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Artículo de revisión

Avances en la lactancia: explorando el papel de la microbiota de la leche materna humana en la maduración intestinal neonatal

Artículos de investigación

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Luxación congénita de rodilla: tratamiento conservador de una serie de casos

Casos clínicos

Malformación pulmonar congénita híbrida: reporte de caso

Masa abdominal secundaria a *fetus-in-fetu* en un neonato: reporte de caso y revisión de la literatura

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Advances in lactation: exploring the role of human breast milk microbiota in neonatal gut maturation

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Abstract

The neonatal microbiota plays a central role in shaping gastrointestinal and immune system maturation, laying the foundation for lifelong health. Prenatally, bacteria in the amniotic fluid and meconium, likely derived from the maternal microbiota, prime the fetal immune system to tolerate beneficial microbes postnatally. At birth, the neonate acquires its initial microbiota through the birth canal or environmental exposure, with breast milk delivering human milk oligosaccharides that selectively nourish beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium*, fostering a protective gut microbiota. Meconium in the colon further supports this process by acting as a barrier against pathogens while promoting colonization by commensal microbes. These early microbial communities enhance intestinal barrier function through tight junction maturation, reduce permeability, and bolster immune defenses, mitigating infection risks. As infants transition to solid foods, microbial diversity increases, supporting intestinal villi development, nutrient absorption, and dietary adaptability. By approximately 3 years of age, the gut microbiota stabilizes, driving critical roles in digestion, vitamin synthesis, and inflammation regulation. This review synthesizes current evidence on the dynamic interaction and influence of maternal factors and breast milk composition on neonatal microbiota development, highlighting current insights into their implications for the infant's immune system and gastrointestinal development.

Keywords: Breast milk. Gastrointestinal development. Neonate. Lactation. Microbiota.

Avances en la lactancia: explorando el papel de la microbiota de la leche materna humana en la maduración intestinal neonatal

Resumen

La microbiota desempeña un papel central en la maduración del sistema gastrointestinal e inmunitario del neonato, sentando las bases para la salud a lo largo de su vida. Antes del nacimiento, las bacterias presentes en el líquido amniótico y el meconio, derivadas de la microbiota materna, preparan al sistema inmunitario fetal para poder tolerar microbios beneficiosos después del parto. Al nacer, el neonato adquiere su microbiota inicial a través del canal de parto o mediante su exposición al ambiente. La leche materna proporciona oligosacáridos que nutren selectivamente bacterias beneficiosas, como *Lactobacillus* y *Bifidobacterium*, iniciando una microbiota intestinal protectora. El meconio en el colon apoya este proceso como

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una barrera mecánica contra patógenos mientras promueve la colonización por microbios comensales. Estas comunidades microbianas tempranas fortalecen la función de la barrera intestinal mediante la maduración de uniones estrechas, reduciendo la permeabilidad y fortalecen las defensas inmunitarias, mitigando los riesgos de infección. A medida que los bebés comienzan a consumir alimentos sólidos, la diversidad microbiana aumenta, fomentando el desarrollo de las vellosidades intestinales, mejorando la absorción de nutrientes y dando paso a la adaptabilidad dietética. Aproximadamente a los tres años, la composición de la microbiota intestinal se estabiliza y desempeña roles críticos en la digestión, la síntesis de vitaminas y en la regulación de la inflamación. Esta revisión sintetiza la evidencia actual sobre la influencia de la composición de la leche materna en el desarrollo de la microbiota neonatal, destacando conocimientos actuales sobre sus implicaciones en el sistema inmunitario y el desarrollo gastrointestinal infantil.

Palabras clave: Leche materna. Desarrollo gastrointestinal. Neonato. Lactancia. Microbiota.

Introduction

Breastfeeding is universally recognized as the optimal mode of infant nutrition, delivering essential nutrients and bioactive compounds critical for newborn growth, development, and long-term health. This review elucidates the physiological intricacies of the mammary gland, the dynamic composition of breast milk, and the vital role of human milk oligosaccharides (HMOs) in infant health. The mammary gland, driven by complex hormonal and metabolic interactions, undergoes distinct developmental phases to produce milk tailored to the infant's evolving needs^{1,2}. Breast milk, a sophisticated biological fluid, not only provides vital energy and nutrients but also fosters physical and emotional well-being for both mother and child, contributing significantly to public health and sustainable food systems^{3,4}. The text further highlights the adaptive nature of breast milk, with its microbiota and bioactive components, such as HMOs, varying across lactation stages and influenced by factors such as maternal diet and mode of delivery⁵⁻⁹. HMOs, the third most abundant component in human milk, play a crucial role in shaping the infant gut microbiota, enhancing intestinal barrier function, and supporting immune development, with notable variations in concentration between colostrum and mature milk, and higher levels in preterm births⁷⁻⁹. This introduction sets the stage for a detailed exploration of the physiological mechanisms, compositional dynamics, and immunological benefits of breastfeeding, emphasizing its foundational role in infant health and development.

Breastfeeding

The mammary gland exhibits distinctive physiological characteristics throughout its developmental process, profoundly impacted by mammatropic hormones closely linked to pregnancy and lactation. In contrast to

exocrine organs such as the salivary gland, which consistently produce saliva, the mammary gland undergoes development only within a specific period of life to complete its function of milk production¹⁰. The development and functionality of the mammary gland constitute intricate processes involving complex hormonal and metabolic interactions. Hormones play a fundamental role in guiding mammary growth from its origin through gland maturation, ensuring the sustained lactation process and efficient ejection of breast milk¹¹.

Breast milk is a highly complex biological fluid that plays a crucial role in the growth and development of newborns¹². Breast milk administration is vital to ensure the health rights of infants, as it provides essential energy and nutrients needed for optimal growth and development. Beyond its nutritional significance, breastfeeding confers primary advantages, fostering both the physical and emotional well-being of both the infant and the mother, with potential enduring effects on their overall lives. Moreover, breastfeeding contributes significantly to public health, positioning breast milk as a cornerstone in establishing a robust and sustainable food system¹³.

The dynamic nature of breast milk composition adapts to the evolving needs of the growing infant throughout the breastfeeding journey. Variations in the microbiota are evident at different stages, spanning from colostrum through transition milk to mature milk, introducing distinctions in microbial content^{14,15}. Infancy constitutes a critical phase in the development of the intestinal microbiota, characterized by its instability and susceptibility to dysbiosis influenced by external factors. Various determinants shape the establishment of infant gut microbiota, including mode of childbirth, feeding practices, nutritional status, and the administration of antibiotics. Nevertheless, the precise origin of the infant gut microbiota remains a topic yet to be fully elucidated¹⁴.

Breast milk composition

Breast milk is a complex secretion that contains proteins and mono-, di-, and oligosaccharides, with oligosaccharides standing as the third principal component after lactose and fat. Breast milk stands out as an abundant reservoir of bioactive compounds, encompassing enzymes, hormones, growth factors, specific proteins, polyamines, nucleotides, and oligosaccharides collectively termed as milk trophic factors¹².

HMOs represent a diverse category of free oligosaccharides, constituting the third-largest group of bioactive molecules in human milk, and serve as essential carbon sources for bacterial species colonizing breast-fed infants¹⁶. Research indicates that HMOs exert direct or indirect effects on the mucosa of infants' intestines and systemic immunity. Some studies have informed the role of HMOs in the proliferation and maturation of intestinal cells, including crypts and goblet cells. In addition, HMOs modulate gene expression in the intestinal epithelium, influencing the functionality of the intestinal barrier, thereby regulating local and systemic immunity¹⁶. Notably, colostrum, the initial milk produced by mothers, has the highest concentration of HMOs at approximately 20-25 g/L. However, as the production of mature milk progresses, the concentration of HMOs decreases to approximately 5-20 g/L. Moreover, the composition of HMOs exhibits variation among women and undergoes changes over the course of lactation, influenced by factors such as diet and other biological parameters^{17,18}.

Studies reveal elevated concentrations of HMOs in the milk of mothers delivering prematurely compared to those giving birth at term^{13,17}. The essential role of HMOs in supporting immune system development and conferring protection against infectious diseases is underscored by their interaction with intestinal epithelial cells or their indirect influence through the modulation of the intestinal microbiota. This modulation, notably driven by bifidobacteria, adds a layer of complexity to the immune-supportive functions of HMOs¹⁸.

Microbiota of the mammary gland

Breast milk harbors a distinctive microbiota, and currently, two theories elucidate the presence of bacteria in breast milk. The first theory suggests that bacteria are introduced through contamination from the surrounding skin of the mammary gland and the neonate's oral cavity. This occurs via a retrograde flow between the mammary ducts and the infant's mouth, facilitating

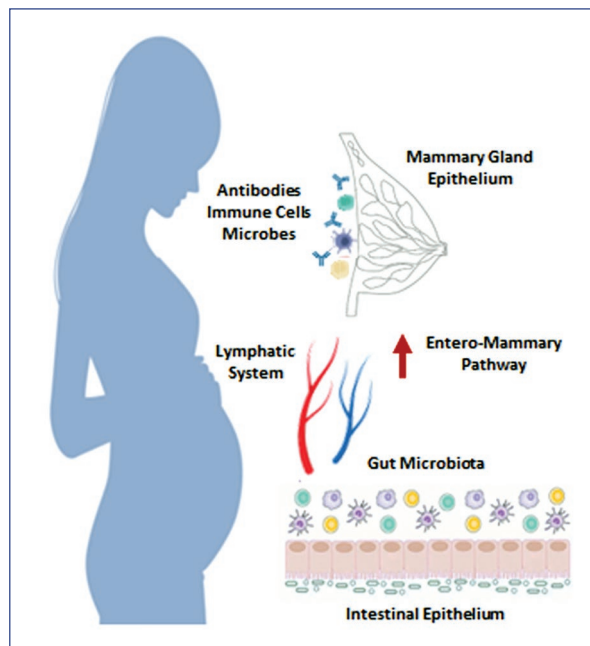


Figure 1. The entero-mammary pathway and mammary-gland microbiota acquisition. This pathway describes the translocation of bacteria from the maternal gut to the mammary glands through the lymphatic and circulatory systems. The establishment of a microbiota in the mammary glands through this pathway is essential for the infant's immune system development and overall health.

bacterial transfer. However, this theory faces challenges. For instance, bifidobacteria, commonly encountered in breast milk, are predominantly anaerobic and may not originate from the mother's skin microbiota. Moreover, some orally administered bacteria to the mother have been subsequently detected in breast milk, indicating active migration¹⁹.

The second theory, active migration, proposes that maternal gut bacteria colonize the mammary gland and transit through breast milk to the neonate. This process has demonstrated efficacy in preventing infectious diseases and contributing to immune system maturation (Fig. 1)¹⁹. A suggested mechanism for active migration involves the ability of intestinal microbiota exopolysaccharides to maintain immunological silence, evading the host's immune response and facilitating migration to the mammary gland²⁰.

