was found, respectively[5].

In this study, the PI was similar across the different generations. This may be explained because all participants had been medical students at some point. Medical students frequently face difficult circumstances during their clinical practice that require from them to develop both a humanistic and a clinical perspective to make appropriate decisions for their patients, in which their conduct is based on professionalism and ethics.

One interesting finding from this study is that the Generation 2021 had a 10% lower percentage of participants in a post-conventional level compared to other generations. Although this difference was not significant, it is relevant to consider that this generation was measured after the 1st year of the COVID-19 pandemic, so the mental health consequences that this health crisis brought[29,30] may have indirectly affected the residents' moral reasoning; thus, more research evaluating the impact of health crises in moral reasoning is needed.

A difference of more than 6 points between female and male participants' PI was found in favor of female participants. Although this difference was not significant, the magnitude of the difference is interesting, especially considering that the PI score of females (43) classified them in a post-conventional level, while the males' PI score (36.6) classified them in a conventional level. There are slight but non-significant differences in moral reasoning between men and women[4,7], so it

would be interesting to continue studying the gender variable in the future.

Healthcare workers face ethical dilemmas in a daily basis in which they must come up with functional answers, since many times the life of a patient depends on those answers. Precise decision-making is a highly important skill for training medical specialists to adequate their clinical practice in an ethical manner. The study and understanding of moral reasoning across different stages of medical education and comparing it to the moral reasoning of individuals with different professional careers might be useful to determine if there is an association between the individual's moral reasoning level and the probability to choose medicine as a career, as well as to understand morality and its' role in a society[31].

Although formal ethics courses are offered in some medical residency programs, resident physicians truly delve into ethical and moral situations during their clinical practice, with their mentor's guidance. Professional conduct is shaped by many complex factors, which highlights the importance of cultivating "virtuous" ethics during the medical education. Ethical orientation and learning content should be present in every stage of the formative process[17,32,33]. Academic education during medical training is highly important for the development of clinical practice skills and medical ethics[17]. Resident physicians consider humanism to be fundamental to their formation, as well as the awareness of their own conditions and abilities to make appropriate decisions, since they think that by being aware of those factors, future medical specialists might improve their moral reasoning level, strengthening it with study and ethical basis. They also consider to be essential to develop ethical, moral, and medical knowledge in real situations for them to be able to apply this knowledge in decision-making[11,13,16].

Ethical learning is not only a crucial component but also a cornerstone of medical education. It is imperative that structured and formal ethics and morals courses are available in all stages of the future physicians' education. It is required that students submerge themselves in real situations, where they can develop ethical abilities and be able to apply them in a practical way in decision-making, transcending the limits of the conventional clinical practice[34,35].

Among the limitations of this study are that moral reasoning scores could have been affected by factors such as participants being sleep deprived among others. These factors were not controlled for the analysis. Another limitation is that the sample may not be representative of other populations. On the other hand, the instrument that was used to assess moral reasoning presents dilemmas concerning general situations, rather than medical context situations. A necessity to develop instruments including dilemmas contemplating specific medical scenarios arises for future research to assess the professionals' moral reasoning facing problems directly related to their job field. This approach could facilitate to determine if the dilemma's modifications contribute to significant variations in moral reasoning, providing a more precise and applied outlook of medical ethics in the clinical practice, for future research.

Conclusion

Physicians who were about to begin their 1st year of pediatric residency training in a tertiary hospital had a moral reasoning PI median of 40, corresponding to a borderline place between a conventional and a post-conventional level according to Kohlberg's theory, where almost half of them were in the latter level. The PI was similar between generations, although Generation 2021 had a lower percentage of participants in the post-conventional level, which could be explained by the COVID-19 pandemic onset.

An appropriate formative education during clinical medical training is essential for the development of clinical and ethical skills. Training physicians acknowledge the importance of the integration of humanism and moral reasoning in their learning process, and they highlight the importance of practical educational situations. Future research should study the influence of gender and other factors on the moral reasoning level of young adults.

