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Temístocles, 315
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Contenido

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Vol. 79 • No. 4 • July-August 2022 www.bmhim.com *Indexed in Scopus and MEDLINE*

Contents

Boletín Médico del
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LETTER TO THE EDITOR

Acute hepatitis of unknown etiology: a proposed diagnostic approach

Hepatitis aguda de etiología desconocida: una propuesta de abordaje diagnóstico

Rubén Peña-Vélez[1], Alfredo Y. Martínez-Vázquez[2], and Lucía Pérez-Ricárdez[3]*

[1]Unidad de Gastroenterología, Hepatología y Nutrición Pediátrica, Hospital General de Puebla Dr. Eduardo Vázquez N.; [2]Servicio de Gastroenterología y Nutrición, Hospital para el Niño Poblano; [3]Servicio Infectología, Hospital para el Niño Poblano. Puebla, Puebla, Mexico

Recently, acute and severe hepatitis cases in children have increased, triggering close epidemiological surveillance worldwide[1]. Between April 5 and May 26, 2022, 650 probable cases have been reported to the World Health Organization (WHO) from 33 countries, with the United Kingdom and the United States reporting most cases, followed by Japan, Spain, and Italy[2].

The WHO defines a probable case as any person presenting with acute hepatitis (not hepatitis A-E) with serum transaminase levels > 500 IU/L (aspartate aminotransferase or alanine aminotransferase) and age ≤ 16 years (Table 1)[3], mainly with gastrointestinal symptoms, such as vomiting, acholia, and jaundice, and respiratory symptoms in a lower percentage (Table 2)[2].

Table 1. Case definitions according to the World Health Organization

Case	Definition
Confirmed	No definition
Probable	Any individual aged ≤ 16 years who presents acute hepatitis (not hepatitis A-E), with serum transaminase levels > 500 IU/L (AST or ALT) since October 1, 2021
Contact	Any individual of any age who presents with acute hepatitis (not hepatitis A-E) and has been in close contact with a probable case since October 1, 2021
Cases with other explanations for clinical presentation should be excluded. Delta testing is not required, as it is only performed in HBsAg-positive individuals to establish the presence of coinfection	

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBsAg, hepatitis B virus surface antigen.

Etiology of acute hepatitis

Cases have tested negative for A-E viruses. A UK study involving 126 children documented the presence of adenovirus in 72% (n = 91). It was also identified in 44% of stool and 29% of respiratory specimens. Twenty-four children (18%) had active SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection. Epstein-Barr, enterovirus, cytomegalovirus, respiratory syncytial virus, and human herpesviruses 6 and 7 were identified less frequently[4-6].

According to the European Centre for Disease Prevention and Control (ECDC), several hypotheses have emerged based on present-day evidence. The most compelling relates to a cofactor affecting children that cause mild adenovirus infections to become more severe or trigger immune-mediated liver damage. This cofactor may be related to susceptibility due to a lack of prior exposure to adenovirus during the pandemic, a previous SARS-CoV-2 infection, or a toxin, drug, or environmental exposure[1,7].

Correspondence:
*Rubén Peña-Vélez
E-mail: rubenpevelez@hotmail.com

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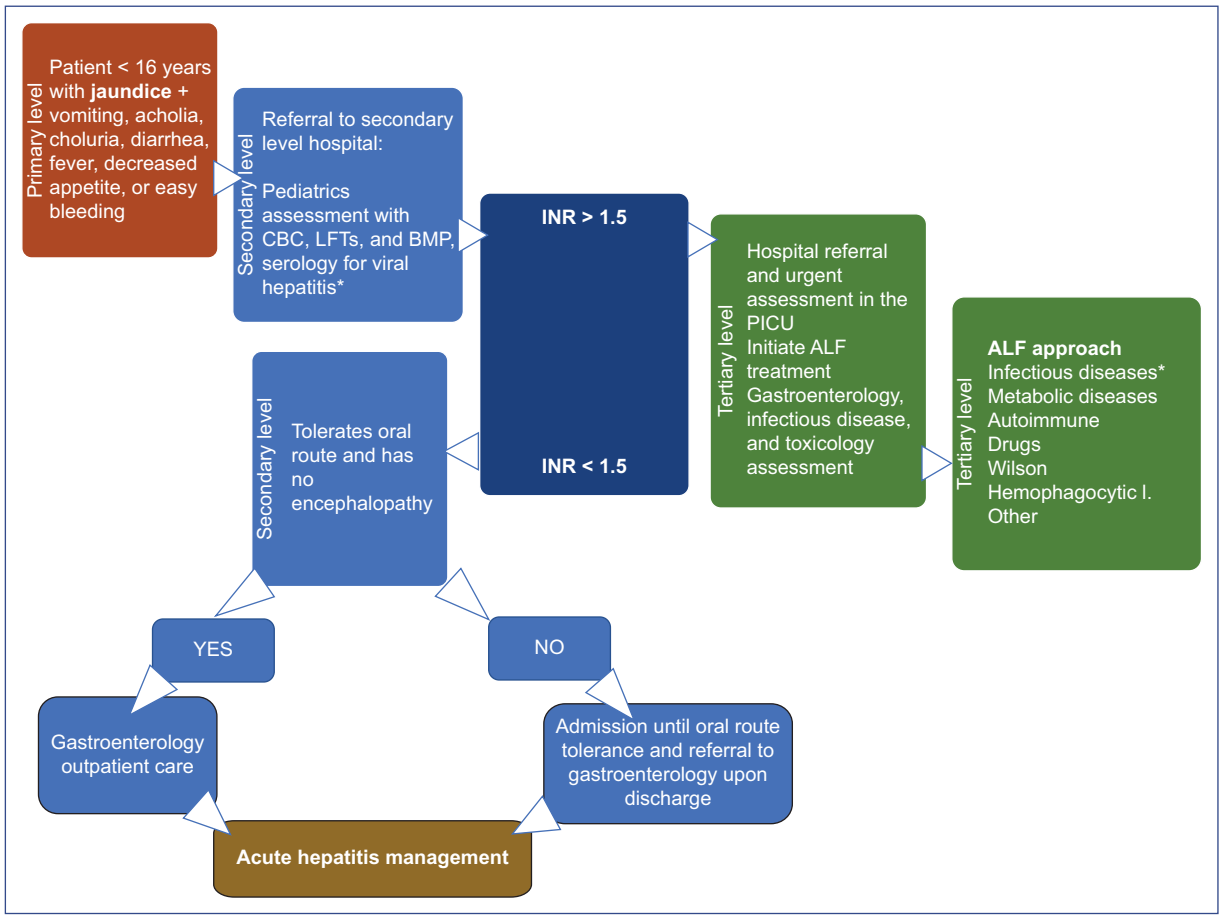

Figure 1. Diagnostic approach to suspected acute hepatitis.
ALF: acute liver failure; BMP: basic metabolic panel; CBC: complete blood count; INR: international normalized ratio; LFTs: liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, albumin, total bilirubin, direct bilirubin, and coagulation tests); PICU: Pediatric Intensive Care Unit.
*Consider hepatitis A, B, C, and E, Epstein-Barr virus, cytomegalovirus, leptospirosis, human parvovirus B19, adenovirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and herpesvirus.

Proposed diagnostic approach

Upon identification of a probable case of hepatitis, the conventional care process should be conducted, allowing for differential diagnosis since acute hepatitis is not a new disease. Throughout history, cases of unknown or idiopathic causes have been documented after searching for the most common causes. For this reason, it is necessary to adopt a systematic evaluation, tiered by the level of care and age group, to manage cases with symptoms consistent with acute hepatitis (Figure 1).

This evaluation is intended to determine the etiology of the liver injury and not ignore other known causes of hepatitis, such as autoimmune, toxic, and other infectious diseases caused by hepatotropic and non-hepatotropic viruses, including hemophagocytic lymphohistiocytosis,

Table 2. Clinical presentation in children with acute hepatitis of unknown etiology

Signs or symptoms	Percentage
Jaundice	71%
Vomiting	63%
Acholia	50%
Diarrhea	45%
Fever	31%
Respiratory symptoms	19%

in which patients present with hepatic inflammation and may develop acute liver failure[8].

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interest.

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REVIEW ARTICLE

Congenital hearing loss: a literature review of the genetic etiology in a Mexican population

Carlos de la Torre-González[1], Dina Villanueva-García[2], Constanza García-Delgado[3], Salvador Castillo-Castillo[4], Marisol Huante-Guido[1], Josefina Chichitz-Madrigal[4], María E. Juárez-Torres[5], Ana L. Sánchez-Sandoval[5], Eira V. Barrón-Palma[5], and Verónica F. Morán-Barroso[6]

[1]Departamento de Otorrinolaringología, Hospital Infantil de México Federico Gómez; [2]Departamento de Neonatología, Hospital Infantil de México Federico Gómez; [3]Departamento de Genética, Hospital Infantil de México Federico Gómez; [4]Departamento de Audiología y Foniatría, Hospital Infantil de México Federico Gómez; [5]Servicio de Medicina Genómica, Hospital General de México Dr. Eduardo Liceaga; [6]Servicio de Genética, Hospital General de México Dr. Eduardo Liceaga. Mexico City, Mexico

Abstract

Hearing loss is the most frequent sensory disorder, with an incidence of 1:1500 live newborns. In more than 50% of patients, it is associated with a genetic cause, while in up to 30% of cases, it is related to syndromic entities. We performed a literature review of studies on congenital hearing loss of genetic origin in the Mexican population. We identified eight reports that showed that the pathogenic variants most frequently associated with hearing loss are related to the GJB2 gene, although in a low percentage (3%). Other mutations were identified in the GJB6, SLC26A4, or CHD23 genes. On this basis, a possible diagnostic strategy in Mexican patients with hearing loss is to consider an initial screening of these three genes. If these genes were negative for pathogenic variants, the following steps would be to consider second-generation sequencing analysis focused on panels of genes associated with hearing loss, isolated or syndromic, and if necessary, to perform exome or whole-genome analysis. Establishing an etiologic cause is critical in clinically evaluating patients with congenital hearing loss and their families. It can help determine rehabilitation strategies, such as hearing aids or cochlear implants and provide information on disease progression and genetic counseling in this population.

Keywords: *Congenital hearing loss. Congenital deafness. Mexican population. GJB2. GJB6.*

Pérdida auditiva congénita: revisión de la etiología genética en la población mexicana

Resumen

La pérdida auditiva es la alteración sensorial más frecuente, con una incidencia de 1:1500 recién nacidos vivos. En más del 50% de los pacientes se asocia con una causa genética, mientras que en más del 30% de los casos se asocia con entidades sindrómicas. Se llevó a cabo una revisión de la literatura de las investigaciones sobre la pérdida auditiva congénita de origen genético en la población mexicana. Se identificaron ocho reportes en los que se demostró que las variantes patogénicas más frecuentemente asociadas con pérdida auditiva se encuentran en el gen GJB2, aunque en un porcentaje bajo (3%). Se identificaron otras mutaciones en los genes GJB6, SLC26A4 o CHD23. Con base en esta información, una posible estrategia diagnóstica en pacientes mexicanos con pérdida auditiva es considerar un primer paso en el tamiz diagnóstico con los tres genes mencionados. Si estos genes fueran negativos para variantes patogénicas, el siguiente paso

Correspondence:
*Verónica F. Morán-Barroso
E-mail: veronicafabiolamoranbarroso@yahoo.com.mx

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sería considerar el análisis por secuenciación de segunda generación enfocado en paneles de genes asociados con pérdida auditiva, tanto aislada como sindrómica, y en caso necesario, realizar el análisis del exoma o del genoma completo. Establecer una causa etiológica es un componente crítico en la evaluación clínica de los pacientes con pérdida auditiva congénita, ya que puede ayudar a determinar las estrategias de manejo y rehabilitación, como el uso de auxiliares auditivos o implantes cocleares, proporcionar información sobre la progresión de la enfermedad y dar asesoramiento genético en esta población.

Palabras clave: *Pérdida auditiva congénita. Sordera congénita. Población Mexicana. GJB2. GJB6.*

Introduction

Hearing loss is the most common sensory disorder, affecting more than 500 million people worldwide. Its incidence is 1:1500 live newborns (LNB); also, the hearing loss is hereditary in 1:1000 LNB and may appear as congenital sensorineural hearing loss that may affect up to 1-3% of individuals in some populations[1-4]. According to the World Health Organization (WHO)[5,6], hearing loss is classified into four groups based on its severity: mild (hearing threshold between 26-40 dB HL); moderate (hearing threshold between 41-60 dB HL); severe (hearing threshold between 61-80 dB HL); profound (hearing threshold > 80 dB HL). Since 2008, a new classification of hearing loss has been proposed by a group of experts belonging to the Global Burden Organization[7]. This proposal defines mild hearing loss in a range of 20 to 34.9 dB HL (which differs from the value of 26 dB HL considered by the WHO classification) in children and adults; it also delineates six different degrees of hearing loss, each defined by a range of 15 dB HL, depending on the better-hearing ear of the patient[8]. Although the Global Burden Organization classification does not go as far as the American Speech-Language-Hearing Association classification—which considers mild hearing loss from 16 dB HL and up to the 25 dB HL threshold, thus including a degree that precedes even the mild hearing loss regarding other classifications—if used, it would show a substantial increase in the number of people around the world who would be considered with a hearing impairment[9]. In either case, using these classifications would increase the global prevalence of mild and severe hearing loss—however, the WHO has not yet officially accepted the new Global Burden Organization classification.

Congenital hearing loss can be classified according to its type as conductive (related to external or middle ear pathology), sensorineural (associated with internal ear and spiral ganglion pathologies), neural (associated with VIII cranial nerve alterations), and mixed (associated with pathologies including two or more of the segments). The classification of hearing impairments has important implications for their treatment. For example, the primary indication for a cochlear implant is exclusively related to the hearing thresholds indicated when congenital hearing loss is classified as severe or profound neurosensorial loss[10]. Congenital hearing loss (of any type) in patients in early childhood has different repercussions on their social and psychological development for the rest of their lives, considering that hearing is the basis of linguistic communication between individuals and their social environment. Besides the genetic assessment, detecting a genetic alteration with hereditary characteristics will allow timely intervention with patients who may require this approach for a better prognosis.

Congenital hearing loss etiology

Although there are several classifications regarding the etiology of congenital hearing loss, the most important to consider is a genetic or non-genetic cause (related to the environment)[1-4,11]. Regarding congenital presentation, more than 50% of early-onset bilateral sensorineural deafness cases have been considered to have a genetic cause[12]. The other half corresponds to non-genetic causes. Environmental factors include, for example, infections such as those associated with TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and HIV), the diagnosis of cytomegalovirus, ototoxic drugs, prematurity, hypoxia at birth, hyperbilirubinemia, or even the permanence of the patient in neonatal intensive care units for more than five days[3,4].

Genetic factors of congenital hearing loss

When analyzing the possible genetic etiology of congenital hearing loss, one of the first aspects to consider is whether it is a syndromic presentation (a situation that represents up to 30% of cases of all types of hereditary hearing loss)[13,14] or whether it is an isolated characteristic (which corresponds up to 70% of patients).

Syndromic genetic causes of hearing loss include Usher, Pendred, Waardenburg, and Norrie syndromes. In this regard, Bahena et al. conducted an interesting study on a group of 59 patients with combined retinal and hearing impairment but no intellectual disability[15]. Most of the patients were Iranian, and seven unrelated Mexican patients were included in this study. Through exome analyses, the authors were able to elucidate all Mexican cases, as several pathogenic or probably pathogenic genetic variants were identified in the *MYO7A* (three patients), *USH1G* (one patient), and *USH2A* (two patients) genes. This study is also an example of the genetic heterogeneity observed in the Mexican population regarding the etiology of syndromic hearing loss.

When non-syndromic causes are considered, hearing loss can be classified according to the inheritance pattern; for example, 75-80% of patients have an autosomal recessive pattern, 20% are autosomal dominant, < 2% are X-linked, and < 1% are of mitochondrial origin[3,4,16]. This information is relevant because, depending on the homozygous or heterozygous condition of the patient, the genetic possibility of expression can vary from 50% risk in the case of autosomal dominant pattern (in which the presence of a single mutated allele is sufficient to cause a clinical manifestation) to 25% risk for autosomal recessive diseases, in which the presence of two mutated alleles is required to generate a clinical alteration. Also, it influences prognosis and response to treatments, including the cochlear implantation[17].

According to the information on the Hereditary Hearing Loss Homepage website, several different genes have been identified to be associated with different inheritance patterns of non-syndromic hearing loss. For example, at the DFNA1 *locus* (OMIM #124900) is the *DIAPH1* gene (OMIM *602121) on 5q31.3; at the DFNA2A *locus* (OMIM #600101) is *KCNQ4* (OMIM *603537) on 1p34.2, and at the DFNA2B *locus* (OMIM #612644) is *GJB3* (OMIM 603324) on 1p34.3; these are examples of autosomal dominant patterns. Examples of congenital hearing loss with an autosomal recessive inheritance pattern include the DFNB1A *locus* (OMIM #220290) with the *GJB2* gene (OMIM 121011) on 13q12.11; *GJB6* (OMIM 604418) on 13q12.11 and *GJB3*; DFNB1B with the mentioned *GJB6,* or *DFNB2* (OMIM #600060) with *MYO7A* (*276903) on 11q13.5[18] (Table 1)[19-25].

Also, it is essential to consider that there are heterozygous compound variants, in which patients carry different pathogenic variants at the same *locus*, or the digenic inheritance, in which pathogenic variants are present in other *loci*. Another representative example of digenic inheritance in patients with hearing loss is the presence of a pathogenic variant in each of the genes encoding connexins 26 and 30, which are doubly heterozygous[2].

The first *locus* associated with pathogenic variants with an autosomal recessive inheritance pattern was mapped in 1994 and corresponded to the *GJB2* gene[26], which encodes the connexin-26 protein. This protein is part of the structure known as connexon, which in turn forms cell-cell junction elements; pathogenic variants of these proteins can cause alterations in the cochlea[4]. Pathogenic variants are the most common cause of autosomal recessive hearing loss and are identified in up to 50% of patients with severe to profound hearing loss. The study of these pathogenic variants is complex, as more than 200 variants have been identified to date[1,4,14]. As described in studies on second-generation DNA analysis, it is still impossible to reach a molecular diagnosis in 100% of the patients[15,23].

An important aspect in diagnosing, managing, and genetic counseling patients with congenital hearing loss is that its distribution is complex, as different variants predominate in different populations. For example, the c.35delG in *GJB2* is the most common variant in Europeans/Americans of European ancestry, and its carrier frequency is ~2.5% in the United States. Carrier prevalence for c. 35delG is 1.5% worldwide, ranging from 0% to 5.7% in Belarus. Another example is a carrier prevalence of 2.5% for the p.V37I variant (from 0% up to 16.7% in Thailand); the c.167delT variant has a carrier prevalence of ~4% in the Ashkenazi population, and the c.235delC variant is the most common in Japan[1-4]. As described above, considering ethnicity is critical when determining the optimal genetic analysis. When sequencing for the diagnosis of congenital hearing loss, there is a wide range of genotype frequency depending on the ethnicity of the patients[27].

Based on these considerations, the alteration's genetic etiology impacts the management and treatment of congenital hearing loss. Therefore, profile determination of the pathogenic variants in different populations allows for determining the resources and prognosis for each patient. As an example, 49 genes were identified in a study that performed genetic analysis of 1119 patients of different ethnicities[28], including 549 Caucasians, 128 Hispanics, 51 African Americans, 40 Asians, 25 Middle Easterns, 8 Ashkenazi Jews, 57 of mixed ethnicity, and seven patients described as of "other" ethnicity. In 75%, hearing loss was associated

Table 1. Comparison of information regarding the different mutations related to hearing impairment in Mexican populations

Author (year)[REF]	Arenas-Sordo et al. (2012)[19]	Mendelsberg-Fishbein et al. (2013)[20]	Hernández-Juárez et al. (2014)[21]	Loeza-Becerra et al. (2014)[22]	Martínez-Saucedo et al. (2015)[13]	Bademci et al.[a] (2016)[23]	Cengiz et al. (2017)[24]	Hernández-Nieto et al.[b] (2020)[25]
Studied population	76 individuals	11 individuals	78 individuals/ deafness	140 individuals/ deafness	Two families	Two Mexican families out of 90 families from several backgrounds	11 individuals out of seven families	805 individuals
Origen of the studied population in Mexico	Not specified	Central[c]: MEX: 6; MICH: 3; GUA: 1; CDMX:1	Northeastern[d]: NLE, SLP, and TAM	West, Northwest, East, Northeast, and Central	Not specified	Not specified	Not specified	From 25 out of 32 states. Ancestry: Latin (640), European (72), Middle East (22), other (3)
Analyzed gene/ Gene and pathogenic variant	*GJB2, GJB6,* del(GJB6-D13S1830) and del(GJB6-D13S1854), m.1555A > G in *MTRNR1*	*GJB2*: c.35delG, c.235delC and c.167delT	*GJB2* IVS1 + 1G > A and *GJB6* deletions	*GJB2, GJB6* y mt.1555A < G	*GJB2*	*CDH23*	*SLC26A4*	*GJB2,* del (GJB6-D13S1830) and del (GJB6-D13S1854).
Methods used for genetic variables identification	*a) GJB2* sequencing b) *GJB6 s*creening (sequencing) for two deletions: del (GJB6-D13S1830) and del (GJB6-D13S1854) c) *MTRNR1* gene (m.1555A>G in)	Three *GJB2* mutations were analyzed: a) c.35delG by direct sequencing b) c.167delT by PCR-RFLP with *Pst*I. c) C.235delC by PCR-RFLP with *Apa*I	*a) GJB2* nucleotide sequencing b) PCR-RFLP analysis to detect IVS1+1G>A c) Real-time quantitative PCR (qPCR) for deletions in *GJB6*	Direct sequencing of a) *GJB2* b) *GJB6* c)mt.1555A>G	Direct sequencing of *GJB2*	a) First *GJB2* mutations were discarded b) Whole-exome sequencing analysis	a) Pre-screening for *GJB2* variants b) Whole-exome sequencing identifying *SLC26A4* and Sanger sequencing for confirmation	Preconception expanded genetic carrier screening; panel test for 283 clinically impactful diseases. Next-generation sequencing was performed for 21 pathogenic variants and the two exons of *GJB2*, the presence or absence of the two upstream deletions of the *GJB2* regulatory region, del(GJB6-D13S1830) and del(GJB6-D13S1854)
Results	Eight previously reported pathogenic variants and two polymorphic variants in *GJB2*.		No deletions were detected in *GJB6* or *GJB2* IVS1 + 1G.	23 Hom mutations, 57 Het mutations, one double Het (*GJB2/GJB6*),	The propositus in family 1 had three mutations:			Twenty-seven cases (3.35%) were carriers of the pathogenic variant in *GJB2*.

(continues...)

Table 1. Comparison of information regarding the different mutations related to hearing impairment in Mexican populations *(continued)*

Author (year)[REF]	Arenas-Sordo et al. (2012)[19]	Mendelsberg-Fishbein et al. (2013)[20]	Hernández-Juárez et al. (2014)[21]	Loeza-Becerra et al. (2014)[22]	Martínez-Saucedo et al. (2015)[13]	Bademci et al.[a] (2016)[23]	Cengiz et al. (2017)[24]	Hernández-Nieto et al.[b] (2020)[25]
	No deletions were identified in *GJB6* or m.1555A>G. Eight cases (10.52%) with biallelic mutations. c.35delG (*GJB2*) was the most frequent pathogenic variant, with six heterozygous and two homozygous individuals. Five rare pathogenic variants were identified, including the autosomal dominant c.551G>A. c.79G>A was the most frequent benign polymorphic variant	c.35delG Hom (1); c.35insG (1); c.34G>T Het (1); c.79G>A (p.V27I) Het (2)	Mutations in *GJB2* were detected in 9.6% of the alleles; c. 35delG was the most frequent. Other six mutations were less frequently detected including (c.645_648delTAGA), (c.35G > A), and one with a possible Mexican origin (c.34G > T). There were no deletions detected in *GJB6* and *GJB2* IVS1 + 1G > A	and 59 wild-type genotypes in *GJB2*. Three Hom c.35delG and 26 Het patients. One patient with a *GJB6* deletion (including the double Het *GJB2/GJB6*). mt.1555A > G was not identified	Tp.S19R/p.R32S/p.E47*; meanwhile, the affected family members had three mutations p.F31I/p.W44*/p.V84M. The parents of both families were Het and had a normal auditive function	Het c.2959 G>A pD987N One compound Het (consanguinity)*	Hom: 3; compound Het: 4, for *SLC26A4* variants Seven families with ten different variants. in *SLC26A4*. A new recurrent variant was identified: t (c.1673A>G (p.N558S) in two families**	c.35delG (10 cases [37%]), c.101T>C (5 cases [18.5%]), c.617A>G (4 cases [14.8%]), c.109G>A (2 cases [7.4%]), other variants (deletion GJB6-D13S1830, c.416G>A, p.Leu90Pro, c.365A>T, c.169C>T, c.269T>C) (one case [3.7%] each
Conclusion	*GJB2* mutations are an important cause of prelingual deafness in the Mexican population	Two polymorphisms and three mutations were identified. The frequency of three different mutations was lower than those reported in the literature	The findings suggested that *DFNB1* mutations are a rare cause of autosomal recessive deafness in the northeastern Mexican population	The type and distribution of the mutations/alleles varied according to the specific analyzed region: 57.86% of patients had *GJB2* or *GJB6* mutated alleles, and 42.14% were wild-type	Two cases with three mutations. This situation reflects the complex patterns of mutations regarding *GJB2*	After excluding pathogenic variants in *GJB2*, a mutation was identified in 56% of the studied families. One Mexican family had a mutation in *CDH23*.	There is a spectrum of variants in *SLC26A4*. No common recurrent variation was identified. *SLC26A4* is a cause of hearing loss in Turkey, Iran, and Mexico	Sequence changes in *GJB2* had a frequency of carriers of 3.35%, and c.35delG (37%) was the most frequently identified. This result is similar to the 2.14% frequency reported in other regions of Mexico[10,13], where c.35del G was also the most commonly identified variant.

[a]Exome sequencing
[b]Preconceptional analysis with second-generation sequencing identified carriers for several diseases, including congenital hearing loss.
[c]MEX, State of Mexico; MICH, Michoacán; GUA, Guanajuato; CDMX, Mexico City.
[d]NLE, Nuevo León; SLP, San Luis Potosí; TAM, Tamaulipas.
Het, heterozygous; Hom; homozygous
*The authors identified pathogenic variants in 56% of the families, which involved 31 genes; 54% of these alterations have not been previously reported. In the remaining families of this study, mutations in the *OTOGL* and *FAM65B* genes were analyzed as new causes associated with hearing loss with autosomal recessive hearing loss.
**The authors identified 27 unique *SLC26A4* variants in 31 probands.

with 10 genes: 22% with *GJB2,* 16% with *STRC*, and 7% with *SLC26A4*. The latter gene encodes a chloride and iodide transporter and, in general, is the second most frequent autosomal recessive presentation and can also cause Pendred syndrome. Pathogenic variants of the *ECTA* genes corresponded to 5% of cases[28,29]. When these authors studied the molecular etiology in 77 patients with a cochlear implant, 13 (18%) had mutations in *GJB2,* and in eight patients, only one mutated allele was identified. Therefore, they were heterozygous for a known autosomal recessive inheritance pattern, although no other variants in other genes were identified, which was a limitation of this study.

It has been reported that patients with congenital hearing loss associated with *GJB2* mutations respond adequately to cochlear implants[17]. Also, patients with cochlear implants and pathogenic variants have shown variations in the language evaluation test according to the associated genetic alteration[30]. In this regard, studies of biallelic mutations in *GJB2* or *SLC26A4* or of patients with no established genetic cause found that patients with *GJB2* mutations would have better auditive nerve functional status than those with *SLC26A4* mutations when compared to either patients with Mondini malformations and dilated vestibular ducts or patients with idiopathic hearing loss[31-33].

Regarding hearing loss with a non-syndromic autosomal dominant inheritance pattern, it has been noted that the hearing abnormality is often less severe than that present in autosomal recessive conditions and manifests between the ages of 10 and 40 years. Some presentations of hearing loss show a unique profile associated with high-frequency hearing loss, such as some pathogenic variants in *KCNQ4,* a gene encoding a potassium channel. Pathogenic variants in the *WFS1* gene cause low-frequency hearing loss (< 2 kHz), and biallelic mutations in *WFS1* cause Wolfram syndrome, with an autosomal recessive inheritance pattern. The characteristic anomalies of this syndrome are described with the acronym DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). Van Beeck et al.[3] performed a study including image analysis and the clinical and genetic characteristics of 423 children with hearing loss. These authors described that the most common etiology of bilateral hearing loss in 67% of children was a genetic disorder, corresponding to 26% of the cases. In children under one year of age with severe hearing loss, 47% of the cases corresponded to a syndromic presentation, and the rest (53%) presented hearing loss as an isolated alteration.

Moreover, in patients with unilateral hearing loss, a temporal bone anomaly was identified in 27%. When considering children with hearing loss due to genetic etiology, 43% had a family history, 39% had a syndrome associated with sensorineural hearing loss, and 18% showed a known pathogenic variant or mutation; among them, a specific mutation for *SLC26A4* (with an autosomal recessive inheritance pattern) was identified. Finally, a unilateral alteration was identified in 20% of patients and a bilateral alteration in 80%.

The response to cochlear implantation is a particularly relevant aspect concerning the management and treatment of congenital hearing loss of genetic etiology. Only a few studies have been performed in pediatric populations on this feature. In a study to determine the etiological profile of 122 Lithuanian children with cochlear implants, 65 cases (53.3%) were diagnosed as non-syndromic hearing loss; in 58 of them, hearing loss was associated with *GJB2*. In contrast, syndromic alterations were identified in eight children (6.6%). Perinatal risk factors for hearing loss, such as prematurity, low birth weight, hypoxia, hyperbilirubinemia, sepsis, ototoxic agents, and meningitis, were associated with hearing loss in 16 (13.1%) and four (3.3%) patients, respectively. Importantly, cytomegalovirus was detected in 12 samples (9.8%). However, even with these results, the origin of hearing loss could not be identified in 17 children. This analysis concluded that *GJB2* alterations were the most frequent cause of hearing loss and that only 14% of patients in this cohort had hearing loss of unknown etiology[11].