Hormonal fluctuations during pregnancy and lactation also contribute to this process. Increased lymph flow and circulation to the mammary gland during pregnancy, aided by hormonal influx, assist in mammary duct dilation. Progesterone hampers phagocytosis by immune cells, interrupts Toll-34 receptor action,

initiates immune signaling, and ensures the inactivity of proinflammatory cytokines such as TNF and interleukin-1 β while not affecting other anti-inflammatory cytokines such as IL-10. Prolactin also plays a significant role in this orchestration¹⁹.

Breast milk assumes a fundamental role in initiating, determining, and regulating the composition of the neonatal microbiota. It provides a spectrum of immunological factors, including immunoglobulins, cytokines, probiotics, and prebiotics, which modulate the colonization of microorganisms (Fig. 2). Presentation of new microorganisms through breast milk introduces approximately 10⁹ microorganisms per liter of milk, establishing it as the primary source of commensal, mutualistic, or probiotic bacteria for infant intestinal colonization. Commonly encountered milk bacteria encompass *Staphylococci*, *Corynebacteria*, *Lactobacilli*, *Micrococci*, and *Bifidobacteria*, with the latter predominantly localized in the nipple and milk ducts. These milk bacteria contribute to the prevention of infectious diseases and the maturation of the immune system²¹. The maturation and development of the microbiota hinge on various factors such as mode of delivery, gestational duration, newborn diet, and host genetics¹².

The role of microbiota in the development of the gastrointestinal system of neonates

Newborn care is characterized by the intricate physiological adjustments accompanying the transition from intrauterine to extrauterine life. This necessitates the orchestration of complex homeostatic mechanisms, involving the maturation of vital organs and systems essential for survival outside the maternal uterus. The gastrointestinal tract encompasses various luminal structures - the oropharynx, esophagus, stomach, duodenum, jejunum, ileum, cecum, and colon - collectively serving neural, endocrine, exocrine, and immune functions, as well as facilitating digestion and nutrient absorption²².

The neonatal period assumes vital importance for the development of innate and adaptive immune functions, coinciding with substantial changes in the gastrointestinal microbiome. While the intrauterine environment was traditionally considered sterile, recent studies have identified microbes in amniotic fluid, placenta, and meconium, suggesting prenatal exposure to microorganisms. This exposure likely contributes to intestinal development, initiating colonization before birth²³. The newborn's intestinal microbiota forms within specialized microbial ecosystems across distinct intestinal

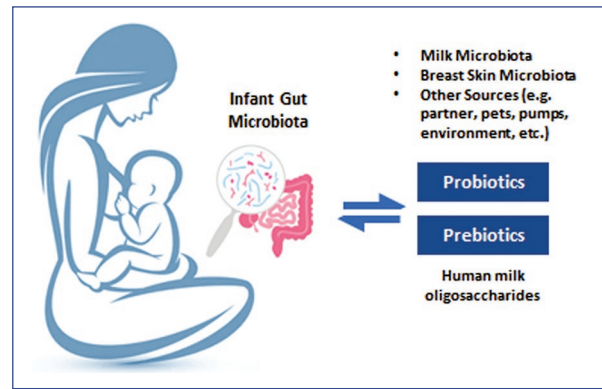


Figure 2. Formation of infant gut microbiota. Lactation plays a crucial role in the transfer of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, through breast milk. In addition, breast milk contains prebiotics, including human milk oligosaccharides (HMOs), which support the growth and activity of these beneficial bacteria. The combined action of these prebiotics and probiotics establishes a healthy gut microbiome, which is vital for neonatal gastrointestinal development, immune function, and overall health.

compartments. Early bacterial colonization is essential for the host's digestive and immune homeostasis, as well as metabolism and behavior²⁴. The neonatal developmental window marks a critical period for establishing the gut microbiota, with the initial contact signaling the commencement of a crucial mutualistic relationship, integral for both short- and longer-term health.

Breast milk serves as a source of active and passive protection for infants due to its rich content of bioactive factors, which can be categorized into three groups: antimicrobial factors, immunomodulatory factors, and factors promoting the development of the gastrointestinal system²⁵. Antimicrobial factors, including immunoglobulin A, lysozyme, lactoferrin, and leukocytes, shield the infant from harmful microorganisms. Immunomodulatory factors, such as platelet-activating factor and polyunsaturated acids, assist in regulating the infant's immune system. Moreover, hormones, growth factors, and gastrointestinal mediators in breast milk contribute to the development of the gastrointestinal system. Breast milk features an increased concentration of cytokine transforming growth factor- β (TGF- β), fostering immune tolerance toward maternal commensal microorganisms and reducing inflammation in response to the evolving intestinal microbiota. Studies indicate that probiotic supplementation in lactating mothers elevates the concentration of TGF- β in breast milk, thereby enhancing intestinal maturation in

newborns²⁶. The maternal microbiome, derived from various sources such as the vaginal and urinary tracts, oral cavity, and intestines, plays a fundamental function in the initial seeding of the neonate's microbiota, while subsequent modifications occur through horizontal transmission due to various exposures²⁰.

The neonate's immune system development is intricately linked to the bacterial density within the *Firmicutes* phylum, encompassing key genera such as *Lactobacillus*, *Actinobacteria*, and *Bifidobacterium*. The establishment of these bacterial phyla creates a conducive environment for the development of *Bacteroidetes*, specifically the class *Bacteroides*, culminating in the formation of enterotype 1²⁷. Anaerobic bacteria, constituting 60-90% of the microbiota, prevail over aerobic bacteria, predominantly belonging to the prominent families of *Bacteroides* (23%) and *Firmicutes* (64%). Furthermore, a fungal species has been identified as a constituent of the intestinal microbiota²⁸.

The continuous expansion and diversification of the microbiome often correlate with dietary changes. Commensal bacteria form a symbiotic relationship with the gastrointestinal (GI) epithelium and mucosal-associated lymphoid tissue. These bacteria, along with their metabolic byproducts, can permeate the submucosa and engage with gastrointestinal lymphoid tissue, influencing immune tolerance. This interaction is vital for coexisting with gastrointestinal microbes without triggering inappropriate inflammatory responses or compromising the immune response to pathogens. In premature infants, the gastrointestinal tracts are underdeveloped, rendering them less adept at defending against enteric pathogens due to compromised mucosal epithelial barriers and deficiencies in immune cells²⁹.

The mode of delivery significantly influences the composition of the adult microbiota. In the initial days of life, the microbiota follows a relatively stable pattern influenced by the development of an anaerobic environment, nutrient availability, and interactions among resident bacteria. The fecal metabolome results from the breakdown of nutrients in milk, microbial colonization, and the infant's physiology³⁰. The infant microbiota attains maturity levels comparable to adults at around 2.5-3 years of age. While feeding patterns and delivery mode play central roles in infant microbiota development, gestational age emerges as the most influential factor³¹. During and shortly after birth, the neonate's gut undergoes colonization by microbes from the mother and the environment until a complex and dense microbiota is established. The succession of microbes

colonizing the intestinal tract is particularly notable during early development, transitioning from breast-feeding to formula feeding, weaning, and the introduction of solid foods³². The composition and function of the microbiota significantly contribute to the development and maturation of the neonatal gastrointestinal tract, thereby holding implications for long-term health outcomes²².

An enriched maternal microbiota holds the potential to directly colonize the neonatal gut or indirectly shape the succession of gut bacteria. The maternal environment plays a fundamental role in fetal and neonatal gut development and maturation through four primary routes: transplacental transfer of maternal blood factors to the fetus, fetal ingestion of amniotic fluid in utero, neonatal gut microbial colonization by maternal microbiota in the perinatal period, and the presence of factors in breast milk. Thus, the transition from prenatal to postnatal life emerges as a critical window for maternal dietary intervention, ensuring the normal development of the infant's gastrointestinal tract and potentially imparting long-term effects on adult health²⁹.

Various factors, spanning the prenatal, perinatal, and postnatal phases, exert influence on the colonization of the newborn's intestinal microbiota, impacting the development of the immune system and the risk of developing allergies. Children with allergic diseases exhibit a distinct composition of their intestinal microbiota during their early years³³. During the intrauterine phase, the fetus develops within an environment closely tied to the maternal microbiome, contributing to the diversity of the fetal microbiota. As gestation progresses, the fetal microbiota is established through hematogenous routes and the ingestion of amniotic fluid. At birth, the formative process continues, with the type of delivery, maternal contact, breastfeeding, and environment all influencing the process. Consequently, the infant's intestinal microbiota develops a characteristic profile analogous to adults by the end of the 1st year, continuing to form a microbiome resembling its parents and environment³⁴. The development of the infant's intestinal microbiota unfolds in four distinct phases: initial acquisition, the remaining period of exclusive breastfeeding, the time between the start of supplementation and the cessation of breastfeeding, and the period of conversion to adult microbiota patterns post-weaning³⁵. The bacterial profile of breast-fed infants undergoes a shift toward that of formula-fed infants following the initiation of dietary supplementation, marked by a decrease in the dominance of bifidobacteria. However, during phases 3 and 4, involving the

introduction of solid foods and weaning, the disparities in fecal microbiota between breast-fed and formula-fed infants dissipate. By the 2nd year of life, the fecal microbiota of infants reflects that of adults³².

Gastrointestinal development of infants

Intestinal development is characterized by the rapid growth of tissue during both prenatal and postnatal periods. The gastrointestinal tract initiates as a simple tubular structure in the 4th week of gestation, swiftly polarizing along the anteroposterior axis. Continuous cell division gives rise to three primary layers - the endoderm, mesoderm, and ectoderm - forming the foundation for the components of the gastrointestinal tract. The embryological gastrointestinal structure is further classified into three sections: the anterior, middle, and posterior intestines, with the gastric mucosa featuring acid-producing parietal, chief, and neuroendocrine cells²⁹. The development and maturation of the gastrointestinal system constitute a continuous process that commences in early fetal stages and persists postnatally.

The process of intestinal maturation unfolds through five distinct phases:

- Phase 1: organogenesis begins in the embryonic phase around the 5th week of gestation.
- Phase 2: this phase witnesses the formation of the primitive intestine, concurrent with the openings of the gastrointestinal tract. Fetal ingestion of amniotic fluid initiates, accompanied by rapid growth and the development of villi and microvilli.
- Phase 3: the late gestational stage is marked by active cell differentiation, with selective apoptosis at the base and ends of the villi.
- Phase 4: postnatally, this phase presents the highest antigenic load and prompts the differentiation between self and non-self.
- Phase 5: initiated during late infancy and extending into childhood, this phase coincides with the transition from milk to complementary feeding. Intestinal maturity, like that of older children, is determined during the second phase of mucosal expansion³⁶.

Commencing at week 12 of development, the fetus begins to ingest amniotic fluid, initiating intestinal peristalsis. By week 20, the fetus possesses hydrochloric acid and all digestive enzymes, albeit in limited quantities. Within the digestive tube, a greenish paste known as meconium forms, comprising bile pigments, digestive tract secretions and shedding, and remnants of amniotic fluid. Typically, meconium is expelled after

birth. Coordination between stomach and intestinal motility patterns is crucial, with normal function relying on feedback from the gastrointestinal tract. Delayed gastric emptying is more prevalent in premature newborns compared to full-term newborns. Small intestine motility patterns are also aberrant, particularly in infants born before 28 weeks of gestation³⁷.