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Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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 is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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CLINICAL CASE

Teenager with persistent facial edema and induration

*Mónica Dávalos-Tanaka and Ma. Teresa García-Romero**

Department of Dermatology, Instituto Nacional de Pediatría, Mexico City, Mexico

Abstract

Introduction: *Acute lymphoblastic leukemia (ALL) is the most common oncological disease in the pediatric population; however, skin infiltration occurs only in 1-3% of the patients and almost always manifests after the diagnosis is made.* **Clinical case:** *A male teenage patient who presented with facial edema and infiltration, associated with systemic symptoms such as asthenia and adynamia. On physical examination, the patient presented facial edema and indurated plaques, as well as cervical, inguinal, and axillary adenopathy. Complete blood count showed pancytopenia and a chest X-ray revealed a mediastinal mass. Due to a high suspicion of malignancy a bone marrow and skin biopsy was taken, both with pre-B ALL. Chemotherapy was started and the patient is now in maintenance phase.* **Conclusions:** *Leukemia cutis manifestations are heterogenous, from a small papule to a big nodule. It is more common in patients with acute myeloid leukemia and it is rare in patients with pre-B ALL, specially in the pediatric population. The diagnosis should be done with a biopsy and the treatment is with systemic chemotherapy. The diagnosis should always be considered in patients with unexplained edematous or indurated lesions, especially in the context of systemic symptoms.*

Keywords: *Leukemia cutis. Pre B acute lymphoblastic leukemia. Pediatric cutaneous leukemia.*

Adolescente con edema e induración facial persistente

Resumen

Introducción: *La leucemia linfoblástica aguda es la enfermedad oncológica más común en la edad pediátrica; sin embargo, la infiltración a la piel solo ocurre en el 1-3% de los pacientes y se manifiesta habitualmente posterior al diagnóstico de leucemia.* **Caso clínico:** *Adolescente varón que acude a urgencias de nuestra unidad por presentar edema facial persistente, junto con astenia y adinamia. En la exploración física presenta edema facial con placas difusas induradas y adenopatía cervical, inguinal y axilar. Se decide realizar una biometría hemática, que muestra pancitopenia, y una radiografía de tórax, que revela una masa mediastinal. Por sospecha de malignidad se decide realizar una biopsia de médula ósea y de piel, dando como resultado leucemia linfoblástica pre-B en ambas. Se inició quimioterapia y actualmente se encuentra en fase de mantenimiento.* **Conclusiones:** *Las manifestaciones clínicas de leucemia cutis son heterogéneas, desde una pápula pequeña hasta lesiones nodulares de diferentes tamaños. Lo más común es verlas en pacientes con leucemia mieloide aguda, y es muy raro en pacientes con leucemia linfoblástica aguda pre-B, especialmente en la edad pediátrica. El diagnóstico se realiza con una biopsia de piel y el tratamiento es con quimioterapia sistémica. Es importante tener en mente este diagnóstico en pacientes con síntomas sistémicos de leucemia.*

Palabras clave: *Leucemia cutis. Leucemia linfoblástica aguda pre-B. Leucemia cutánea pediátrica.*

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Introduction

Leukemia is a neoplasm of the hematopoietic system very common in the pediatric population[1]. It can also have manifestations in other organs, including the skin. The skin manifestations, called leukemia cutis (LC), are very heterogeneous and non-specific, it can also be present previous to the systemic manifestations even though it is rare. The most common type of leukemia associated with LC is acute myeloid leukemia (AML) and the least common pre B acute lymphoblastic leukemia (ALL). We report the case of a teenager who presented with facial edema and infiltration and systemic symptoms as the initial manifestation of pre-B ALL.

Clinical case

A previously healthy 14-year old male developed facial edema that worsened in the mornings and improved spontaneously during the evenings, associated with asthenia and adynamia. He consulted several physicians without obtaining any specific diagnosis or treatment; during this time, a complete blood count (CBC) was done and found to be normal. Due to persistent edema he was brought to our clinic 2 months later. Physical exam was notable for facial edema, diffuse indurated plaques affecting the cheeks, palpebral erythematoedematous plaques (Fig. 1), bilateral cervical, inguinal and axillary adenopathy, and splenomegaly. A new CBC was taken showing pancytopenia, and a chest X-ray revealed a mediastinal mass. Bone marrow (BM) biopsy was taken as part of the diagnostic protocol revealing small to medium cells with scarce cytoplasm, and immunohistochemistry (IHC) positive for TdT and PAX5. A skin biopsy of the cheek showed a dense dermal inflammatory infiltrate composed of atypical lymphocytes (Fig. 2A), IHC was positive for TdT and PAX5 and negative for CD56 (Fig. 2B). With these pathology results, pre-B ALL with skin infiltration (LC) was confirmed.