In a similar analysis in Polish children, 196 patients with severe prelingual hearing loss were evaluated[29]. The study described a good response to cochlear implants in 149 children with DFNB1-related hearing loss. Furthermore, better hearing development was described in children who underwent implantation before 12 months of age. This analysis also demonstrated that cochlear implantation was the most successful treatment in patients with hearing loss associated with the DFNB1 *locus*. These findings underscore the importance of determining the molecular genetic etiology in congenital hearing loss.

Molecular profile of hearing loss in Mexico

Few studies have been conducted in Mexico to determine the etiology of congenital hearing loss in the Mexican mestizo population (Table 1). In research

conducted at the Hospital Infantil de México Federico Gómez (HIMFG) in children with hearing loss (Table 1), a population of almost 100 patients was evaluated to establish the cause of the hearing loss[16]. Molecular analysis was performed in 11 patients with a c.35delG homozygous, a c.35insG heterozygous, a c.34G>T heterozygous, and heterozygous patients for the c.79G>A polymorphism, all in *GJB2*, were identified. Interestingly, several factors suggesting non-genetic causes were identified, including a positive TORCH test in 1% and infections or the use of ototoxic drugs in 3% of patients. Regarding this aspect, it is essential to mention that ototoxic drugs only cause hearing damage in patients with specific genotypes[34]. This aspect has been studied in patients requiring the use of aminoglycosides as a treatment for infectious diseases; it has been shown that some genetic alterations in mitochondrial DNA confer greater sensitivity to these drugs and, therefore, to the risk of presenting non-syndromic deafness associated with their use. Several mutations in the 12S rRNA region of mitochondrial DNA have been described in various populations[14,35], including T961insC, T961C, T961+C(n)ins, T1095C, C1494T, and A1555G. However, these pathogenic mitochondrial variants are rare, and their frequency may even vary among different ethnic groups, as has been studied in the Mexican population by Meza et al. (2011)[31]. In their study of 65 subjects, the authors did not identify any previously reported mutation related to aminoglycoside hypersensitivity, and only two of the patients treated with the aminoglycoside streptomycin had a T1189C variant of the previously mentioned 12S rRNA region, which was considered a possible mutation related to the aminoglycoside hypersensitivity.

Molecular genetics research has been conducted on hearing loss etiology in Mexican mestizo populations (Table 1). For example, in a study conducted in northeastern Mexico, a pathogenic variant of *GJB2* was identified in 78 patients. A mutation in *GJB2* was identified in 9.6% of the alleles; c.35delG was the most frequently identified, and six other mutations were also detected. Interestingly, the IVS1+1G>A *GJB2* variant was not detected. This study determined that mutations in the *DFNB1 locus* are a rare cause of autosomal recessive non-syndromic sensorineural hearing loss in this population[21].

In a cohort of patients attending the Hospital General de México Dr. Eduardo Liceaga, mutations in *GJB2*, *GJB6,* and mt.1555A<G were studied, and a double heterozygous (*GJB2*/*GJB6*) was detected in this group, as well as three patients homozygous for c.del35 in *GJB2*, while 26 patients were heterozygous for this gene. Conversely, the mt.1555A<G mutation was not detected. In this cohort, 57.86% of patients showed one or two affected alleles of *GJB2* or *GJB6*[22].

As described in the previously mentioned studies performed in Mexico in specific populations with hearing loss, the most frequent pathogenic variants have been identified in well-known genes such as *GJB2* and *GJB6*. However, it was impossible to identify a genetic alteration in a significant percentage of patients. Therefore, genomic analyses should be performed using next-generation sequencing (NGS) techniques, including gene panels or whole exome, or genome studies[30]. Implementing this technology will allow efficient simultaneous screening of multiple genes[25].

An example of the scope of NGS is that with exome sequence analysis was possible to establish the etiology in 27% of patients in a group of children with development anomalies with no previous diagnosis. Also, genomic studies can provide a timely diagnosis in managing infants in neonatal intensive care units[36]. This situation underlines the importance of using these molecular techniques in diagnosing diseases such as congenital hearing loss in patients without a definitive etiology.

Several populations with congenital hearing loss in different parts of the world have been studied by NGS, including a small group of Mexican patients with congenital hearing loss in whom an alteration in *GJB2* was excluded before NGS. Bademci G et al. studied 160 families (including two of Mexican origin) by exome analysis for all known genes associated with non-syndromic congenital hearing loss[23]. In this research, the authors identified a novel variant c.2959G>A, p.D987N in the *CDH23* gene in one of the Mexican families. Cengiz et al. identified mutations in *SLC26A4* in Mexican patients (Table 1), corresponding to three homozygous and four compound-heterozygous patients[24].

Hernández-Nieto et al.[25] conducted an interesting analysis in which they analyzed data from 805 individuals with NGS (Table 1). The population examined differed from those described in other hearing loss studies since the patients requested a preconception NGS analysis due to genetic counseling. The population analyzed included patients born in Mexico. Different population origins were identified by ancestry analysis, most of them corresponding to the Latino population, and several carriers of other diseases were identified. Among these abnormalities, congenital hearing loss genes were found in 27 cases (3.35%), corresponding to carriers of *GJB2* gene pathogenic variants. This frequency is similar to those reported by other authors in

northeastern Mexico[19,22]. Although it came from a population that consulted for a situation unrelated to congenital hearing loss (among other characteristics that may contribute to some bias of this study), this information is interesting as a reference to the frequency of carriers in the general Mexican population for pathogenic variants of *GJB2*.

Congenital hearing loss is a public health problem in Mexico. As in other populations, its etiology is diverse. Although few studies have been conducted in Mexico, they have shown *GJB2* pathogenic variants, compound heterozygous, and the presence of pathogenic variants in other genes such as *GJB6* or *SLC26A4* in this population; there are also some families with particular characteristics due to the genes involved. Interestingly, the frequency (3.35%) of the c.35delG variant in *GJB2* was found in a population analyzed by exome who consulted for preconception genetic diagnosis[25]. The studies reviewed here indicate the genetic heterogeneity of congenital hearing loss in the Mexican population and the importance of establishing the diagnosis, etiology, and genetic counseling when the most frequent causes have been excluded. Also, the studies showed the implications of genetic diagnosis for patient management, such as that related to cochlear implants. As discussed in this review and summarized in Table 1, the most frequent pathogenic variants associated with hearing loss in the Mexican population are related to the *GJB2* gene, although in a low percentage, followed in frequency by pathogenic mutations in *SLC26A4* and mutations in *CHD23* in third place. Based on these data, a possible diagnostic strategy would be screening for these three genes in Mexican patients. If the result is negative for pathogenic variants at these *loci*, the following step would be a second-generation sequencing analysis focused on panels of genes already associated with isolated and syndromic hearing loss. If these analyses are not informative, second-generation sequencing should be considered, first by whole-exome analysis, and, in the case of negative results, whole-genome sequencing should be performed.

As proposed for other populations[37], these data reflect the importance of genetic evaluation with molecular studies to establish the genetic etiology of congenital hearing loss in Mexican patients.

In conclusion, establishing an etiological cause is critical in the clinical evaluation of infants and children with congenital hearing loss and their families, as has been emphasized by many authors[38]. Identifying underlying causes could help choose rehabilitation strategies, such as hearing aids or cochlear implants. This will provide insights into disease progression, facilitate monitoring of clinical manifestations and associated complications, and provide parents information on the risk of recurrence. Finally, this review is critical because it summarizes all the research conducted in Mexico on the genetic etiology of hearing loss.

Ethical disclosures

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

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

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

Conflicts of interest

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ARTÍCULO DE REVISIÓN

Fibrosis quística: patogenia bacteriana y moduladores del CFTR (regulador de conductancia transmembranal de la fibrosis quística)

*Silvia Y. Vargas-Roldán[1,2], José L. Lezana-Fernández[3,4], Jorge F. Cerna-Cortés[2], Santiago Partida-Sánchez[5,6], José I. Santos-Preciado[1] y Roberto Rosales-Reyes[1]**

[1]Unidad de Investigación en Medicina Experimental, Facultad de Medicina, Universidad Nacional Autónoma de México, Ciudad de México, México; [2]Laboratorio de Microbiología Molecular, Departamento de Microbiología, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Ciudad de México, México; [3]Laboratorio de Fisiología Respiratoria y Clínica de Fibrosis Quística, Hospital Infantil de México Federico Gómez, Ciudad de México, México; [4]Dirección Médica, Asociación Mexicana de Fibrosis Quística, Ciudad de México, México; [5]Center for Microbial Pathogenesis, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, Ohio, Estados Unidos de América; [6]Department of Pediatrics, College of Medicine, The Ohio State University, Columbus, Ohio, Estados Unidos de América

Resumen

La fibrosis quística es una enfermedad hereditaria autosómica recesiva que se origina por mutaciones en el gen regulador de conductancia transmembranal de la fibrosis quística (CFTR, cystic fibrosis transmembrane conductance regulator). El CFTR es una proteína que transporta iones a través de la membrana de las células epiteliales pulmonares. La pérdida de su función conlleva la producción de un moco pegajoso y espeso, donde se pueden establecer y adaptar diversos patógenos bacterianos que contribuyen a la pérdida gradual de la función pulmonar. En este artículo de revisión se dará evidencia de los mecanismos moleculares que utilizan Pseudomonas aeruginosa *y* Burkholderia cenocepacia *para sobrevivir y persistir en el ambiente pulmonar. Adicionalmente, se describirán las nuevas estrategias de terapia a base de moduladores de la función del CFTR.*

Palabras clave: *Fibrosis quística.* Pseudomonas aeruginosa. Burkholderia cenocepacia. *Moduladores de CFTR.*

Cystic fibrosis: bacterial pathogenesis and CFTR (cystic fibrosis transmembrane conductance regulator) modulators

Abstract

Cystic fibrosis is an autosomal recessive inherited disease caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR). CFTR is a protein that transports ions across the membrane of lung epithelial cells. Loss of its function leads to the production of thick sticky mucus, where various bacterial pathogens can establish and adapt, contributing to the gradual loss of lung function. In this review, evidence of the molecular mechanisms used by Pseudomonas aeruginosa *and* Burkholderia cenocepacia *to survive and persist in the pulmonary environment will be provided. Additionally, new therapeutic strategies based on CFTR function modulators will be described.*

Keywords: *Cystic fibrosis.* Pseudomonas aeruginosa. Burkholderia cenocepacia. *CFTR modulators.*

Correspondencia:
*Roberto Rosales-Reyes
E-mail: rrosalesr@ciencias.unam.mx

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Introducción

La fibrosis quística (FQ) es una enfermedad genética con herencia autosómica recesiva que afecta a casi 1 de cada 3000 nacidos vivos en el norte de Europa, aunque su frecuencia varía entre diferentes orígenes étnicos. Por ejemplo, para los Estados Unidos de América, la incidencia es de 1 por 4000 nacidos vivos, mientras que para los hispanos es de 1 por 8000-10,000[1]. En los Estados Unidos de América, la Cystic Fibrosis Foundation[2] reporta que cada año se diagnostican aproximadamente 1000 nuevos casos, con una esperanza de vida de 37 años, mientras que en el Reino Unido la esperanza de vida llega a ser de casi 47 años[3]. En México, en el año 2006, se determinó que la sobrevida promedio de 521 pacientes fue de 17.6 años (intervalo de confianza al 95%: 16.8-18.4)[4].

Patogenia de la fibrosis quística

La FQ se origina por la presencia de mutaciones en el gen CFTR, que codifica para la proteína reguladora de la conductancia transmembranal de la fibrosis quística (CFTR, *cystic fibrosis transmembrane conductance regulator*). Esta proteína transporta iones cloruro y bicarbonato a través de las membranas de las células epiteliales pulmonares[3]. A la fecha se han descrito más de 2000 mutaciones en este gen, aunque la más común es la de fenilalanina en la posición 508 (ΔF508)[5]. La pérdida de la expresión o de la función del CFTR ocasiona que se produzca y acumule un moco deshidratado y pegajoso en las vías respiratorias que gradualmente disminuye el aclaramiento mucociliar, lo que ocasiona obstrucción pulmonar. El cúmulo de este moco propicia que diversos patógenos bacterianos colonicen el tejido y se produzca una infección crónica que conlleva la pérdida de la función pulmonar[3].

Patógenos bacterianos asociados con la fibrosis quística

Los primeros patógenos bacterianos cultivables que se aíslan de las expectoraciones de pacientes con FQ son *Staphylococcus aureus* y *Haemophilus influenzae* no tipificable. Con la edad, *Pseudomonas aeruginosa* se convierte en la bacteria dominante que perdura hasta el final de la vida. Recientemente se ha demostrado que las vías respiratorias de los individuos con FQ también son colonizadas por *Burkholderia cenocepacia,* un patógeno oportunista que contribuye al rápido deterioro de la función pulmonar y a la muerte del individuo afectado[6,7]. Además, las vías respiratorias también pueden ser colonizadas por *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, micobacterias no tuberculosas y hongos[7].

En este trabajo se describen los mecanismos que utilizan *P. aeruginosa* y *B. cenocepacia* para colonizar, adaptarse y persistir en el ambiente pulmonar de los individuos con FQ. Asimismo, se describen las nuevas estrategias de tratamiento basadas en el uso de moduladores y potenciadores de la expresión del CFTR. Esta información pretende ayudar a establecer mejores estrategias de prevención y tratamiento en los individuos afectados con FQ.

Pseudomonas aeruginosa

P. aeruginosa es un patógeno oportunista que puede infectar de forma crónica al pulmón. Se calcula que el 30% de los niños menores de 1 año están colonizados por *P. aeruginosa* y la prevalencia puede alcanzar hasta el 50% durante el tercer año de vida[8]. En México, el 47% de los niños están colonizados por *P. aeruginosa*[9]. La persistencia de *P. aeruginosa* se asocia con un proceso de adaptación que le permite sobrevivir y convertirse en el patógeno dominante en la edad adulta, con una prevalencia de casi el 70%[8,10].

Patogenia de la infección

La adherencia de *P. aeruginosa* a las células epiteliales permite que el *Toll Like Receptor 4* (TLR4) reconozca al lipopolisacárido (LPS) y el receptor TLR5 a la flagelina. Este reconocimiento conlleva que las células epiteliales produzcan interleucina (IL) 6, IL-8, IL-10, factor de necrosis tumoral alfa, IL-17A y pro-IL-1β (Fig. 1 A). Como las bacterias adheridas a la membrana plasmática son rápidamente internalizadas, *P. aeruginosa*, desde su localización intracelular, utiliza el sistema de secreción tipo III (SST3) para inyectar las proteínas efectoras ExoS (activadora de las pequeñas Rho GTPasas), ExoT (con actividad ADP-ribosiltransferasa), ExoU (con actividad de fosfolipasa A_2) y ExoY (con actividad de adenilato ciclasa) al citosol[11,12]. Al mismo tiempo, las moléculas bacterianas, como la flagelina, PscI y PscF (componentes del SST3), logran ingresar al citosol, donde son reconocidas por el inflamasoma NLRC4[13,14]. En contraste, la localización del LPS bacteriano en el citosol conlleva la activación de la caspasa 11 y, a su vez, de la gasdermina D (Fig. 1 A). *P. aeruginosa* produce y secreta la toxina ExlA, la cual, al insertarse en la membrana plasmática, causa un

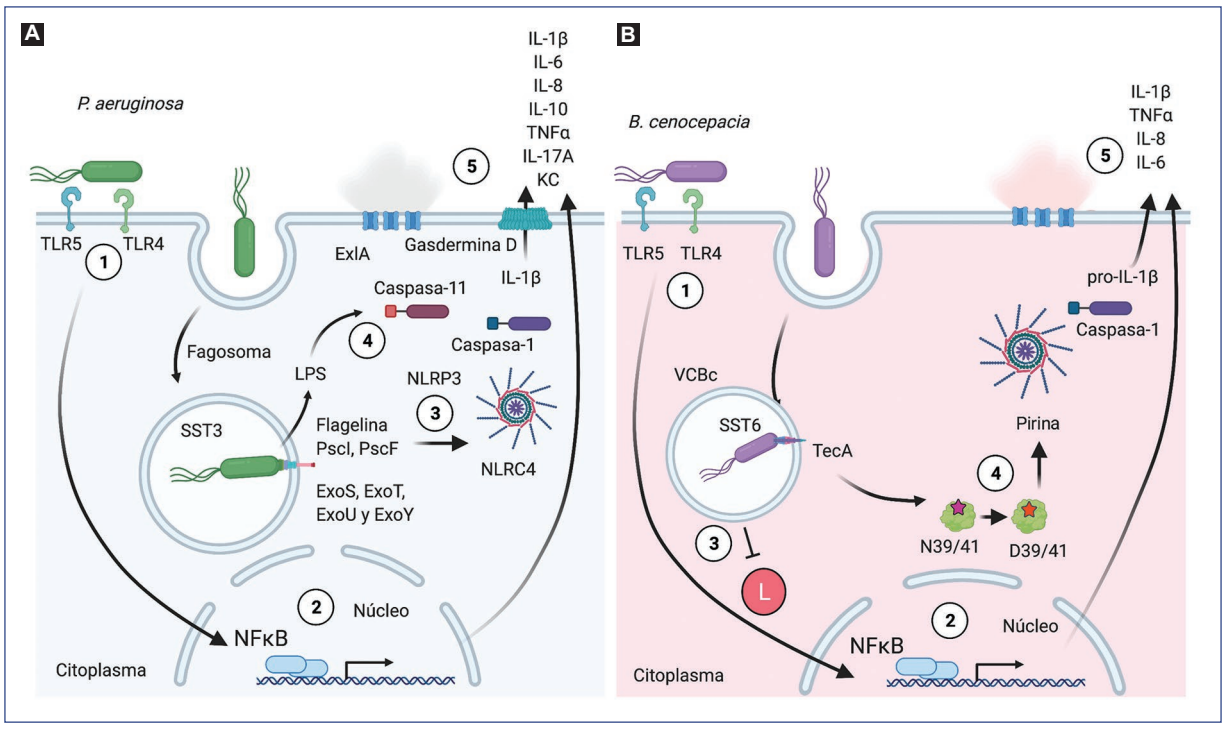

Figura 1. Interacción de *Pseudomonas aeruginosa* y *Burkholderia cenocepacia* con células eucariontes. **A:** al ser reconocida en la membrana plasmática (1), *P. aeruginosa* promueve la síntesis de citocinas proinflamatorias (2). A su vez, el SST3 promueve la liberación de PscI y PscF, proteínas que son reconocidas por el inflamasoma NLRC4 (3). Por su parte, las toxinas ExoS, ExoT, ExoU y ExoY modulan funciones celulares. El lipopolisacárido (LPS) activa a la caspasa-11, y esta, a su vez, a la gasdermina D para generar poros en la membrana plasmática (4). Al formar poros en la membrana plasmática, la toxina ExlA permite la activación del inflamasoma NLRP3, lo cual produce la liberación de IL-1β y la muerte celular por piroptosis (5). **B:** al ser reconocida por TLR4 y por TLR5 en la membrana plasmática (1), *B. cenocepacia* promueve la síntesis de citocinas proinflamatorias (2). La bacteria reside dentro de la vacuola VCBc, desde donde retarda la fusión con los lisosomas (3). El SST6 daña la membrana de la VCBc, lo que activa al inflamasoma NLRP3/ASC (4). Al mismo tiempo, el SST6 transfiere a la proteína efectora TecA, la cual, al desamidar a RhoA, activa al inflamasoma pirina (5), lo que promueve la liberación de IL-1β madura y la muerte celular por piroptosis. Figura generada en BioRender.com.

desbalance iónico que favorece la activación del inflamasoma NLRP3[15].

P. aeruginosa produce tres tipos de exopolisacáridos: alginato, Psl y Pel. Estos dos últimos se relacionan con la formación de agregados de *P. aeruginosa* en el esputo de pacientes con FQ. Por otro lado, se sabe que Pel producido en las vías respiratorias mantiene una carga positiva, lo cual le confiere la capacidad de interactuar con algunos componentes negativos encontrados en la biopelícula, como el DNA extracelular (eDNA). Dicha interacción aumenta la gravedad de la enfermedad, ya que las biopelículas dependientes de Pel secuestran el eDNA en la matriz extracelular y permiten a *P. aeruginosa* una mayor tolerancia al tratamiento con tobramicina. Además, el complejo Pel-eDNA protege al eDNA de la digestión por las DNAasas[16]. Se ha documentado *in vivo* que LasR promueve la secreción de proteasas, por lo que las cepas deficientes (LasR$^-$) no secretan estas proteasas. Las mutantes deficientes en LasR permiten un aumento en la expresión de la molécula celular mICAM-1 *in vivo,* lo que permite un mayor grado de infiltración de neutrófilos y, con ello, un incremento en el daño tisular[17].

Tratamiento con antimicrobianos

El tratamiento contra las infecciones agudas y crónicas por *P. aeruginosa* se basa en la administración oral de fluoroquinolonas[18] y de tobramicina por nebulización[19]. El tratamiento también incluye penicilinas semisintéticas (carbenicilina, ticarcilina y piperacilina), cefalosporinas de tercera generación (ceftazidima) y carbapenemes (meropenem). Los macrólidos no presentan una actividad eficiente debido a que su mecanismo

de acción es muy lento; sin embargo, sí mejoran el pronóstico de los pacientes[20]. Por otra parte, la combinación de una penicilina semisintética y un aminoglucósido mejora la terapia antimicrobiana[21]. La aparición de aislados con resistencia a múltiples fármacos (MDR, *multidrug-resistant*) condujo a que la Organización Mundial de la Salud la clasificara como patógeno de prioridad crítica para la búsqueda de nuevos antibióticos.

Burkholderia cenocepacia

B. cenocepacia forma parte del complejo de *Burkholderia cepacia*. Los miembros del complejo de *B. cepacia* se agrupan en nueve genomovares, de los cuales *B. cenocepacia* pertenece al genomovar III[22]. La colonización pulmonar por esta bacteria es de mal pronóstico. Se sabe que entre el 60% y el 80% de los individuos infectados fallecen al desarrollar el síndrome de cepacia (presencia de neumonía necrosante y sepsis)[22]. Esta bacteria es altamente transmisible entre personas; de hecho, las cepas ET12 y PHDC fueron causantes de brotes epidémicos en centros de FQ de Canadá y Europa[22]. Al parecer, su transmisibilidad se asocia con la expresión de la adhesina denominada cable (Cbl) pili[23].

En México se ha reportado que los miembros del complejo de *B. cepacia* han causado brotes nosocomiales[24,25], y su transmisibilidad se ha asociado con una interacción persona a persona y con la contaminación extrínseca de soluciones parenterales.

Patogenia de la infección

Los pulmones de los individuos infectados con *B. cenocepacia* presentan una intensa respuesta inflamatoria que contribuye a un rápido deterioro de la función pulmonar[22]. El reconocimiento del LPS y la flagelina de *B. cenocepacia* por TLR4 y TLR5 media la producción de IL-1β[26] e IL-8[27] (Figura 1 B). En los macrófagos, *B. cenocepacia* sobrevive en el interior de una vacuola (VCBc), desde donde la bacteria retarda la fusión de la VCBc con los lisosomas a través de la inactivación de la pequeña GPTasa Rab7. *B. cenocepacia* transfiere a TecA al citosol a través del SST6 para inactivar a RhoA y mediar la activación del inflamasoma pirina[28]. La expresión del SST6 inactiva a Rac1 y retrasa así el ensamble y la activación del complejo NADPH-oxidasa en la membrana de la VCBc[29].

Recientemente se demostró que durante la adaptación de *P. aeruginosa* en el microambiente pulmonar, la bacteria deja de expresar SST6, situación que aprovecha *B. cenocepacia*, que transfiere toxinas con su propio SST6 al interior de *P. aeruginosa* para eliminarla de la comunidad polimicrobiana[30], lo que la convierte en el patógeno dominante del ambiente pulmonar.

Tratamiento con antimicrobianos

B. cenocepacia presenta una resistencia intrínseca a los betalactámicos, ceftazidima, meropenem, ticarcilina-clavulanato, levofloxacino, trimetoprima-sulfametoxazol, polimixina B, minociclina y cloranfenicol[31]. El tratamiento contra esta infección incluye al doripenem y la tobramicina[22]; sin embargo, no se observa una mejoría en la función pulmonar. También se han usado combinaciones dobles y triples de moxifloxacino, ceftazidima y metanosulfonato de colistina[31].

Moduladores de CFTR

Se han descrito más de 2000 mutaciones en el gen CFTR en la FQ[5]. Estas mutaciones se han clasificado en seis tipos, acorde con la alteración que se genera en la proteína CFTR: las mutaciones de tipo I y II se caracterizan por la falta de expresión de la proteína; las de tipo III inducen una disminución de la apertura del canal; las de tipo IV generan una conductancia iónica deficiente; las de tipo V originan una reducida expresión de la proteína funcional, y las de tipo VI reducen la cantidad de la proteína funcional en la membrana celular (Figura 2)[32]. El modelado de las proteínas mutadas ha permitido el desarrollo de diversos compuestos para corregir su función. La introducción de moléculas moduladoras de la función de CFTR ha logrado un gran éxito terapéutico[33] y ha permitido un mejor manejo de la enfermedad, ya que estos compuestos representan una alternativa de tratamiento dirigido[34]. A la fecha, existen dos clases de compuestos: los potenciadores, que incrementan la actividad de CFTR y mejoran el transporte de iones, y los correctores, que mejoran el procesamiento del CFTR y dirigen su tránsito celular hacia la membrana plasmática (Tabla 1)[35].

Dentro de los potenciadores se encuentra el ivacaftor (Kalydeco®), aprobado en 2012 para su uso en pacientes mayores de 6 años que portan al menos una mutación de clase III (Figura 2), como la G551D (Tabla 1)[36]. Este fármaco actúa aumentando el flujo de iones cloruro[37]. Al administrarlo a pacientes, se observaron una disminución en la concentración de cloruros en el sudor, una reducción en el número y la frecuencia de exacerbaciones pulmonares, y una evidente mejoría en la función pancreática e intestinal[33]. Actualmente, el ivacaftor se utiliza en pacientes que presentan 38 mutaciones

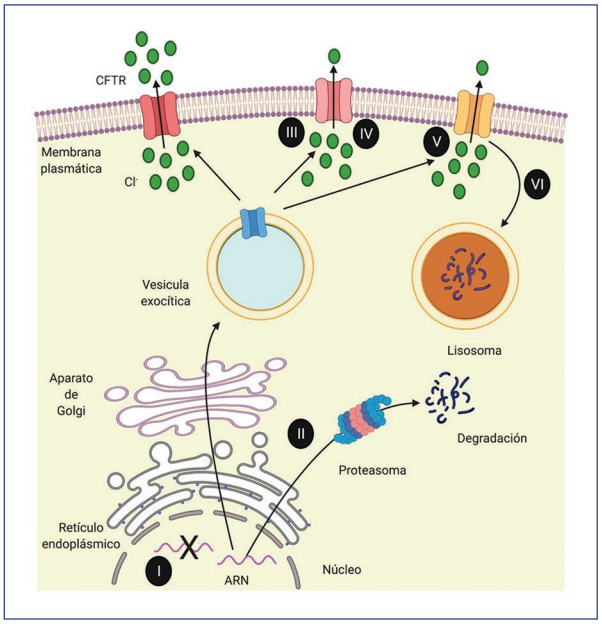

Figura 2. Mutaciones asociadas con CFTR (proteína reguladora de la conductancia transmembranal de la fibrosis quística). Las mutaciones de tipo I impiden la expresión de CFTR; las de tipo II promueven su degradación; las de tipo III producen una apertura reducida de la proteína; las de tipo IV generan una proteína con conductancia iónica deficiente; las de tipo V producen la baja expresión de la proteína funcional, y las de tipo VI presentan una estancia reducida en la membrana plasmática. Figura generada en BioRender.com.

diferentes en CFTR y su uso se ha indicado en niños de hasta 6 meses de edad. Sin embargo, el ivacaftor únicamente cumple su función cuando CFTR se expresa en la membrana celular[34]. El GLPG1877 es un potenciador que se encuentra en fase II de ensayos clínicos en pacientes con mutaciones en G551D y S1251N[38].

Al día de hoy, únicamente tres correctores han sido aprobados por la Food and Drug Administration y se encuentran disponibles para su venta: lumacaftor, tezacaftor y elexacaftor[34]. El lumacaftor (VX-809) es un corrector que aumenta la función de CFTR en células epiteliales bronquiales *in vitro*. En pacientes homocigotos para ΔF508 se observa una disminución en la producción de iones cloruro en el sudor (Figura 2), pero con poco beneficio en la función respiratoria (Tabla 1)[33].

Como los correctores actúan mejorando el plegado y el transporte de CFTR hacia la membrana, aunque sin ejercer un efecto directo sobre la función de esta, se ha optado por utilizar la combinación de potenciadores y correctores[34]. La combinación de lumacaftor con ivacaftor (Orkambi®) ha dado muy buenos resultados. De hecho, se han observado una mejora en la función pulmonar y una reducción de las exacerbaciones pulmonares en pacientes homocigotos para ΔF508[39]. El efecto de Orkambi® también se ha evaluado en la composición microbiana de las vías respiratorias de pacientes adultos con FQ, en los que se observó que dicha combinación, además de restaurar la función del canal de cloruro de manera transitoria, generó un cambio en la composición del microbioma pulmonar, lo cual se evidencia por la disminución de la colonización por *P. aeruginosa* después de 6 meses de tratamiento[40].

El tezacaftor es un corrector de CFTR que actúa aumentando la expresión de la proteína en la membrana celular; generalmente se utiliza en combinación con ivacaftor (Symdeko®) en pacientes homocigotos para ΔF508 a partir de los 6 años de edad. En estos pacientes, la cantidad de iones cloruro producidos en el sudor disminuyó, así como las exacerbaciones pulmonares[33,41]. Es importante mencionar que el tezacaftor es un corrector que aún se encuentra en investigación clínica.

Por otro lado, el elexacaftor es un corrector de CFTR que se utiliza en combinación con tezacaftor e ivacaftor (Trikafta®). Esta combinación condujo a una clara mejoría en las espirometrías, en la función respiratoria y en la reducción de la producción de iones cloruro en el sudor de los pacientes ΔF508[42]. En la actualidad se están realizando estudios para determinar la seguridad de Trikafta® en niños de 6 a 11 años de edad.