Stomach postnatal development depends on breastmilk and microbiota interaction

The development of the human stomach is a complex process, significantly influenced by the interaction between breast milk and microbiota. The stomach begins as a fusiform dilation of the foregut in the 4th week of development, lined by endodermal cells, which give rise to the mucosa layer³⁸. The stomach mucosa comprises several cell types, including parietal cells (which produce hydrochloric acid), Chief zymogenic cells (which produce pepsinogen), and mucus-secreting cells, among others. The development of the stomach epithelium can be divided into several stages as the histological structures and differentiated cells emerge³⁹. The first phase occurs during embryogenesis, when gastric epithelial stem cells start to exhibit a columnar appearance. The second phase is characterized by the formation of primitive gastric glands through stem cell proliferation and cell differentiation. The final phase occurs in the late fetal stage, involving the differentiation of fundic and pyloric glandular cells. Although the stomach's mucosal layer acquires most of its morphological features by the 15th week, the functional establishment differs between cell types during prenatal and postnatal development⁴⁰.

For instance, the maturation of chief cells, responsible for pepsin production, coincides with the thickening of the glandular region. In the human fetus, chief cell granules appear at around 16 weeks, and pepsinogen is detectable in the stomach by 17-18 weeks⁴⁰. However, at birth, pepsin levels in the newborn's stomach are low. After birth, proteolysis and protease activity increase with the infant's maturity, with preterm infants showing lower pepsin activity compared to full-term infants⁴¹. This increase in pepsin activity is driven by exposure to the microbiome and breast milk, though full maturation occurs postnatally⁴². Interestingly, interruptions in breastfeeding can disrupt the development of the gastric mucosa, potentially leading to permanent abnormalities in zymogenic cell differentiation⁴³, which could impair stomach function later in life – a phenomenon that warrants further investigation.

Parietal cells begin developing in the 8th week and are regularly observed in the stomach mucosa by the end of the first trimester⁴⁴. Although hydrochloric acid secretion starts during the fetal phase and increases as birth approaches, the most significant increases occur postnatally⁴⁵. In the first 2 months after birth, gastric acid production doubles⁴⁶, indicating that part of the maturation of parietal cells depends on interaction with external factors such as breastfeeding. However, the exact relationship and significance of these factors in postnatal life require further research. Notably, preterm infants produce less gastric acid than full-term infants, making them more susceptible to gastrointestinal infections, especially if they are not breastfed⁴¹. Adequate maturation of parietal cells is crucial, as less acidic stomach contents and faster gastric emptying in neonates can allow pathogenic species, such as *Salmonella*, to survive and colonize the small intestine⁴⁷. Regarding the microbiota, *Lactobacillus* is a predominant bacterial group in the stomach during postnatal life. Vaginally born, full-term infants typically exhibit *Lactobacillus* colonization, while preterm infants born via cesarean section often display *Ureaplasma* colonization⁴⁸. These differences in microbial colonization could influence variations in cell differentiation between preterm and full-term infants. Although the functional maturation of the stomach is complex and involves numerous factors, the interaction between breast milk and the microbiota is likely essential for the stomach's postnatal development.

Intestinal postnatal development depends on breastmilk and microbiota interaction

During the morphogenesis of the intestinal mucosa, the endodermal-derived pseudostratified intestinal epithelium begins to give rise to villi as early as 8-10 weeks of gestation. By weeks 11-12, proliferating cells accumulate in the intervillus pockets, which subsequently form the crypts⁴⁹. As villi emerge in the small intestine, the differentiation of various cell types lining the intestinal mucosa follows, including mucus-producing goblet cells, absorptive enterocytes, hormone-secreting enteroendocrine cells, and stem cells. During later stages, immune-related cells such as Paneth and M cells also appear. Although the development of villi and crypts begins in the later embryonic stages, much of their maturation occurs during the fetal phase⁵⁰. However, full maturation is not completed until postnatal stages, as the fetal gastrointestinal tract typically exhibits shorter villi, smaller crypts, and fewer epithelial

cells⁵¹. Complete differentiation and functionality of the various cell lineages are achieved only after the epithelial layer interacts with the microbiota postnatally.

Enterocyte differentiation begins after the formation of villi⁵², allowing for some absorptive functions to be active during prenatal development. Nonetheless, these cells fully differentiate after birth, enhancing the absorptive area through the expansion of apical microvilli and the modification of apical transporter expression involved in nutrient uptake⁵³. Notably, HMOs have been shown to enhance both general and enterocyte-specific markers of differentiation *in vitro*⁵⁴. In addition to their role in absorption, enterocytes contribute to the formation and regulation of intestinal permeability. Tight junctions, which regulate the paracellular transport of antigens from the intestinal lumen, begin to form as early as 10 weeks of gestation⁵⁵. However, newborns have a highly permeable intestinal barrier, a characteristic that may be necessary for immune system maturation, promoting tolerance rather than activation or inflammation⁵⁶.

Interestingly, regardless of gestational age, this increased permeability decreases within the 1st week of life, suggesting that the interaction of microbiota and breastmilk is essential for this process⁵¹. In preterm neonates, breast milk intake is associated with a reduction in intestinal permeability, which can occur in the 1st month after birth, with higher breast milk feeding levels positively correlated with reduced permeability⁵⁷. Furthermore, *in vitro* evidence suggests that even colostrum applied apically to pediatric enteroid monolayers reduces ion permeability, promotes epithelial cell differentiation, and enhances tight junction function, thereby reducing intestinal permeability⁵⁸. In addition, recent findings indicate that anomalous composition of microbiota in postnatal life could cause epithelial barrier dysfunction and could increase the obesity risk in children⁵⁹.

Goblet cells are the most abundant secretory epithelial cells in the gastrointestinal tract, primarily responsible for secreting Muc2, the main gel-forming mucopolysaccharide in the intestinal mucus barrier. Goblet cell differentiation begins during prenatal development as villi form, with a significant increase in their numbers after the 3rd month of gestation⁶⁰. However, the number of functional goblet cells remains constant between the 5th month of gestation and birth⁵². In the fetal intestine, Muc2 glycans are not fully modified post-translationally with sulfate, sialic acid, or fucose, modifications that are essential for proper mucin interaction with microbiome⁶¹. As the gastrointestinal tract

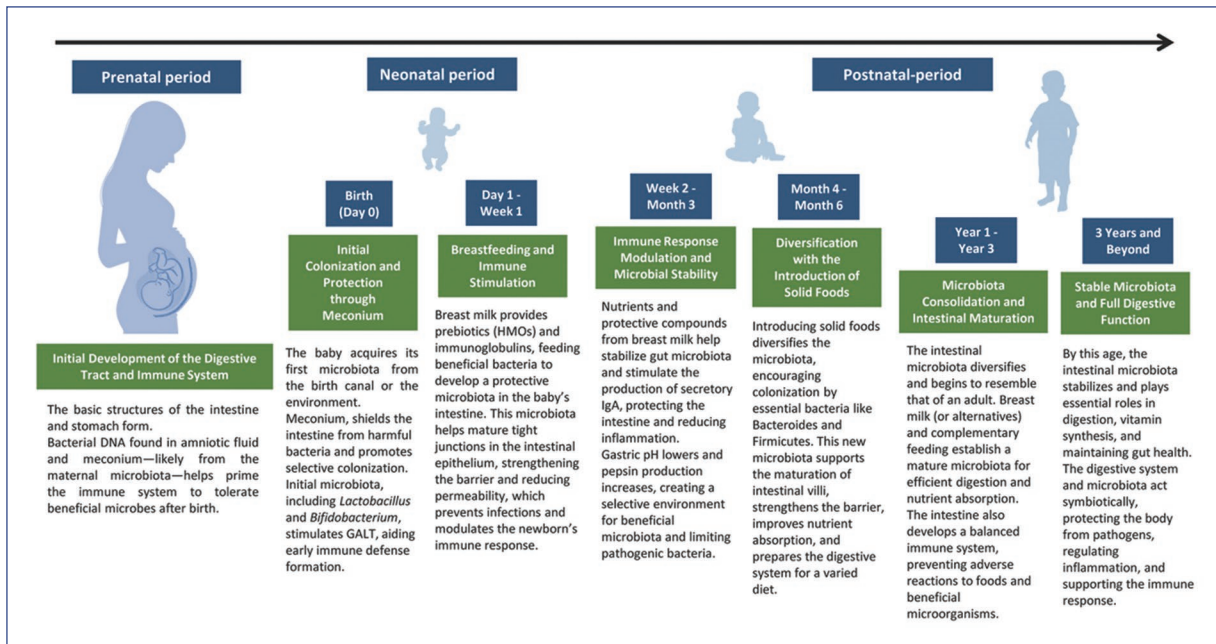


Figure 3. Relationship between neonatal microbiota and gastrointestinal development. Neonatal microbiota and gastrointestinal development across prenatal, neonatal, and postnatal periods. Highlighting key stages – initial colonization at birth, breastfeeding and immune stimulation in the 1st week, immune response modulation by month 3, dietary diversification by month 6, and microbiota consolidation by years 1-3 – showing how maternal and environmental factors shape the digestive tract and immune system over time.

transitions to its role as the primary site of nutrient absorption, interaction with breastmilk and/or the microbiota induces goblet cell maturation. This maturation is characterized by the overexpression of Muc2 and the acquisition of specific glycosylation patterns necessary for intestinal mucus function⁶². Moreover, exposure to commensal bacteria further increases the size and number of goblet cells, leading to enhanced mucus production; in germ-free mice, the absence of goblet cells is observed, underscoring the importance of microbial interaction⁶².

Paneth cells, which appear as early as the 13th week of gestation, eventually settle at the base of the crypts in the intestine⁶³. These cells produce antimicrobial peptides and increase in number as gestation progresses, with full maturation occurring after birth⁶⁴; the final count of Paneth cells is influenced by the type and timing of microbiota colonization in postnatal life⁶⁵. Paneth cells play a crucial role in the pathogenesis of necrotizing enterocolitis, a neonatal disease characterized by severe inflammation of the intestine, bacterial invasion, and subsequent cellular damage leading to colon necrosis. Premature infants with necrotizing enterocolitis have been found to have significantly lower concentrations of Paneth cells in their small

intestines compared to controls⁶⁶. Interestingly, colonization with *Lactobacillus* has been shown to promote Paneth cell differentiation and reduce the severity of necrotizing enterocolitis⁶⁷. In addition, breast milk is essential to produce α -defensin, an antimicrobial peptide that modulates cytokine production and prevents the apical release of proinflammatory cytokines in the gut⁵⁸.

The development of the immune system in the gut begins early in gestation but is largely completed postnatally. One of the first immune cells to interact with the microbiota is the microfold cell, which originates from the stem cell niche in the crypts. Microfold cells are responsible for transferring microbial antigens from the intestinal lumen to antigen-presenting cells, thereby inducing the production of IgA by plasma cells. Microfold cells begin to develop late in the fetal stage, around the 17th week of gestation, and their numbers increase after birth^{51,68}. The antigen transfer by microfold cells is a crucial step for the effective induction of intestinal secretory IgA (sIgA), even before breastfeeding ceases⁶⁸. However, their role is somewhat diminished due to the presence of sIgA in breast milk⁶⁹. The absence of maternal breast milk-derived IgA has been associated with decreased mucosal barrier integrity

and an altered microbiome in adults, as sIgA plays a key role in shaping the intestinal microbiome⁷⁰. Both breastmilk and microfold cell differentiation are essential for promoting the growth of obligate anaerobes, such as *Bacteroides* and *Firmicutes*, while limiting the proliferation of inflammatory facultative anaerobes such as *Enterobacteriaceae*⁷¹.