The clinical differential diagnoses of facial edema and palpebral erythema include cellulitis, nephrotic syndrome, superior vena cava syndrome and parasitosis (such as onchocerciasis). The patient also presented facial induration and systemic symptoms which extends the differential diagnoses to include lymphoproliferative diseases infiltrating the skin. Pancytopenia and a mediastinal mass leads to a high suspicion of LC, confirmed by histopathology.

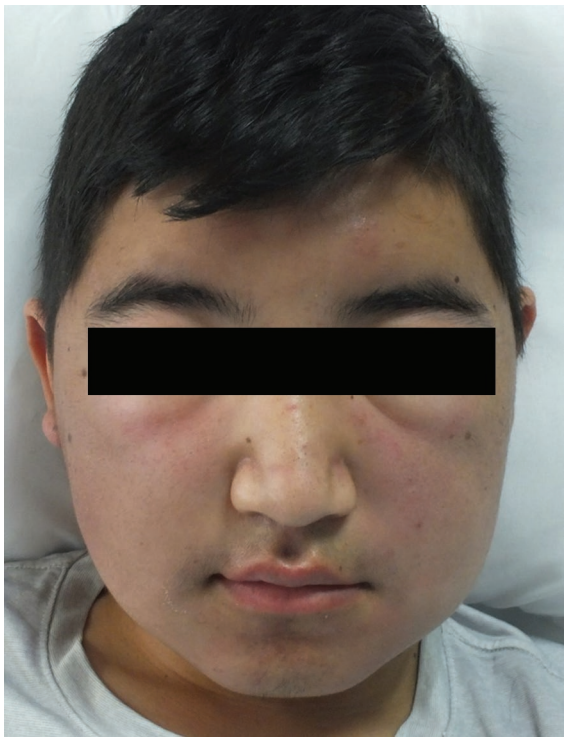

Figure 1. Facial edema, diffuse indurated plaques on the cheeks.

Discussion

ALL is one of the most frequent oncological diseases in children[1], affecting the BM first and subsequently appearing in peripheral blood and other organs, including the skin[2].

LC refers to cutaneous infiltration of neoplastic leukocytes (myeloid or lymphoid) and LC occurs more frequently in patients with myeloid leukemias, especially in subtypes with monocytic components (AML)[1]. Skin involvement is more common in children, occurring in up to 50% of patients with AML, 4-20% with chronic lymphocytic leukemia (CLL), and around 1-3% in ALL. It is particularly uncommon in pre B-cell ALL[3,4].

Usually LC occurs after the diagnosis of leukemia (55-70%) and up to 30% patients have concomitant systemic and cutaneous involvement[2,4]. LC may also be the presenting sign of tumor relapse or recurrence and generally is a poor prognostic sign, however the exact survival rate of patients with LC secondary to pre-B ALL in unknown[3,5]. Aleukemic LC refers to cutaneous involvement without other manifestations, affecting up to 7% of patients, and may precede