La terapia con moduladores y correctores corrige, en gran medida, el tránsito intracelular de CFTR, al mismo tiempo que incrementa su función[32]. El estudio del microbioma antes y después de la terapia con moduladores muestra el impacto considerable de su uso. Por ejemplo, el ivacaftor demostró tener capacidades antiinfecciosas parecidas a las de las quinolonas contra *S. aureus*[43]. Después de 6 meses de terapia con ivacaftor se ha observado una disminución considerable en la positividad del cultivo de *P. aeruginosa*[44]. En un estudio sobre el efecto del tratamiento con ivacaftor durante más de 2 años en la carga bacteriana en el esputo de pacientes de 22 a 57 años de edad, se observó una reducción de la abundancia relativa de *P. aeruginosa;* sin embargo, hubo un aumento de la abundancia relativa de bacterias comensales, como *Streptococcus*[45]. A partir de estos resultados, se infiere que el uso de moduladores de CFTR altera el microbioma de las vías respiratorias como consecuencia de la corrección de la funcionalidad del canal de cloro, lo cual genera una mejoría en el aclaramiento mucociliar, que a su vez reduce la producción de moco pegajoso y deshidratado, y con ello disminuyen la carga bacteriana y el desarrollo de infecciones

Tabla 1. Potenciadores y correctores utilizados en la fibrosis quística

	Clase I	Clase II	Clase III	Clase IV	Clase V	Clase VI
Defecto	Se produce un ARN inestable, por lo que no se produce la proteína	Defecto en la estructura, por lo que la proteína se destruye	Presenta función defectuosa	Presenta una conductancia disminuida	Hay baja expresión de CFTR en la membrana plasmática	Las moléculas desaparecen para ser degradadas en los lisosomas
Mutaciones descritas	G542X, W1282X, del2,3(21kb), R553X	F508del, N1303K, I507del	G551D, G551S, G1349D, S549N, S1251N V520F, R11H	R117H, R334W, R347P, D1152H	3849+10kbC→T, 2789+5G→A, A455E, 2780+5G→A	N287Y, 4326delTC, 427insA
Posible terapia	No existe	Lumacaftor/ ivacaftor, tezacaftor/ ivacaftor	Ivacaftor	Ivacaftor	Tezacaftor/ ivacaftor	Tezacaftor/ ivacaftor

ARN: ácido ribonucleico; CFTR: regulador de conductancia transmembranal de la fibrosis quística.

crónicas[46,47]. Por otra parte, se ha documentado que la combinación de ivacaftor/lumacaftor o ivacaftor/tezacaftor actúa disminuyendo la secreción de IL-18. En particular, la combinación de ivacaftor/tezacaftor disminuye la producción de IL-1β y aumenta la producción de IL-10 en pacientes con FQ[48]. Estos resultados indican que la combinación de estos moduladores contribuye al establecimiento de una respuesta antiinflamatoria. De esta manera, se sugiere que las propiedades antiinflamatorias se relacionan con la modificación del microbioma pulmonar de los pacientes con FQ[47].

A pesar de que la terapia con moduladores y potenciadores contribuye a restaurar la función y el tráfico de CFTR a la membrana plasmática, es importante destacar que no restaura completamente la deficiencia funcional de CFTR, por lo que es necesario que se establezcan nuevas estrategias para mejorar la eficiencia y la estabilidad de los moduladores y potenciadores. Con ello se podrán disminuir la colonización bacteriana y la inflamación pulmonar[47] para mejorar la calidad y la expectativa de vida de los individuos con FQ.

Para concluir, la presencia de mutaciones en CFTR en la FQ conlleva la pérdida de función y la producción de un moco pegajoso que facilita la colonización por *S. aureus, P. aeruginosa* y *B. cenocepacia*. Con frecuencia, estos patógenos se adhieren, adaptan, persisten y generan una respuesta inflamatoria crónica que conduce gradualmente a la pérdida de la función pulmonar, e incrementa el riesgo de muerte del individuo afectado. La erradicación parcial o total de estos microorganismos requiere el uso de antimicrobianos por vía intravenosa o en aerosol. A pesar de esto, los individuos continúan con una deficiencia en la expresión de CFTR, por lo que se sigue generando ese moco pegajoso sobre el cual se establecen nuevas infecciones bacterianas. En los últimos años se ha logrado restaurar la expresión y la función de CFTR con el uso de moduladores y potenciadores, lo que ha mejorado la función pulmonar. Desafortunadamente, aún no se utilizan moduladores que contribuyan a restaurar la función pulmonar en México, por lo que se siguen produciendo infecciones bacterianas que con frecuencia derivan en la muerte del paciente. La terapia utilizada al día de hoy va encaminada a eliminar este tipo de microorganismos con antimicrobianos. En conclusión, el uso combinado de antimicrobianos y de moduladores/potenciadores de CFTR podría contribuir a una mejor función pulmonar en los individuos afectados, así como evitar las exacerbaciones y el riesgo de muerte.

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Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

Responsabilidades éticas

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

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

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

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RESEARCH ARTICLE

Analysis of predictors of response to high-flow oxygen nasal cannula therapy in a pediatric intensive care unit

Irene Baquedano-Lobera[1], *Cristina Bardella-Gil*[2], *and Juan P. García-Iñiguez*[3]

[1]*Servicio de Pediatría, Hospital Clínico Universitario Lozano Blesa;* [2]*Servicio de Pediatría, Hospital Universitario Miguel Servet;* [3]*Unidad de Cuidados Intensivos Pediátricos del Hospital Universitario Miguel Servet. Zaragoza, Spain*

Abstract

Background: *Bronchiolitis is one of the most frequent reasons for admission to pediatric intensive care units. Medical treatment is primarily supportive. The usefulness of high-flow oxygen (HFO) nasal cannula in these patients has been described. This study evaluated the clinical and analytical variables of patients admitted to our Pediatric Intensive Care Unit (PICU) for initiation or continuation of HFO for respiratory distress and to identify any variable that may be a predictor of success or failure of this technique.* **Methods:** *We conducted a retrospective observational study that included infants aged < 24 months admitted to our PICU due to bronchiolitis between January 2015 and March 2019 for HFO.* **Results:** *We analyzed the characteristics between responders (n = 112) and non-responders (n = 37). No statistically significant differences were observed between groups regarding sex, age, weight, comorbidities, nasopharyngeal aspirate result, hours of evolution, and respiratory and heart rate. However, a pCO_2 ≥ 75 mmHg (p = 0.043) and a SCORE of bronchiolitis severity (p = 0.032) were predictors of HFNC failure.* **Conclusions:** *The pCO_2 level and SCORE of bronchiolitis severity are predictors of this respiratory support modality.*

Keywords: *High-flow oxygen nasal cannula. Bronchiolitis. Non-invasive respiratory support. Pediatric Intensive Care Unit (PICU).*

Análisis de factores predictores de respuesta a la oxigenoterapia de alto flujo en una unidad de cuidados intensivos pediátricos

Resumen

Introducción: *La bronquiolitis es uno de los motivos más frecuentes de ingreso en las Unidades de Cuidados Intensivos Pediátricos (UCIP); el tratamiento médico es básicamente de soporte. Se ha descrito la utilidad de la oxigenoterapia de alto flujo (OAF) en estos pacientes. El objetivo de este estudio fue evaluar algunas variables clínicas y analíticas de los pacientes que ingresan en nuestra UCIP para inicio o continuación de OAF ante cuadros de dificultad respiratoria e identificar cualquier variable que pueda ser factor predictor del éxito o fracaso de esta técnica.* **Métodos:** *Se realizó un estudio retrospectivo observacional, incluyendo lactantes menores de 24 meses ingresados en la UCIP entre enero de 2015 y marzo de 2019 para OAF ante cuadros de bronquiolitis.* **Resultados:** *Se analizaron las características entre el grupo de respondedores (n = 112) y no respondedores (n = 37). No se observaron diferencias estadísticamente significativas en cuanto al sexo,*

Correspondence:
*Irene Baquedano Lobera
E-mail: irenebaquedano.l@gmail.com

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edad, peso, comorbilidades, resultado del aspirado naso-faríngeo, horas de evolución, frecuencia respiratoria, frecuencia cardiaca entre ambos grupos. Sin embargo, una pCO_2 ≥75 mmHg (p = 0.043) y un SCORE de gravedad de la bronquiolitis mayor (p = 0.032) fueron factores predictores de fracaso de la OAF. **Conclusiones:** *El nivel de pCO_2 y el SCORE de gravedad de la bronquiolitis son factores predictores de esta modalidad de soporte respiratorio.*

Palabras clave: *Oxigenoterapia de alto flujo. Bronquiolitis. Soporte respiratorio no invasivo. Unidad de Cuidados Intensivos Pediátricos (UCIP).*

Introduction

Acute bronchiolitis is the first episode of respiratory distress with wheezing or decreased alveolar air entry caused by inflammation of the lower airway in infants under two years of age. It is usually preceded by a catarrhal presentation of the upper airways with rhinitis, cough, or fever[1-4]. Its diagnosis is essentially clinical[2,5,6]. Bronchiolitis is a pathology affecting the lower respiratory tract, usually of viral etiology[2,7]. Although most cases are self-limited and can be managed at home, bronchiolitis is the leading cause of hospital admission in infants during the winter months[1,2,8]. Between 1-5% of patients require hospital admission, and 5-15% need respiratory support in a Pediatric Intensive Care Unit (PICU). Acute bronchiolitis is the most frequent infectious cause of hospitalization in infants with no underlying chronic disease[1,7,9,10].

Treatment options are limited as the available evidence does not support the routine use of bronchodilators, anticholinergics, inhaled or systemic corticosteroids, antiviral drugs, or antibiotics. Respiratory support remains the mainstay of treatment due to the lack of effective medications to treat this pathology[2,10-13].

In recent years, high-flow oxygen (HFO) therapy with nasal cannula has been described as a valuable and safe alternative to conventional oxygen therapy to treat these patients[2,8,14,15]. It has been observed that its use reduces the need for invasive and non-invasive respiratory support to treat respiratory distress[12,16-20]. In addition, it could provide adequate comfort with fewer side effects[21-24]. However, as it has not been established in which patients its success may be more likely, it is not known who would be suitable candidates for its application[2,10,24,25].

On this basis, the main objective of this study was to characterize the patients with bronchiolitis in whom HFO is used in our PICU. As secondary objectives, we sought to evaluate the effectiveness of HFO in these patients and the response rate and to analyze possible variables associated with a greater probability of success or failure that could serve as predictors for the management of these patients.

Methods

We conducted a cross-sectional, retrospective, observational study on infants < 24 months (including patients < 28 days) admitted to the Pediatric Intensive Care Unit of the Hospital Universitario Miguel Servet de Zaragoza for respiratory distress between January 2015 and March 2019. We included patients admitted for respiratory distress in the presence of bronchiolitis. We excluded those patients who were already receiving intensive respiratory support (invasive or non-invasive mechanical ventilation) at the time of admission to the unit.

Microsoft Excel and SPSS (Statistical Package for the Social Sciences) for Windows were used to create the database and analyze the data.

The descriptive results were expressed as the arithmetic mean, median, and standard deviation. The Kolmogorov-Smirnov test was used to analyze the distribution of quantitative variables since the sample size was > 30 patients. The variables were considered to follow a normal distribution when a *p*-value > 0.05 was obtained.

HFO success was established when patients did not require intensification of respiratory support and HFO failure in cases where non-invasive or invasive mechanical ventilation was needed. The validated SCORE Wood-Downes-Ferrés bronchiolitis severity scale was applied to all patients to standardize the severity assessment.

For the contrast of hypotheses between two qualitative variables, we applied the χ^2 test. To compare quantitative variables related to the success or failure of the HFO, we used the Student's t-test for variables with a normal distribution or the Mann-Whitney's U test for those variables that did not follow a normal distribution.

To compare two or more quantitative variables, we applied ANOVA if the quantitative variable followed a normal distribution or the Kruskal-Wallis test in the opposite case.

For linear correlation between quantitative variables with normal distribution, Pearson's correlation was

applied, and for correlation between qualitative variables with no normal distribution, Spearman's correlation was used.

The limit of statistical significance accepted for the analysis was 95%. A statistically significant difference was considered when the *p*-value < 0.05.

For the present study, we followed the protocols established by the hospital for access to medical record data, publication of patient data, and divulgation among the scientific community, always respecting patient privacy.

Results

We included 149 patients who received HFO as the first respiratory support therapy on admission (or continued with its application if they had started such treatment in their hospital of origin). The mean age at admission was 4.58 months ± 6.41 (median 2 months), and 60.4% were male and 39.6% female. Clinical variables before the onset of HFO are shown in Table 1.

In 112 patients (75.2%), an adequate response to HFO was observed and did not require escalation to other respiratory support modalities. In 37 patients (24.8%), HFO failed, and escalation or change to another respiratory support modality was necessary.

No statistically significant differences were found in sex, age (in months), age group, and weight between patients who responded adequately to HFO and those in whom this measure failed. There were also no differences in terms of the history of prematurity, respiratory pathology, bronchopulmonary dysplasia, neurological pathology, or cardiac pathology between the responder and non-responder groups. Similarly, no statistically significant differences were found between the two groups in the nasopharyngeal aspirate virus results (Table 2).

Regarding clinical variables before initiating oxygen therapy (respiratory rate and heart rate), it was observed that the group of HFO responders showed lower heart and respiratory rates at admission than the group of non-responders. However, these differences were not statistically significant (Table 3). Regarding gasometry variables, higher pCO_2 levels were found in HFO non-responders than responders (Table 3). However, these differences were not significant (p = 0.083). Given this tendency, we analyzed whether there was a pCO_2 level at which HFO failure could be predicted. We found that a baseline pCO_2 level ≥ 75 mmHg was a predictor of HFO therapy failure (p = 0.043). The SCORE for bronchiolitis severity was significantly higher in the group in which HFO failed than the group in which it was effective (p = 0.032). The SCORE for bronchiolitis severity could also be a predictor of HFO therapy failure (Table 3).

Discussion

Acute bronchiolitis in infants is the leading cause of hospital admission in the winter months, and up to 5-15% of them require admission to a PICU[1,2,7,8].

Recently, HFO with nasal cannula has been described as a valuable and safe alternative to conventional oxygen therapy for treating patients with acute respiratory distress[14]. Multiple studies have concluded the efficacy and adequate clinical response of patients after initiating this respiratory support system[2,11,21-23]. In addition, other reports support this system in an inpatient ward or pediatric emergency room due to the good results obtained and the reduced need for admission to an Intensive Care Unit[8,11,26].

Due to the increased use of HFO in infants with bronchiolitis, research has been conducted to determine which demographic, clinical, or analytical characteristics of the patients could select or predict a greater probability of success when using this respiratory support. It has been described that pCO_2 levels, pH, respiratory rate, and heart rate[14,22,27-29] before initiating HFO therapy may be related to its success or failure.

Here, we analyzed a sample of 149 patients. Most of them were infants < 6 months of age who were admitted to initiating HFO for respiratory failure. In this population, the success rate of HFO was 75%, with 15 patients requiring invasive mechanical ventilation for nonresponse. Other studies have reported a similar response rate (between 60-90%, depending on the source)[3,12,17].

When analyzing patient characteristics, no statistically significant differences were observed between the responder and non-responder groups regarding sex, age (in months), weight, history of prematurity, bronchopulmonary dysplasia, respiratory disease, neurological disease, or cardiac disease. Other studies that also analyzed these differences between responders and non-responders to HFO have reported similar results[14,22,27-29].

Lower heart rate and respiratory rate were observed in patients who responded adequately to HFO compared to non-responders. However, these differences were not significant. In contrast, statistically significant differences in respiratory rate between responders and

Table 1. Variables before starting high-flow oxygen therapy

	Mean	Median	Standard deviation	Min	Max
pCO_2 pre-HFO	58.19 mmHg	56.50 mmHg	17.82	29	123
HR pre-HFO	165 bpm	165 bpm	27	94	257
RR pre-HFO	60 Bpm	60 Bpm	14	22	98
$SatO_2$ pre-HFO	95.85%	97%	5.47	82	100
FiO_2 pre-HFO	0.39	0.35	0.173	0.21	1
SCORE	7	7	2	2	11

HR: heart rate (beats per minute); RR: respiratory rate (breaths per minute); pCO_2: partial pressure of carbon dioxide (mmHg); $SatO_2$: oxygen saturation; FiO_2: fraction of inspired oxygen; SCORE: validated Wood-Downes-Ferrés bronchiolitis severity scale.

Table 2. Distribution of variables between the group of responders vs. non-responders

	HFO success (n = 112)		HFO failure (n = 37)		*p*-value
Sex					
Male	72	64.3%	18	48.6%	0.092
Female	40	35.7%	19	51.4%	
Age (months)	4.40		4.46		0.88
Age (months)					
< 28 days	24	21.4%	8	21.6	0.395
1 – 6	62	55.4%	23	62.2%	
6 – 12	14	12.5%	2	5.4%	
12 – 18	8	7.1%	3	8.1%	
18 – 24	4	3.6%	1	2.7%	
Weight (kg)	5.29		5.16		0.58
History of prematurity					
No	78	70%	24	64.5%	0.588
Yes	34	30%	13	35.1%	
History of bronchopulmonary dysplasia					
No	103	91.7%	34	92%	0.98
Yes	9	8%	3	8.1%	
History of respiratory disease					
No	90	80.4%	30	81%	0.923
Yes	22	19.6%	7	18.9%	
History of cardiac disease					
No	87	77.7%	30	81%	0.662
Yes	25	22.3%	7	19%	
History of neurological disease					
No	98	87.5%	30	81%	0.267
Yes	14	12.5%	7	19%	
NPA					
Negative	26	23.3%	9	28.1%	0.89
Positive	86	76.7%	28	71.8%	

HFO: high-flow oxygen therapy; NPA: nasopharyngeal aspirate.

non-responders were found in other studies[22,27,28] where the respiratory frequency was higher in the group in which oxygen therapy failed. Consistent with other studies[14,22,27], no statistically significant differences were found in heart rate between the HFO responder and non-responder groups.

Differences in pCO_2 levels obtained by measuring blood gases before initiating HFO were also observed in

Table 3. Differences between clinical and blood gas variables among responders and non-responders

	HFO responders	HFO non-responders	*p*-value*
HR (bpm)	160	170	0.521
RR (BPM)	58 ± 14	63 ± 16	0.13
pCO_2 (mmHg)	56.59 ± 15.31	62.54 ± 23.04	0.083
SCORE	6	7	0.032
Hours of evolution	36	48	0.39
$SatO_2$ (%)	97	96	0.425
FiO2	0.35	0.35	0.655
$SatO_2/FiO_2$	279.3 ± 83.2	270.9 ± 82	0.597

FiO_2: fraction of inspired oxygen; HFO: high-flow oxygen therapy; HR: heart rate (beats per minute, bpm); RR: respiratory rate (breaths per minute, bpm); pCO_2: partial pressure of carbon dioxide; $SatO_2$: oxygen saturation; SCORE: validated Wood-Downes-Ferrés bronchiolitis severity scale.
The table shows the means and standard deviations for the variables that follow a normal distribution and the medians for those with a non-normal distribution. Mann-Whitney's U test (nonparametric test), Student's t test (parametric test). *p*-value < 0.05 was considered statistically significant.

this study between responder and non-responder groups. The pCO_2 levels were higher in the nonresponder group than in the responder group. In addition, moderate-severe hypercapnia with a pCO_2 level ≥ 75 mmHg was identified as a predictor of HFO failure (p = 0.043). These results are consistent with other studies[14,22,27], in which elevated pCO_2 levels were also associated with HFO failure.

When analyzing the differences between responder and non-responder groups, the SCORE for bronchiolitis severity was also significantly higher in the group of non-responders (p = 0.032).

In summary, we identified moderate-severe hypercapnia with a pCO_2 level ≥ 75 mmHg and a higher level of respiratory symptoms severity (according to the SCORE Wood-Downes-Ferrés bronchiolitis severity scale) were predictors of HFO failure in a PICU. The rest of the variables analyzed were not related to a higher probability of success or failure of HFO.

Based on these results, initial moderate-severe hypercapnia (pCO_2 level ≥ 75 mmHg) and SCORE of bronchiolitis severity according to the Wood-Downes-Ferrés rating scale are proposed as predictors of HFO failure. The presence of these factors represents a possible risk in the initial evaluation of the patient and increases the probability of requiring intensive respiratory support with non-invasive or invasive mechanical ventilation. However, these data come from a single center. Thus, given the limited sample size, further evidence is required to extrapolate these results and conclusions.

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. This study involved a retrospective review of medical records, for which approval was obtained from a formally constituted review board (Institutional Review Board or Institutional Ethics Committee).

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Effectiveness of kangaroo mother care on maternal resilience and breastfeeding self-efficacy using the role-play method in a neonatal intensive care unit

Fateme Mohammadi[1], Behnaz Basiri[2], Majid Barati[3], Salman Khazaei[4], Seyedeh Zahra-Masoumi[5], Efat Sadeghian[6], Mark Gillespie[7], and Khodayar Oshvandi[8]

[1]Chronic Diseases (Home Care) Research Center and Autism Spectrum Disorders Research Center, Department of Nursing, Hamadan University of Medical Sciences, Hamadan, Iran; [2]Department of Pediatrics, School of Medicine, Fatemieh Hospital, Hamadan University of Medical Sciences, Hamadan, Iran; [3]Department of Public Health, School of Health, Autism Spectrum Disorders Research Center, Hamadan University of Medical Sciences, Hamadan, Iran; [4]Department of Epidemiology, Health Sciences Research Center, Health Sciences & Technology Research Institute Hamadan University of Medical Sciences, Hamadan, Iran; [5]Department of Midwifery, School of Nursing and Midwifery, Mother and Child Care Research Center, Hamadan University of Medical Sciences, Hamadan, Iran; [6]Department of Nursing, School of Nursing and Midwifery, Chronic Diseases (Homecare) Research Center, Hamadan University of Medical Sciences, Hamadan, Iran; [7]School of Health Nursing and Midwifery, University of the West of Scotland, Paisley, Scotland; [8]Department of Medical-Surgical Nursing, School of Nursing and Midwifery, Mother and Child Care Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

Abstract

Background: *Kangaroo mother care (KMC) offers several benefits for neonates and mothers. Although many studies have evaluated the effectiveness of KMC on infants, only few studies have examined the effects on mothers. This study aimed to evaluate the effectiveness of KMC on maternal resilience and breastfeeding self-efficacy via the role-play method in a neonatal intensive care unit.* **Methods:** *We conducted a randomized controlled trial. Mothers were randomized into two groups. Mothers in the intervention group were trained using the role-play method. Questionnaires were administered before and after the intervention. Data were analyzed with SPSS version 22.* **Results:** *The training demonstrated a statistically significant difference in resilience score and breastfeeding self-efficacy in each group after the intervention. In addition, a statistically significant difference was revealed between both groups in resilience scores and breastfeeding self-efficacy after the intervention.* **Conclusions:** *KMC training with the role-play method was most effective. Role-play and routine methods are recommended as methods of therapeutic care in clinical settings to improve maternal resilience and breastfeeding self-efficacy.*

Keywords: *Kangaroo mother care. Role-play. Resilience. Breastfeeding self-efficacy. Neonatal Intensive Care Unit.*

Eficacia de los cuidados madre canguro sobre la resiliencia de la madre y la autoeficacia de la lactancia materna mediante el método de juego de roles en una unidad de cuidados intensivos neonatales

Resumen

Introducción: *El cuidado madre canguro ofrece una gran cantidad de beneficios para el neonato y la madre. Aunque muchos estudios han evaluado la eficacia del cuidado madre canguro en los bebés, solo pocos estudios han examinado los efectos en las madres. El propósito del presente estudio fue evaluar la efectividad del cuidado madre canguro sobre la resiliencia*

Correspondence:
*Khodayar Oshvandi
E-mail: saraghaderi6392@yahoo.com

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de la madre y la autoeficacia de la lactancia mediante el método de juego de roles en la unidad de cuidados intensivos neonatales. **Métodos:** *Se llevó a cabo un ensayo controlado aleatorio. Las madres se asignaron en dos grupos al azar. Las madres del grupo de intervención fueron capacitadas mediante el método de juego de roles. Se aplicaron cuestionarios antes y después de la intervención. Los datos se analizaron utilizando SPSS versión 22.* **Resultados:** *El entrenamiento demostró una diferencia estadísticamente significativa en la puntuación de la resiliencia y la autoeficacia de la lactancia en cada grupo después de la intervención. Además, se reveló una diferencia estadísticamente significativa entre ambos grupos en la puntuación de resiliencia y la autoeficacia de la lactancia después de la intervención.* **Conclusiones:** *La capacitación del cuidado madre canguro mediante el método de juego de roles fue más efectiva. Se recomienda el juego de roles y los métodos de rutina como métodos de atención terapéutica en entornos clínicos para mejorar la resiliencia de la madre y la autoeficacia de la lactancia.*

Palabras clave: *Cuidado madre canguro. Juego de roles. Resiliencia. Autoeficacia de la lactancia. Unidad de Cuidados Intensivos Neonatales*

Introduction

The neonatal period is considered the most critical and essential in growth and development[1] because newborns experience unstable conditions in the first hours and days after birth, challenging them to adapt to extrauterine life. Moreover, preterm infants show a reduced ability to adapt to the surrounding world[1,2]. Consequently, many preterm infants may be admitted to neonatal intensive care units due to respiratory problems, instability in temperature, blood pressure, heart rate, respiratory and cardiac distress, and neurological diseases in the first days of life[3]. Epidemiological studies reveal that 9.6 to 12.9 million premature infants are born annually, accounting for 5-15% of live births worldwide[4]. In this regard, 1.6 million births occur in Iran each year, of which 160,000 newborns are preterm (8-12%) and require specialized care in neonatal intensive care units[3,4].

Mothers of preterm babies are faced with a newborn who needs special equipment and is being cared for to survive. After a complicated delivery process, they experience severe emotional shock. As a consequence of this shock, mothers do not have sufficient capacity and strength to care for the baby[5] since facing a premature baby, or a patient admitted to the Neonatal Intensive Care Unit (NICU) is one of the most sensitive and stressful stages in the life of parents, especially mothers. This confrontation is considered a major emotional crisis and can have adverse and long-term effects on the lives of mothers[6]. The negative impact of preterm birth on mothers consists of feelings of inability and intolerance, incompatibility, sadness, anxiety, fear, worry, guilt, anorexia, failure to breastfeed, depression, and sleep disorders[7,8]. These mothers also experience significant changes in family relationships, work, social activities, family responsibilities, and parenting roles[9].

Seeing a premature infant inside an incubator or warmer under a ventilator or oxygen therapy, with multiple intravenous lines connected, cause these mothers to doubt their ability to care for their babies. As a result, many have not been able to adapt to the baby's condition and needs and have subsequently expressed intolerance to caring for their baby[8]. This is why resilience is an essential concept of positive psychology and refers to the dynamic process of positive adaptation to bitter and unpleasant experiences[10]. Resilience is also defined as measuring a person's ability to cope with stressors and factors that threaten a person's mental health[11]. Therefore, improving resilience and increasing mothers' threshold of tolerance to stressful conditions can moderate their helplessness under stressful situations and boost their mood, mental and physical health, and involvement in caring for their baby[10,11].

Mothers with low resilience are less active in the pediatric section and are not sufficiently involved in caring for their babies and performing their role as mother[12]. In addition, one of the fundamental functions of mother-infant attachment is breastfeeding[13]. Consequently, developing a sense of self-efficacy in breastfeeding mothers of preterm infants improves their ability to care for their infants to achieve a stable condition. In other words, breastfeeding self-efficacy means believing in one's ability to breastfeed and care for the baby[14].

Breastfeeding self-efficacy is influenced by four essential factors, including past breastfeeding experiences, surrogate experiences (observing mothers who have been successful at breastfeeding), verbal encouragement from influential people in the mother's life (spouse, friends, family, and treatment team, especially nurses), and physical and mental illness (postpartum depression, anxiety, and fear)[14,15]. Medical staff, particularly nurses in the NICU, can promote mother-infant interaction and attachment and reinforce resilience and

self-efficacy in breastfeeding. In addition, they can encourage and support them to stay in bed with their baby and engage in care procedures[16,17]. By counseling and assisting the mothers of these infants, nurses can promote a sense of self-efficacy in breastfeeding. Mothers may experience a sense of empowerment, self-efficacy, and reassurance[18].

As mentioned in previous studies, kangaroo mother care (KMC) is one of the most influential participatory care in promoting infant health and improving mothers' sense of empowerment. Kangaroo care involves skin-to-skin contact between mother and infant and addresses infant health, mother-infant relationship, and maternal satisfaction and empowerment[17]. Recent studies examining the effect of KMC on preterm infants and their mothers have been conducted. In particular, research has shown that kangaroo care improves physical health indicators in preterm infants[13,19]. However, as this care is a bidirectional interaction pattern between mother and baby, it may also affect the physical and mental health indicators of the mothers[12,13,19].

KMC stimulates oxytocin secretion and decreases cortisol. As a result of these biochemical changes, the mother's sense of calm, vitality, and pain tolerance is increased, and stress, anxiety, and worry are reduced[20]. However, only a few studies have examined the effects of kangaroo care on mothers, especially on mothers of preterm infants admitted to the NICU[7,18,21]. In this regard, de Macedo et al. (2007), Bigelow et al. (2012), and Faramarzi et al. (2014) have shown that KMC relaxes mothers and helps them feel better, empowers them, and helps them to be more tolerant, reinforcing these feelings[8,17,22]. In addition, Widström et al. (2019), Yilmaz et al. (2020), and Zhang et al. (2020) have reported that kangaroo care increases mothers' confidence in caring for their infants[13,23,24]. These studies also found that mothers needed less help with breastfeeding and demonstrated more self-efficacy in breastfeeding[13]. Most of these investigations evaluated the impact of KMC on resilience and breastfeeding self-efficacy with educational booklets and videos and reported its benefits. Heidarzadeh et al. (2013) and Mohammadi et al. (2021) also found that KMC is a safe, effective, and feasible method of care for low-birth-weight infants that increases maternal engagement in NICU care and leads to successful exclusive breastfeeding, and can be a good substitute for CMC (conventional methods of care) in NICU in Iran[25,26]. However, Namnabati et al. (2016) argued that several challenges are faced for KMC in NICUs in Iran, such as maternal-related and organizational barriers and the need for a physician's order to perform KMC. These cross-cultural differences between Iran and other developed countries, such as the United States, limit KMC in NICUs in Iran[27].