Peyer's Patches (PP) are among the most crucial sites for the development of the gut's adaptive immune response, becoming observable by 24 weeks of gestation⁶³. The presence and interaction of B and T cells in the gut, particularly within PP and lamina propria, have been documented as early as the second trimester⁷². During fetal development, the intestinal environment is primed for the recruitment of naïve T cells and the generation of memory T cells⁷³, with Th1 cells being the second most common phenotype in prenatal life⁷³. B cells are also active during prenatal stages but undergo significant activation and maturation postnatally, acquiring antibody-producing capabilities upon exposure to a more diverse microbiome⁷³, a process further influenced by breastfeeding. Interestingly, components of the breast milk play a vital role in promoting the proliferation of a well-balanced and diverse microbiota, which in turn supports a balanced Th1/Th2 immune response and activates T-regulatory cells by specific breast milk-stimulated organisms such as *Bifidobacteria*, *Lactobacillus*, and *Bacteroides*⁷⁴.

Furthermore, immune cells present in breast milk, especially colostrum, contribute to the regulation of the neonatal immune response. Colostrum is rich in activated, motile leukocytes, including myeloid precursors, neutrophils, immature granulocytes, and non-cytotoxic T cells⁷⁵. The relative frequencies of neutrophils and immature granulocytes significantly increase in mature milk compared to colostrum, with variations observed between term and preterm mothers⁷⁶. These maternal immune cells are likely important in establishing the newborn's immune response as they begin to interact with the developing microbiota.

Conclusions

Based on the literature review performed in the current study, we provide insights into physiological, microbiological, and pediatric aspects, as summarized in [figure 3](#). Our findings underscore that microbiota, ubiquitous throughout the human body, undergo development from pregnancy due to microorganisms transmitted from the mother to the fetus during its gestation. Within

the process of delivery, fecal and vaginal microorganisms are transferred either from the mother or the surrounding environment in the case of a cesarean section. These processes represent the early stages of intestinal microbiota colonization. Diverse factors, including blood type, diet, environment, physical activity, and delivery mode, exert an influence on this complex process. Breastfeeding plays an important role in the establishment of the neonate's microbiota, providing essential nutrients and microorganisms that facilitate its generation and maintenance. This microbial equilibrium is established around 3 years of age, undergoes alterations during adolescence, stabilizes in adulthood, and experiences further changes in old age.

The neonate's intestinal microbiota begins its journey before birth, gaining enrichment at the time of delivery through contact with the mother's body. This colonization is indispensable, acting as a barrier against environmental microorganisms and certain pathogens, preventing them from freely accessing and infecting the neonate's epithelia. Subsequently, breast milk serves as a continual conduit for microbial transmission from the mother's body to the infant's microbiota, along with oligosaccharides (HMO) that foster the proliferation of the neonate's microbiota and uphold its equilibrium. However, it is crucial to note that the infant's gastrointestinal system is not fully developed, relying on both diet and the microorganisms it harbors. Therefore, the proper development of microbiota is intricately linked to cellular, physiological, and immunological aspects, contributing to overall intestinal health.

Understanding the microbiota, its functions, and its impact on the functioning and homeostasis of the human body is vital in developing perception about the benefits of exclusive breastfeeding for the optimal development of the neonate. Moreover, beyond conferring advantages to the newborn, such as preventing certain gastrointestinal diseases and allergies, breastfeeding for more than 12 months can reduce the mother's risk of breast cancer. In conclusion, the complex interplay between breast milk and microbiota is crucial for the postnatal development and functional maturation of the intestinal mucosa, underscoring the essential role of these factors in establishing lifelong gastrointestinal health and immune competence.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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Distribution of childhood cancer types using the International Classification of Childhood Cancer, third edition classification in a tertiary hospital in northwest Mexico

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Abstract

Background: In Mexico, childhood cancer is the leading cause of death by disease in children between 5 and 14 years of age, and the sixth leading cause of death in children under 5 years of age. In addition, it represents almost 70% of the total cancer burden in the pediatric population. It comprises a heterogeneous group of malignancies with different clinical patterns, etiologies, therapeutic options, and survival prognoses. **Methods:** Descriptive cross-sectional study that included confirmed cases of childhood cancer in patients between 1 and 18 years of age, diagnosed with hematolymphoid neoplasms and solid tumors. The study was carried out in a third-level hospital of the Instituto Mexicano del Seguro Social UMAE N71, located in northwest Mexico, during the year 2024. The International Classification of Childhood Cancer, third edition (ICCC-3), was used for the analysis and classification of cases. **Results:** The mean age of the patients was 8 years, with a distribution of 40.4% in females and 59.5% in males. Leukemia was the most common pediatric cancer, with acute lymphoblastic leukemia standing out in 45% of cases. This was followed by solid tumors in the central nervous system (CNS), representing 20.2%, the most frequent being astrocytomas, ependymomas, and other types of gliomas. **Conclusions:** Leukemias and CNS tumors were identified as the most frequent types of childhood cancer in the northwestern region of Mexico. The use of the classification (ICCC-3) represents a fundamental tool for the standardization of diagnosis and epidemiological analysis of childhood cancer.

Keywords: Cancer. Leukemia. Hospitals. Mortality.

Distribución de los tipos de cáncer infantil utilizando la clasificación ICCC-3 en un hospital terciario del noroeste de México

Resumen

Introducción: En México, el cáncer infantil es la primera causa de muerte por enfermedad en niños de entre 5 y 14 años, y la sexta en menores de 5 años. Además, representa casi el 70% de la carga total de cáncer en la población pediátrica. Comprende un grupo heterogéneo de neoplasias malignas con distintos patrones clínicos, causas, opciones terapéuticas y pronósticos de supervivencia. **Métodos:** Estudio descriptivo transversal, que incluyó casos confirmados de cáncer infantil

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en pacientes de entre 1 y 18 años de edad, diagnosticados con neoplasias hematolinfoides y tumores sólidos. El estudio se llevó a cabo en un hospital de tercer nivel del Instituto Mexicano del Seguro Social UMAE N71 ubicado en el noroeste de México, durante el año 2024. Para el análisis y clasificación de los casos, se utilizó la Clasificación Internacional del Cáncer Infantil, tercera edición (ICCC-3). **Resultados:** La edad media de los pacientes fue de 8 años, con una distribución del 40,4% en mujeres y el 59,5% en hombres. La leucemia fue el cáncer pediátrico más común, destacándose la leucemia linfoblástica aguda en el 45% de los casos. A continuación se ubicaron los tumores sólidos en el sistema nervioso central, representando el 20,2%, siendo los más frecuentes los astrocitomas, epéndimos y otros tipos de gliomas. **Conclusiones:** Se identificó que las leucemias y los tumores del sistema nervioso central constituyen los tipos de cáncer infantil más frecuentes en la región noroeste de México. La utilización de la clasificación ICCC-3 representa una herramienta fundamental para la estandarización del diagnóstico y análisis epidemiológico del cáncer infantil.

Palabras clave: Cancer. Leucemia. Hospitales. Mortalidad.

Introduction

Childhood cancer represents a serious public health issue worldwide. Cancer is one of the main causes of mortality among children and teenagers in the world; each year, approximately 280,000 cancer cases are diagnosed in a population of ages 0-19. The World Health Organization (WHO) estimates that by 2030, secondary deaths to cancer will represent 70% of deaths in developing nations¹. In Mexico, there are approximately 7000 new cancer cases during childhood and adolescence annually, showing a great increase in acute leukemia, which currently represents 50% of all malignant conditions between the ages of 0 and 18². Childhood cancer is the second leading cause of death in people < 18 years old, among which the most common are leukemia, lymphoma, and tumors of the central nervous system (CNS)^{3,4}. It comprises a group of medical conditions with specific clinical features, which separate them from the disease in adults, such as the anatomical location, histologic type, and different behavior. The most common childhood neoplasms are leukemia (30-50%), lymphomas (17.1%), and tumors of the CNS (11.9%)⁵. The different types of cancer that develop in children differ from those diagnosed in people of a more advanced age in terms of their biology, behavior, symptoms, presenting symptoms, treatment options, and results⁶. It is important to mention that childhood cancers comprise a heterogeneous group of cancers in which adult-type carcinomas, which also support the definition of the codification system CIE-10⁷, are rare. At present, childhood cancers are classified based on morphology (histology) and topography (location); the International Classification of Childhood Cancer (ICCC), currently in its third edition (ICCC-3)⁸, groups cancers coded according to the third revision of the WHO International classification of diseases for oncology (CIE-O)⁹ into 12 main diagnostic

groups, which reflect the types of cancer found in children.

There is currently great difficulty in measuring the global and regional incidence of cancer with precision, given that most of the world's population is not properly included in cancer monitoring records and cancer registries. In Mexico, there are only data about the incidence of cancer in children in Mexico City and IMSS beneficiaries, and about the frequency of these conditions in some states around the Republic¹⁰⁻¹². Records are crucial to grasp the magnitude and impact of childhood cancer locally, regionally, and globally. They allow the identification of risk factors, the monitoring of the effectiveness of treatments, and the improvement of public policies aimed toward the prevention and treatment of the disease. To face these challenges, it is vital to invest in the creation and strengthening of updated records of childhood cancer on a global basis, in addition to personnel training and the development of technological systems that facilitate efficient data analysis and collection. Childhood cancer represents a serious public health problem mainly in developing countries such as Mexico, where cancer is one of the leading causes of mortality among individuals aged 0 to 18 years, with an increasing incidence in recent years. All of this is based on the fact that the High Specialty Medical Unit (UMAE) N71, where these epidemiological data are to be collected, serves four states in the northwest region of the Mexican Republic: Coahuila, Chihuahua, Durango, and Zacatecas. Currently, at the UMAE N71, a great number of patients with these types of high-incidence pediatric malignant neoplasms are treated. Therefore, the objective of the present study is to issue the epidemiological description of pediatric patients diagnosed with malignant neoplasms being treated at the Mexican Social Security Institute (IMSS) (UMAE N71), a tertiary-level hospital in the northwest region of Mexico.

Methods

Study design and participants

A cross-sectional descriptive study of pediatric patients within an age range of 0-19 years of age with a confirmed diagnosis of malignant neoplasms (hematolymphoid or solid organ oncologic pathology) treated in 2024 at the Specialty Hospital UMAE N71 in the city of Torreon, Coahuila, Mexico. These patients were treated by the pediatric oncology department and were identified using the patient's record, which is part of the epidemiological surveillance protocol of childhood cancer (ONCOCREAN). They were also beneficiaries of the High Specialty Medical Unit No.71 of the IMSS from January 01, 2023, to December 31, 2024. The ICCC-3 was used, currently in its third edition (ICCC-3)⁸, which groups cancers-coded according to the third revision of the International Classification of Diseases for Oncology (CIE-O), into 12 main diagnostic groups, which reflect the types of cancer found in children.