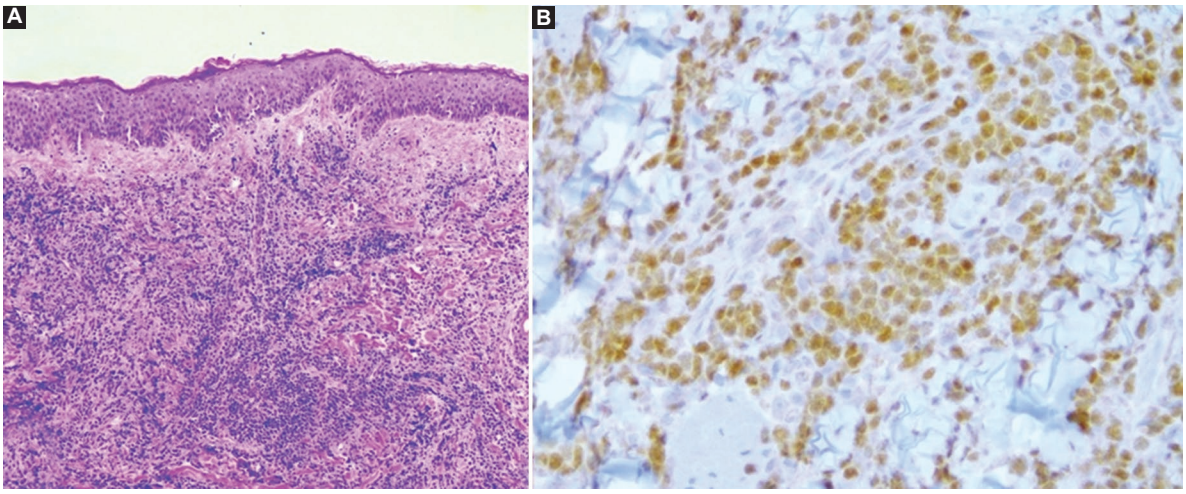

Figure 2: A: the dermis has a dense infiltrate of small blastic monomorphic cells (×10). **B:** inmunohistoquímica de Pax – 5 positiva para células blásticas linfoides de linaje B (×40).

peripheral blood or BM disease for several months or years[2].

The clinical presentation of LC is heterogeneous varying from hemorrhagic papules or violaceous nodules to plaques of different sizes; erythematous papules and nodules are the most frequently seen[4]. Different skin lesions can be seen in the same patient during the course of the disease. The most commonly involved sites are the extremities (particularly lower), followed by arms, back, chest, scalp, and face[4]. In pre-B cell ALL, the most common findings are infiltrated nodules and plaques on the head and neck[5].

The diagnosis of LC is based on histopathologic findings characterized by: a Grenz zone (superficial dermis without any inflammatory cells), a lymphocytic infiltrate that can be perivascular and periadnexial or dense diffuse or nodular involving the dermis and subcutis, with numerous mytoses and necrotic cells[3,4]. IHC is important to determine the cell lineage. In ALL the B lymphoblasts are positive for CD79a, CD19, PAX - 5 and TdT, the combination of the last two being the most useful[2,4]. T lymphoblasts to CD1a, CD3, CD43 and TdT. CLL lymphocytes express CD5, CD19, CD20, CD43[2,4]. In AML the most frequently used markers and are positive are: NASD, MPO, CD43, lysozyme and CD74[3,4]. Additional to the skin biopsy, a BM biopsy as well as peripheral blood analysis is necessary to confirm the diagnosis[3,4].

The treatment is aimed to eradicate systemic disease; systemic chemotherapy and local therapy, such as local radiation or surgery, is indicated[4]. At the same time as remission of hematological findings, there is partial or complete resolution of cutaneous manifestations[2].

Conclusion

LC may present heterogeneously and is a poor prognostic factor in patients with leukemia[3]. The diagnosis should always be considered in patients with unexplained edematous or indurated lesions, innocent as these may look. The presence of LC in patients with pre-B cell ALL is extremely rare and only a few are reported in the literature.

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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. Además, los autores han reconocido y seguido las

recomendaciones según las guías SAGER dependiendo del tipo y naturaleza del estudio.

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

Uso de inteligencia artificial para generar textos. Los autores declaran que no han utilizado ningún tipo de inteligencia artificial generativa en la redacción de este manuscrito ni para la creación de figuras, gráficos, tablas o sus correspondientes pies o leyendas.

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CLINICAL CASE

Linear IgA bullous dermatosis in a latin adolescent treated with cyclosporine and prednisone

Andrea Ríos-Sánchez[1], Juan A. Godínez-Chaparro[2], Marissa de J. Quintal-Ramírez[3], and Ixchel R. Ramírez-Ricarte[4]*

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Abstract

Introduction: *Linear IgA bullous dermatosis (LABD) is a rare autoimmune disease. Although dapsone is the initial treatment, other immunomodulators are used in resistant cases or when dapsone is unavailable.* **Case report:** *A 12-year-old Mexican child, with no relevant medical history, developed in May 2023 a disseminated dermatosis affecting all body segments, including mucous membranes, characterized by erythematous patches and plaques evolving into the formation of serous and serosanguinous blisters and vesicles, distributed in a "string of pearls" pattern. LABD was suspected and confirmed by skin biopsy, which showed a subepidermal blister with neutrophilic infiltration and linear Immunoglobulin A deposits at the dermo-epidermal junction by direct immunofluorescence.Treatment with prednisone (2 mg/kg/day) and cyclosporine (5 mg/kg/day) resulted in improvement and lesion remission within 2 weeks. Both drugs needed to be discontinued for 3 months due to intermittent blistering. Cyclosporine was continued as maintenance therapy at a dose of 4 mg/kg/day for 8 months.* **Conclusions:** *The report highlights the use of cyclosporine as an alternative immunomodulator for DAAL, an immunosuppressive agent used in autoimmune disorders. Few cases, including this one, have described complete remission and control of the dermatosis with cyclosporine, accompanied by prednisone at the start of treatment.*