Examining the influence of KMC through role-playing before an actual performance may be practical and valuable for maternal physical and mental health. Since this effect is unknown, we decided to study the influence of KMC on the resilience and self-efficacy for breastfeeding in mothers of preterm infants admitted to the NICU with the role-play method. We hypothesized that KMC through role-playing is more effective than the routine method in increasing the resilience and improving breastfeeding self-efficacy in mothers of neonates admitted to the NICU.

This study aimed to evaluate the effect of kangaroo care through role-playing on resilience and self-efficacy in breastfeeding in mothers of infants admitted to the NICU.

Methods

Study design

From November 2020 to March 2021, we conducted a single-blind randomized controlled trial with an intervention and a control group in a hospital with two NICUs affiliated with the University of Medical Sciences in western Iran.

Ethical considerations

The Ethics Committee approved the study of the Hamadan University of Medical Sciences (Umsha.rec.1399.1042) and prospectively registered in Clinical Trials (number IRCT20190703044082N4). At the beginning of the study, the researcher introduced herself and explained the study's objectives. After providing participants with sufficient information about the study, those who agreed to participate signed an informed consent form. Participants were assured that all information would remain confidential. The researcher offered participants the possibility of withdrawing from the study at any time and assured them that their non-participation or withdrawal would not have any consequences.

Study population and sample size

Mothers of preterm infants admitted to two neonatal intensive care units participated in this study. Inclusion criteria included preterm infants ≤ 1,800 g, an Apgar score ≥ 7 at 5 minutes after birth and ≥ 30 weeks of

gestation. It had to be a delivery of a single, healthy neonate without severe physical disorders and not having undergone surgery. It should be noted that these babies were not undergoing phototherapy. According to the opinion of a medical specialist, the neonate should also be in a condition to leave the incubator and the warmer and had to be able to breastfeed. Mothers' absence of psychiatric problems (depression, bipolar disorder, among others) and the non-consumption of psychiatric drugs and tobacco were also considered. Mothers should be ≥ 18 years of age and able to read and write. Finally, the mothers had to be willing to participate in the study.

Exclusion criteria included the occurrence of unexpected physical problems in the infants during the study, mothers' unwillingness to continue the investigation, death, transfer of the infant to another hospital, and mothers' absence for one day of the intervention (because if the mother did not show up one day, kangaroo care was not performed).

The sample size in this study was calculated according to Yilmaz et al. (with $\beta = 80\%$ and $\alpha = 0.05$)[13]. A total of 78 mothers were randomly assigned to the experimental or control group. The sample size was estimated at 39 individuals with a 10% loss in each group. Three infants in each group were excluded from the study due to changes in physical status or transfer to another hospital (Figure 1).

Recruitment and allocation

After determining the sample size, a total of 78 patients were screened for eligibility; they were then randomly assigned to one of two groups by block randomization with a volume of 2 and an allocation ratio of 1:1 using a computer-generated randomization program stratified by parity (two strata: first and second). This study was conducted in a single-blind manner, so the questionnaires were collected by a researcher unaware of the assignment of individuals to groups.

Intervention

In the experimental group, each mother attended two 30-minute individual sessions in the hospital conference room. These mothers were taught how to hold a baby dummy in their arms. To do this, the researcher first talked to the mothers in this group and answered their questions about how to care for, hold, look at, and cuddle the baby. The researcher then helped them wear a particular blouse designed according to the KMC standard and protocol. These blouses mainly were loose-fitting, with short sleeves and buttons on the front of the garment that could be easily opened and closed. The mother would then sit in a chair in whatever position she felt comfortable for the next steps. The researcher placed the model baby with only a cap and diaper upright position between the mother's breasts to teach her kangaroo care. After this step, the researcher closed the bottom buttons of the mother's blouse. The model dummy was entirely placed between the mother's breast and the cloth, reducing the possibility of falling and hypothermia. The researcher then stood next to the mother and asked her to try to make eye contact with the model while smiling, looking, caressing, and talking to the model baby. After training in embrace care by role-playing method, mothers in the intervention group performed this training three times a day (once per shift) for 30 minutes for 7 days with full supervision and accompaniment by the researcher. Mothers in the control group received a booklet training routine. All mothers completed the questionnaires several times: before the intervention, one day after, and one week after discharge. These questionnaires were applied by a researcher unaware of the allocation of individuals into the intervention and control groups.

Connor and Davidson Resilience Scale

We used the scale designed by Connor et al. (2003) in the United States to measure resilience[28]. This scale has 25 questions on five areas: individual and general competence (eight questions), tolerance to adverse effects and strength against stress (seven questions), positive acceptance of the change (five questions), self-control (four questions), and spiritual impact (five questions). The questions of this scale are scored from zero (completely incorrect) to four (always correct) according to Likert scores. The maximum score for this questionnaire is 100, and the minimum score is zero. Higher scores indicate more resilience. The face validity, content, and reliability of this questionnaire have been estimated by Ahangarzadeh et al. (2015). This study mentioned that the reliability of this instrument had been reported through Cronbach's alpha method with a value of approximately 0.82[29].

Breastfeeding self-efficacy questionnaire

One of the most important instruments to measure breastfeeding self-efficacy in this study was the Breastfeeding Self-Efficacy Scale designed in 1999 by Dennis. This instrument can measure the confidence

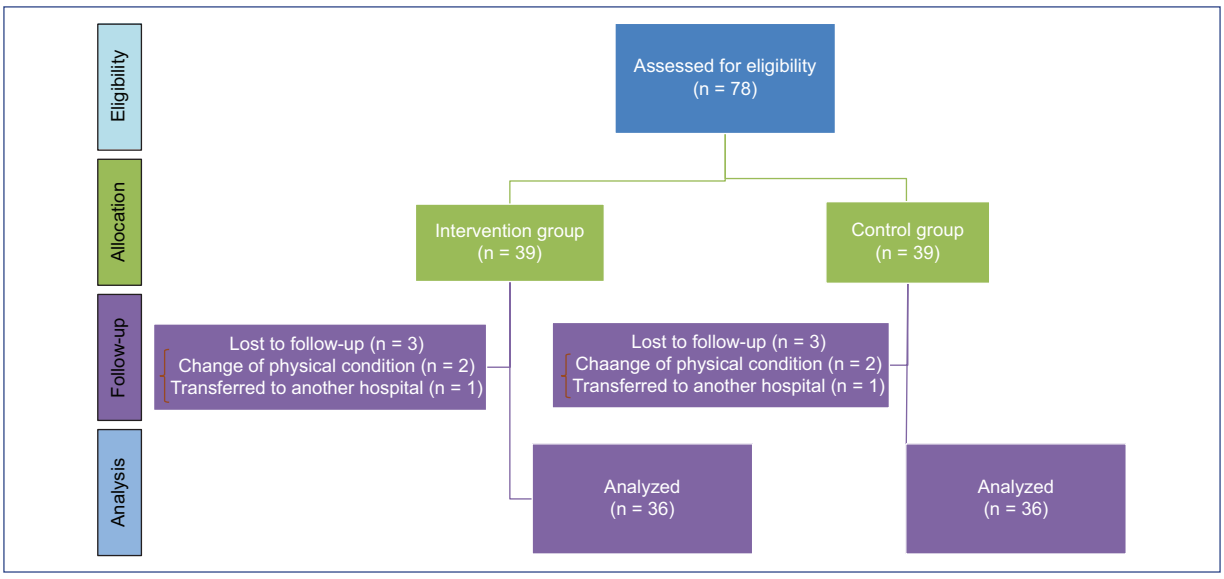

Figure 1. Study design flow chart.

and ability of breastfeeding mothers based on 5-point Likert-type items through 33 questions: 1 strongly disagree to 5 strongly agree. All questions in this questionnaire are positive, and the score range is 33 to 165. A higher score indicates higher self-efficacy for breastfeeding in mothers. Dennis performed face validity, content, and reliability of this questionnaire, and its reliability was estimated at 0.96 by Cronbach's alpha method[30]. In Iran, Farhadieh et al. evaluated this questionnaire's face validity, content, and reliability and considered it a suitable instrument for research[31].

Data analysis

Data were analyzed with SPSS version 22 software. Descriptive statistics (frequency, percentage, mean, and standard deviation) were used for this purpose. After confirming the normal data distribution by the Kolmogorov–Smirnov test, the paired t-test was used to compare the mean of resilience and breastfeeding self-efficacy between the two groups on three measures. Finally, repeated measures analysis of variance was used to compare the mean of resilience and breastfeeding self-efficacy in each group three times of measurement. The statistical significance value was considered as 0.05.

Results

Most of the mothers in this study were graduates and self-employed. The mean age of the mothers was 37.31 ± 1.57 years in the intervention group and 37.42 ± 1.41 in the control group; the mean monthly income of the participants was $120 in both groups.

Most of the neonates in both groups were male. Their mean weight of the infants was 1721.42 ± 1.92 g in the intervention group and 1756.21 ± 1.74 g in the control group, and their mean gestational age was 31.42 ± 1.52 weeks in the intervention group, and 31.61 ± 1.06 weeks in the control group. No statistically significant differences were observed in the distribution of demographic characteristics between the two groups ($p > 0.05$) (Table 1).

Resilience in mothers of premature neonates

Before the intervention, the resilience score in both groups was not statistically significant ($p = 0.71$). However, repeated measures analysis of variance demonstrated a statistically significant difference in the resilience score in each group one day and one week after performing the intervention ($p < 0.001$). Cohen's d for resilience in the intervention and control groups showed the high impact of the intervention. Moreover, the independent t-test revealed a statistically significant difference between both groups in the resilience score one day and one week after the intervention ($p \leq 0.01$). Therefore, the role-playing method was more effective than the routine method (booklet training) (Table 2).

Table 1. Demographic information of the participants

Variable	Intervention group, n (%)	Control group, n (%)	*p*-value
Mother's age (years)			
24-33	11 (28.20)	12 (30.77)	0.87*
34-44	16 (41.03)	16 (41.03)	
45-55	12 (30.77)	11 (28.20)	
Mother's education			
Illiterate	2 (5.12)	3 (7.69)	0.79**
Primary	11 (28.21)	12 (30.78)	
Diploma	18 (46.15)	17 (43.58)	
Bachelor	7 (17.95)	6 (15.38)	
Master's degree and higher	1 (2.57)	1 (2.57)	
Father's education			
Illiterate	3 (7.69)	3 (7.69)	0.77**
Primary	10 (25.64)	12 (30.78)	
Diploma	18 (46.16)	18 (46.15)	
Bachelor	5 (12.82)	4 (10.26)	
Master's degree and higher	3 (7.69)	2 (5.12)	
Mother's job			
Self-employed	11 (28.21)	13 (33.34)	0.71*
Employee	10 (25.64)	9 (20.51)	
Housewife	18 (46.15)	18 (46.15)	
Father's job			
Self-employed	19 (48/71)	18 (46.15)	0.77*
Employee	7 (17.95)	7 (17.95)	
Livestock and farmer	13 (33.34)	14 (35.90)	
Number of children			
2	19 (48/71)	19 (48/71)	0.89*
3	13 (33.34)	14 (35.90)	
≥ 4	6 (15.38)	5 (12.82)	
Sex of neonates			
Male	20 (51.29)	21 (53.85)	0.98*
Female	19 (48/71)	18 (46.15)	
Gestational age (weeks)			
30-33	21 (53.85)	20 (51.29)	0.98*
34-36	18 (46.15)	19 (48/71)	

*x^2 test; **Fisher exact test.

Breastfeeding self-efficacy in mothers of premature neonates

At the beginning of the study, mothers in both groups showed a poor performance in breastfeeding self-efficacy, with no statistically significant difference between their breastfeeding self-efficacy scores (p = 0.83). However, after KMC training, mothers in both groups made significant progress in their breastfeeding self-efficacy scores. Intragroup comparison of the breastfeeding self-efficacy scores was statistically significant in each group (p = 0.001), demonstrating that KMC education by both methods (role-playing and routine) was effective. In addition, Cohen's d for breastfeeding self-efficacy in the showed the high impact of the intervention. Furthermore, a statistically significant difference was observed between both groups one day and one week after performing the intervention (p = 0.01). Hence, the role-playing method proved more effective than the routine method (booklet training) (Table 3).

Discussion

The results of the present study revealed that role-playing and routine methods effectively promote resilience and breastfeeding self-efficacy. However, the two groups showed statistically significant differences in improving resilience and breastfeeding self-efficacy. The role-play method seems more effective than the routine method in promoting resilience and breastfeeding self-efficacy in mothers of premature infants in the NICU.

Table 2. Comparison of resilience scores between both groups

Study days / Study groups	Before intervention Mean (SD)	One day after intervention Mean (SD)	One week after intervention Mean (SD)	F, mean difference, *p*-value for time* group
Control group	43.74 ± 3.46	54.65 ± 3.22	66.43 ± 3.42	10.75, 0.67, 0.001**
Intervention group	43.84 ± 3.96	87.87 ± 3.22	92.74 ± 3.11	29.54, 0.82, 0.001**
t, mean difference, *p*-value	0.01, 1.02, 0.71*	33.22, 2.76, < 0.01*	26.31, 3.98, < 0.01*	

SD, standard deviation.
*Student's t-test; **Repeated measure test.

Table 3. Comparison of breastfeeding self-efficacy scores between both groups

Study days / Study groups	Before intervention Mean (SD)	One day after intervention Mean (SD)	One week after intervention Mean (SD)	F, mean difference, *p*-value for time* group
Control group	23.14 ± 2.76	62.95 ± 2.12	73.65 ± 2.76	10.32, 0.69, 0.001**
Intervention al group	23.32 ± 2.96	91.17 ± 2.41	112.04 ± 2.31	24.51, 0.81, 0.001**
t, mean difference, *value**	0.26, 1.42, 0.83*	28.22, 3.64, < 0.01*	38.39, 4.14, < 0.01*	

SD, standard deviation.
*Student's t-test; **Repeated measure test.

In the literature, we found no data on the effect of KMC training by role-play method on resilience and breastfeeding self-efficacy in mothers of premature neonates. Therefore, the impact of KMC on resilience and breastfeeding self-efficacy is discussed broadly as follows.

Consistent with our findings, Ghazi et al. (2021) stated that a home visiting program based on the continuation of KMC positively affected maternal resilience in mothers of premature infants. These authors found a statistically significant difference in mothers' mean resilience score one month after discharge between the intervention and control groups[32]. Although the results of this study show the efficacy of KMC in improving maternal resilience, the researchers taught KMC to mothers only with the routine method (booklet training), and the experimental group continued the KMC after discharge at home. Murty et al. (2018) found that KMC improves the resilience of families with low-birth-weight infants. Home-based KMC motivates families to manage problems effectively, ultimately saving the newborn from neonatal death[10]. This finding indicates that KMC is an effective method for improving the tolerance and resilience of families, especially mothers with preterm and low-birth-weight infants, consistent with our results. However, in the same study by Murty et al., mothers were also trained in KMC only with the routine method (booklet training)[10]. It seems that if education is conducted with more objective and effective methods, such as role-playing, it can help families manage the preterm birth crisis and increase tolerance and resilience more effectively.

Furthermore, in line with the present study, Rossman et al. (2017) remarked that the mother's training and ability to care for her infant in the NICU positively affect maternal resilience and adaptability to conditions[11]. Herizchi et al. (2018) also showed that KMC improved maternal adaptability and tolerance. Thus, the authors suggest that KMC be taught continuously and with more efficient training methods to mothers of premature infants to promote maternal adaptation and improve the newborn's condition[33].

This study showed that breastfeeding self-efficacy of mothers of preterm infants admitted to the NICU improved in both the role-playing and routine education groups. However, the best results in promoting breastfeeding self-efficacy were observed in the role-play group. Although many studies have examined breastfeeding self-efficacy in mothers of term infants, few studies have examined the effect of KMC on breastfeeding self-efficacy in mothers of preterm infants admitted to the NICU. In this regard, Zhang et al.

demonstrated that mothers in the intervention group (KMC) reported higher frequency and quality of breastfeeding than the control group. Therefore, it can be said that KMC significantly improved the number and quality of breastfeeding in mothers of preterm infants[24], consistent with our observations. However, in the present study, the mean score of breastfeeding self-efficacy was higher in both groups. A possible explanation could be a difference in how KMC is taught.

Also consistent with the present study, Yilmaz et al. reported that KMC effectively promotes breastfeeding self-efficacy and creates a sense of empowerment in mothers, which consequently helps them to achieve better infant development[13]. Our results are consistent with published evidence reporting that frequent skin-to-skin contact between mother and infant is crucial for the successful transition to direct breastfeeding in preterm infants[6,24,30,34] and the initiation of exclusive breastfeeding in healthy full-term infants[13,24].

One of the notable limitations of the present study was the small sample size of the participants. Therefore, similar studies in different communities and with larger samples are recommended in future years. Moreover, in this study, mothers were followed up for one week after the intervention; we suggest following the effect of KMC on breastfeeding self-efficacy in mothers of preterm infants for more weeks.

This study showed that teaching KMC through role-playing and routine methods effectively promotes resilience and breastfeeding self-efficacy. However, the role-play method is more effective than standard methods in promoting resilience and breastfeeding self-efficacy. We recommend role-playing and routine methods as therapeutic care methods in clinical settings at the beginning of infants' admission to the NICU to improve maternal resilience and breastfeeding self-efficacy.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Perception of neonatology staff regarding the availability of equipment and supplies for the care of patients in need of nCPAP

Lorenzo Osorno-Covarrubias[1], Raúl Villegas-Silva[2], Alma Sánchez-de la Vega[3], Francisco J. Vázquez-Cortés[4], Raúl H. Muro-Flores[5], and Daniel Martínez-Sánchez[6]*

[1]Servicio de Pediatría, Neonatología, Hospital Star Médica, Mérida, Yucatán; [2]Servicio de Neonatología, Hospital Infantil de México, Federico Gómez, Mexico City; [3]Servicio de Neonatología, Hospital General de Tampico, Tampico, Tamaulipas; [4]Consulting board, Federación Nacional de Neonatología de México; [5]Servicio de Neonatología, Hospital General de Zona 46, Dr. Bartolomé Reynés Berezaluce, Instituto Mexicano del Seguro Social, Villahermosa, Tabasco; [6]Servicio de Neonatología, Hospital Materno Infantil Instituto de Seguridad Social del Estado de México y Municipios, Toluca, State of Mexico. Mexico

Abstract

Background: *Respiratory distress syndrome (RDS) is Mexico's second leading cause of neonatal mortality. The 75% reduction in mortality due to RDS has been attributed to the use of nasal continuous positive airway pressure (nCPAP). A survey was conducted to determine the perception of the medical staff regarding the availability of nCPAP equipment and supplies in Mexican hospitals with neonatal intensive care units (NICUs).* **Methods:** *We sent a survey via e-mail to several neonatologists in each state of the country, requesting only one response per hospital. We performed statistical analysis with SPSS software.* **Results:** *We received 195 surveys from private (HPri) and public (HPub) hospitals with NICUs nationwide: 100% of HPri and 39% of HPub. More than 75% of the nursing and medical staff had received formal training in nCPAP in 11% of HPri and 5% of HPub. The perceived availability of CPAP equipment was 83.7% vs. 52.1%; nasal cannula supply, 75.5% vs. 36.3%; air/oxygen blender availability, 51.0% vs. 32.9%, in HPri and HPub, respectively. The observed differences were statistically significant. Significant differences were also found among healthcare institutions.* **Conclusions:** *The availability of CPAP equipment and consumables between HPub and HPri is unbalanced and is lower in public institutions. Bubble CPAP is not included essential equipment in the national catalog of instruments and equipment for public hospitals, and its request is complicated. The training of CPAP staff and the availability of bubble CPAP and supplies in public hospitals should be improved.*

Keywords: *Respiratory distress syndrome. Nasal continuous positive airway pressure. Newborn. Hospital equipment and supplies. Secondary and tertiary care hospital. Neonatal care.*

Percepción del personal de neonatología sobre la disponibilidad de equipo e insumos para la atención de pacientes con necesidad de nCPAP

Resumen

Introducción: *El síndrome de dificultad respiratoria (SDR) es la segunda causa de mortalidad neonatal en México. La reducción del 75% de la mortalidad por SDR se le ha atribuido al uso de la presión positiva nasal continua de las vías respiratorias (nCPAP). Se realizó una encuesta con el objetivo de conocer la percepción del personal médico acerca de la disponibilidad del equipo e insumos para nCPAP en hospitales de México que cuenten con unidades de cuidados intensivos*

Correspondence:
*Lorenzo Osorno-Covarrubias
E-mail: lorenzo.osorno.covarrubias@gmail.com

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neonatales (UCIN). **Métodos:** *La encuesta se envió por correo electrónico a varios neonatólogos de cada estado del país y se solicitó una sola respuesta por cada hospital. El análisis estadístico se realizó con el software SPSS.* **Resultados:** *Se recibieron 195 encuestas respondidas tanto de hospitales privados (HPri) como públicos (HPub) que cuentan con UCIN a escala nacional: el 100% de HPri y el 39% de HPub. Más del 75% del personal de enfermería y médico recibió una capacitación formal en nCPAP en el 11% de HPri y el 5% de HPub. La percepción de disponibilidad de equipos de presión positiva continua de las vías respiratorias (CPAP) fue del 83.7% vs. el 52.1%; el abasto de cánulas nasales, del 75.5% vs. el 36.3%; la disponibilidad del mezclador aire/oxígeno, del 51.0 % vs. el 32.9%, en HPri y HPub, respectivamente. Las diferencias fueron estadísticamente significativas. También se encontraron diferencias significativas entre las instituciones de salud.* **Conclusiones:** *La disponibilidad de equipo y material de consumo para CPAP entre HPub y HPri es desequilibrada, y es menor en las instituciones públicas. El CPAP burbuja no se encuentra incluido en el cuadro básico de equipo médico y se dificulta su solicitud. Debe mejorarse la capacitación del personal en CPAP y la disponibilidad de CPAP burbuja e insumos en los hospitales públicos.*

Palabras clave: *Síndrome de dificultad respiratoria. Presión positiva continua en la vía aérea nasal. Recién nacido. Equipo e insumos hospitalarios. Hospital segundo y tercer nivel. Cuidado neonatal.*

Introduction

Respiratory distress syndrome (RDS) continues to be a leading cause of neonatal mortality and morbidity in many countries worldwide[1-4].

In the United States, mortality due to RDS decreased by 95% between 1970 and 2005. During this period, RDS dropped from being the first to the eighth leading cause of neonatal death[5,6]. Between 1970 and 1985, 75% of this decrease occurred when continuous positive airway pressure (CPAP) was initiated for neonates with RDS before surfactant therapy became available. Non-invasive use through a nasal cannula (nCPAP)[7] began in 1974. Other improvements in care that contributed to reducing mortality were the development of ventilators designed for neonates (in the 90s), exogenous surfactants, and, more recently, the development of ventilators with gentler ventilation modes[5].

In Mexico, mortality due to RDS decreased 46% from a rate of 2.6 to 1.4/1,000 live births between 1998 and 2017[8,9]. In many hospital centers, RDS is no longer among the leading causes of death[10,11]. However, in the Instituto Mexicano del Seguro Social (IMSS), RSD is still the second leading cause of neonatal mortality nationwide[12]. Despite advances in its management, mortality due to RDS in Mexico is 13.5 times higher than in the United States (1.4/1,000 live births vs. 0.103/1,000 live births)[13].

Furthermore, the decrease in RDS mortality is accompanied by an increase in bronchopulmonary dysplasia (BPD), a condition that is a frequent consequence in RDS survivors worldwide. Mechanical ventilation plays a predominant role in the generation of BPD[14,15].

Early use of CPAP at birth reduces the need for mechanical ventilation and decreases the combined outcome of BPD or death[16]. According to some reports, the rate of BPD is two to three times higher than in developed countries[17-19].

In Mexico, retinopathy of prematurity (ROP) is associated with mechanical ventilation, uncontrolled oxygen exposure, and prematurity. ROP is 2.4 times higher than in developed countries and is also the cause of infant blindness in 34% of those attending schools for the blind[20,21].

Continuous flow devices can generate positive airway pressure: bubble CPAP, conventional ventilator-generated CPAP, and variable flow devices.

Bubble CPAP is the most efficient and inexpensive of these devices[22]. It consists of an air/oxygen mixer, a flowmeter, a servo-heated humidifier, an inspiratory circuit with a heating cable to reduce condensation, and an interface for its application in the neonate (nasal cannula or nasal mask) with its fixation system. It also has an expiratory circuit at its distal end connected to the pressure generator, which consists of a bottle with distilled water where the end of the expiratory course is submerged as many centimeters as centimeters of water pressure are desired to be generated. It is essential to have each one of its components for its correct operation (Figure 1).

Since the late 70s, bubble CPAP has been used in developing countries by adapting a nasal cannula and a circuit to a nebulizer.

Unfortunately, it is often misused: without the air/oxygen mixer because there is no mixer in each oxygen port, and there is only one mixer on mechanical ventilators. For approximately 15 years, bubble CPAP devices with all the required elements and safety measures have been marketed in Mexico, but their use is not widespread.

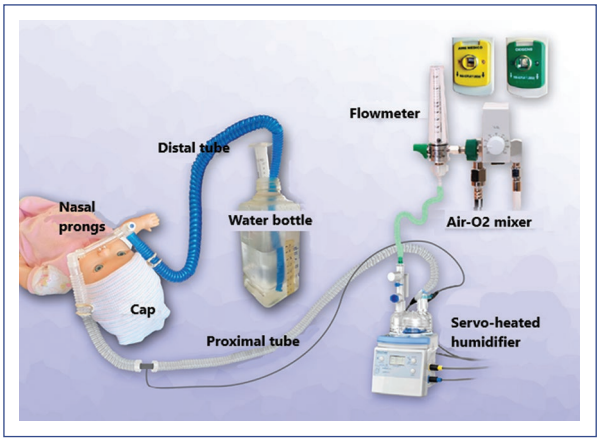

Figure 1. Components of bubble CPAP (continuous positive airway pressure).

In the treatment guidelines for this disease, which have been developed in different countries, including Mexico, CPAP is the treatment of choice for stabilizing newborns. CPAP should be started early to reduce morbidity and mortality due to this disease and reduce the possibility of reintubation after extubation[23-25]. Since the equipment and supplies necessary for its use are suspected to be not adequately provided in the numerous neonatal care centers in the country, the Commission on CPAP and Best Practices for Ventilatory Support in Neonates of the National Federation of Neonatology of Mexico (Federación Nacional de Neonatología de México) decided to investigate the availability of CPAP equipment and supplies.

This study aimed to determine neonatal medical personnel's perception of the availability of CPAP equipment and supplies in public and private secondary and tertiary level hospitals in Mexico.

Methods

To know the perception of the availability of equipment and supplies to provide nCPAP in Mexican hospitals with neonatal intensive care units (NICU), we developed a survey using Google forms. The link to answer the survey was sent to the presidents of the associations belonging to the Federación Nacional de Neonatología de México A.C. in each state of the country. They were asked to answer the questions related to the hospital(s) in which they worked and to send this link to their colleagues in public and private hospitals at the secondary and tertiary levels of care in the different health institutions in their city or state. One response per hospital was requested, and those who responded were followed up. Survey responses were received between June 16 and August 31, 2021.

The survey consisted of 27 questions. The demographic questions were about professional training (neonatologist, pediatrician, nurse, other), working hospital, level of care (public tertiary level, public secondary level, private tertiary level, private secondary level), affiliation institution (IMSS, Instituto de Salud para el Bienestar [INSABI], State or Municipal Secretariat, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado [ISSSTE], PEMEX, SEDENA, SEMAR, or private), number of births/year, percentage of premature births, and state of the republic.

The dichotomous questions (with YES or NO answers) were the following:

1. Does the delivery room have CPAP?
2. Does the delivery room have an air/oxygen mixer?
3. Does the delivery room have a pulse oximeter?
4. Is there a CPAP for transfer?
5. Is the number of equipment to provide CPAP in the NICU sufficient for the demand for care?

The same questions were asked for the delivery room and intermediate care areas:

1. Do all CPAP devices have an air/oxygen mixer?
2. Is a complete tower to provide CPAP (CPAP equipment integrated into a rolling pedestal with all its components) available?

Regarding consumables, the questions were as follows:

1. Is the supply of *nasal cannulae* sufficient and timely?

The same question was asked for caps, circuits, CPAP generators, and surfactants.

Response options were based on an analog scale from 1 to 5 with extreme values of 1-never and 5-always. This variable was re-coded as a dichotomous variable, assigning the values 1 to 3 as NO and 4 to 5 as YES, to unify the presentation of the responses and facilitate analysis.

The nominal questions (with response options) were as follows:

1. What device do you primarily use to provide CPAP? Bubble, ventilator-generated, variable flow, invasive/non-invasive ventilator.
2. What type of nasal cannula do you primarily use? Hudson, Fisher & Paykel, Drager, or others.
3. What surfactant do you use? Beractant or poractant.
4. Is CPAP equipment provided by purchase, commodate, or both?
5. Are consumables supplied by purchase, commodate, or both?

6. The usual surfactant application technique in your unit is INSURE, LISA, or conventional intubation-ventilation-extubation?
7. The percentage of healthcare staff (medical and nursing) formally trained in CPAP is less than 25%, 25-50%, 50-75%, or more than 75%?

One of the authors captured the responses and exported them to the SPSS statistical program (IBM Statistics SPSS 20) for descriptive and comparative analysis. The χ^2 test was performed to compare equipment and provision of CPAP supplies in public and private hospitals, by the level of care, and by the healthcare institution. A p-value < 0.05 was considered statistically significant. The percentage difference in responses between public and private hospitals was calculated. The 95% confidence intervals (95%CI) were calculated on the Statology.org website[26].

The percentage of hospitals surveyed in relation to the total number of hospitals with public and private NICUs in Mexico was calculated according to data from the Dirección General de Información en Salud (DGIS) and the Instituto Nacional de Estadística y Geografía (INEGI), respectively[27,28].