Data collection

The frequencies of the different types of childhood cancer were analyzed according to sex, and age groups were defined as follows: Q1 (0-4 years), Q2 (5-9 years), Q3 (10-14 years), and Q4 (15-19 years), state of residence, as well as the incidence of pediatric malignant neoplasms in patients < 19 years old. The demographic and clinical data obtained from the patient's records were collected and centralized in a database for further statistical analysis. The results were reported using descriptive statistics.

Statistical analysis

The analysis was carried out employing STATA 18 software (StataCorp LP, College Station, Texas). Descriptive statistics tools were used according to the type of variable. Qualitative variables were reported as frequency and percentage; quantitative variables were reported as mean and standard deviation if they complied with the normality assumptions according to the Kolmogorov–Smirnov test.

Ethical considerations

The present study is aligned with the ethical principles of the Declaration of Helsinki, General Health Law, and legislation with regard to health research, as well

as institutional regulations of the IMSS. This article reports a retrospective descriptive study based on patients' medical records; therefore, no interventions were carried out on the individuals. All information from the patients' records was handled with strict confidentiality. The study was approved by the Research Ethics Committee and Health Research Committee No. 501 of the Specialty Hospital UMAE N71, registry number R-2023-501-055.

Results

A total of 188 pediatric patients diagnosed with childhood cancer during the period between January 1 and December 31, 2024, were included. The mean age of the patients was 8.5 years; 76 (40.4%) were women and 112 (59.5%) men. Patients were stratified into four age groups: Q1 = 40 (0-4 years), Q2 = 74 (5-9 years), Q3 = 46 (10-14 years), and Q4 = 28 (15-19 years). The states of origin of the pediatric patients diagnosed with childhood cancer were Coahuila (41.4%), Durango (31.3%), Chihuahua (15.4%), and Zacatecas (9.5%); thus covering the northwest region of Mexico. The general clinical characteristics of the pediatric patients are shown in [table 1](#). The results of the most frequent childhood cancers during 2023 and the type of diagnoses indicated that within the classification group ICCC-3 ([Table 2](#)), leukemia was the most frequent type of pediatric cancer, with acute lymphoblastic leukemia (ALL) as the most common (n = 86), representing 45.2% of all registered cases. In the second place, there are the tumors of the CNS, with a frequency of 20.2%; among these, the most frequent types were astrocytomas, ependymomas, and other gliomas. The ratio of pediatric patients based on their type of childhood cancer diagnosis is: ALL (45.2%), acute myeloid leukemia (AML) (5.32%), Hodgkin lymphoma (2.14%), non-Hodgkin lymphoma (4.28%), tumors of the CNS (20.21%), astrocytoma (2.6%), ependymoma (0.53%), retinoblastoma (2.13%), nephroblastoma (5.85%), hepatoblastoma (1.06%), osteosarcoma (0.53%), soft-tissue sarcoma (7.98%), and germ cell tumors (3.72%). In male children, the most frequent cancers were leukemia (42.8%), tumors of the CNS (22.3%), sarcomas (8.1%), and renal tumors (4.4%). On the other hand, among the most frequent cancers in female children were leukemia (50%), tumors of the CNS (17.1%), and other types of gliomas (14.4%) ([Table 3](#)). The 2023 registry shows the frequency of the different types of childhood cancer according to the ICCC-3, registered at the High Specialty Medical

Table 1. General characteristics of pediatric patients with childhood cancer at the IMSS-UMAE 71 specialty hospital during the year 2024

Characteristics	Total pediatric patients (n = 188)	
Age, years	Mean ± SD	
	8.5 ± 1.2	
	n	%
Q1 (0-4 years)	40	21.28
Q2 (5-9 years)	74	39.36
Q3 (10-14 years)	46	24.47
Q4 (15-19 years)	28	14.89
Sex		
Female	76	40.43
Male	112	59.57
State of origin		
Coahuila	78	41.49
Durango	59	31.38
Chihuahua	29	15.43
Zacatecas	18	9.57
Other	4	2.13
Mortality	12	6.38
	Mean ± SD	
Months of follow-up	6	1.3

n: total number of patients; %: mean and standard deviation (SD).

Unit N71 in 2024. In accordance with the ICC-3 diagnostic group, the most common age group showed as follows: ALL (Q2 group, Leukemia) showed with greater frequency in patients between the ages of 5 and 9 (48.8%); however, neuroblastoma (Q1 group, Renal Tumors) was more frequent in patients between the ages of 0 and 4. Non-Hodgkin lymphoma (Q3 group, Lymphomas) predominated in patients between the ages of 10 and 14; tumors of the CNS (Q3 group, CNS Tumors) showed mostly in patients between the ages of 5 and 9 (39.4%), and soft-tissue sarcomas showed a little less frequently (Q3 group, Sarcomas) in patients between the ages of 10 and 14 (33.3%). Another interesting finding was a high prevalence of other types of gliomas in the pediatric age range of 5-9 years. The results of the patients hereof are shown in [table 4](#). Among the 188 pediatric cancer cases analyzed, a total of 12 deaths were documented. ALL accounted for the highest number of fatalities (seven cases), followed by Hodgkin lymphoma (three cases), AML (one case), and astrocytoma (one case).

Discussion

Childhood cancer is a heterogeneous group of malignant neoplasms that affects children and teenagers generally from birth up to 19 years of age. It is a disease characterized by the growth and abnormal dissemination of cells in the body. It is estimated that there will be around 13.7 million new childhood cancer cases globally between 2020 and 2050, an increase of 32% with respect to 2018. If no investment is made for children to have access to better medical attention or treatment, 11.1 million patients will die. In addition, it is known that 9.3 million children with cancer (84.1%) will live in low- and lower-middle-income countries¹³. Early diagnosis is crucial in cancer care since it improves the perspective on this disease and offers less morbidity, thus improving the quality of life of the patient, in comparison with intense treatments given to children in advanced stages of the disease¹⁴. There are children of ages 0-14 with cancer who never receive a diagnosis, which indicates that there is a misdiagnosis, which in turn is not considered in estimates of incidence¹⁵. Timely identification and referral of suspicious childhood cancer cases in Mexico are of utmost importance since they allow effective access to health services.

A recent study in the central-south region of Mexico reported 388 cases of ALL, with an age-standardized incidence rate (0-14 years) of 51.5 cases/million, varying across Puebla (53.2), Tlaxcala (54.7), and Oaxaca (47.7). In the 0-19-year age group, rates ranged from 44.3 to 49.6/million. B-cell ALL was the predominant subtype in all three states. Our findings are consistent with a recent study in marginalized populations of central-south Mexico, where, as in the northwest region of the country, ALL was the most predominant type of childhood cancer in children and adolescents.

The present study gathers epidemiological information from the northwest region of Mexico. As a tertiary-level hospital, it receives patients from the states of Coahuila, Chihuahua, Durango, and Zacatecas, and ALL is the most frequent childhood cancer in our medical unit. Leukemia is the most frequent childhood cancer in the world, with ALL as the most common type¹⁶. A global peak incidence is observed between the ages of 2 and 5, with a greater prevalence in the male sex^{17,18}. This matches with our study, in which the most frequent diagnosis occurred in the age group of 1-8. In contrast, American literature reports that the greater incidence of ALL occurs between the ages of two and three, probably because there is easier access to healthcare services and early diagnosis. Despite the

Table 2. Distribution of childhood cancer types using the International Classification of Childhood Cancer (ICCC-3) in the Unidad Médica de Alta Especialidad (UMAE) No. 71

Number	Diagnosis	Group ICCC-3	Total cases (n = 188) (%)	Female (n = 76) (%)	Male (n = 112) (%)
1	Acute lymphoblastic leukemia	Group I (Leukemias)	86 (45.2)	38 (45.7)	48 (55.8)
2	Acute myeloid leukemia	Group I (Leukemias)	10 (5.32)	7 (70)	3 (30)
3	Hodgkin lymphoma	Group II (Lymphomas)	4 (2.14)	1 (75)	3 (25)
4	Non-Hodgkin lymphoma	Group II (Lymphomas)	8 (4.28)	1 (12.50)	7 (87.50)
5	CNS tumors (central nervous system)	Group III (CNS tumors)	38 (20.21)	13 (34.21)	25 (65.79)
6	Astrocytoma (CNS) tumor	Group III (CNS tumors)	5 (2.66)	1 (20)	4 (80)
7	Ependymoma (CNS) tumor	Group III (CNS tumors)	1 (0.53)	1 (99.9)	0 (0)
8	Other gliomas	Group III (CNS tumors)	32 (17.02)	11 (34.38)	21 (65.63)
9	Retinoblastoma	Group V (retinoblastomas)	4 (2.13)	2 (50)	2 (50)
10	Nephroblastoma	Group VI (renal tumors)	11 (5.85)	6 (54.55)	5 (45.45)
11	Hepatoblastoma	Group VII (hepatic tumors)	2 (1.06)	0 (0)	2 (99.9)
12	Osteosarcoma	Group VIII (bone tumors)	1 (0.53)	1 (99.9)	0 (0)
13	Ewing sarcoma	Group VIII (bone tumors)	1 (0.53)	0 (0)	1 (99.9)
14	Soft-tissue sarcomas	Group IX (sarcomas)	15 (7.98)	6 (40)	9 (60)
15	Germ cell tumors	Group X (germ cell tumors)	7 (3.72)	2 (28.57)	5 (71.43)
16	Other	Group XII (other and unspecified malignant neoplasms)	1 (0.53)	1 (99.9)	0 (0)

ICCC-3: International Classification of Childhood Cancer, third edition.