Keywords: *Linear immunoglobulin A bullous dermatosis. Prednisone. Cyclosporine. Case report.*

Dermatosis ampollosa por IgA lineal en un adolescente latino tratado con ciclosporina y prednisona

Resumen

Introducción: *La dermatosis ampollosa por IgA lineal es una enfermedad autoinmunitaria rara. Aunque la dapsona es el tratamiento inicial, se usan otros inmunomoduladores en casos resistentes o cuando la dapsona no está disponible.* **Caso clínico:** *Un niño mexicano de 12 años, sin antecedentes relevantes, desarrolló en mayo de 2023 una dermatosis diseminada a todos los segmentos corporales, incluyendo las mucosas, caracterizada por manchas y placas eritematosas que evolucionaron hacia la formación de ampollas y vesículas serosas y serohemáticas, distribuidas en forma de «cadena de perlas». Se sospechó dermatosis ampollosa por IgA lineal y se confirmó mediante biopsia cutánea, que mostró una ampolla subepidérmica con infiltrado neutrófilo y depósitos lineales de IgA en la unión dermoepidérmica mediante*

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inmunofluorescencia directa. El tratamiento con prednisona (2 mg/kg al día) y ciclosporina (5 mg/kg al día) resultó en mejoría y la remisión de las lesiones a las 2 semanas. Fue necesario dejar ambos fármacos durante 3 meses debido a la aparición intermitente de ampollas. Se dejó ciclosporina como terapia de mantenimiento a dosis de 4 mg/kg al día por 8 meses. **Conclusiones:** *El reporte destaca el uso de ciclosporina como inmunomodulador alternativo para la dermatosis ampollosa por IgA lineal, un agente inmunosupresor utilizado en trastornos autoinmunitarios. Pocos casos, incluido este, han descrito la remisión completa y el control de la dermatosis con ciclosporina, acompañada de prednisona al inicio del tratamiento.*

Palabras clave: *Dermatitis ampollosa por IgA lineal. Prednisona. Ciclosporina. Reporte de caso.*

Introduction

Linear IgA bullous dermatosis (LABD), also known as chronic bullous disease of childhood, is a rare autoimmune subepidermal vesiculobullous disease that affects mucocutaneous tissues. The disease derives its name from the linear deposition of autoantibodies, primarily immunoglobulin A (IgA), along the dermoepidermal junction[1]. LABD has an annual incidence of 0.5-2.3 cases per million people and is more prevalent in Asian and African populations. This bullous disease represents the most common autoimmune form in childhood and follows a chronic course[2-4].

The initial and maintenance management of LABD is with dapsone; however, this drug is difficult to access and unavailable in certain countries. In addition, there are cases that have shown resistance to first-line treatment, which includes dapsone and prednisone. Furthermore, there is a lack of randomized controlled trials on the treatment of LABD; therefore, the described management options are mostly anecdotal[2]. This article presents the case of a Latin patient with LABD whose disease onset occurred during adolescence and was treated with ciclosporin and prednisone. The patient responded favorably to the initial treatment with ciclosporin and prednisone and achieved adequate therapeutic control solely with ciclosporin in the following months.

Clinical case

A 12-year-old male patient, native and resident of Mexico City, presented with no significant personal or family medical history. He has completed age appropriate immunizations. His current condition began in May 2023 when he suddenly developed a localized dermatosis on the trunk characterized by patches and wheals. In the following weeks, tense vesicles and blisters appeared, causing intense itching. The dermatosis spread to involve all body segments, including oral and genital mucosa, in the following days. The patient consulted multiple physicians, but no clinical diagnosis was issued. He received treatment with antihistamines, steroids, and topical drying agents for 2 weeks without clinical improvement.