Results

A total of 241 surveys were received from 195 hospitals. Only one survey per hospital was included. We excluded 18 surveys sent more than once by the same respondent in the same hospital, 26 repeated surveys from the same hospital by different respondents, and two incomplete surveys (multiple or essential items unanswered). The exclusion of repeated surveys from the same hospital sent by different respondents was based on the following criteria: key or multiple unanswered items and inconsistencies with other responses from the same hospital. When more surveys from the same hospital remained after applying the above criteria, only one survey was randomly selected.

Surveys were received from 30 states in Mexico with a mean ± standard deviation (SD) of 6.5 ± 4.7 hospitals per state.

According to data from the DGIS, 368 public hospitals with NICUs are registered in Mexico[23]. A total of 195 hospitals were surveyed, representing 39% of those with NICUs.

From January 1, 2020, SSA hospitals and several hospitals of the State and Municipal Health Secretariats became part of INSABI, so they were grouped in this classification.

Table 1. Surveyed hospitals classified by health institution and level of care

Healthcare institution	n	%
State or Municipal Health Secretariat	60	30.8
Private	50	25.6
IMSS	41	21.0
ISSSTE	19	9.7
INSABI	18	9.2
PEMEX, SEDENA, SEMAR	5	2.6
IMSS Bienestar	2	1.0
Total	195	100
Level of care	**n**	**%**
Public		
Tertiary level	35	17.9
Secondary level	110	56.4
Private		
Tertiary level	22	11.3
Secondary level	28	14.4
Total	195	100

IMSS: Instituto Mexicano del Seguro Social (Mexican Social Security Institute); INSABI: Instituto de Salud para el Bienestar (Health Wellness Institute); ISSSTE: Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (Institute of Security and Social Services for State Workers); PEMEX: Petróleos Mexicanos (Mexican Petroleum); SEDENA: Secretaría de la Defensa Nacional (Secretary of National Defense); SEMAR: Secretaría de Marina (Secretary of the Navy).

According to INEGI (health statistics in private facilities 2019), 47 private hospitals with NICUs are registered in Mexico[24]. Fifty private sector hospitals were included in the survey.

The distribution of the number and percentage of surveyed hospitals from different healthcare institutions and public and private hospitals according to the level of care is shown in Table 1.

The distribution according to the number of births/year was as follows: 78% of hospitals with < 5,000 births; 16% of hospitals with 5,000-10,000 births; 4% of hospitals with 10,000-15,000 births; and only 1% hospital with > 15,000 births.

The rate of prematurity was 8-10% in 38%; 10-12% in 29%; 12-14% in 16%; 15-16% in 5% and > 16% in 13% of the surveyed hospitals.

The professional training of the respondents was neonatologist in 90%, pediatrician in 8%, pediatric intensivist in 1%, nurse in 0.5%, and postgraduate (MSc) in 0.5%.

Regarding equipment in the delivery room, CPAP was found in 65%, pulse oximeter in 64%, CPAP with air/oxygen mixer in 36%, and CPAP for transport in 40%.

Table 2. Continuous positive airway pressure (CPAP) equipment and supplies availability in public and private hospitals

Availability of equipment and consumables	Hospitals		Difference (%)	95% CI*	*p*-value
	Private (n = 50)	Public (n = 145)			
CPAP in the delivery room	79.6%	60.2%	19.4%	[0.0568, 0.3312]	0.014
Mixer in CPAP devices	51.2%	30.6%	20.6%	[0.0484, 0.3636]	0.017
Pulse oximeter in the delivery room	81.6%	57.9%	23.7%	[0.1029, 0.3711]	0.003
Complete CPAP bubble tower	77.6%	36.3%	41.3%	[0.2734, 0.5526]	<0.001
All CPAP have a mixer	51.0%	32.9%	18.1%	[0.0227, 0.3393]	0.023
Sufficient CPAP devices in NICU	83.7%	52.1%	31.6%	[0.1853, 0.4467]	<0.001
Adequate and timely nasal cannula supply	75.5%	36.3%	39.2%	[0.2494, 0.5346]	<0.001

95%CI, confidence interval for differences; CPAP: continuous positive airway pressure; NICU: Neonatal Intensive Care Unit.

The CPAP device used in the delivery room was a CPAP bubble (60%), a T-piece resuscitator (26%), and a flow-inflated resuscitation bag with positive end-expiratory pressure (PEEP) control (13%).

Regarding which CPAP device was mainly used in all care areas, the most frequent was bubble CPAP (66%), followed by conventional ventilator applied (18%), invasive/non-invasive ventilator (7%), variable flow CPAP (6%), and spring-loaded valve device (3%).

On whether devices to provide bubble CPAP were complete, 37% reported that all CPAP had an air/oxygen mixer, and 47% reported that all CPAP had a complete bubble CPAP tower.

Concerning the sufficiency of equipment for the demand for care in the different neonatal care areas, 60% sufficiency was reported in the NICU, 62% in intermediate care, and 46% in the delivery room.

Supplies for CPAP devices were considered sufficient and timely in 43% to 51% of nasal cannulas, caps, circuits, and pressure generator bottles.

The most frequent method of acquiring equipment and supplies was purchase (74% and 77%, respectively), followed by commodate (5% and 4%, respectively), and both in approximately 20%.

Surfactant supply was rated as sufficient and timely in 71% of hospitals. The surfactant types supplied were poractant (59%) and beractant (41%).

Regarding the usual surfactant delivery technique, the following was observed: intubation, surfactant, extubation (INSURE) in 55%; intubation, invasive ventilation, surfactant, conventional extubation in 31%; less invasive surfactant administration (LISA) in 12%.

The preferred interface was Hudson tips (58%); F&P, Dräger, and other tips (22%); Infant Flow (8%); F&P nasal mask (6%); and others (5%).

Regarding formal CPAP training, 5% of the hospitals had trained > 75% of the nursing staff, and 11% of the units had trained at least 75% of the physicians.

When comparing public and private hospitals regarding the availability of CPAP equipment and consumables, a statistically significant difference was observed: private hospitals showed greater availability of equipment and consumables in the delivery rooms and NICUs (Table 2).

The primary device to provide CPAP at all levels was bubble CPAP, followed by conventional ventilator, invasive/non-invasive ventilator, variable flow, and spring-loaded valve (Figure 2).

The most frequently available surfactant in public and private secondary and tertiary level hospitals was poractant compared to beractant (p = 0.037) (Figure 3).

The most frequent surfactant application method was INSURE in public and private secondary and tertiary level hospitals, followed by invasive ventilation-intubation-conventional extubation and, less frequently, LISA (Figure 4).

The availability of equipment and supplies by the level of care in public and private hospitals are shown in Table 3. The results of responses by the level of care in public and private hospitals are shown in Table 3.

There was a significant difference in the availability of equipment and consumables among healthcare institutions. Private hospitals had higher availability of equipment and consumables. Among public sector hospitals, State or Municipal Secretariats, INSABI, Pemex, and ISSSTE had better availability of

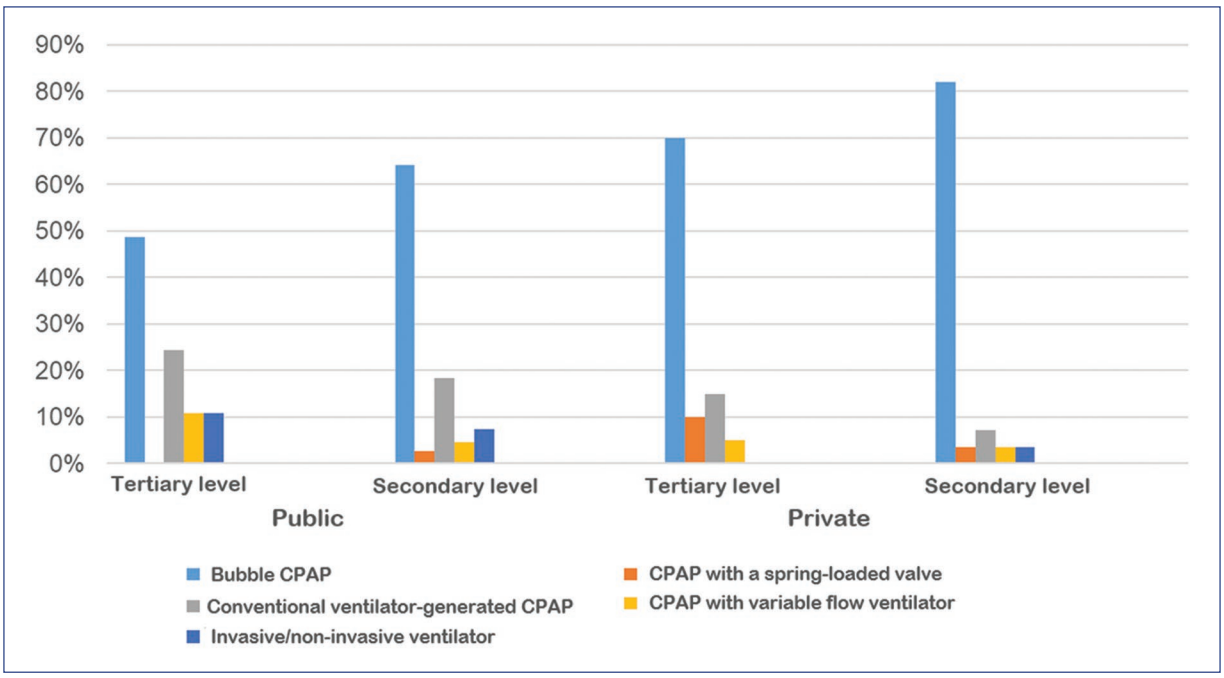

Figure 2. CPAP (continuous positive airway pressure) device mainly used according to the level of care.

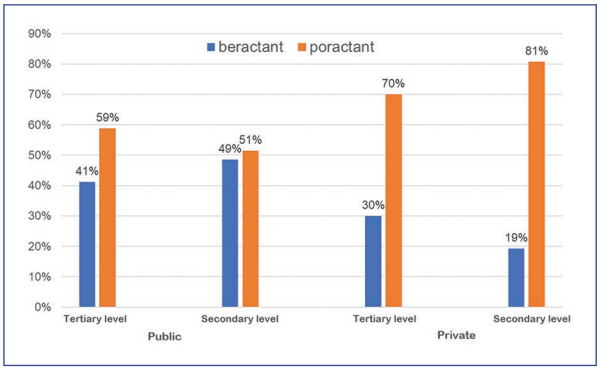

Figure 3. Surfactant availability by the level of care.

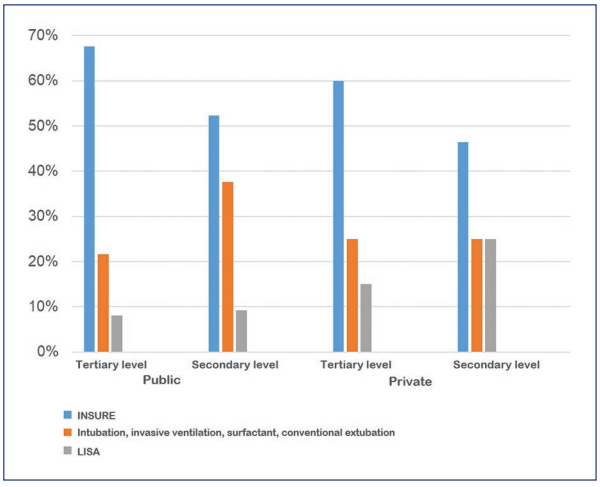

Figure 4. Method of surfactant application by the level of care. INSURE: intubation surfactant extubation; LISA: less invasive surfactant administration.

equipment and consumables than IMSS. Because IMSS Bienestar received responses only from two hospitals, several answers appear as 0 (Table 4).

The distribution of the devices mainly used to provide CPAP by healthcare institutions is shown in Figure 5. In all institutions, the primary device used was bubble CPAP, followed by CPAP supplied by the conventional ventilator, invasive/non-invasive ventilator, variable flow CPAP, and spring-loaded valve. The proportion varied from one institution to another.

The type of surfactant available, its distribution (Figure 6), and its method of administration (Figure 7) are shown for each healthcare institution.

Discussion

Some limitations of the present study are that only one response per hospital was requested, which limits the representativeness of the perception of the availability of equipment and supplies; however, responses were reasonably consistent among health institutions and levels of care. Fifty private hospitals with NICUs were reported, while INEGI reports only 47; this means that some neonatology

Table 3. Availability of equipment and supplies by the level of care in public and private hospitals

Level of care	Private		Public		*p*-value
	Tertiary (n = 22)	Secondary (n = 28)	Tertiary (n = 35)	Secondary (n = 110)	
Availability of equipment in the delivery room					
CPAP available in the delivery room	86.4%	78.6%	66.7%	57.7%	0.022
Air/oxygen mixer in the delivery room	81.0%	30.9%	43.5%	25.3%	< 0.001
Oximeter available	95.5%	71.4%	66.7%	55.2%	0.003
CPAP available for transfer	81.8%	46.4%	43.8%	43.1%	0.010
Availability of CPAP in the neonatology wards					
Bubble CPAP with all its components	95.6%	67.9%	37.1%	34.5%	< 0.001
All CPAP has an air/oxygen mixer	77.3%	35.7%	48.6%	26.4%	< 0.001
Sufficiency of equipment by care area					
In the NICU	95.5%	75.0%	68.6%	46.4%	< 0.001
In the intermediate care unit	95.5%	78.6%	71.4%	47.3%	< 0.001
In the delivery room	77.3%	60.7%	55.6%	32.7%	< 0.001
Adequate and timely supplies					
Nasal cannulas	95.5%	64.3%	54.3%	29.1%	< 0.001
Caps	95.5%	67.9%	51.4%	23.9%	< 0.001
Circuits	100%	64.3%	62.9%	33.6%	< 0.001
CPAP bottle	100%	66.9%	61.3%	35.8%	< 0.001
Surfactant	100%	67.9%	82.9%	62.7%	0.002

CPAP: continuous positive airway pressure; NICU: Neonatal Intensive Care Unit.

Table 4. Availability of equipment and consumables in each healthcare institution

Health institution	Private (n = 50)	St-Mun (n = 60)	INSABI (n = 18)	ISSSTE (n = 19)	P-S-S (n = 5)	IMSS (n = 41)	IMSS-B (n = 2)	*p*-value
Availability of equipment in the delivery room								
CPAP	82.0%	73.6%	64.3%	42.1%	20.0%	53.8%	0.0%	0.001
Devices have an air/oxygen mixer	54.5%	39.1%	50.0%	30.8%	25.0%	9.1%	0.0%	0.003
Oximeter	82.0%	69.8%	57.1%	52.6%	80.0%	43.6%	0.0%	0.005
CPAP for transfer	62.0%	59.3%	52.9%	10.5%	20%	35.9%	0.0%	< 0.001
Availability of CPAP in the neonatology wards								
Bubble CPAP with all its components	80.0%	39.0%	55.6%	42.1%	40.0%	14.6%	50.0%	<0.001
All CPAP have an air/oxygen mixer	54.0%	35.0%	38.9%	36.8%	0.0%	26.8%	0.0%	0.058
Sufficiency of CPAP equipment								
In the NICU	84.0%	61.7%	38.9%	57.9%	60.0%	38.9%	50.0%	0.012
In the intermediate care unit	86.0%	61.7%	44.4%	63.2%	100%	34.1%	50.0%	< 0.001
In the delivery room	68.0%	49.1%	35.7%	44.4%	20.0%	23.1%	0.0%	0.001
Adequate and timely supplies								
Nasal cannulas	78.0%	45.0%	44.4%	26.3%	60.0%	19.5%	0.0%	< 0.001
Caps	80.0%	36.7%	50.0%	27.8%	20.0%	17.1%	0.0%	< 0.001
Circuits	80.0%	46.7%	50.0%	36.8%	60.0%	29.3%	0.0%	< 0.001
CPAP bottle	82.0%	49.2%	56.3%	31.6%	80.0%	25.6%	0.0%	< 0.001
Surfactant	82.0%	73.3%	50.0%	68.4%	100%	63.4%	50.0%	0.099

CPAP: continuous positive airway pressure; IMSS: Instituto Mexicano del Seguro Social; IMSS-B: IMSS Bienestar; INSABI: Instituto de Salud para el Bienestar; ISSSTE: Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado; NICU: Neonatal Intensive Care Unit; P-S-S, PEMEX (Petróleos Mexicanos)-Secretaría de la Defensa Nacional-Secretaría de Marina; St-Mun: State or Municipal Health Secretariat.

services providing intensive care to neonates with no official NICU registry were cataloged as having one. In addition, the survey did not define the criteria for assigning whether the hospital was a secondary or tertiary care setting, leaving it to the informant's judgment. Furthermore, the results from IMSS Bienestar (two) and PEMEX-SEDENA-SEMAR (five) hospitals surveyed should be interpreted with caution due to the small sample size.

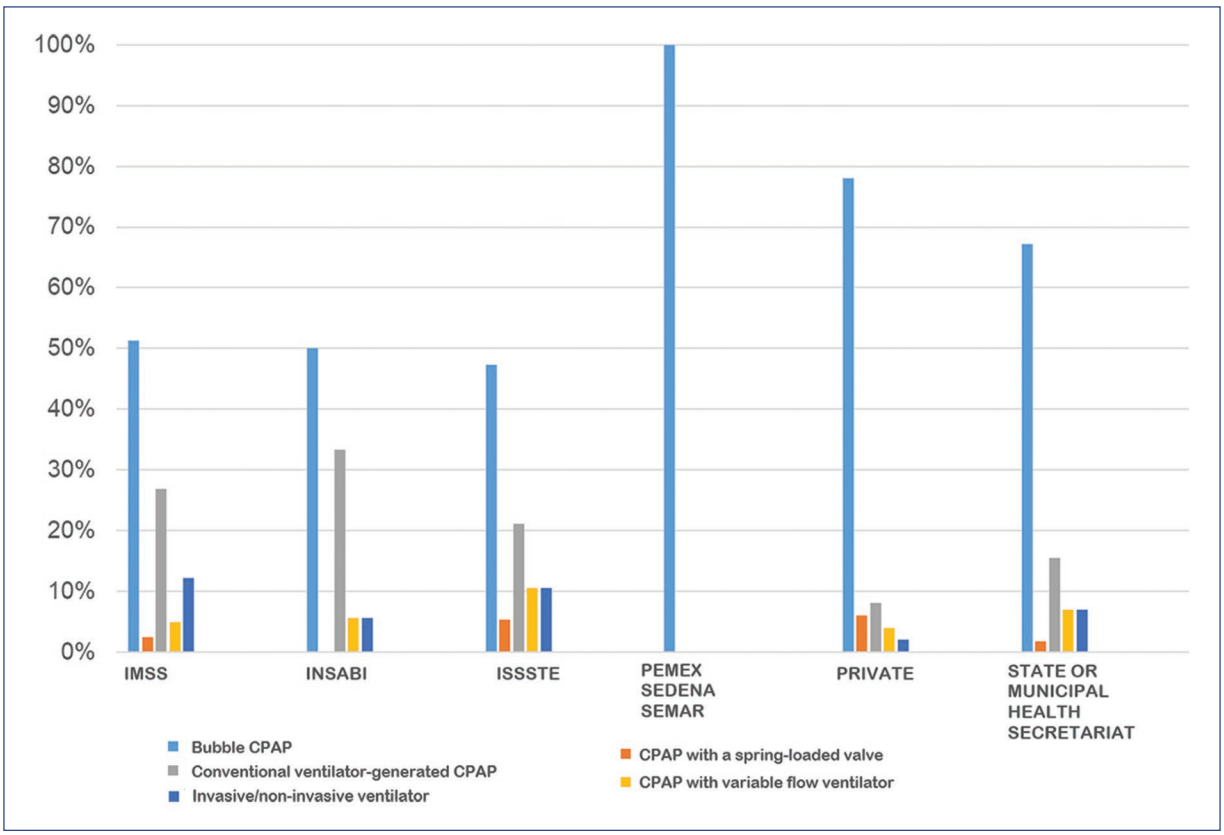

Figure 5. CPAP (continuous positive airway pressure) device distribution by healthcare institutions.
IMSS: Instituto Mexicano del Seguro Social; INSABI: Instituto de Salud para el Bienestar; ISSSTE: Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado; PEMEX: Petróleos Mexicanos; SEDENA: Secretaría de la Defensa Nacional; SEMAR: Secretaría de Marina.

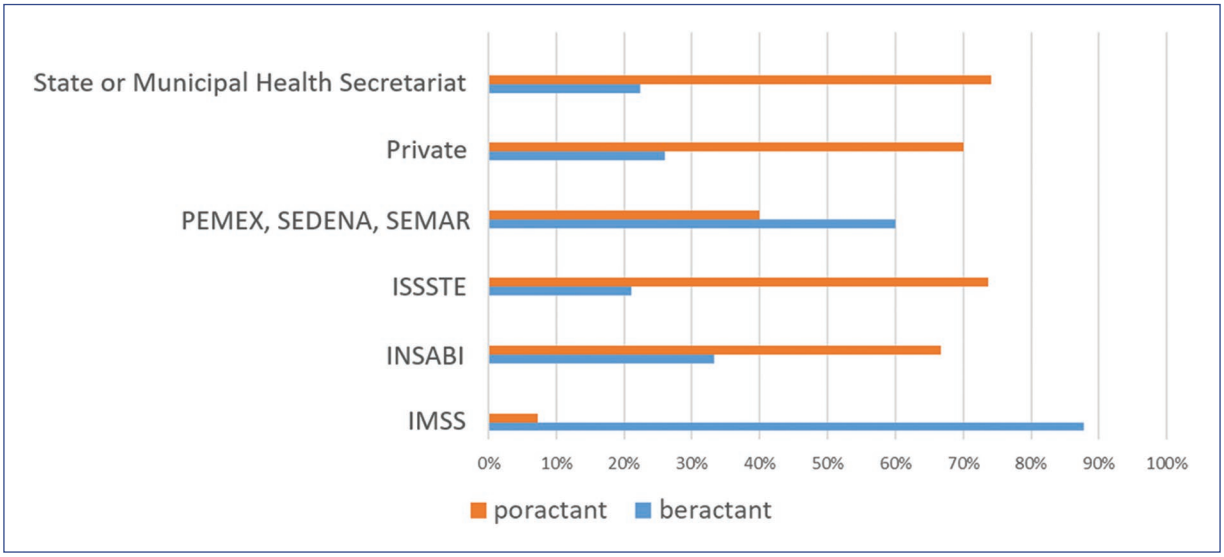

Figure 6. Type of surfactant available and its distribution by healthcare institutions.
IMSS: Instituto Mexicano del Seguro Social; INSABI: Instituto de Salud para el Bienestar; ISSSTE: Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado; PEMEX: Petróleos Mexicanos; SEDENA: Secretaría de la Defensa Nacional; SEMAR: Secretaría de Marina.

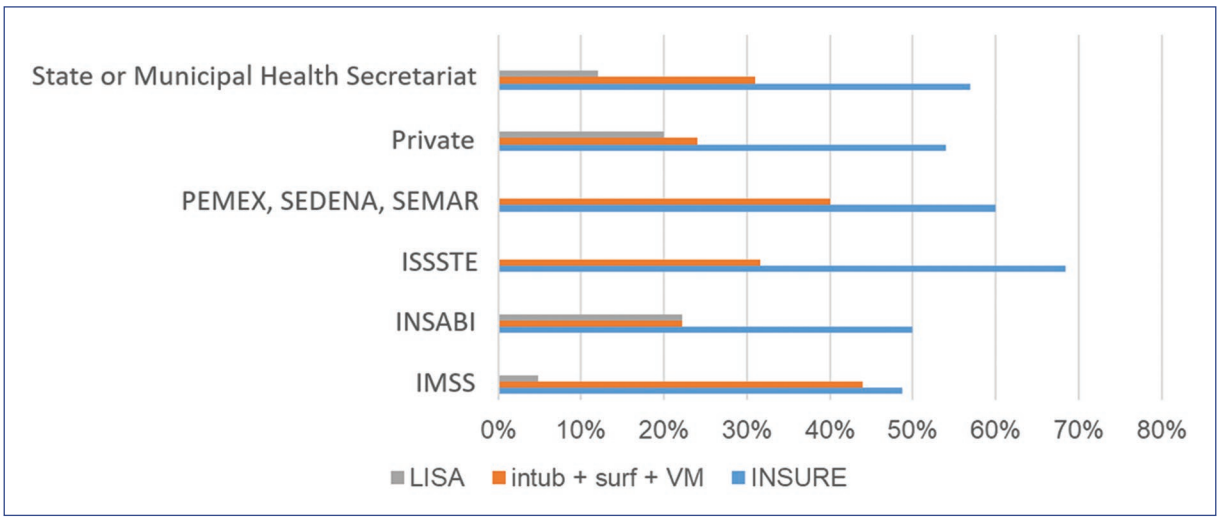

Figure 7. Method of surfactant administration by healthcare institutions.
IMSS: Instituto Mexicano del Seguro Social; INSABI: Instituto de Salud para el Bienestar; INSURE: intubation surfactant extubation; intub + surf + MV: intubation-surfactant-mechanical ventilation; ISSSTE: Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado; LISA: less invasive surfactant administration; PEMEX: Petróleos Mexicanos; SEDENA: Secretaría de Defensa Nacional; SEMAR: Secretaría de Marina.

Improvements in the quality of newborn care, including nCPAP training, bubble CPAP equipment, and adoption of best care practices (prenatal steroids, CPAP from birth, early surfactant, avoidance of unnecessary intubation, early extubation) have an impact on reducing bronchopulmonary dysplasia, sepsis, neonatal ventilation, reduced surfactant use, and reduced ROP[29-31]. These interventions have been evaluated as cost-effective in developed and developing countries[32-38].

In Mexico, there is a significant disparity in the availability of CPAP equipment and consumables between public and private sector hospitals and the different institutions surveyed, leading to the assumption that availability depends on economic and administrative factors.

The equipment to provide bubble nCPAP, the most commonly used device for this purpose, is not included as complete equipment in the basic list of medical instruments and equipment in the health sector[39,40]. The lack of an adequate mixer and humidifier exposes the neonate to the risk of short-and long-term morbidity and mortality, and the physician and the healthcare institution to malpractice, as it contravenes patient care and safety standards. Only the nasal cannula and circuit are included in the basic table of consumables[41].

The increased availability of equipment and consumables in private hospitals could be related to the increase, in recent years, in the use of major medical health insurance among the middle and upper-class population, which has allowed private hospitals to have resources for equipment and consumables for their NICUs.

The purchasing and resource prioritization schemes could also explain the difference between IMSS and other public hospitals.

The catastrophic expense insurance granted resources to public hospitals accredited by the SSA and the State or Municipal Health Secretariats to care for newborns with respiratory failure and prematurity. To be accredited, the hospital had to meet quality standards regarding facilities, personnel, equipment, and organization to care for neonates with this pathology[42].

In IMSS, equipment acquisition is programmed annually and adjusted according to the availability of resources and priorities. The disadvantage of this scheme is that the needs of a critical and priority health area compete with the multiple needs of the entire hospital, so the limited resources often do not reach where they are most needed.

Mortality and morbidity associated with RDS are still relevant problems in Mexico. Consequently, it would be advisable for public health institutions to improve their mechanisms for acquiring equipment and supplies to address priority areas with a high impact on morbidity and mortality.

Public health sector hospitals and institutions have an excellent opportunity to optimize resources by acquiring equipment for non-invasive ventilatory support of the neonate, prioritizing CPAP bubble complete equipment. In parallel, improvements in neonatal care are required with the training of multidisciplinary perinatal care personnel and the adoption of better care practices.

The initial cost of investing in this nCPAP equipment and supplies can be considered a significant saving due to a future decrease in morbidity and time of care in these infants, as well as a significant decrease in mortality associated with this condition—which should not be underestimated.