Table 3. Distribution of childhood cancer types by sex in the medical unit

Childhood cancer types ICCC-3	Female (n = 76)	Male (n = 112)
	n (%)	n (%)
Group I (Leukemias)	38 (50)	48 (42.8)
Group III (CNS tumors)	13 (17.1)	25 (22.3)
Group III (Other gliomas)	11 (14.4)	21 (18.7)
Group IX (sarcomas)	6 (7.8)	9 (8.1)
Group VI (renal tumors)	6 (7.8)	5 (4.4)

ICCC-3: International Classification of Childhood Cancer, third edition.

evidence which suggests that the recent improvements in survival have been greater for AML than those for ALL, in many countries¹⁹ the survival rate for ALL is still systematically superior to that of AML in Europe²⁰, the United States²¹, and worldwide²². A recent cross-sectional study in the Democratic Republic of Congo²³

revealed that the most frequent cancers in children were retinoblastoma, with an incidence of 29.3%, followed by renal tumors (23.2%), lymphomas (13.1%), and leukemia (12.1%), taking into consideration all combined forms. By comparison, our study found a frequency in retinoblastomas of 2.1%, followed by renal tumors (5.8%), lymphomas (6.4%), and leukemia (50.5%). Non-Hodgkin lymphoma (4.28%) showed a greater incidence in our study in patients between the ages of 11 and 18. Tumors of the CNS in children are the most common after leukemia, which accounts for a large share of pediatric cancers. It is important to mention that tumors of the CNS were identified as the second cause for childhood neoplasms in Fajardo's study²⁴, which matches our study findings. Genetic and molecular factors play a vital role in childhood oncogenesis, which serves as evidence that sex can be a risk factor in certain types of cancer due to specific genetic variants^{25,26}. In our study, the distribution of childhood cancers based on sex showed that the most frequent types in children are leukemia (42.8%), tumors of the CNS

Table 4. Age-based distribution of childhood cancer types at tertiary-level Hospital UMAE No. 71, northwest Mexico, 2024

Number	Diagnosis	Group ICCC-3	Q1 (0-4 years)	Age		Q4 (15-19 years)
				Q2 (5-9 years)	Q3 (10-14 years)	
			n = 40 (%)	n = 74 (%)	n = 46 (%)	n = 28 (%)
1	Acute lymphoblastic leukemia	Group I (Leukemias)	16 (18.6)	42 (48.84)	18 (20.93)	10 (11.63)
2	Acute myeloid leukemia	Group I (Leukemias)	4 (40)	1 (10)	4 (40)	1 (10)
3	Hodgkin lymphoma	Group II (Lymphomas)	0 (0)	2 (50)	2 (50)	0 (0)
4	Non-Hodgkin lymphoma	Group II (Lymphomas)	0 (0)	1 (12.5)	4 (50)	3 (37.5)
5	CNS tumors (central nervous system)	Group III (CNS tumors)	6 (15.79)	15 (39.47)	10 (26.32)	7 (18.42)
6	Astrocytoma (CNS) tumor	Group III (CNS tumors)	2 (40)	2 (40)	1 (20)	0 (0)
7	Ependymoma (CNS) tumor	Group III (CNS tumors)	0 (0)	1 (99.9)	0 (0)	0 (0)
8	Other gliomas	Group III (CNS tumors)	4 (12.5)	13 (40.63)	8 (25)	7 (21.88)
9	Retinoblastoma	Group V (retinoblastomas)	3 (75)	1 (25)	0 (0)	0 (0)
10	Nephroblastoma	Group VI (renal tumors)	6 (54.55)	5 (45.45)	0 (0)	0 (0)
11	Hepatoblastoma	Group VII (hepatic tumors)	2 (99.9)	0 (0)	0 (0)	0 (0)
12	Osteosarcoma	Group VIII (bone tumors)	0 (0)	1 (99.9)	0 (0)	0 (0)
13	Ewing sarcoma	Group VIII (bone tumors)	1 (99.9)	0 (0)	0 (0)	0 (0)
14	Soft-tissue sarcomas	Group IX (sarcomas)	3 (20)	4 (26.67)	5 (33.33)	3 (20)
15	Germ cell tumors	Group X (germ cell tumors)	0 (0)	1 (14.29)	2 (28.57)	4 (57.14)
16	Other	Group XII (other)	1 (99.9)	0 (0)	0 (0)	0 (0)

ICCC-3: International Classification of Childhood Cancer, third edition; CNS: central nervous system.

(22.3%), sarcomas (8.1%), and renal tumors (4.4%). Other types of pediatric tumors can be linked to life-style. With the introduction of combination therapy, the survival rate for childhood cancer has improved significantly in the last five decades. One possible limitation of the study is the presence of selection bias, as other hospitals in the area may treat cancer patients, which could influence the representativeness of the sample. Some limitations of our epidemiological study of childhood cancer include the fact that only data from the children treated in the High Specialty Medical Unit N71 were collected from January to December 2023.

However, these data provide us with a current picture of the tendency of childhood cancer in the northwest region of Mexico. A prospective registry will allow the collection of standardized data about the incidence and characteristics of childhood cancer, enabling the identification of patterns, tendencies, and risk factors. It is crucial to conduct more detailed research to have a better understanding of the epidemiology of childhood cancer and how socio-economic factors, health determinants, and diagnostic capability interact with each other. These elements are decisive and influence childhood cancer statistics both globally and in Mexico.

Conclusions

It was identified that leukemia and tumors of the CNS are the most common types of childhood cancer in the northwest region of Mexico. However, epidemiological data about the distribution of childhood cancer in the country are still limited. It is vital to implement monitoring programs for proper treatment to contribute to the decrease of the early mortality rate from childhood cancer in Mexico.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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Cross-sectional and longitudinal relationships between abdominal fat depots and cardiometabolic risk in a sample of Mexican adolescents

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Abstract

Background: The relationship between abdominal fat depots and cardiometabolic risk among youth is inconclusive due to the cross-sectional nature of existing studies and limitations in assessment methods. In this study, we examined cross-sectional and longitudinal associations of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) with cardiometabolic risk indicators among Mexican adolescents. **Methods:** Participants ($n = 169$ at baseline and 134 at follow-up) were assessed for diastolic or systolic blood pressure (DBP or SBP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, glucose, and insulin. VAT and SAT were measured using magnetic resonance imaging. Measures were repeated at 1-year follow-up. Using multilevel linear regression models, the associations among fat depots and cardiometabolic risk indicators were examined. **Results:** At baseline, SAT measures were cross-sectional and positively associated with glucose, insulin, TC, triglycerides, SBP, and BDP in boys, and DBP in girls, but negatively with HDL-C. VAT measures were cross-sectional and positively associated with glucose, insulin, and SBP and DBP in boys. VAT at L1-L2 was longitudinal and positively associated with insulin, TC, LDL-C, and DBP in boys. **Conclusions:** Higher levels of SAT and increases in VAT during adolescence may be particularly detrimental to cardiometabolic health, contributing to an increased risk of future diseases. Future intervention and treatment strategies should target VAT to reduce disease risk in this population.

Keywords: Cardiovascular risk. Metabolic syndrome. Total body fat. Regional body fat. Subcutaneous adipose tissue. Visceral adipose tissue.

Relaciones transversales y longitudinales entre depósitos de grasa abdominal y riesgo cardiometabólico en una muestra de adolescentes mexicanos

Resumen

Introducción: La mayoría de los estudios sobre la relación de los depósitos específicos de grasa abdominal con el riesgo cardiometabólico han sido transversales. El objetivo del presente estudio fue analizar las asociaciones transversales y longitudinales del tejido adiposo subcutáneo (TAS) y el tejido adiposo visceral (TAV) con indicadores de riesgo cardiometabólico en adolescentes mexicanos. **Métodos:** Se evaluaron características antropométricas, presión arterial diastólica (PAD) o sistólica (PAS), colesterol total, colesterol HDL, colesterol LDL, triglicéridos, glucosa e insulina de los participantes ($n = 169$

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en la medición basal y 134 en el seguimiento). El TAV y el TAS se midieron mediante resonancia magnética. Las mediciones se repitieron al año de seguimiento. Se estimaron modelos de regresión lineal multinivel. **Resultados:** Las mediciones de TAS se asociaron transversal y positivamente con glucosa, insulina, colesterol total, triglicéridos, presión arterial en niños y PAD en niñas, pero negativamente con el colesterol HDL. Las mediciones de TAV se asociaron transversal y positivamente con glucosa, insulina y presión arterial en niños. El TAV entre las vértebras lumbares 1 y 2 se asoció longitudinal y positivamente con insulina, colesterol total, colesterol LDL y presión arterial en niños. **Conclusiones:** Niveles altos de TAS y el incremento del TAV durante la adolescencia pueden ser perjudiciales para la salud cardiometabólica. Para reducir el riesgo cardiometabólico en esta población, las intervenciones deben enfocarse en prevenir el incremento del TAV.

Palabras clave: Riesgo cardiovascular. Síndrome metabólico. Grasa corporal total. Grasa subcutánea. Grasa visceral.

Introduction

As in most of the world, children and adolescents in Mexico have experienced an increase in overweight and obesity. This is concerning, given the negative effects that excessive adiposity can have on health and well-being both in childhood and across the lifespan into adulthood. Total fat is a predictor of the development of cardiometabolic abnormalities, and fat deposits in the abdominal area can be especially detrimental¹. In adults, abdominal visceral adipose tissue (VAT) is a stronger predictor of poor cardiometabolic outcomes compared to subcutaneous adipose tissue (SAT)². However, in children and adolescents, the relationship between VAT and SAT with cardiometabolic abnormalities is inconclusive and differs across race, ethnicity, and even nationality. For example, among children and adolescents with overweight or obesity who are of European³⁻⁷ and Asian⁸ ancestry, VAT is positively related to cardiometabolic risk factors. Yet, in the U.S., the association of VAT with metabolic risk factors, such as insulin sensitivity, has been observed in African and Hispanic children and adolescents, but not in youth with European ancestry⁹. In contrast, SAT, but not VAT, has been shown to be related to metabolic abnormalities in Mexican¹⁰ and Italian children with overweight or obesity¹¹. Furthermore, additional studies have demonstrated that sex differences exist among associations of SAT and VAT with cardiometabolic risk factors^{12,13}.

With exceptions¹⁴⁻¹⁶, most studies focused on the relationship between fat depots and disease risk are cross-sectional and use less accurate measures of fat depots. Cross-sectional comparisons suggest that associations between body fat depots and cardiometabolic risk are more strongly observed as youth transition from early childhood to adolescence as they undergo puberty^{7,12,17}. However, more research is needed to understand the longitudinal relationship between fat depots and cardiometabolic risk factors among Mexican children during the critical life stage of

adolescence. Although some research has been conducted in the US with American Hispanic pediatric subjects¹⁵, there is scarce research on adolescents born and raised in Latin America. The purpose of this study was to analyze the longitudinal association of changes in total body fat (TBF), SAT, and VAT with cardiometabolic risk indicators in a sample of Mexican adolescents. The secondary aim was to examine the relationship among SAT, VAT, and cardiometabolic risk indicators across sex.

Methods

The ethical approval for this research was granted by the Council of Biological and Health Sciences of the Metropolitan Autonomous University campus Xochimilco (agreement number 5/21.10.2). Written consent from the guardians and the assent of the adolescents were obtained. After the assessments, adolescents and their guardians received their individual results. When any alteration was detected, they received the invitation to receive nutritional orientation.

Participants

A longitudinal study was conducted with a convenience sample of adolescents who were measured in both the 1st and 2nd years of junior high school. Participants were recruited from five secondary schools in Mexico City. Although schools were selected by convenience, the counties in which they are located represent different socioeconomic levels. Three high schools were in low-income counties (Iztapalapa and Xochimilco), while the other two were situated in a middle-income county (Coyoacán). The first high school was public, and the second was private. These schools were selected due to their proximity to the university campuses where the assessments were to be carried out.

All students were invited to participate in the study. Adolescents were ineligible if they had any medical diagnosis (e.g. hypothyroidism, Cushing's syndrome, hypertension, or diabetes) and/or were taking any medications (e.g., prednisone, Ritalin, or growth hormone) known to affect body composition or metabolism, those who used wheelchairs or crutches, had a metallic implant or prosthesis, or had undergone a radiological study 7 days before the evaluation.