In June 2023, he presented to the pediatric dermatology service at La Raza National Medical Center, Mexican Social Security Institute. Initial somatometry measurements were as follows: weight 41.4 kg, height 1.50 cm, blood pressure 100/60 mmHg, heart rate 91 bpm, respiratory rate 18 rpm, and oxygen saturation 91%. On physical examination, he exhibited a disseminated dermatosis affecting all body segments, including oral and genital mucosa. It consisted of erythematous patches that coalesced, annular, and serpiginous erythematous plaques, with tense vesicles and blisters containing serous and serosanguineous fluid. The distribution pattern resembled a “string of pearls,” with erosions and hemorrhagic crusts forming on rupture (Fig. 1). The rest of the physical examination was unremarkable. Laboratory studies revealed a complete blood count with a hemoglobin level of 13.6 g/dL, hematocrit of 42.6%, leukocytosis of 12,115 K/uL with neutrophilia of 8660 K/uL, and platelet count of 323,000 K/uL. Renal function tests, including serum creatinine, were within normal limits.

On clinical suspicion of LABD, a skin biopsy was performed. Histopathology with hematoxylin and eosin staining revealed a subepidermal blister with a predominance of neutrophilic infiltration in the papillary dermis (Fig. 1). Direct immunofluorescence showed linear deposits of IgA at the dermoepidermal junction (Fig. 1). The diagnosis of LABD was confirmed, and treatment was initiated with prednisone at 2 mg/kg/day and cyclosporine at 5 mg/kg/day. Improvement and lesion remission were observed within 2 weeks of therapy initiation. Both medications had to be continued for 3 months due to the intermittent appearance of blisters during this period. Finally, cyclosporine was continued as maintenance therapy at a dose of 4 mg/kg/day for 8 months without any recurrence of blisters reported up to the time of this publication. No adverse drug effects were reported.

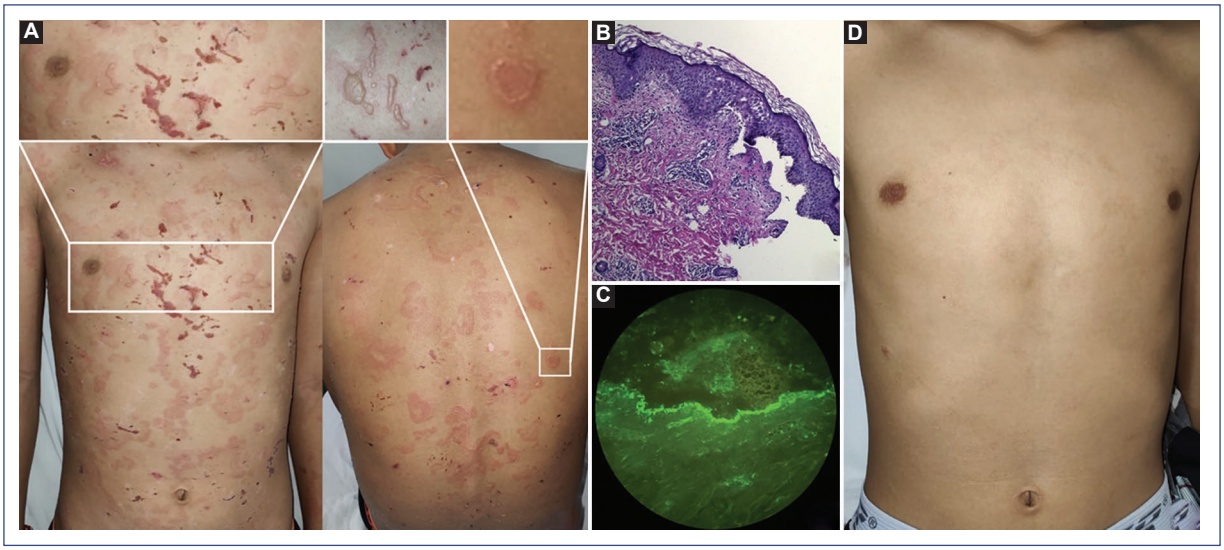

Figure 1. A: dermatosis with annular patches and serpiginous wheals, vesicles, and blisters forming a "string of pearls" pattern and hemorrhagic crusts due to scratching. **B:** subepidermal blister edge with neutrophilic infiltrate in the papillary dermis. **C:** direct immunofluorescence showing linear deposits of immunoglobulin A at the basement membrane. **D:** healthy skin after treatment.