On this basis, there is an excellent opportunity for public and private hospitals to improve the availability of complete bubble CPAP devices for neonatal non-invasive ventilatory support and training of healthcare personnel in the adoption of best practices for non-invasive ventilatory support and less invasive surfactant application to have an impact on RDS mortality and associated morbidities, such as BPD and ROP.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Idiopathic left fascicular ventricular tachycardia in children and adolescents

Enrique Velázquez-Rodríguez[1], *Norberto García-Hernández*[1], *Elsa Silva-Oropeza*[1], *Santiago Jiménez-Arteaga*[2], *Arturo Martínez-Sánchez*[2], *Carlos Alva-Espinoza*[2], *Felipe David-Gómez*[2], *and Lucelli Yáñez-Gutiérrez*[2]

[1]*Servicio de Electrofisiología, Unidad Médica de Alta Especialidad Hospital de Cardiología, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social;* [2]*Servicio de Cardiopatías Congénitas, Unidad Médica de Alta Especialidad Hospital de Cardiología, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social. Mexico City, Mexico*

Abstract

Background: *Idiopathic ventricular tachycardia (VT) in children with structurally normal hearts is generally unrelated to the risk of sudden arrhythmic death. Still, it may be associated with deterioration in the quality of life. VT involving the fascicular conduction system is the most typical form of idiopathic left VT. In this retrospective study, we describe the experience of the clinical presentation, catheter ablation, and long-term follow-up of left fascicular VT in children.* **Methods:** *An electrophysiological study was performed on consecutive children at a single tertiary center. Clinical fascicular left VT was induced by programmed stimulation, and catheter ablation was guided searching for Purkinje potentials.* **Results:** *We included 18 patients (0.8 patients/year): 14 (77.8%) males and four females. The mean age of the first VT episode was 8.5 ± 5 years. Intravenous verapamil administration was effective for paroxysmal fascicular VT but not for prevention of recurrences. The mean age at the time of catheter ablation was 11.1 ± 3.8 years (8 months-16 years). The mean weight was 36.8 ± 16.4 kg (8.7-58 kg). A 100% success rate was observed with catheter ablation after repeated procedures without major complications. Mean follow-up was 2.0 ± 1.2 years (1.0-4.0 years, median 1.5), with permanent success in all patients and no antiarrhythmic drug administration.* **Conclusions:** *Fascicular VT has an adverse clinical course in children. In most cases, this condition is drug refractory. Catheter ablation is successful and safe treatment and should represent the first-line approach in symptomatic children.*

Keywords: *Fascicular ventricular tachycardia. Verapamil-sensitive ventricular tachycardia. Idiopathic left ventricular tachycardia. Electroanatomical mapping. Purkinje potentials. Catheter ablation in children.*

Taquicardia ventricular fascicular izquierda idiopática en niños y adolescentes

Resumen

Introducción: *La taquicardia ventricular (TV) idiopática en niños con corazón estructuralmente normal generalmente no se relaciona con el riesgo de muerte súbita arrítmica, pero puede asociarse con deterioro de la calidad de vida. La TV que involucra el sistema de conducción fascicular es la forma más común de TV izquierda idiopática. En este estudio retrospectivo se describe la experiencia de presentación clínica, ablación con catéter y seguimiento a largo plazo de TV fascicular*

Correspondence:
*Enrique Velázquez-Rodríguez
E-mail: enve@prodigy.net.mx

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en niños. **Métodos:** *Se llevó a cabo un estudio electrofisiológico en niños consecutivos en un centro terciario. La TV fascicular clínica se indujo mediante la estimulación programada y la ablación con catéter fue guiada buscando el registro de potenciales de Purkinje.* **Resultados:** *Se incluyeron 18 pacientes (0.8 pacientes/año): 14 (77.8%) de sexo masculino y cuatro de sexo femenino. La media de edad a la cual ocurrió el primer episodio fue de 8.5 ± 5 años. La administración intravenosa de verapamilo fue eficaz para la TV fascicular paroxística, pero no para prevención de recurrencias. La media de edad de la ablación con catéter fue de 11.1 ± 3.8 años (8 meses-16 años). La media del peso fue 36.8 ± 16.4 kg (8.7-58 kg). Se observó el 100% de éxito con la ablación con catéter después de procedimientos repetidos sin complicaciones mayores. La media de seguimiento fue de 2.0 ± 1.2 años (1.0-4.0, mediana de 1.5 años) con éxito permanente en todos los pacientes y sin administración de fármacos antiarrítmicos.* **Conclusiones:** *En niños, el curso clínico de la TV fascicular es adverso. Además, en la mayoría de los casos, esta condición es refractaria a fármacos. La ablación con catéter resulta exitosa y segura y debe representar el abordaje de primera línea en niños sintomáticos.*

Palabras clave: *Taquicardia ventricular fascicular. Taquicardia ventricular sensible a verapamilo. Taquicardia ventricular izquierda idiopática. Mapeo electroanatómico. Potenciales de Purkinje. Ablación con catéter en niños.*

Introduction

Few data exist on the incidence of spontaneous ventricular tachycardia (VT) in a random pediatric population. The prevalence of VT detected in asymptomatic children is low according to school-based heart screening (2 to 8 per 100 000 children)[1,2]. VT after palliative repair of congenital heart disease is relatively infrequent but is a known cause of early and late morbidity and mortality. Pediatric VT is primarily idiopathic in patients without underlying heart disease. Idiopathic VT in children with structurally normal hearts although not related with risk of sudden arrhythmic death, it may be associated with significant deterioration in their quality of life. Idiopathic VT includes right ventricular infundibulum tachycardia, left VT involving the fascicular conduction system, and fascicular VT (also called verapamil-sensitive VT). Fascicular VT has been classified into four subtypes: left posterior, left anterior, upper septal, and papillary muscle fascicular VT[3,4]. Fascicular VT that involves the left posterior fascicle is the most common type of ifiophatic VT. In cases with high diagnostic suspicion, specific 12-lead electrocardiogram (ECG) signs and typical responses to intravenous drug therapy are essential features to consider.

We conducted a retrospective study on the experience regarding clinical presentation, definitive treatment with catheter ablation, and long-term outcomes of pediatric patients with idiopathic left fascicular VT.

Methods

Study sample

This single tertiary heart center study received 62 children with VT treated between September 1995 and February 2018. Of these, 43 patients had right or left idiopathic type VT. Here, we studied 18 children with idiopathic left fascicular VT variant who were referred to the arrhythmia clinic for electrophysiological study and definitive treatment with catheter ablation. Structural heart disease was excluded after a detailed medical history and examination, with 12-lead ECG, chest X-ray, echocardiography, and, if necessary, right or left ventriculography. Echocardiography excluded the presence of false tendon or fibromuscular band extensions from the posteroinferior left ventricle (LV) to the basal septum in all patients. Follow-up was conducted jointly with the interventional electrophysiology and congenital heart disease services. All parents signed informed consent for the interventional electrophysiological study and catheter ablation.

Electrophysiological study and catheter ablation protocols

Antiarrhythmic drugs (AAD) were withdrawn for at least five half-lives before the procedure. Electrophysiological study and catheter ablation protocols were performed under local anesthesia. In younger children or patients with anxiety, procedures were performed under conscious sedation, and in infants, under general anesthesia. 6-Fr Josephson-curve quadripolar catheters were inserted through the femoral vein and placed in the high right atrium, the His-bundle region, and the right ventricular apex. In selected cases, a steerable decapolar catheter was put into the coronary sinus or along the LV septum under fluoroscopic guidance. In infants, three 2-Fr fixed-curve quadripolar catheters were introduced through a single 6-Fr long sheath trio multi-lumen introducer (Trio/Ensamble™ Arrow Medical, Pasadena CA, USA) via the femoral vein. Programmed pacing was performed from the right ventricular apex and right atrium

and, when necessary, intravenous infusion of orciprenaline or aminophylline for VT induction. Intracardiac bipolar electrograms were filtered between 30 to 500 Hz and displayed at a sweep speed of 100 to 200 mm/s. Left fascicular VT was confirmed by the relative activation times of Purkinje and His-bundle electrograms; the origin of VT was determined by identifying the site of earliest ventricular activation during VT, and mapping was performed searching for Purkinje electrograms extending from the left basal septum to apical areas. In four cases, a three-dimensional (3D) electroanatomical mapping system, EnSite Velocity NavX™ (St Jude Medical, St Paul, MN, USA), and the Electroview™ 3D (Bard Electrophysiology, Lowell, MA, USA) were used.

LV endocardial geometry was performed in these cases, followed by local activation time mapping. Catheter ablation was advanced retrogradely across the aortic valve. Radiofrequency current (RFCA) was delivered between a quadripolar 7-Fr, 4-mm distal-tip electrode steerable catheter (B-curve Mansfield/Webster™, Watertown, or RF MARINR™ MC Medtronic, Minneapolis, MA, USA) or the Therapy Cool Path™ ablation catheter irrigated (St Jude Medical) and a dispersion pad applied to the left subscapular region in selected cases. Heparin was administered intravenously at 100 U/kg after femoral artery access, followed by additional doses every hour as needed. RFCA was delivered setting power of 30 to 35 W and a maximum temperature of 65°C; for the cooled catheter, 35 W and 45°C. After each RFCA pulse, VT reinduction was attempted by programmed stimulation. For successful pulses, RFCA was applied for 120 seconds; otherwise, it was interrupted at 10 seconds. For infants, a 5-Fr ablation catheter (RF MARINR™ SC, Medtronic, curve reach 35 mm) was used with RFCA power of 30 W at 55°C for 60 seconds. All patients were observed overnight in the pediatric postoperative intermediate intensive care ward and then transferred to the pediatric cardiology area for clinical observation, ECG, and echocardiographic monitoring for possible complications before discharge after 24 hours. Patients were discharged on aspirin 100 mg/day for the next 2 months. Follow-up was performed in the outpatient clinic every 3 months until discharge, at least up to one-year post-ablation. Recurrence was defined as the return of clinical symptoms or ECG documented left fascicular VT.

Statistical analysis

Continuous and categorical variables were described as mean ± standard deviation (SD) and percentages.

Results

Over 22 years and 5 months, 18 patients (0.8 patients/year) were followed up to evaluate idiopathic left fascicular VT: 14 (77.8%) males and four females. The mean age at the first episode of VT was 8.5 ± 5 years (7 months-15 years, median 9 years) with a mean evolution time of 1.3 ± 0.8 years (1 month-3 years, median 1.2 years). The mean age at the time of catheter ablation treatment was 11.1 ± 3.8 years (8 months-16 years, median 12 years) with a mean weight of 36.8 ± 16.4 kg (8.7-58 kg, median 35 kg). The 8-month-old infant weighed 8.7 kg and measured 0.76 cm (BSA 0.41 m^2).

Clinical characteristics

All patients presented symptoms with a predominance of palpitations and dyspnea (60%), palpitations only (40%), and coexisting dizziness or fainting sensation (10%); no patient presented syncope or was resuscitated (Table 1). An 8-month-old infant male showed fatigue, food refusal and irritability, and incessant tachycardia as auscultatory findings. A 14-year-old female with two years of evolution, initially with episodes of paroxysmal VT, progressed to the persistent form of left fascicular VT with symptoms of congestive heart failure. The echocardiogram showed a pattern of dilated cardiomyopathy (categorized and confirmed as tachycardia-induced cardiomyopathy) published as a case report[5].

Antiarrhythmic treatment and outcome

In paroxysmal fascicular VT, acute treatment in the emergency room was always successful with intravenous (IV) verapamil but not autonomic maneuvers, adenosine, esmolol, or amiodarone (which only partially slowed the VT rate). During clinical follow-up, an outpatient regimen of oral AAD was prescribed, with a mean of 2 ± 1 without success, including AADs such as verapamil, β-blockers, propafenone, and only in one case, amiodarone. Initially, AADs were used as monotherapy, followed by a combination of AADs in 86.5%.

ECG characteristics

In 17 of the 18 cases (94.4%), VT was detected on the resting 12-lead ECG during an episode of paroxysmal VT, and in one patient, VT was identified by a 24-hour-Holter ECG (Table 2). The sustained monomorphic form of VT was identified in 16 patients, the non-sustained or

Table 1. Clinical characteristics

Variables	Patients (n = 18)
Mean weight, kg (range)	36.8 ± 16.4 (8.7-58)
Age of onset, mean ± SD (range)	8.5 ± 5 (7 months-15 years)
Age at ablation, mean ± SD (range)	11.1 ± 3.8 (8 months-16 years)
Male, n (%)	14 (78)
Female, n (%)	4 (22)
Symptoms	100 %
Palpitations/dyspnea	60 %
Only palpitations	40 %
Coexisting dizziness or fainting sensation	10 %
Congestive heart failure, n (%)	1 (5.5)
Syncope	0
Cardiac arrest	0
Previous antiarrhythmic drugs, mean ± SD	2 ± 1

SD: standard deviation.

premature ventricular complexes (PVCs) ran in one patient, and the third patient showed both types. The 12-lead ECG pattern indicative of a left posterior fascicular type of VT [right bundle branch block (RBBB) with left axis deviation] was found in 17 (94.4%) children. Of this group, one case involved both left posterior and left anterior (RBBB with right axis deviation) fascicles (Figure 1), another case involved left posterior and upper septal fascicular VT type (narrow QRS and normal axis) (Figure 2), and one more case involved the Purkinje network of the posterior papillary muscle (RBBB with extreme right axis deviation). The mean VT rate was 176 ± 17 beats/min (150-205 bpm, median 170 bmp), and the mean QRS width, relatively narrow, of 106 ± 10 ms (90-120 ms, median 100 ms), except for the upper septal VT with narrow QRS. Indications for interventional treatment were refractoriness to AAD and hemodynamic intolerance during VT in 16 patients and incessant VT in two, one of whom had tachycardia-induced cardiomyopathy.

Mapping and catheter ablation

Clinical left fascicular VT was reproducibly induced under baseline conditions in the 15 patients with a history of sustained paroxysmal VT: 13 patients by right ventricular apex extra stimuli (86.7%), four by atrial pacing and ventricular extra stimuli (27%), and two patients (13.3%) by ventricular burst pacing. We also found one case with non-sustained recurrent spontaneous VT or non-sustained PVC runs despite orciprenaline or aminophylline infusion. A reentrant mechanism was considered in all cases except for non-sustained recurrent VT (with a possible triggered activity mechanism). The rationale was the inverse relationship between the coupling interval and the first beat of the tachycardia echo interval. Also, the finding that the VT was reproducibly induced and terminated by pacing was considered. Entrainment pacing was not routinely used. The mean baseline AH interval was 69.2 ± 18.7 ms, and the HV interval of 45.7 ± 9 ms, both within normal limits before and post-RFCA. During VT, 15 patients (83.3%) had ventricular-atrial (VA) dissociation, and three patients (16.7%) had constant VA conduction. In these cases, the use of adenosine caused temporary VA dissociation and allowed the differential diagnosis of VT.

In most cases (14), only conventional endocardial mapping was performed during sustained VT, and in one patient, it was performed during both VT and sinus rhythm (SR). In the left posterior fascicular VT, the earliest ventricular activation was recorded in the apical posteroinferior zone; in the left anterior fascicular VT, in the anterosuperior zone; and in upper septal fascicular VT, in the superior medial septum. In all cases, the His-bundle was retrogradely activated during VT with a mean VH interval of 11.7 ± 5 ms, except in the case of upper septal fascicular VT with a retrograde His-bundle recorded before the QRS complex. Mapping was conducted to search for the earliest presystolic Purkinje (PP) potential and mid-diastolic Purkinje potential (DP) electrograms. In 16 patients, the earliest local activation of the left ventricle during sustained VT was preceded by a sharp, high-frequency PP potential electrogram that was the main target of ablation. Two patients obtained PP and mid-DP potentials simultaneously (Figures 3, 4, and 5).

During VT, the mean earliest PP potential preceded QRS onset by -19 ± 7 ms and was recorded within the posteroapical third of the LV septum. Total procedure time had a mean of 148.7 ± 95 min (60-250 min, median 142.5 min) and a mean fluoroscopy time of 15.7 ± 6.9 min (5-19 min, median 12.9 min). Fluoroscopy time in 3D electroanatomical mapping cases was between 4 and 7 minutes of intermittent

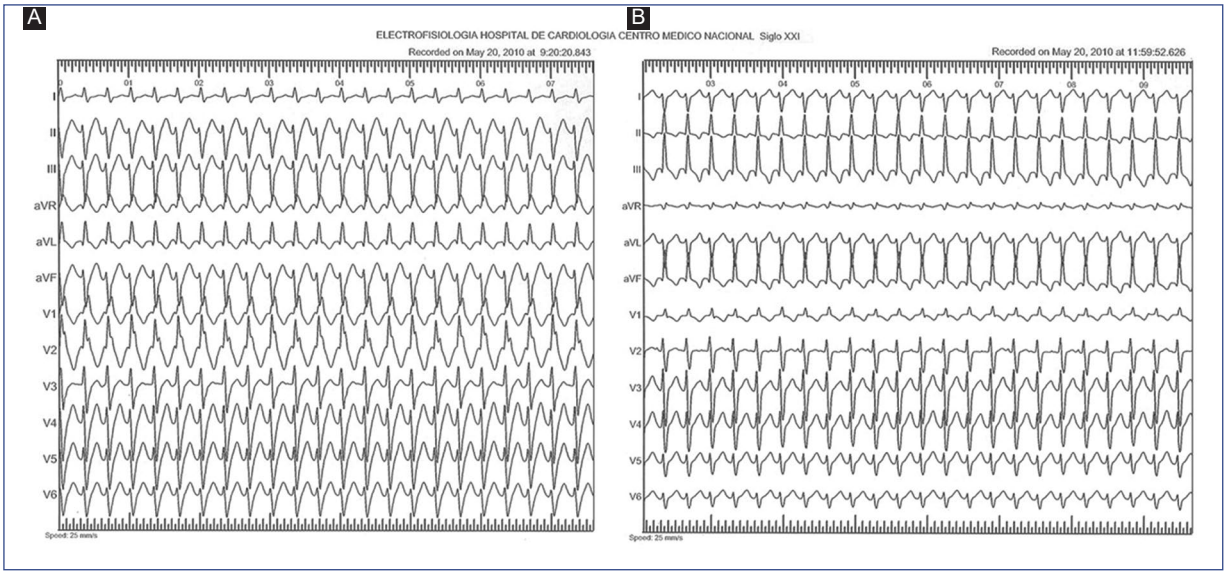

Figure 1. Fascicular ventricular tachycardia in a 12-year-old male. **A:** left posterior fascicular VT (right bundle branch block with left axis deviation). **B:** left anterior fascicular VT (right bundle branch block with right axis deviation).

Table 2. Ventricular tachycardia characteristics.

Variable	Cases (n = 17)
Median VT rate (bpm), mean ± SD (range)	176 ± 17 (150-205)
Paroxysmal VT, n (%)	16 (89)
Incessant VT, n (%)	2 (11)
Non-Sustained, n (%)	1 (5.5)
Verapamil-sensitive	100%
Adenosine-sensitive	0
QRS morphology	
QRS width (ms), mean ± SD (range)	106 ± 10 (90-120)
RBBB—left axis, n (%)	17 (94)
RBBB—right axis, n (%)	1 (5.5)
RBBB—extreme right axis, n (%)	1 (5.5)
Induced in basal conditions, n (%)	15 (100)
Right ventricular apex, n (%)	13 (87)
Atrial and ventricle, n (%)	4 (27)
Burst ventricular pacing, n (%)	2 (13)
Constant VA conduction, n (%)	3 (17)
Ablation procedure	
Conventional mapping, n (%)	14 (78)
Total procedure time (min), mean ± SD (range)	148.7 ± 95 (60-250)
Acute success rate, n (%)	15 (83.3)
Recurrences, n (%)	3 (16.6)
Re-ablation, n (%)	3 (16.6)
Total success, n (%)	18 (100)
RF (pulses), mean ± SD (range)	6.0 ± 5.0 (1-17)
Fluoroscopy time (min), mean ± SD (range)	15.7 ± 6.9 (5-19)
Complications	0
Follow-up (years), mean ± SD (range)	2.0 ± 1.2 (1-4)

RBBB, right bundle branch block; RF, radiofrequency; SD, standard deviation; VA, ventricular-atrial; VT, ventricular tachycardia.

fluoroscopy. The procedure was used to assist in the placement of diagnostic catheters, ablation catheters for retrograde passage of the aortic valve, and construction of the LV endocardial map. The interventional procedure with RFCA was acutely successful in 15 of 18 (83.3%) children; two children underwent a second and one child a third intervention to achieve 100% success. The mean number of RFCA pulses was 6.0 ± 5.0 (1-17, median 5).

Recurrence of left fascicular VT with the same 12-lead ECG morphology was documented in three patients (16.6%: 14, 43, and 86 days, respectively, after the initial ablation procedure). These patients underwent a second session with satisfactory results. In the case of the 8-month-old infant, RFCA was successful for the presentation of incessant left posterior fascicular VT but not for the induced paroxysmal upper septal fascicular VT. In the latter, each application caused transient left bundle branch block; therefore, it was decided to abandon the ablation procedure because of the high risk of atrioventricular block. The outcome was the spontaneous disappearance of this type of tachycardia.

The mean follow-up time of all children after RFCA was 2.0 ± 1.2 years (1-4 years, median 1.5 years), with permanent success and no need for AAD in all groups. No major or minor complications were related to the vascular approach or passage through the aortic valve (confirmed by echocardiography). One case had a

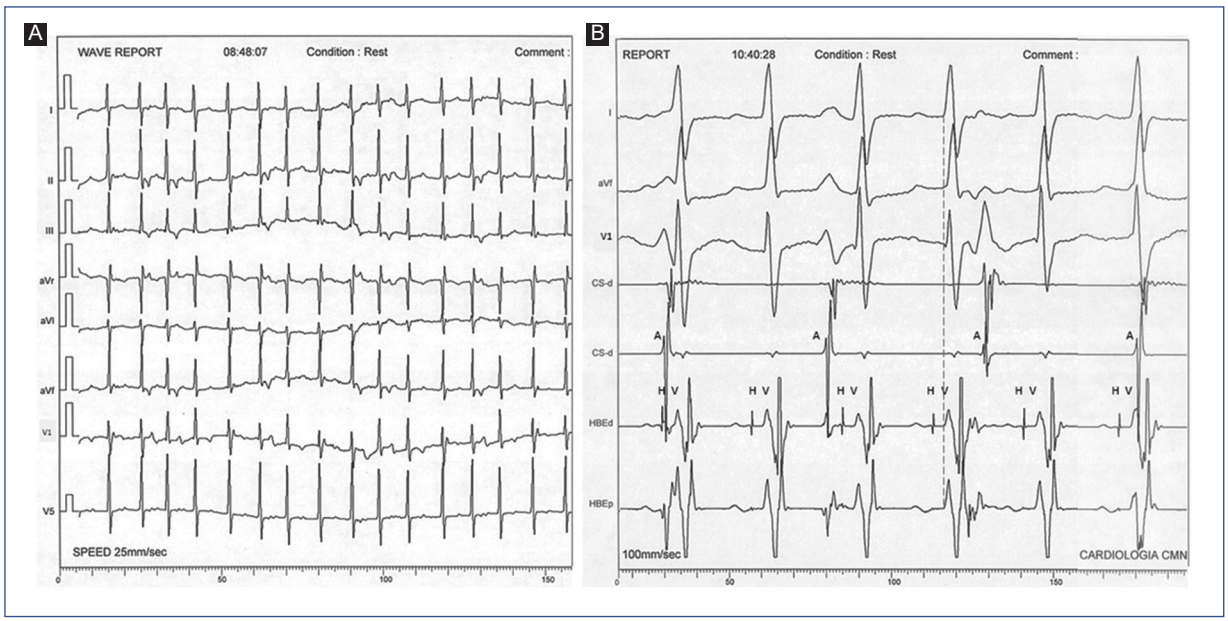

Figure 2. Fascicular ventricular tachycardia in an 8-month-old male infant. **A:** upper septal fascicular VT (narrow QRS and normal axis). **B:** intracardiac electrograms of the same case, where the ventricular-atrial dissociation can be observed. A, left atrial electrograms; HBE, His-bundle electrograms (H); V, ventricular electrograms; CS, coronary sinus electrograms.

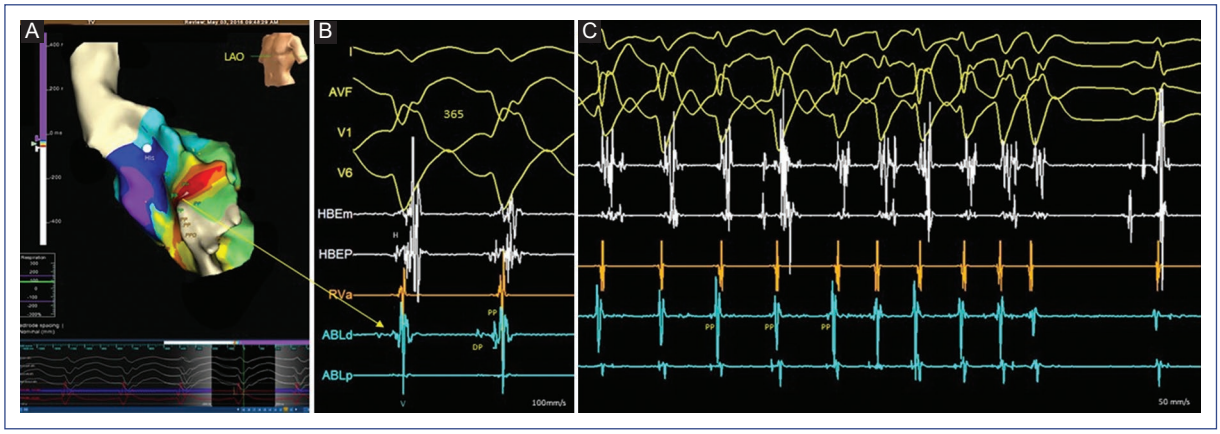

Figure 3. Electroanatomical mapping (EnSite NavX) in a 16-year-old female. **A:** LV endocardial geometry with isochronal local activation time (LAT) map during sustained VT. Purkinje electrogram (PP) recordings extend from the left basal septal to the apical sites marked on the LV geometry. Early and late transition areas (from the small white to the purple area) can be identified. **B:** intracardiac electrograms from the ablation catheter (ABLd) corresponding to the LAT map with simultaneous recording of a mid-diastolic Purkinje potential (DP) and an early presystolic Purkinje (PP) potential (yellow arrow). **C:** at this site, the radiofrequency pulse interrupts ventricular tachycardia. HBE: His-bundle electrograms (H); V: ventricular electrogram.

periprocedural transient left bundle branch block during RFCA pulses applied in the region above the LV mid-septal region derived from the ablation procedure. After the RFCA session and follow-up, no 12-lead ECG showed the criteria of a new fascicular block.

Discussion

VT is a rare cardiac arrhythmia in the pediatric population. Clinically, most cases are idiopathic with no structural heart disease; within these, left fascicular VT stands out for its clinical characteristics and electrophysiological properties.

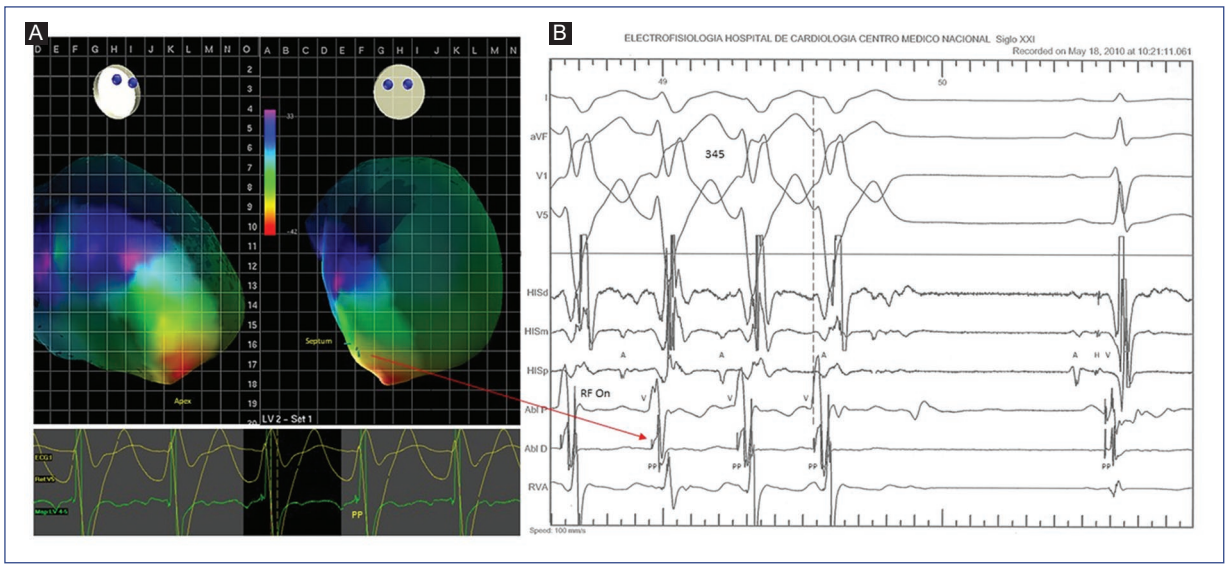

Figure 4. Mapping and catheter ablation in a 10-year-old male. **A:** electroview 3D mapping system with local activation time (LAT) map. During sustained VT, the early activation site (PP potential) is recorded within the posterior-apical third of the left ventricular septum (red arrow). **B:** intracardiac electrograms from the ablation catheter (ABL D) recording PP potentials at -8 ms of QRS onset (dotted line) corresponding to the LAT map; successful radiofrequency site (RF On, second pulse).

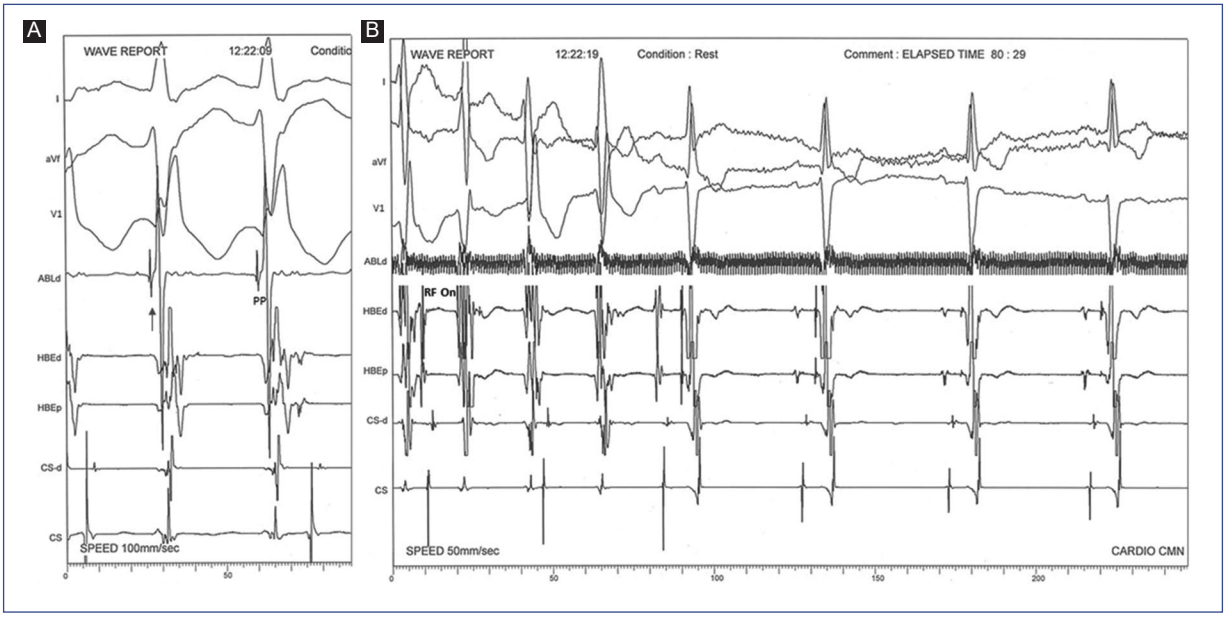

Figure 5. Mapping and catheter ablation in an 11-year-old female. **A:** conventional mapping during sustained VT in the left posterior fascicle; intracardiac electrograms from the ablation catheter (ABL d) recording PP potentials (arrow) simultaneously with QRS onset. **B:** target site of the successful radiofrequency pulse (RF On).