All measurements were conducted at the Xochimilco (located in the Coyoacán county) and Iztapalapa (located in the Iztapalapa county) campuses of Metropolitan Autonomous University. It was considered that the proximity of secondary schools to university campuses would encourage participation and reduce the transportation burden. Baseline measurements were conducted from January to November 2015 with the participation of 169 adolescents. A follow-up evaluation of 134 adolescents was carried out 1-year later, from February to November 2016. Only participants with at least one valid measurement of VAT or SAT were considered. For each variable, the number of participants with data varied. This was due to various reasons related to the fieldwork. For example, some children did not have all the magnetic resonance scans because they were unable to remain still. In some cases, not enough blood was obtained for the various biochemical tests. Furthermore, some samples were hemolyzed.

Procedures

At baseline and follow-up, blood samples were taken, and total and abdominal adiposity were assessed. Participants arrived at the Xochimilco campus in the morning after an overnight fast, and a venous blood sample was obtained. The blood sample was used to determine the levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, glucose, and insulin. Blood pressure (BP) was measured following American guidelines¹⁸.

After consuming a breakfast (usually a soybean drink or juice, torta, and apple or banana) provided by the research team, anthropometric measurements were taken. Height was measured using a standardized technique¹⁹ using a Seca stadiometer. Previously trained and standardized interns from the Bachelor's Degree in Human Nutrition make the anthropometric measurements. The World Health Organization height-for-age Z-score scores were calculated²⁰.

TBF was measured using dual-energy X-ray absorptiometry with a densitometer, Hologic Discovery Wii. Manufacturer instructions (Hologic Inc., Bedford, MA) and guidelines²¹ were followed to conduct the scans. Using the Hologic APEX software, version 3.3.0.1, the images were analyzed. The technician's variation coefficients were 1.27% for TBF (kilograms) and 1.04% for the percentage of TBF (%TBF).

Participants were then transferred to the Iztapalapa campus for the magnetic resonance imaging (MRI) assessment. Imaging of the abdomen without contrast was performed to obtain four cross-sectional images from the lumbar region. A standardized technician handled the 3-Tesla MRI scanner (Phillips Inc.). Four slices were obtained for each adolescent around every 8 mm, starting at the twelfth thoracic vertebra and ending at the sacral vertebra slice. The thickness of each image was a voxel of $2.3 \times 3.3 \times 8.0$ mm. Four slices were evaluated: between lumbar 1 and 2 (L1-L2), between lumbar 2 and 3 (L2-L3), between lumbar 3 and 4 (L3-L4), and between lumbar 4 and 5 (L4-L5). Images were analyzed to distinguish between visceral and subcutaneous fat using the ImageJ software. The area (cm²) was estimated based on the quantification of pixels. Analysis of images and estimation of VAT and SAT were conducted by the same observer, who had technical errors of 1.55% and 2.55%, respectively¹⁰.

Sexual maturity was assessed using the Pubertal Development Scale²², which is a self-reported measurement that classifies youth as pre-pubertal, pubertal, or post-pubertal²³.

Statistical analysis

Statistical analysis was performed using STATA software version 26. Values equal to or lower (higher) than twice the interquartile range plus percentile 25 (percentile 75) were considered outliers and therefore were treated as missing. Descriptive statistics (mean, standard deviation, minimum, and maximum) were estimated for all variables. The Pearson correlation coefficient was estimated to determine the relationship between TBF, SAT, and VAT.

Multilevel linear regression models (MLRM)^{24,25} were estimated to analyze the association between fat depots and cardiometabolic risk factors. In all models, the dependent variables were the cardiometabolic risk factors. The main predictors were SAT and VAT, and TBF was considered a secondary predictor. Estimation of the models was done in three steps: (a) TBF, SAT,

or VAT (and their interaction with age) were introduced in separate models. These models aim to distinguish between cross-sectional (the main effect of the fat depot variable) and longitudinal (the interaction term of the fat depot variable by time) associations. (b) When the interaction term of time with TBF, SAT, or VAT was not significant ($p > 0.099$), it was removed to verify whether the main effect of SAT or VAT was significant. (c) The main effects and interactions of SAT and VAT (but not TBF) that were significant ($p \leq 0.050$) in previous steps were introduced in the same model. Below are described additional elements that were considered in building the final models.

For all models, continuous variables were centered. Age was introduced as a random slope; whereas schools' identification was considered a random intercept, i.e., participants were clustered within schools. In some cases (models for BP and with SAT and VAT at L4-L5), the random intercept of school identification was excluded because models did not converge. All models were adjusted for sex (except for the BP variables), sexual maturity, and height-for-age index. Sexual maturity was considered a categorical variable.

Another models were estimated to include the interaction term of sex by time. An interaction was considered significant when $p < 0.100$. This model was estimated to identify sexual dimorphism in the changes in cardiometabolic risk factors. The adolescents' age in years was considered a time variable. The sex by time interaction term was only significant for BP variables; therefore, separate models were conducted for boys and girls for these variables.

The suggestions of Garson²⁶ were followed to assess the existence of the following assumptions of the MLRM:

- Data at the lower level (i.e., repeated measures) are nested or clustered within units of the higher level (i.e., each participant or school). This is the opposite of ordinary least squares (OLS) regression, which assumes that data are independent. In other words, MLRM considers the intra-subject dependence of the repeated measurements (i.e., the measurements in one moment are correlated with the ones obtained at follow-up). To verify intra-subject dependence, an empty model using the identification variable of adolescents as a random intercept was estimated. Based on this model, the intra-class correlation (ICC) coefficient was estimated for each cardiometabolic risk factor and body fat depot variable. The ICC is a statistic of intra-subject dependence.

- Linearity of the associations of VAT and SAT with cardiometabolic risk factors. For each cardiometabolic risk factor, two models were fitted through maximum likelihood: (a) in one model, only the interaction of age by fat depot (SAT or VAT) was introduced, which implies a linear association, and (b) in another model, the interaction of age by the quadratic term of fat depot age was also introduced. These two models were compared using a likelihood-ratio test. In most cases, there was no difference between models with linear or quadratic terms. Searching for parsimony, models with linear relationships are a more suitable option. When there was a difference between models ($p < 0.050$), Schwarz's Bayesian information criterion (BIC) was considered to compare models' fit. The models with quadratic terms were dismissed because those with linear association had a lower BIC (a difference of > 2.0 between models).
- Lack of multicollinearity among predictors. Dealing with this problem in the topic of our study is complex. From a clinical perspective, the research on regional fat depots (VAT and SAT) aims to identify their effects on cardiometabolic health independent of each other and of TBF. At the same time, from a statistical perspective, multicollinearity can artificially change the size, sign, and standard errors of the regression coefficients of predictors. It can be expected that there is a correlation between TBF, SAT, and VAT. Therefore, our decisions were based on considering both perspectives. The first way we assessed multicollinearity was by estimating Pearson correlation coefficients (r) among VAT, SAT, and TBF. A rule of thumb for considering the risk of collinearity is a $r \geq 0.80$. Another way we addressed multicollinearity is by examining the regression coefficients of VAT and SAT in models with only one of them and models including both variables. Two scenarios were suggestive of multicollinearity: (a) the sign of the regression coefficients changed when both variables were included in the same model and (b) the significance of the VAT and SAT's regression coefficients was lost in the models including them at the same time. In these cases, only one of the two variables (SAT or VAT) was included in the final model. To decide which variable to introduce, the BIC of their models was considered (see above). When neither of the two scenarios was observed, both variables were kept. Finally, a typical measure of multicollinearity in OLS regression models is the variance inflation factor (VIF) statistic.

Table 1. Descriptive statistics of adiposity and cardiometabolic risk at baseline and follow-up

Variables	Basal (2015)				Follow-up (2016)				ICC	95% CI
	n	M	SD	min/max	n	M	SD	min/max		
Age, months	169	153.6	6.4	128/185	134	165.3	5.5	144.0/181.0		
Height-for-age, Z-score	169	0.0	1.0	-2.5/4.4	134	-0.2	1.0	-2.5/2.0	0.90	0.88/0.92
Total body fat, %	168	31.3	8.9	12.2/49.8	134	32.1	10.0	12.0/52.4	0.90	0.89/0.92
SAT L1-L2, mm ²	137	140.5	81.3	36.9/405.1	128	123.8	86.4	13.8/408.4	0.78	0.73/0.83
SAT L2-L3, mm ²	165	159.4	92.5	15.5/387.9	132	150.6	102.1	13.7/481.3	0.70	0.64/0.75
SAT L3-L4, mm ²	168	196.5	101.7	28.2/451.6	132	182.8	111.3	13.4/452.7	0.69	0.64/0.74
SAT L4-L5, mm ²	84	233.5	102.3	48.3/483.6	126	210.5	120.8	12.7/504.6	0.74	0.67/0.81
VAT L1-L2, mm ²	134	62.6	39.8	4.7/169.2	126	43.7	29.1	7.8/145.8	0.53	0.42/0.64
VAT L2-L3, mm ²	164	65.8	34.4	7.7/167.2	132	49.1	29.6	4.9/156.5	0.41	0.30/0.52
VAT L3-L4, mm ²	168	60.6	31.0	5.7/154.9	132	45.8	30.0	3.7/176.9	0.35	0.24/0.46
VAT L4-L5, mm ²	164	58.9	26.0	7.3/155.4	128	40.6	24.1	6.7/136.1	0.74	0.67/0.80
Glucose, mg/dL	159	91.6	7.5	78.0/110.0	127	87.8	6.1	73.0/112.0	0.43	0.33/0.54
Insulin, μ U/mL	152	11.4	5.6	1.5/30.4	124	10.5	5.3	2.0/30.1	0.64	0.57/0.72
Total cholesterol, mg/dL	163	158.6	25.3	101.0/226.0	128	154.5	27.7	93.0/226.0	0.69	0.63/0.75
LDL-C, mg/dL	158	92.6	20.8	44.0/152.0	125	93.1	21.5	36.0/154.0	0.72	0.67/0.78
HDL-C, mg/dL	162	43.1	9.3	24.0/67.0	128	41.9	9.3	22.0/72.0	0.64	0.62/0.74
Triglycerides, mg/dL	159	108.8	48.3	36.0/251.0	125	96.8	41.5	29.0/242.0	0.61	0.52/0.70
Systolic BP – boys, mmHg	71	116.3	11.6	91.0/147.0	60	114.3	10.9	87.0/140.0	0.46	0.32/0.61
Diastolic BP – boys, mmHg	70	70.1	8.3	50.0/87.0	59	68.5	7.2	55.0/87.0	0.40	0.24/0.57
Systolic BP – girls, mmHg	95	114.2	11.2	89.0/146.0	70	108.4	10.6	82.0/137.0	0.43	0.28/0.58
Diastolic BP – girls, mmHg	96	72.5	8.7	42.0/94.0	70	69.3	7.3	53.0/84.0	0.31	0.15/0.47

M: mean; SD: standard deviation; Min: minimum; Max: maximum; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ICC: intra-class coefficient; 95% CI: 95% confidence interval.

However, VIF cannot be derived from MLRM. Therefore, we estimated equivalent OLS regression models for the final MLRM. In all cases, VIFs were lower than 5.0.