Discussion

LABD involves circulating IgA antibodies against the basement membrane, identified by immunoelectron microscopy in the lamina lucida and sublamina densa. Onset can be triggered by infections, vaccinations, autoimmune diseases, oncological processes, and medications. In some cases, especially in children, no triggering factors are identified[4-6].

The infantile variant of LABD begins in the abdominal and perioral areas and progresses to the rest of the body. It presents with transparent or serohematic vesicles and blisters on normal, erythematous, or target lesion skin, causing itching, excoriations, and blood crusts. New blisters characteristically form at the periphery of resolving lesions, creating a ring pattern known as a "crown of jewels" or "string of pearls."[4] Mucous membranes may be affected. The Nikolsky sign and large skin erosions are more common in drug-induced LABD than in the idiopathic type[5].

The confirmatory diagnosis of LABD is established through the comprehensive evaluation of clinical, histopathological, and immunological findings. Two diseases that can be confused with this condition are dermatitis herpetiformis and bullous pemphigoid (Table 1)[4].

The treatment of choice for managing LABD is dapsone at a dose of 0.5-2 mg/kg/day, often complemented with systemic corticosteroids to control the dermatosis[2,6]. In regions with limited access to dapsone, such as Mexico, other immunosuppressants are used. In cases of glucose-6-phosphate dehydrogenase deficiency, sulfa allergy, therapeutic failure, or unavailability of the drug, and systemic corticosteroids at doses of 0.5-1 mg/kg/day are recommended. If the clinical response is unsatisfactory, alternative drugs such as antibiotics (penicillins, erythromycin, or tetracyclines), intravenous immunoglobulin, colchicine, rituximab, the combination of nicotinamide/niacin + tetracycline, mycophenolate mofetil, methotrexate, cyclosporine, tumor necrosis factor-α inhibitors, omalizumab, sulfasalazine, azathioprine, and thalidomide have been used, though their efficacy is primarily based on case reports rather than clinical studies[2].

Cyclosporine is an immunosuppressant used in autoimmune disorders, including dermatological conditions, by inhibiting the proliferation of activated T lymphocytes through the blockade of Interleukin-2 production[15]. It has been used in severe and resistant cases of LABD along with other immunomodulators like dapsone and corticosteroids[16-19]. In addition, as a steroid-sparing drug, it allows for the reduction or discontinuation of steroids or dapsone, serving as a maintenance option to prevent recurrences over prolonged periods.[4]

Table 1. Comparative table of linear IgA bullous dermatosis of childhood compared to its main differential diagnoses