Clinical differential diagnosis

A clinically significant fact is that 100% of our cases were initially misdiagnosed as supraventricular tachycardia (SVT) with aberrancy, even in this or other specialized centers. This misdiagnosis might be because this pathology usually occurs in young patients with a structurally normal heart, a relatively narrow QRS

during tachycardia, and the characteristic response to IV verapamil. Moreover, the diagnostic challenge is even more significant since we need to differentiate between idiopathic VT and SVT with aberrancy in infants. Thus, initial misdiagnosis of idiopathic VT as SVT can occur between 30% (in infants)[6] and 100% (in adolescents) without high clinical and electrocardiographic suspicion. A practical suggestion is that if children with no structural heart disease present with a pattern of RBBB and left axis deviation during tachycardia with a lack of response to adenosine (virtually in 100% of patients), a distinct electrocardiographic entity should be assumed until proven otherwise, and the presence of left fascicular VT should be rapidly suspected[7].

From the electrocardiographic perspective, and unlike VT associated with structural heart disease, there is a high incidence of AV dissociation (from 50% in infants[7] to 73% in young people[8]) in this pathology that may be due to a relatively narrow QRS complex that facilitates the identification of P waves in the 12-lead surface ECG (Figure 6). Indirect data of AV dissociation (fusion and capture beats) are present in ≥ 25% of cases, and another relevant feature is an RS interval ≤ 80 ms in precordial leads[8]. As in our experience, IV verapamil is practically 100% effective in treating paroxysmal fascicular VT (hence so-called verapamil-sensitive VT). This efficacy is presumed to result from the blockade of a slow conduction area (calcium channel-dependent) within the antegrade arm of the tachycardia circuit adjacent to the left fascicle[9]. According to recent experience, IV verapamil is effective and safe in infants and children, following a particular dosing strategy and method of administration[10]. However, oral treatment and other conventional AADs have limited success, as in our case series[11]. During follow-up, it was present in ≥ 75% of patients; thus, all children continued with recurrent episodes of fascicular VT, a situation well recognized in other series; this determined the indication for interventional treatment in several cases.

Electrophysiological characteristics

The exact mechanism of the tachycardia circuit has not been fully elucidated. From an electrophysiological perspective, a small macro-reentrant pathway involving the posterior Purkinje network is considered. Left ventricular mapping shows a focal origin during VT; antegrade conduction descends from the basal septum through a zone of slow conduction in the ventricular

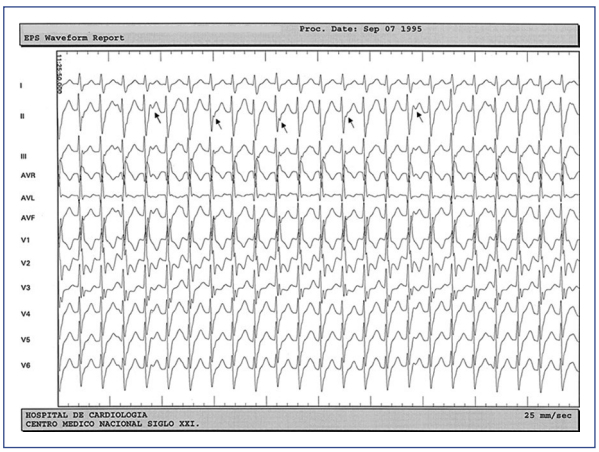

Figure 6. The 12-lead ECG `during sustained left posterior fascicular VT in an 11-year-old female. A classic right bundle branch block pattern with left axis deviation and AV dissociation (arrows).

septum resulting in a mid-DP potential and continues to the apical septum and the posterior septal myocardium. Retrograde conduction proceeds passively over the left posterior fascicle (≥ 94%) or the Purkinje fibers close to the left posterior fascicle originating a PP potential that precedes the onset of QRS during tachycardia[12-14], whereas in the SR, the mid-DP follows the local ventricular complex and surface QRS (retro-DP), which also allows mapping and ablation in the SR.

Electrophysiological differential diagnosis

The most important feature for diagnosing left fascicular VT is recording the PP electrogram preceding the earliest local ventricular activation of the LV posteroapical septum, followed by early retrograde conduction of the His-bundle and anterograde activation of the proximal branch of the right bundle branch. At the same site, but during SR, the PP potential is recorded after the His-bundleelectrogram and before the onset of the QRS complex. During the electrophysiology study, the specialist should perform the differential diagnosis between SVT with aberrancy and actual fascicular VT with continuous conduction of the VA and other VTs. During sustained VT, if there is continuous 1:1 conduction of the VA, rapid atrial pacing may show AV dissociation favoring the diagnosis of fascicular VT. Another more straightforward maneuver is to use adenosine to block the AV node evidencing transient dissociation of the VA without interrupting or changing QRS morphology and tachycardia cycle length. In SVT with

aberrancy, the His-bundle is anterograde, and the HV interval is the same as in SR; the opposite occurs in fascicular VT. Other verapamil-sensitive tachycardias, such as interfascicular VT or idiopathic mitral annulus VT, have a typical RBBB morphology with left or right axial deviation and can simulate fascicular VT. Another interesting VT to consider is verapamil-sensitive fascicular VT, which affects the Purkinje network around the posterior papillary muscle and is characterized by RBBB and extreme right axis deviation[15].

Interventional treatment

Once the mechanism is determined to be a reentrant involving branches of the Purkinje network emanating from the posterior or anterior left fascicles, consideration is needed to search for the appropriate endocardial site of the reentrant circuit guided by specific electrograms of the Purkinje to perform catheter ablation. With improvements in catheter and mapping technology, catheter ablation has become the standard treatment for children and adolescents with idiopathic VT, although reports are primarily of single cases and small series[16,17]. Therefore, experience related to catheter ablation of VT in pediatric patients has been limited. One of the first and largest retrospective series on fascicular VT ablation procedures in the pediatric population (102 cases, mean age 12.5 ± 3.6 years) derived from an international multicenter study (22 hospitals) reported 82% of acute success rate and 72% at a median follow-up of two years[18]. However, some limitations of the study were the different treatment approaches, success rates, and follow-up among institutions. More recent reports of single-center experiences (44 children, 73% ≥ 10 years old, and 32 children, 8.6 ± 3.7 years, mean BW 34.3 ± 14.9 kg)[6,19] showed a similar or higher acute success rate of 90% and 97%, respectively, with a recurrence rate after ablation of 10% to 14% and success rate ≥ 90% at 2 to 4 years of follow-up. Another small series (6 cases, aged 3 to 17 years) proposed that the approach technique of creating a partial fascicular block was effective and safe[20]. Data from a systematic review of the literature confirmed that catheter ablation is an effective and safe treatment for left fascicular VT. However, the success rate was lower in observational pediatric case series (90% after repeated procedures, 95%CI 82.1-94.6%) compared to adult cases (94.3%, 95%CI 92.2-95.9%, $p < 0.001$)[21]. Catheter ablation in children with the rare left anterior fascicular VT presents some difficulties, essentially due to the challenge of identifying tachycardia circuits, a high recurrence rate, and some complications[22]. Electroanatomic 3D mapping systems can facilitate the procedure and minimize the child's exposure to fluoroscopy. In a small series of four patients with a mean age of 14.5 years (4-20 years), success was achieved in all cases using noncontact mapping (EnSite ArrayTM)[23]. Two recent studies with EnSite NavXTM totaling 53 children reported an acute success rate of 95% and 100%, with a median fluoroscopy time between 1.25 and 5.1 minutes[24,25], although fluoroscopy was not used in 91% of cases[23].

A recurrence rate of 20% and 3% was recorded during short- and long-term follow-ups. Repeat ablations achieved permanent success in all cases[24,25]. Only the last four cases were performed in our series with 3-D mapping after introducing this technology in our center. Overall, 3D mapping in adults improved the success rate compared to fluoroscopy, especially after the index procedure. However, there are no comparative studies in the pediatric population, and for now, the main advantage of 3D mapping is the limitation of fluoroscopy. Idiopathic infant-onset VT may be more likely to disappear spontaneously, with a mean age of 1.9 ± 1.1 years (0.1-3.2 years)[26], as was the isolated case in our series with the upper septal fascicular VT, the rarest type.

Electrophysiological studies and catheter ablation procedures in infants present difficulties, essentially due to the lower weight and height of the patients. Left fascicular VT is rare in infants but can be persistent and lead to tachycardia-induced cardiomyopathy refractory to AAD. In our series, the patient with incessant VT (left posterior fascicular VT type) underwent a successful RFCA. Two isolated cases of infants aged 8 and 12 months (BW 7.7 and 10 kg, respectively) with persistent fascicular VT and heart failure refractory to AAD and electrical cardioversion have been described in the literature. Recovery of SR by RFCA, used as a life-saving procedure, was associated with improved systolic function without needing AAD. Thus, an attempt at ablation may be justified when tachycardia-induced cardiomyopathy is present or suspected, regardless of body weight[27,28]. In most patients, catheter ablation has no severe acute or chronic complications. Still, minor complications have been described, such as persistent left bundle branch block (0.9%)[18] without major complications[19,20,23-25] or permanent atrioventricular block. The latter was present in the uncommon left anterior fascial VT because, in some cases, it is located in the mid-anterior LV septum, close to the His-bundle[22].

Finally, in exceptional cases, life-threatening periprocedural ventricular arrhythmias have been reported[18].

The prevalence and incidence of VT detected in children are relatively low, and the prognosis of idiopathic VT differs according to its origin. In the case of fascicular VT, our experience revealed an adverse clinical evolution in the pediatric population at medium or long-term follow-up, showing refractoriness to AAD in most patients. Fascicular VT represents a particular condition in which pediatricians and emergency physicians should always consider the 12-lead ECG pattern clues and its typical response to IV verapamil. The mechanism of fascicular VT is a macro-reentry involving the Purkinje system (mainly the left posterior fascicle) and the Purkinje-ventricular myocardium junction. Therefore, ablation targeting with characteristic Purkinje potential electrograms can eliminate this type of idiopathic VT. Catheter ablation is a safe treatment for fascicular VT in children with a high success rate and should represent the first-line approach in symptomatic patients. If the 3D electroanatomic mapping system is available, it should be preferred to minimize exposure to fluoroscopy.

Limitations

This study represents the experience of a single center specialized in a rare clinical condition. We report a relatively small group of patients, so the limitations are those inherent to retrospective studies; however, not enough reports were found in our setting. Although we presented relatively few cases, we had the opportunity to treat different types of idiopathic left fascicular VT. The results are consistent with some Asian reports, where the incidence and prevalence of left fascicular VT are higher than in other geographic areas.

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. This study involved a retrospective review of medical records, for which approval was obtained from a formally constituted review board (Institutional Review Board or Institutional Ethics Committee).

Conflicts of interest

The authors declare no conflicts of interest.

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COCHRANE REVIEW SUMMARY

Interventions to improve compliance with hand hygiene in patient care

Leticia A. Barajas-Nava[1], Ismael Barrañon-Rivera[2], and Bernardo Briones-Aguirre[3]

[1]Unidad de Investigación de Medicina Basada en Evidencias, Centro Asociado Cochrane, Hospital Infantil de México Federico Gómez, Mexico City; [2]Facultad de Medicina, Benemérita Universidad Autónoma de Puebla, Puebla, Puebla; [3]Academia de Salud Pública, Epidemiología y Nutrición Medica, Facultad de Medicina, Benemérita Universidad Autónoma de Puebla, Puebla, Puebla. Mexico

Abstract

Healthcare-associated infections are a significant cause of morbidity and mortality. Hand hygiene is considered an effective method of prevention. This article summarizes the results of a Cochrane systematic review evaluating methods for improving hand hygiene compliance in patient care.

Keywords: *Compliance. Hand hygiene. Patient care. Infection. Systematic review.*

Intervenciones para mejorar el cumplimiento de la higiene de manos en la atención al paciente

Resumen

Las infecciones asociadas con la atención médica son una causa importante de morbilidad y mortalidad. La higiene de las manos se considera un método eficaz de prevención. Este documento resume los resultados de una revisión sistemática Cochrane que evalúa los métodos para mejorar el cumplimiento de la higiene de manos en la atención al paciente.

Palabras clave: *Cumplimiento. Higiene de manos. Atención al paciente. Infección. Revisión sistemática.*

Introduction

The following is a summary of a Cochrane systematic review that evaluated the success of methods to improve compliance with hand hygiene recommendations and determined if hand hygiene decreased healthcare-associated infection rates[1].

Hospital-acquired infections are a severe public health problem worldwide. Over the past two decades, hospitalized patient care (PC)-related infections have increased. Also, infections caused by antimicrobial-resistant gram-negative bacteria have further increased. According to reports from the U.S. Centers for Disease Control and Prevention (CDC), about 1.7 million hospitalized patients each year acquire healthcare-associated infections while being treated for other health problems. In addition, one in 17 patients dies from these infections (more than 98,000). Several studies report a prevalence of healthcare-associated infections between 4 and 11.9%. The most frequent are urinary tract and lower respiratory tract infections[2]. These infections can be considered a serious threat to patient health and an additional

Correspondence:
*Leticia A. Barajas-Nava
E-mail: Leticiaa.barajas@gmail.com

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healthcare cost. The cost estimate per case of a hospital-acquired infection varies between $2,027 and $12,197, resulting in a financial burden of $96-$147 billion per year.

Most hospital-acquired infections are transmitted by direct, person-to-person contact, mainly by healthcare personnel. Hand hygiene is a primary method of infection prevention, as it blocks the transmission of pathological microorganisms. Transmission of pathogens by healthcare personnel in contact with patients or within a sterile area is prevented mechanically by washing hands with soap and water or with an antiseptic liquid. Similarly, rubbing hands with an alcohol-based disinfectant eliminates some of the pathogens that cause hospital infections.

Different groups worldwide have established standards and recommendations for hand washing.

Multiple interventions have been implemented at the healthcare level to improve hand hygiene in an individual or multimodal group. However, the most effective method has not yet been determined. Therefore, the main objectives of this Cochrane systematic review were to evaluate strategies, both in the short- and long-term, to improve hand hygiene compliance in patient care and to determine if increasing hand hygiene compliance can reduce rates associated with healthcare-associated infection.

Methods

The Cochrane review from which this summary was extracted included randomized controlled clinical trials and non-randomized trials, controlled before/after studies, and interrupted time series in which any intervention for the improvement of hand hygiene with soap and water or alcohol-based products, or both, was evaluated in nurses, physicians, and other healthcare workers in any healthcare setting[1].

Time-series studies had to show a clearly defined time for the intervention and at least three points at which data were collected before and after the intervention. Studies that promoted hand hygiene or adherence to infection prevention and control methods were potentially eligible. Studies in which an artificially controlled environment was evaluated or took place outside the clinical setting were excluded.

The following outcomes were assessed in the review:

– Hand hygiene compliance, measured through observation or an indicator of compliance (effective use of soap or sanitizer for hand hygiene). Healthcare workers' self-report of hand hygiene methods was not considered a valid measure of compliance.
– Decrease in healthcare-associated infections.
– Decrease in colonization by clinically significant nosocomial pathogens.

The review was conducted following the Cochrane methodology and the Cochrane Effective Practice and Organisation of Care (EPOC) group[3].

Bibliographic searches were performed in the central electronic databases to identify the studies: Cochrane Central Register of Controlled Trials, PubMed, Embase, CINAHL, Clinical Trials, and the World Health Organization (WHO) international clinical trials registry platform, as well as other relevant resources from 2009 to October 2016.

Study selection, data extraction, and methodology assessment were performed by three independent reviewers using the criteria and methods standardized in the Cochrane EPOC Group. The evaluation of the included studies was performed with the bias detection mechanism[4]. Data analysis was performed with Review Manager 5 statistical software (RevMan 5 Version 5.3)[5]. Results were reported using the measures of effectiveness described in the studies. These measures varied among them: adjusted odds ratios (OR), adjusted relative risks (RR), and mean differences (MD). Two independent reviewers evaluated the quality of evidence using the GRADE methodology[6].

It was impossible to perform a metanalysis of the data due to the heterogeneity among the studies.

Results

A total of 4,219 bibliographic entries were identified for the review[1], of which 3,685 were excluded because they did not meet the inclusion criteria. Subsequently, 534 articles were reviewed, and finally, 26 studies were included (23 studies were eligible after the search, and three had already been included in a previous version of the review)[7].

According to the type of study, 14 of the 26 included studies were randomized controlled studies (two randomized clinical trials, nine cluster-randomized trials, two stepped-wedge cluster-randomized trials, and one randomized trial with cross-over), two non-randomized clinical trials, and ten interrupted time series. The studies were conducted in long-term care facilities, primary care, anesthesia ward, and hospital critical care units (23 studies).

The studies reported the results of multimodal hand hygiene campaigns with complex interventions similar to or based on WHO recommendations on either some or all of the five recommended actions for hand washing[8]. Only three studies reported using the five moments[8] as part of promotional material to inform staff about

hand hygiene. Eighteen studies used more than one intervention. Some studies considered additional methods such as social promotion or personnel participation in the development of the campaign. Six studies reported a single intervention (educational sessions, electronic teaching games, posters, purposeful feedback with additional components). Studies measured hand hygiene compliance by direct observation (20 studies), video observation (one study), or electronic monitoring (one study). In addition, the studies evaluated the proportion of nurses complying with hourly hand hygiene and the development of healthcare-associated infections.

According to the results in the review, hand hygiene compliance increased in all studies, regardless of the intervention or outcome measure employed, study design, or setting. However, the increase and compliance level varied at the intervention's beginning and end. The evidence from the review showed that when feedback and compliance training are implemented as a single strategy, better hand hygiene outcomes are achieved. It was also observed that close placement of an alcohol-based hand sanitizer as the only method used slightly increases slightly hand hygiene compliance. In 11 studies, hand hygiene compliance measures were long-term (12 months or longer). Four studies reported a decrease in infections, with the most commonly reported microorganism, methicillin-resistant *Staphylococcus aureus* (MRSA). Only one study reported a reduction in mortality.

Overall, the risk of bias in the studies was high, with at least two items with high or unclear risk. In addition, the evidence obtained from these studies showed low or moderate reliability.

The WHO recommendations for hand hygiene promotion interventions are the most comprehensive and applicable in all healthcare settings. However, they should be adapted according to the needs and resources available in each location.

Multimodal interventions that include some (but not all) of the WHO-recommended strategies and those that have all of the recommended procedures (plus additional ones) may slightly improve hand hygiene compliance and be more effective in some groups and settings than in others.

It is unclear whether multimodal interventions containing all WHO-recommended strategies (alcohol-based hand gel, training, reminders, compliance feedback, and support) increase hand hygiene compliance or even offer an advantage over individual interventions, as the evidence shows a lesser degree of reliability.

Implications for practice

As healthcare personnel probably transmit most hospital-acquired infections, hand washing should reduce these infections. Several international bodies have promoted the WHO recommendations. Because these recommendations are practical, they tend to be adapted to different locations depending on the resources available and the strategies used.

There is sufficient evidence to justify implementing measures to improve hand hygiene. However, it is not clear whether interventions should be multimodal. Therefore, it will be necessary for organizations to evaluate their performance and revise such interventions accordingly.

New study designs evaluating the efficacy of interventions to improve hand hygiene compliance and reduce healthcare-associated infections need to optimize their methodology and report potential biases. These studies must include sufficient pre-and post-intervention data collection sites and information on the period during which each phase of the study took place. Studies also need to use consistent measures of effect. More detailed designs and analyses are required to determine the value of the individual components.

In addition, there is a need for more efficient communication of the results of studies on interventions to improve hand hygiene compliance, which would facilitate their implementation and adaptation to different healthcare settings.

Healthcare institutions and organizations should be expected to consider relevant measures to improve hand washing compliance by healthcare personnel, contributing to decreasing nosocomial infections and improving healthcare quality.

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. In accordance with the statutes of the Cochrane Collaboration, the Cochrane Associated Centre Hospital Infantil de México Federico Gómez is authorized to publish this Cochrane review summary in Mexico.

Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL CASE

Treatment-refractory heart failure as a manifestation of aortic arch atresia

Luis A. González-Ramos[1], Erika M. Martínez-Carballo[2], Jesús E. Anaya-García[3], Jessica Sánchez-Cárdenas[2], Kenya N. Velázquez-Fontes[2], and Daniel Mazariego-Pedraza[4]

[1]Servicio de Cardiología; [2]Servicio de Neonatología; [3]Servicio de Cirugía Cardiovascular; [4]Servicio de Pediatría Médica. Hospital Infantil del Estado de Sonora, Hermosillo, Sonora, Mexico

Abstract

Background: *Distal segment atresia (isthmus) is an extremely rare anatomical variant of obstructive aortic arch anomalies.* **Case report:** *We present the case of a newborn who, at 48 hours of life, presented a clinical picture of heart failure. The initial echocardiogram showed a congenital interrupted aortic arch type A, patent ductus arteriosus, and ventricular septal defect. Prostaglandins were initially indicated. Subsequently, a second echocardiogram showed the absence of ductus arteriosus; the CT angiography study confirmed this finding and revealed blood flow to the descending aorta through small intercostal blood vessels. The possibility of atresia of the distal segment (isthmus) of the aortic arch was considered and confirmed at the time of surgery.* **Conclusions:** *Aortic atresia should be considered a diagnostic possibility in the presence of type A interrupted aortic arch since the hemodynamic behavior between them is similar. Surgical medical treatment should be individualized since this condition is frequently an emergency in the neonatal period. However, this is not always the case, as other cases have been reported in schoolchildren and adults.*

Keywords: *Aortic atresia. Aortic interruption. Aortic arch.*

Falla cardiaca refractaria a tratamiento como manifestación de atresia de arco aórtico

Resumen

Introducción: *La atresia de segmento distal (istmo) de arco aórtico es una variante anatómica extremadamente rara de las anomalías obstructivas del arco aórtico.* **Caso clínico:** *Se presenta el caso de un recién nacido que a las 48 horas de vida presentó un cuadro clínico de insuficiencia cardiaca. El estudio de ecocardiograma inicial mostró una anomalía congénita de interrupción de arco aórtico tipo A, conducto arterioso y comunicación interventricular. De inicio se indicaron prostaglandinas. Posteriormente, el segundo ecocardiograma mostró la ausencia del conducto arterioso; el estudio de angiotomografía confirmó este hallazgo y también reveló flujo sanguíneo hacia aorta descendente a través de pequeños vasos sanguíneos intercostales. Se consideró la posibilidad de atresia del segmento distal (istmo) de arco aórtico y se confirmó al momento del acto quirúrgico.* **Conclusiones:** *La atresia aórtica debe ser considerada como posibilidad diagnóstica en presencia de interrupción de arco aórtico tipo A, ya que el comportamiento hemodinámico entre ellos es similar. El tratamiento médico quirúrgico debe individualizarse, ya que es frecuente que sea una urgencia en el periodo neonatal. Sin embargo, no sucede así siempre, ya que se han reportado casos en escolares y adultos.*

Palabras clave: *Atresia aórtica. Interrupción aórtica. Arco aórtico.*

Correspondence:
*Luis Antonio González Ramos
E-mail: gonralu@hotmail.com

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Introduction

Obstructive anomalies of the aortic arch (OAA) include a group of anatomical malformations that are differentiated by the lack of anatomical continuity of the aortic arch (interruption of the aortic arch). OAA can present with anatomical continuity of the aorta in which there is a fibrous segment causing a total obstruction (aortic atresia), or there is only a reduction of the vessel lumen, causing a circumscribed partial obstruction (coarctation of the aorta). The clinical behavior of these anomalies is similar. We previously reported our experience in OAA in a study of autopsy cases from the Hospital Infantil del Estado de Sonora and found that coarctation of the aorta was the most frequent finding, followed by interruption of the aortic arch; no case of aortic arch atresia was found[1]. Reports on this anomaly in the medical literature are scarce and are generally isolated clinical cases. As this is the first clinical case of atresia of the distal segment (isthmus) of the aortic arch diagnosed in our institution, we decided to report it.

Clinical case

We describe the case of a male neonate born at term vaginally, the product of the third gestation, with a birth weight of 2.5 kg. The mother was aged 24 years with apparent good health, and the father was 34 years with positive addiction to crystal meth and marijuana. The patient was referred from a secondary level care hospital where he arrived for presenting food refusal, irritability, and crying without tears in the first 48 hours of life. At the hospital, the patient showed acrocyanosis, generalized pallor, dry oral mucosa, respiratory distress, and hypothermia signs. During the hospital stay, the patient was diagnosed with congenital heart disease, interruption of the aortic arch type A with ventricular septal defect and patent *ductus arteriosus*, right ventricular systolic dysfunction, and moderate secondary tricuspid and mitral regurgitation. Prostaglandin was indicated at a dose of 0.01 μg/kg/min. The patient was transferred to the Hospital Infantil del Estado de Sonora in Hermosillo, Sonora, where he received supplemental oxygen through nasal cannulas at 2 L/min with an oxygen saturation of 92% and was admitted to the Neonatal Intensive Care Unit. Physical examination revealed marmoreal skin, systolic murmur in the aortic area, and a third murmur in the mitral area; upper extremity pulses were brisk, and lower extremity pulses were diminished in intensity. A central venous catheter was placed through the right subclavian puncture. The patient was evaluated by a pediatric cardiologist, who found a normal phenotype on physical examination, with hemodynamic instability, earthy tinge, and tachypnea. Auscultation showed a low left parasternal third sound and no precordial murmur. The heart rate was 155 bpm, according to the monitor. The hepatic border was palpated 4-5 cm below the right costal border. Bulging pulses were detected in the upper limbs that were not found in the lower limbs. The sphygmomanometer on the right upper limb recorded a pressure of 128/87mmHg, the left upper limb 107/81mmHg, and the lower limb 86/57mmHg.

Chest X-ray showed grade IV cardiomegaly with a dilated right atrium and capillary congestion in the lung fields. The echocardiogram study indicated *situs solitus* with dilatation of cardiac cavities. In the atrial septum, color Doppler demonstrated a unidirectional left-to-right shunt through a 2.5 mm diameter *foramen ovale*. At the tricuspid valve, continuous and color Doppler showed regurgitant flow with a velocity of 4.19 m/s and a gradient of 70.2 mmHg. Therefore, concordant atrioventricular and ventricular-arterial connections were found. In addition, a membranous ventricular septal defect of 3.5 mm in diameter was observed, and color Doppler demonstrated a bidirectional shunt at this level. The pulmonary artery trunk was found with confluent branches, and no *ductus arteriosus* shunt was observed at this level. The left ventricular outflow tract was free, and the aortic valve showed no alterations. The aortic arch was visible on the left and was incomplete due to a lack of continuity with the descending aorta in its distal segment. The presence of three supra-aortic vessels was visualized, and the interruption of the aortic arch was observed after the origin of the left subclavian artery (Figure 1A and 1B).

Due to the findings, a CT angiography study with image reconstruction was indicated, in which the interrupted segment following the left subclavian artery and the absence of communication between the pulmonary artery and the descending aorta through the *ductus arteriosus* were visualized (Figure 2A and 2B). The interrupted space between the aortic arch and descending aorta measured 12.3 mm. The descending aorta showed good size, receiving blood flow through two small-caliber intercostal arteries in its upper segment (Figure 3). The interrupted aortic arch type A diagnosis was proposed against the differential diagnosis of aortic arch atresia, and urgent surgical intervention was indicated. The patient presented a sudden respiratory deterioration with a decrease in oxygen saturation

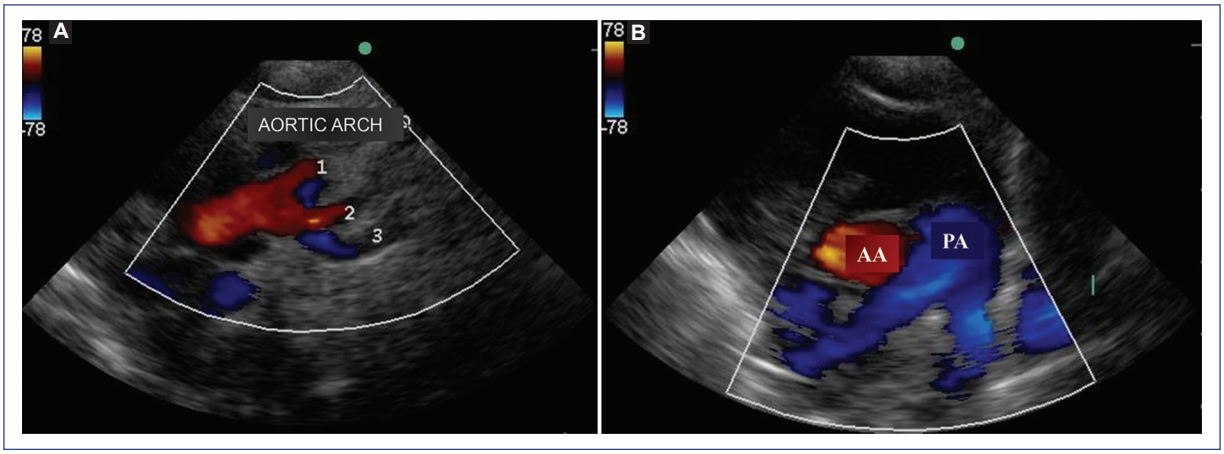

Figure 1. Echocardiogram. **A:** the aortic arch and three supra-aortic vessels with no continuity with the descending aorta are observed. **B:** pulmonary artery (PA), ascending aorta (AA), and confluent branches are shown. Absence of *ductus arteriosus*.

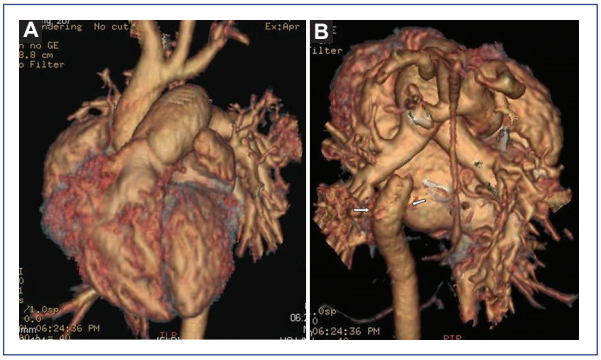

Figure 2. CT angiography. **A:** three supra-aortic vessels and interruption of the aortic arch behind the left subclavian artery are observed. **B:** pulmonary artery and confluent branches are shown. Connection of two small intercostal arteries (⇨) in the upper part of the descending aorta.