Variable/disease	Linear IgA bullous dermatosis	Dermatitis herpetiformis	Bullous pemphigoid
References	Yang et al.[3], Mori et al.[4], Bernett et al.[6], Díaz et al.[7], Schultz and Hook[8]	Schultz and Hook[8], Mirza et al.[9], Tekin et al.[10], Reunala et al.[11]	Schultz and Hook[8], Patsatsi et al.[12], Oranje and van Joost[13], Bernard and Borradori[14]
Global incidence (per million population annually)	0.5-2.3 cases	0.8-1.8 cases	6-13 cases
Pediatric onset age	Rare in childhood. Most cases occur in preschoolers aged 3-5 years (mean onset age of 4.5 years).	Rare in children (4% of cases). It is more common between the ages of 2 and 7 years.	Rare in children. Two groups: (a) childhood (under 12 years with a mean onset age of 8.3 years) and (b) juvenile cases (13-18 years, mean age 14.9 years).
Etiology	Autoimmune Autoantibodies mainly IgA Association with HLA haplotypes B8, DR3, DQ2, Cw7	Autoimmune Genetic association with HLA-DQ2 and HLA-DQ8. First-degree relatives have a higher risk. Gluten and tissue transglutaminase are important environmental factors.	Autoimmune Association with alleles DQB1*0301, DRB1*04, DRB1*1101 and DQB1*0302
Physiopathology	Autoantibodies IgA directed against the basement membrane zone. Microscopy identifies two types: one in the lamina lucida and another in the sublamina densa.	Formation of circulating IgA-transglutaminase 3 immune complexes originating from the intestine and deposited in the dermis.	Autoantibodies IgG and/or IgA against specific antigens in the hemidesmosomes that damage the adhesion structure of the dermoepidermal basement membrane zone.
Target antigens (morphological structures)	– LAD Antigen (Anchoring filaments) – BP230/BPAG1e (Hemidesmosomal plaque) – BP180/BPAG2/Collagen XVII (Hemidesmosomal plaque/ Anchoring filaments) – Type VII collagen (Anchoring fibrils)	– Transglutaminase	– BP180/BPAG2/Collagen XVII (Hemidesmosomal plaque/ Anchoring filaments) – BP230/BPAG1e (Hemidesmosomal plaque)
Morphology	Tense vesicles and blisters in a polycyclic configuration over an erythematous annular background resembling a "crown of jewels" or "string of pearls."	Pruritic eruption consisting of blisters, papules, and erythema. Symmetrical lesions. Acral purpura is more common in children.	Tense blisters, sometimes hemorrhagic, on normal, erythematous, or urticarial skin. The blisters exhibit an arciform or rosette pattern. May or may not involve mucous membranes.
Topography	Trunk at abdominal level and proximal extremities. Progresses to the rest of the body. Affects mucous membranes.	Extensor surfaces of forearms, knees, and buttocks followed by back, abdomen, and face.	All body segments. Predilection sites include the face, neck, skin folds, palms, and soles of the feet. Mucous membranes may be affected as well.
Itchiness	Intense	Intense	Intense
Histopathology	Subepidermal blisters with an inflammatory infiltrate composed of neutrophils, some eosinophils, and lymphocytes in the underlying dermis.	Subepidermal blisters with a predominance of neutrophilic infiltrate or formation of microabscesses in the dermal papillae.	Subepidermal blister with infiltration of scattered eosinophils within the blister accompanied by a perivascular infiltrate of neutrophils, numerous eosinophils, and lymphocytes.
Direct immunofluorescence	Linear deposits of IgA at the dermoepidermal junction	Granular deposits of IgA in the dermal papillae.	Linear deposits of IgG and/or C3 along the basement membrane in a "chicken wire" pattern.

(Continues)

Table 1. Comparative table of linear IgA bullous dermatosis of childhood compared to its main differential diagnoses *(continued)*

Variable/disea-se	Linear IgA bullous dermatosis	Dermatitis herpetiformis	Bullous pemphigoid
Treatment	Choice: Dapsone 0.5-2 mg/kg/day. Other options include antibiotics, other immunomodulators such as steroids, cyclosporine, and azathioprine.	Gluten-free diet, dapsone at 0.5 mg/kg/day at the beginning of treatment, and sulfonamide.	Topical steroids or systemic prednisone at a dose of 1-2 mg/kg/day in combination with immunomodulators such as dapsone, azathioprine, mycophenolate mofetil, or erythromycin/nicotinamide.
General associations	Triggers: infectious agents, drugs, other associated autoimmune conditions (systemic lupus erythematosus, rheumatoid arthritis, psoriasis), oncological processes, autoimmune lymphoproliferative syndrome, and gastrointestinal pathology (celiac disease, Crohn's disease, ulcerative colitis).	Celiac disease T-cell or B-cell lymphoma associated with enteropathy. Other autoimmune diseases such as diabetes mellitus, atopic dermatitis, alopecia areata, vitiligo, and thyroid diseases.	Autoimmunity, primary immunodeficiencies, transplant patients. Vaccinations as possible triggers.

IgA: immunoglobulin A; IgG: immunoglobulin G; BP230/BPAG1e: bullous pemphigoid antigen 1; BP180/BPAG2: bullous pemphigoid antigen 2.

Only two anecdotal cases have been documented in the pediatric population where cyclosporine was used with other immunomodulators to treat LABD[16,17]. Ikeya et al., reported a 12-year-old adolescent with LABD following HPV vaccination, who did not improve with erythromycin and required oral prednisolone and cyclosporine[16]. Tate et al., described a 5-year-old child with LABD without identified triggering factors, whose difficult-to-control disease required treatment in a burns unit, receiving dapsone, prednisolone, and cyclosporine[17].

Conclusion

Cyclosporine is a useful pharmacological alternative for controlling LABD. Publishing positive clinical experiences in rare diseases is crucial to generate more scientific evidence, evaluate its efficacy and safety in the disease in the future, and develop standardized therapies.

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Conflicts of interest

The authors declare no conflicts of interest.

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 no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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