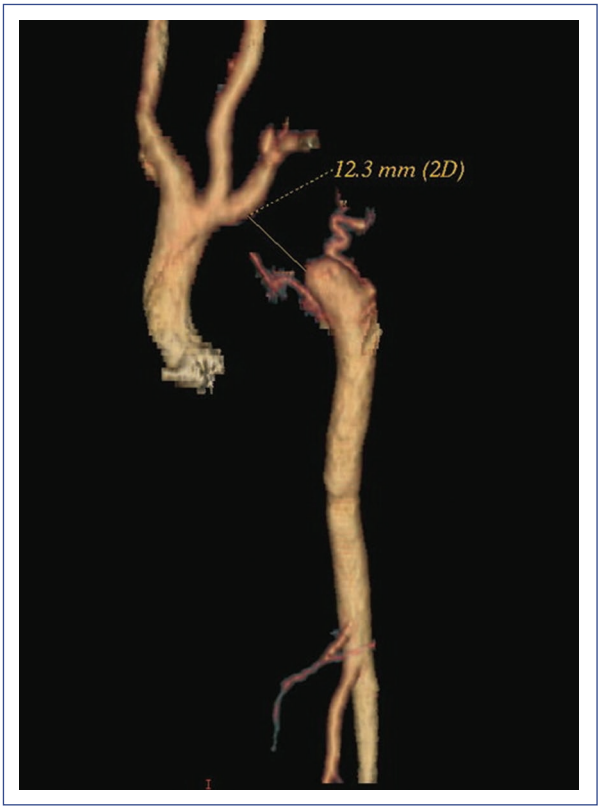

Figure 3. CT angiography. Aortic arch with supra-aortic vessels, discontinuity with the descending aorta, and small intercostal arterial vessels in the upper segment of the descending aorta are observed.

reaching 60% and bradycardia of 70 bpm with poor respiratory effort, for which it was decided to maintain the airway with assisted mechanical ventilation. Due to hypoxemia, the patient presented a state of mixed acidosis. The patient underwent surgery through a left postero-lateral thoracotomy. Vascular structures were dissected and identified, allowing visualization of the continuity of the aortic arch with the descending aorta through an obliterated fibrous tissue. In addition, the *ductus arteriosus* was obliterated, and proximal and distal clamping was performed for section and ligation of the *ductus arteriosus* (Figure 4). Aortic advancement was performed to anastomose the aortic arch and descending aorta, and the subclavian artery was used for a wide junction. Clamping was released, and hemostasis was checked; however, the patient presented gradual and progressive hemodynamic deterioration. Support was given with direct cardiac massage

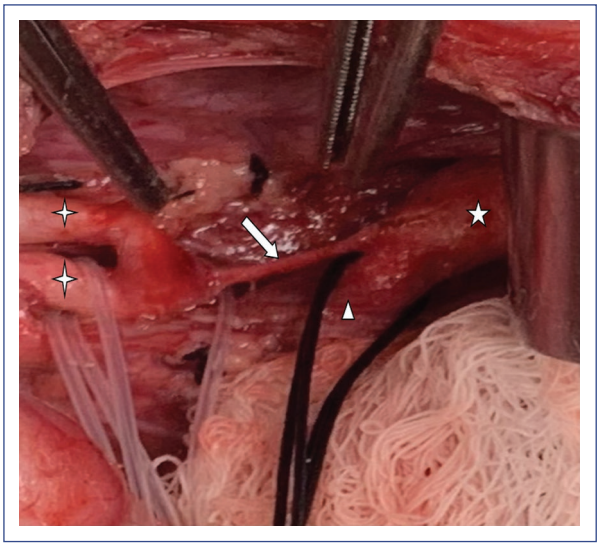

Figure 4. Intraoperative image. Supra-aortic vessels (✧) in continuity with the aortic segment with atresia (⇨) and the descending aorta (☆). Presence of obliterated *ductus arteriosus* ligament (△) connecting with the descending aorta.

maneuvers for 5 minutes with an adequate response. Regardless, after 10 minutes, the patient deteriorated again into asystole but with no response to management.

Discussion

Of the OAAs, atresia of the aortic arch's distal segment (isthmus) is extremely rare. In our previous report on obstructive anomalies of the aortic arch, aortic atresia was not included[1]. The present report is the first clinical case of a patient with aortic atresia diagnosed in a term male newborn with a normal phenotype. OAAs have been associated with genetic syndromes such as 22q·11 deletion, DiGeorge syndrome, and Down syndrome[1,2]. The presentation of this clinical picture in the first 48 hours of life may be related to hemodynamic adjustments that occur in vascular resistance, mainly at the pulmonary level. Newborns and infants present severe heart failure with a tendency to develop shock, which results in death within a few days of birth if untreated[3]. In cases of OAA, the *ductus arteriosus* is usually the structure that allows systemic blood flow along with high pulmonary vascular resistances at birth; subsequently, the *ductus arteriosus* may begin to close, and with it begin the signs and symptoms of hemodynamic imbalance. The use of prostaglandin E_1 is indicated when the specific diagnosis of this ductus-dependent congenital heart disease is established to prevent the closure of the *ductus arteriosus*. The dose of prostaglandin to be administered by infusion is 0.01 μg/kg/min, which may vary according to the clinical condition; in case of circulatory collapse due to closure of the *ductus arteriosus*, a dose of 0.1 μg/kg/min is used.

The presence of cardiomegaly and capillary congestion in the radiological study of the thorax reflects the clinical hemodynamic state in which the patient was received. Some patients may survive infancy without the need for surgical treatment, as they usually have a *ductus arteriosus* and well-developed collateral arteries that carry blood flow to the descending aorta; in the absence of *ductus arteriosus*, early development of collateral arteries of adequate caliber may replace the function of the *ductus arteriosus*[4]. In other cases, when the *ductus arteriosus* is obliterated and collateral arterial vessels are not well developed, a pressure difference can occur in the segments of the obstructed aortic arch and the descending aorta, triggering heart failure, as in this case[2]. The association of patent *ductus arteriosus* in this anomaly has been described in 98%, and ventricular septal defect in 90%[5]. These two anomalies were present in this case, but the *ductus arteriosus* presented early closure, as observed in the echocardiographic and CT angiographic studies. Other associated anomalies reported are aortic and sub-aortic valvular stenosis.

Although the distinction between interruption and atresia of the aortic arch is complex, the hemodynamic consequence of these two anatomical lesions is similar. The surgeon identifies them at the time of surgery, as occurred in this case and in others reported previously[6,7]. Echocardiography remains the preferred method for evaluating patients with suspected congenital heart disease. Furthermore, in the case of OAA, it is possible to define the site of obstruction. Echocardiography can be performed from the prenatal stage, allowing early detection of cardiac malformations and referring the patient to a medical center for optimal care, improving the patient's prognosis. CT angiography studies, especially with multi-slice technology and magnetic resonance imaging (MRI), have gained relevance in studying vascular anomalies, mainly in neonates and infants. In this case, the CT angiography confirmed the echocardiographic findings and provided information on the collateral circulatory state that carried flow to the descending aorta through small intercostal vessels (Figure 3)[8,9]. Cardiac catheterization in the critical clinical condition of the neonate is not an option as it was

previously. Immediate medical care and timely diagnosis contribute to a stable clinical condition, maintaining the *ductus arteriosus* with prostaglandin supply and allowing better hemodynamic stability before surgery. This clinical condition, however, was not present in our patient due to hemodynamic deterioration with pulmonary compromise and hypoxemia that caused a state of mixed acidosis during the critical evolution of this case. Echocardiographic evaluation of this patient found pulmonary arterial hypertension as part of an unstable hemodynamic situation. The patient underwent surgery to connect the aortic arch with the descending aorta through an aortic advancement and using the subclavian artery to create a wide anastomosis[10]. However, the patient deteriorated and presented irreversible cardiac failure at the end of the surgical procedure.

The prognosis of patients with OAA who undergo surgery in medical centers is good. A survival rate of 100% has been described in an average follow-up of 9 years after corrective surgery for this malformation[11]. We consider relevant the state of hypoxemia and mixed acidosis that this group of patients usually present since, for this reason, any pharmacological or surgical intervention may be unsuccessful. We should consider the diagnostic possibility of aortic atresia in the presence of interruption of the aortic arch.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL CASE

Acute generalized exanthematous pustulosis

Gustavo A. Lizardo-Castro[1] *and Gina W. Guillén-Mejía*[2]

[1]*Departamento de Pediatría, Servicio de Dermatología, Hospital Escuela, Universidad Nacional Autónoma de Honduras;* [2]*Facultad de Ciencias Médicas, Universidad Nacional Autónoma de Honduras, Tegucigalpa, Honduras*

Abstract

Background: *Acute generalized exanthematous pustulosis is a rare disease. Although it is usually related to drug intake, it is occasionally associated with infections, especially in the pediatric age. It is characterized by the sudden onset of sterile non-follicular pustules on an erythematous fundus, fever, and leukocytosis, with frequent and prompt spontaneous resolution. It mainly affects adults and is uncommon in childhood. Complications have been reported in approximately 20% of cases.* **Case report:** *We report the case of a 10-year-old female patient with a 5-day history of fever and dermatosis characterized by countless non-follicular pustules, predominantly on the trunk, inguinal folds, and proximal thighs but not involving palms, soles, and mucous membranes. The patient reported an incident of upper respiratory tract infection that occurred 7 days earlier. Histopathological examination confirmed the diagnosis of acute generalized exanthematous pustulosis. Spontaneous resolution occurred within 2 weeks.* **Conclusions:** *This disease is one of the severe cutaneous adverse reactions that usually have a self-limited and benign course within a few weeks. We propose that a previous respiratory infection triggered the acute generalized exanthematous pustulosis in this pediatric case. Knowledge of this pathology by the medical professionals, in general, and the pediatricians, in particular, will prevent an aggressive and inappropriate approach and management.*

Keywords: *Acute generalized exanthematous pustulosis. Severe cutaneous adverse reactions. Drugs. Infections. T cells. Children*

Pustulosis exantemática generalizada aguda

Resumen

Introducción: *La pustulosis exantemática generalizada aguda es una enfermedad rara. Aunque usualmente se relaciona con el consumo de drogas, ocasionalmente se asocia con infecciones, sobre todo en edad pediátrica. Se caracteriza por el inicio súbito de pústulas no foliculares estériles sobre un fondo eritematoso, fiebre y leucocitosis, con frecuente y pronta resolución espontánea. Afecta principalmente a los adultos, y no es frecuente en la niñez. Se han reportado complicaciones en cerca del 20% de casos.* **Caso clínico:** *Se presenta el caso de una paciente de 10 años con fiebre e historia de dermatosis de 5 días de evolución caracterizada por incontables pústulas no foliculares de predominio en tronco, pliegues inguinales y parte proximal de muslos, respetando palmas, plantas y mucosas. Refirió antecedente de infección respiratoria alta 7 días antes. El examen histopatológico confirmó el diagnóstico de pustulosis exantemática generalizada aguda. Presentó resolución espontánea en el transcurso de 2 semanas.* **Conclusiones:** *Esta enfermedad es una de las reacciones adversas cutáneas severas, que tiene un curso usualmente autolimitado y benigno en pocas semanas. Proponemos que la pustulosis*

Correspondence:
*Gustavo A. Lizardo-Castro
E-mail: glizardoc@yahoo.com

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exantemática generalizada aguda en este caso pediátrico fue desencadenada por la infección respiratoria previa. El conocimiento de esta patología por parte del gremio médico, en general, y del pediatra, en particular, evitará un abordaje y manejo agresivo e inapropiado.

Palabras clave: *Pustulosis exantemática generalizada aguda. Reacciones adversas cutáneas severas. Drogas. Infecciones. Células T. Niños.*

Introduction

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction. AGEP is characterized by the sudden development of numerous millimetric, sterile, disseminated, non-follicular pustules on an erythematous-edematous base and is usually associated with fever and leukocytosis[1]. Drugs cause approximately 90% of cases; the remainder is caused by viral and bacterial infections and contact with mercury and spider bites[2]. Its worldwide incidence is 1 to 5 cases per million individuals per year. It is more frequent in adult women and rare in children[2-4].

In 1968, Baker and Ryan published on five patients with no history of psoriasis who presented with pustular eruptions of sudden onset, rapid remission, and no recurrence. They named the pathology exanthematous pustular psoriasis, suspecting that drugs or infections were the triggers. In 1980, Beylot et al.[5] introduced the term acute generalized exanthematous pustulosis. In 1991, Roujeau et al. initially described diagnostic criteria using the European Study of Severe Cutaneous Adverse Reactions (EuroSCAR)[6]:

1. Acute pustular rash
2. Fever > 38 ºC
3. Neutrophilia with or without eosinophilia
4. Subcorneal or intraepidermal pustule on skin biopsy
5. Spontaneous resolution in less than 15 days[3]

In 2001, based on these criteria, Sidoroff et al. included a more detailed, rigorous, and specific scoring system, validated by the EuroSCAR study group[5,6].

This study aims to encourage physicians, in general, and pediatricians and first contact physicians, in particular, to learn more about this rare disease in children. Although AGEP is a severe cutaneous adverse reaction, it is usually benign and uncomplicated. Therefore, a thorough understanding of this disease will prevent aggressive and inappropriate management.

Clinical case

We present the case of a 10-year-old female scholar with pruritic dermatosis associated with a fever of five days' evolution. The patient reported that a week before the onset of the symptoms, she had had a transient, febrile upper respiratory tract infection resolved with symptomatic management. On examination, the patient was in good general condition, with a temperature of 39 ºC, 31.5 kg of weight, and 134.5 cm of height. The patient complained of pruritus and a burning sensation in the lesions distributed on the trunk, inguinal region, and proximal thighs (Figure 1A). The lesions consisted of numerous 1-3 mm small non-follicular pustules, some confluent, on an erythematous base (Figure 1B), with no involvement of the palms, soles, and mucous membranes. A skin biopsy was performed, and symptomatic management with oral hydroxyzine and an emollient cream was indicated. Two days later (at 7 days of evolution), pustules were no longer observed, but erythema and pruritus with residual desquamation persisted (Figure 1C). Laboratory studies reported the following results: culture for pustule bacteria, negative; immunoglobulin (Ig)G and IgM for herpes simplex type 1 and Tzanck's test, negative; hemoglobin (Hb), 13.6 g/dL; hematocrit (HCT), 40.8%; platelets, 370,000/µL; leukocytes, 6,420/µL; neutrophils, 2,620/µL; lymphocytes, 2,630/µL; eosinophils, 460/µL; glucose, cholesterol, triglycerides, transaminases, uric acid, blood urea nitrogen (BUN), and creatinine levels were normal. Biopsy confirmed the diagnosis of AGEP (Figure 2). According to the EuroSCAR scale for AGEP, the following diagnostic scores are used for the diagnosis: 1-4, possible; 5-7, probable; 8-12, definitive. As the patient obtained a score of 11, the diagnosis of AGEP was definitive.

Discussion

AGEP mainly affects adults and is infrequent in children. The estimated global incidence of this condition is 1 to 5 cases per million individuals per year. In contrast, it is approximately 1 case per million children per year[7]. Pediatric publications on AGEP are mainly case reports and a case series with few patients[7-9]. In a systematic review, RegiSCAR reported 49 pediatric cases up to 2014[10]. AGEP is usually observed around the sixth decade of life, with a slight predominance in females. Its

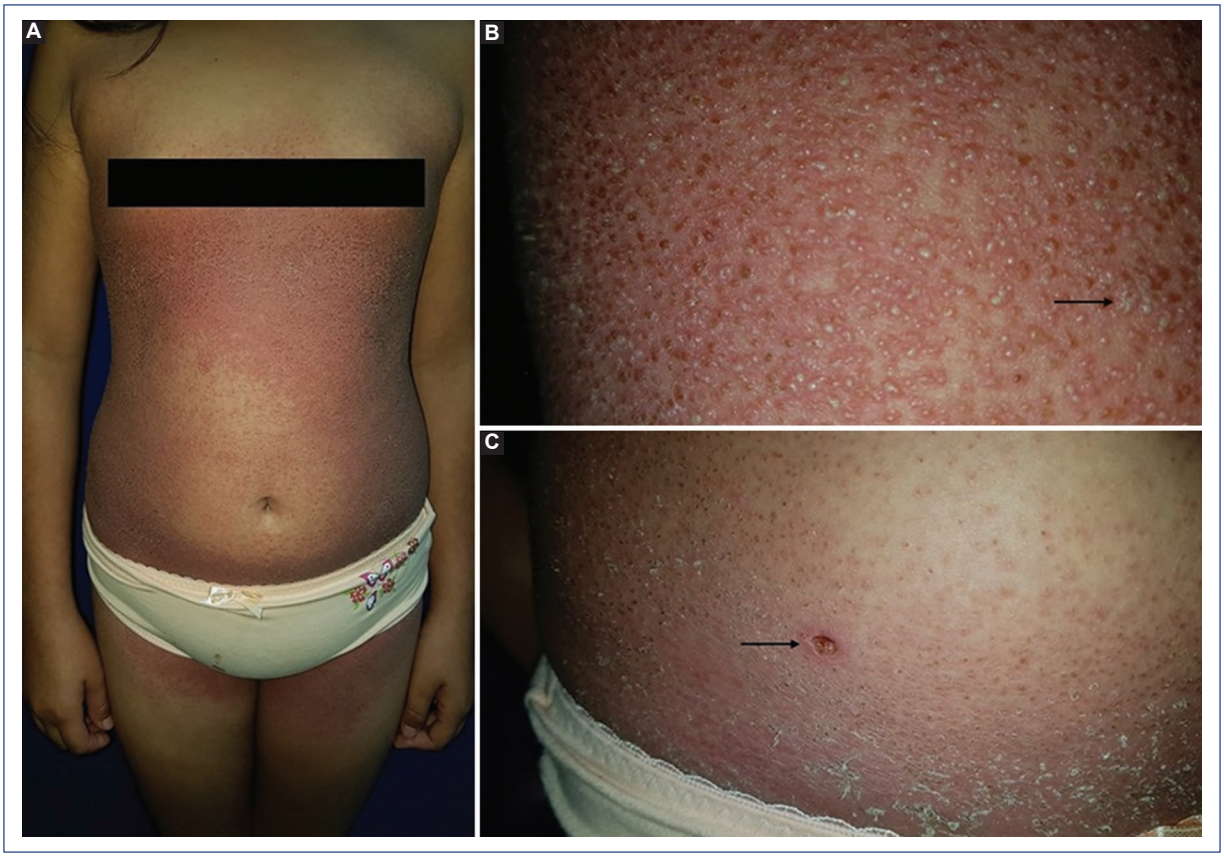

Figure 1. A: acute generalized exanthematous pustulosis. Dermatosis on trunk, inguinal region, and thighs. **B:** hundreds of non-follicular pustules on an erythematous base are observed in the lumbar region, some confluent (arrow). **C:** two days later, erythema persists, but pustules are no longer observed. Post-pustular desquamation is also observed. The arrow indicates the biopsy site.

main risk factors are drug intake, the mean age of 50, and other comorbidities such as diabetes mellitus, psoriasis, and a history of drug hypersensitivity. Seventeen percent of individuals with AGEP have a previous history of psoriasis[11,12].

Drug intake causes more than 90% of the reported cases of AGEP, most frequently antibiotics, mainly beta-lactams and macrolides[3]. Other drugs involved include aminoglycosides, sulfonamides, quinolones, antifungals, antimalarials, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), antihypertensives, calcium channel blockers, and antiepileptics[11,13,14]. The remaining 10% of the cases of AGEP have been associated with viral (enterovirus, adenovirus, parvovirus B19, cytomegalovirus, hepatitis B, Epstein Barr, among others), bacterial (*Chlamydia pneumoniae*, *Escherichia coli*, *Mycoplasma pneumoniae*, among others), and mycotic (pustulosis caused by fungi) infections, spider bites, mercury poisoning[15,16], parasites, and food allergens, as well as radiotherapy, chemotherapy, and pregnancy[11,13,14]. It has been suggested that viral infections could be the most frequent trigger in the pediatric population[2]. The latency between drug exposure and the onset of AGEP varies from a few hours to 1 to 2 weeks, classically ranging from 48 to 72 hours; in the case of antimicrobials, it is usually less than 24 hours[1,16].

Research studies on the pathophysiology have suggested that AGEP is a T-cell-mediated disease. Following drug exposure, specific CD4+ and CD8+ T cells are activated, proliferate, and migrate to the dermis and epidermis. CD8+ T cells induce apoptosis of keratinocytes within the epidermis by forming subcorneal and intraepidermal vesicles using perforin/B-granzyme and Fas ligand mechanisms. CD4+, CD8+ T cells, and natural killer (NK) cells have also been shown to express granulysin in different reactions to drugs or AGEP, suggesting that this substance may also play a role in pathogenesis. During the initial phase, vesicles formed from keratinocyte apoptosis contain mainly

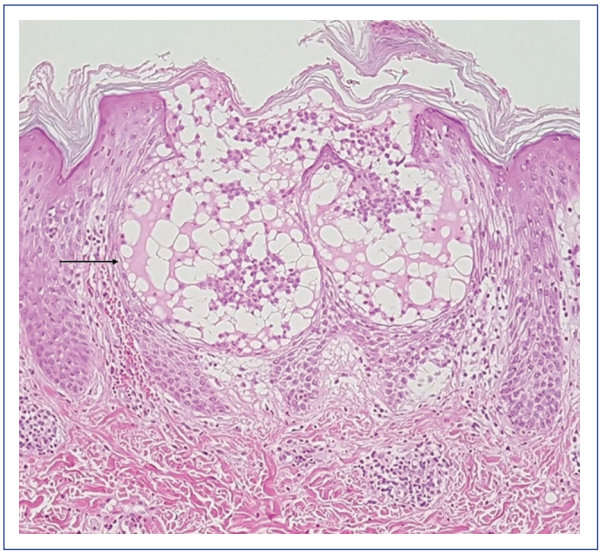

Figure 2. Acute generalized exanthematous pustulosis. Subcorneal blister in the stratum of Malpighi containing fibrin, few neutrophils, and eosinophils (arrow). Spongiosis and lymphocyte exocytosis are observed. Papillary and upper reticular dermis with mild lymphocytic inflammatory infiltrates and few eosinophils with perivascular distribution and intravascular neutrophils. Dilated capillaries with mild wall edema, some congestive with focal erythrocyte extravasation (hematoxylin-eosin stain, 10x).

drug-specific CD4+ T cells and keratinocytes, which release large amounts of a potent neutrophil cytokine (CXCL8). CXCL8 transforms vesicles into sterile pustules by neutrophil chemotaxis[1,17]. Analysis of drug-specific CD4+ T cells from AGEP patients shows a predominant Th1 profile with increased production of interferon-gamma (IFN-γ) and granulocyte/macrophage colony-stimulating factor (GM-SCF), which increases neutrophil survival by enhancing sterile pustule formation.

IFN-γ and GM-SCF can induce the release of CXCL8 by keratinocytes, promoting neutrophil accumulation. Furthermore, CD4+ T cells of some AGEP patients have a Th2 profile with elevated production of IL-4 (interleukin 4) and IL-5 (a potent stimulator of eosinophil growth and proliferation), which explains the eosinophilia found in up to 30% of AGEP cases[1]. A higher level of IL-17 expression by neutrophils, mast cells, and macrophages and a lower level by T cells has been described in patients with AGEP, suggesting that innate cells may be involved in pathogenesis[17]. *IL36RN* gene mutations and increased CXCL8-mediated neutrophilic chemotaxis have been found in some patients with AGEP, suggesting their involvement in its pathogenesis[7]. The genetic predisposition for the development of AGEP is unknown; however, there might be a correlation between mutations of *IL-36RN*, which encodes the interleukin-36 receptor antagonist (IL-36Ra), and the development of generalized pustular eruptions after drug consumption. This suggests that patients with such a mutation are predisposed to develop AGEP [1,17]. In addition, IL-36 Ra deficiency in some patients with AGEP appears to play a role in the increased expression of several proinflammatory cytokines and chemokines, such as IL-1, IL-6, IL-12, IL-23, IL-17, tumor necrosis factor-alpha (TNF-α) and CXCL8/IL-8, which enhances the recruitment and activation of neutrophils[1].

In cases of AGEP of infectious etiology, there is no precise pathophysiological mechanism. However, it is hypothesized that infectious antigens could cross-react with drug antigens, act as haptens, or synergistically with some drugs, triggering the same immunologic reaction as in classical drug-induced AGEP[16]. Regarding the underlying pathogenesis, it has been proposed that drug-like infections lead to T-cell activation[7].

AGEP manifests clinically as a cutaneous eruption of acute onset and is characterized by the appearance of numerous sterile, non-follicular pustules < 5 mm in diameter on an erythematous and edematous base. The dermatosis predominates on the trunk, upper extremities, and intertriginous regions, mainly the neck, axillae, and inguinal areas. However, it may be disseminated without affecting the face, palms, and soles, as in the present case. Occasionally, pustules may coalesce and lead to superficial collarette-shaped desquamation at the sites of the previous lesions[18]. The reaction is limited to less than 15 days after discontinuation of the causative agent or remission of the infection. It may be accompanied by fever, leukocytosis, neutrophilia, and sometimes eosinophilia, depending on the case. Systemic involvement with hepatic, renal, or pulmonary involvement has been described in 17% of patients[17]. Other symptoms include pruritus or burning sensation and mucosa involvement in up to 20% of cases, generally in severe forms and usually restricted to the oral mucosa or rarely to the conjunctivae[1,16]. Edema of the scrotum, hands, face, purpura, petechiae, vesicles, blisters and target lesions have been reported in 50% of patients[11,17]. In addition, severe atypical presentations of AGEP have occasionally been described. These extreme forms have been considered the overlap between AGEP and toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS). They may present with a clinical course similar to these conditions but with the histopathology of AGEP[6,16,17].

The diagnosis of AGEP is based on clinical and histological criteria validated by the EuroSCAR study group[3]. A more precise evaluation based on morphology, course, and histopathological findings was proposed by Sidoroff et al. and validated by the EuroSCAR group. According to the score obtained, the case can be classified as possible (1 to 4 points), probable (5 to 7 points), or definitive (8 to 12 points)[5,6,19]. According to this scale, the reported case was diagnosed as definitive for AGEP, scoring 11 points.

Histopathology confirmed the clinical diagnosis. Usually, subcorneal or intraepidermal spongiform pustules, edema of the papillary dermis, perivascular infiltrates of neutrophils, and some eosinophils are observed (Figure 2). In addition, focal keratinocyte necrosis and leukocytoclastic vasculitis are occasionally detected[17,20].

Patch tests are helpful when it is necessary to identify the drug involved[4]. A multicenter study showed that 58% of AGEP patients showed positive patch tests[4,10]; another study found positivity in 80%[19]. A negative test does not rule out the involvement of a particular drug. Dermoscopy with polarized light can be helpful: in the early stages, small, milky macules and papules, round globules, and sparsely scattered crusts on a pinkish/reddish background are observed[21].

The differential diagnosis of AGEP should be made primarily with generalized pustular psoriasis of the von Zumbusch type. However, it is sometimes difficult to differentiate, as both may present with a similar clinical picture and unclear histopathology. In the latter, however, there is usually a previous history of psoriasis, fever, and a rash that persists longer, has a more generalized distribution with a tendency to recur, and can be fatal if not adequately treated[11,17]. The history, clinical picture, and histopathological findings can easily exclude other pustular eruptions of bacterial or fungal origin and neutrophilic dermatoses[17]. Differential diagnoses with drug-induced skin disorders such as DRESS syndrome, Stevens-Johnson syndrome, and NET should be considered in severe cases[3]. The most critical factor for differential diagnosis is the faster resolution time observed in AGEP[17].

Although AGEP is benign and self-limited in most cases, it can present renal, hepatic, pulmonary, and bone marrow complications[17]. These complications are infrequent and occur mainly in the elderly, patients with comorbidities, or those with mucous membrane involvement[1,11]. Visceral involvement occurs in < 20% of cases, and amoxicillin is the most commonly implicated drug[16]. In these cases, it can cause death due to multiorgan dysfunction and disseminated intravascular coagulation, although mortality occurs in < 5% of cases[1].

Cases have been reported of patients with AGEP presenting with systemic involvement: hepatomegaly, anemia, acute respiratory failure, hypotension, acute renal failure, cholestasis, and spinal cord involvement, as well as elevated liver function test values (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase), and increased urea and creatinine[20]. In addition, high absolute neutrophil count and C-reactive protein levels were associated with systemic organ involvement[1].

There are no evidence-based treatment guidelines for the management of AGEP[16]. However, since its resolution is usually spontaneous, treatment is supportive, so topical corticosteroids, moisturizers, emollients, antipyretics, and oral antihistamines are frequently adequate[15]. The most critical measure is the suspension of the causative drug (or the remission of the infectious condition). With this, the cutaneous and even systemic involvement resolution occurs in < 15 days[16], as in this case. In the pustular phase, moist dressings with antiseptic solutions and topical steroids can be used, while in the desquamative (post-pustular) phase, emollients could optimize the barrier function[16,17]. Antibiotics are counter-indicated unless there is superinfection of the lesions[1,13]. Medium and high potency topical corticosteroids are used for symptomatic relief of pruritus and inflammation[22]. Systemic corticosteroids are not usually necessary. Some authors consider them effective in cases of extensive cutaneous involvement (prednisone 0.5-1 mg/kg/day)[3,13], although two cases of oral corticosteroid-induced AGEP have been reported[17]. The usefulness of cyclosporine and etanercept in patients resistant to corticosteroid treatment has also been described[18]. In cases of AGEP mimicking NET, intravenous immunoglobulin has been used[16]. Reintroducing the implicated drug should be avoided because of the risk of recurrence, usually with a more rapid onset[13].

The prognosis of this disease is generally favorable, even if there is systemic involvement[13]. The condition resolves spontaneously approximately 10-15 days after discontinuation of the causative drug. Initially, pustules and fever disappear, followed by the collarette-shaped desquamation[6]. The same evolution is observed in cases of AGEP with infectious etiology, which is more frequent in children, as in the case described.

In conclusion, AGEP is a rare disease in pediatric patients. However, this condition should be considered a possible diagnosis in the presence of a sudden onset picture with numerous non-follicular pustules on an erythematous base and associated with fever. Pharmacological etiology is predominant,

although AGEP is often associated with infections in children. The EuroSCAR scale facilitates the confirmation of the diagnosis. In most cases, treatment is supportive with an excellent prognosis. Knowledge of this pathology will improve the diagnostic and therapeutic approach to avoid aggressive and inappropriate management.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interest.

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