- Homogeneity of error variance or the homoscedasticity assumption. When this premise is not met (i.e., heteroscedasticity is present), the use of cluster-robust standard errors based on the “sandwich estimator” is recommended (option *vce(robust)* in STATA). In addition, the use of the heterogeneous or unstructured variance model (option *cov(unstruct)* in STATA) is a better option because it does not assume error variance is the same in each group. The final models were estimated with both options.

The normality of distribution of variables was not assessed, as it has been proven that in MLRM, the violation of normality does not influence the accuracy of parameter estimates or their standard errors²⁷.

Results

Baseline descriptive statistics for body composition and cardiometabolic risk indicators of adolescents are presented in [table 1](#). High ICC was observed for TBF. The ICC was stronger for SAT measurements (from 0.69 to 0.78) than for VAT ones (from 0.35 to 0.74). The ICC for cardiometabolic risk indicators was moderate (insulin, TC, LDL-C, HDL-C, and triglycerides) to low

(glucose, DBP, and SBP). Distribution of participants according to sexual maturity at basal and follow-up assessments was as follows: 26.0% and 16.4%, respectively, were in early puberty; 64.5% and 63.4% were midpubertal; and 9.5% and 20.2% were late pubertal (data not shown in the table).

At baseline, there was a strong correlation between TBF and SAT (r from 0.75 to 0.82) (Table 2). The correlation of VAT and TBF was low to moderate (r from 0.27 to 0.60).

The results of the SAT and VAT, as introduced in different models, are reported in supplementary tables 1 and 2. The final models are presented in tables 3 and 4. In these models, only the significant main and interaction terms were retained, and when appropriate, the VAT and SAT variables were introduced simultaneously. At baseline, SAT measures were positively associated with glucose (SAT at L4-L5), insulin (four slices of SAT), TC (SAT at L3-L4), triglycerides (four slices of SAT), SBP in boys (SAT at L3-L4, and L4-L5), DBP in boys (SAT at L1-L2, and L3-L4), and DBP in girls (four slices of SAT), but negatively with HDL-C (four slices of SAT). The interaction term of SAT measures by age was negatively associated with insulin (SAT at L2-L3 and L3-L4), and TC (SAT at L3-L4).

In models in which fat depots were introduced separately, SAT at L1-L2 was related to TC and DBP in girls (Supplementary Table 1). However, these associations lost their significance after VAT was introduced in the same model (Table 3). The same occurred with the relationship of SAT at L2-L3 to SBP and DBP in boys.

At baseline, VAT measures were positively associated with glucose (SAT at L1-L2), insulin (four slices of SAT), and SBP (SAT at L2-L3) and DBP (SAT at L2-L3) in boys. The interaction term of VAT at L1-L2 by age was positively associated with insulin, TC, LDL-C, and SBP and DBP in boys.

In models in which fat depots were introduced separately, VAT at baseline was related to HDL-C (VAT L1-L2, L3-L4, and L4-L5), triglycerides (four slices of VAT), and SBP (VAT L3-L4 and L4-L5), and DBP (VAT L3-L4 and L4-L5) in boys (Supplementary Tables 1 and 2). However, these associations lost their significance after the SAT was introduced in the same model (Tables 3 and 4). The same occurred with the relationship of glucose with the interaction term of VAT at L4-L5 by age.

At baseline, TBF was positively associated with glucose, insulin, TC, LDL-C, and triglycerides, as well as SBP and DBP in boys, and DBP in girls; however, it was negatively associated with HDL-C (Table 5).

Table 2. Correlations at baseline between TBF, %, abdominal SAT, and abdominal VAT

Variables	%TBF-SAT	%TBF-VAT	SAT-VAT
	r	r	r
Lumbers 1-2	0.82	0.60	0.70
Lumbers 2-3	0.81	0.55	0.62
Lumbers 3-4	0.79	0.46	0.51
Lumbers 4-5	0.75	0.27	0.36

R: Pearson correlation coefficient. For all coefficients $p < 0.001$.
TBF: total body fat; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue.

Discussion

Cardiometabolic diseases, including type 2 diabetes and hypertension, are the leading causes of death in Mexico, highlighting the need to identify predictive markers in childhood to allow for early intervention to prevent future disease²⁸. This study examined various fat depots and their cross-sectional and longitudinal associations with cardiometabolic risk indicators in a sample of Mexican adolescents.

An unexpected finding was that, on average, adolescents experienced a reduction of SAT and VAT. During the study, no nutritional or physical activity intervention was implemented that could yield these changes. One possibility is that puberty (especially in boys) can be associated with loss of abdominal fat. Future analysis of our data can explore this issue.

It is relevant to know whether different measures of adiposity are independently associated with cardiometabolic risk. At the same time, as expected, total adiposity can be correlated to specific depots of fat. In our sample of Mexican adolescents, SAT was strongly correlated with TBF, whereas the relationship with VAT was mild to moderate. Other studies have demonstrated that TBF is strongly associated with total SAT ($r > 0.93$)^{10,29}. In addition, changes in SAT are similar to those of TBF; however, changes in VAT are independent of TBF³⁰. These findings suggest that SAT can be considered a proxy for total adiposity. If this is the case, it is not adequate to adjust the associations of SAT with cardiometabolic risk factors by TBF, as multicollinearity will arise. For this reason, our final models were only adjusted by SAT and VAT.

In our sample of Mexican adolescents, associations of SAT and TBF with cardiometabolic risk factors were similar: both measures of adiposity were cross-sectional and positively associated with glucose, insulin,

Table 3. Multilevel linear regression models having cardiometabolic indicators as outcomes and abdominal and visceral SATs between lumbar vertebrae 1-2 and 2-3 as predictors in a sample of Mexican adolescents

Dependent variables	Lumbar vertebrae 1 and 2						Lumbar vertebrae 2 and 3					
	Constant	Age, yr	SAT, mm ²	SAT × age	VAT, mm ²	VAT × age	Constant	Age, yr	SAT, mm ²	SAT × age	VAT, mm ²	VAT × age
	A	B	B	B	B	B	A	B	B	B	B	B
Glucose, mg/dL	-	-	-	-	-	-	-	-	-	-	-	-
Insulin, µU/mL	-0.56	0.96	0.03 ^c	-	0.05 ^c	0.04 ^c	-1.83	0.07	0.03 ^c	-0.01 ^a	0.06 ^c	0.03 ^a
Total cholesterol, mg/dL	-7.48	2.65	0.01	-0.01	0.07	0.11 ^b	-	-	-	-	-	-
LDL-C, mg/dL	-7.51	3.85 ^c	-	-	0.07	0.05 ^b	-	-	-	-	-	-
HDL-C, mg/dL	-1.67	0.17	-0.03 ^c	-	-0.00	-	-1.56	0.21	-0.03 ^c	-	-0.01	-
Triglycerides, mg/dL	-0.60	-10.40 ^b	0.16 ^c	-	0.03	-	7.26	-9.31 ^d	0.13 ^c	-	-	-
Boys												
Systolic blood pressure, mmHg	1.50	2.20	0.04 ^a	-	-0.02	0.05 ^a	-5.27 ^a	5.93 ^c	-	-	0.06 ^b	-
Diastolic blood pressure, mmHg	0.97	0.14	0.02	-	0.00	0.06 ^c	-3.80 ^a	0.83	-	-	0.05 ^b	-
Girls												
Systolic blood pressure, mmHg	-	-	-	-	-	-	-	-	-	-	-	-
Diastolic blood pressure, mmHg	0.86	-1.48 ^d	0.02 ^b	-	-	-	-2.38	-2.26	0.01 ^d	-	-	-

^ap ≤ 0.050.^bp ≤ 0.010.^cp ≤ 0.001.

-, because the regression coefficient was not significant, it was removed from the final model. Abdominal subcutaneous adipose tissue (SAT) and abdominal visceral adipose tissue (VAT) were included in the same model. Models adjusted for sex (except blood pressure variables), sexual maturity, and height-for-age Z-score. In models, schools and participants' identification were added as random intercepts, and participants' age was added as a random slope. A: constant; B: regression coefficient. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

triglycerides, TC, and BP but negatively with HDL-C. TBF (but not SAT) was related to LDL-C. In addition, cross-sectional associations of VAT with HDL-C, triglycerides, and BP disappeared after adjusting for SAT. In Mexican school children, SAT was also associated with cardiometabolic risk indicators¹⁰. Equally, systematically among U.S. Hispanic^{31,32} and Latinoamerican³³ youth, TBF has been related to cardiometabolic risk indicators. These findings suggest that higher total adiposity is directly associated with alterations in lipid profile and glucose metabolism, indicating that excess body fat during this life phase may contribute to the development of atherosclerosis and cardiovascular disease later in adulthood.

An unexpected finding is that increases in SAT were negatively associated with insulin and cholesterol. However, in some adult samples, SAT has not been related to cardiometabolic risk or even been shown to be protective against it^{34,35}. Compared to VAT, SAT has higher vascularization, but less fibrosis and infiltration of

macrophages³⁶. These properties of SAT can emerge protective, at least in early ages. More research is required.

In this sample, the intra-individual correlation of SAT and TBF was high, whereas that of VAT was moderate to low. This finding suggests that the variability of the VAT across time is higher than that of other adiposity measurements and therefore. It looks like VAT is a trait more independent of total adiposity.

In our sample, only increases in VAT at L1-L2 and L4-L5 over the 1-year follow-up period were positively associated with insulin, TC, LDL-C, and DBP in boys. In addition, VAT was cross-sectionally associated with insulin and BP in boys. Increased VAT has been associated with decreased beta-cell and metabolic function². According to the spillover hypothesis, when SAT reaches its capacity for expansion, fat deposition in the VAT increases, which can have a more deleterious impact on metabolic risk indicators.¹⁵ VAT increases as puberty progresses and, therefore, it can have a greater effect on cardiometabolic factors during adolescence compared to childhood^{7,12,15-17}.

Table 4. Multilevel linear regression models having cardiometabolic indicators as outcomes and abdominal and visceral SAT between lumbar vertebrae 3-4 and 4-5 as predictors in a sample of Mexican adolescents

Dependent variables	Lumbar vertebrae 3 and 4						Lumbar vertebrae 4 and 5					
	Constant	Age, yr	SAT, mm ²	SAT × age	VAT, mm ²	VAT × age	Constant	Age, yr	SAT, mm ²	SAT × age	VAT, mm ²	VAT × age
	A	B	B	B	B	B	A	B	B	B	B	B
Glucose, mg/dL	-	-	-	-	-	-	7.55 ^c	-4.80 ^b	0.01 ^b	-	-	-
Insulin, µU/mL	-1.90	0.02	0.02 ^c	-0.01 ^b	0.05 ^c	-	-0.98	0.17	0.02 ^c	-	-	-
Total cholesterol, mg/dL	-3.14	2.39	0.02	-0.02 ^c	-	-	-	-	-	-	-	-
LDL-C, mg/dL	-	-	-	-	-	-	-	-	-	-	-	-
HDL-C, mg/dL	-0.85	0.35	-0.02 ^c	-	-0.02	-	-1.05	-0.75	-0.01 ^b	-	0.01	-
Triglycerides, mg/dL	1.36	-7.96	0.10 ^a	-	0.12	-	-12.18	-12.18 ^a	0.08 ^b	-	0.11	-
Boys												
Systolic blood pressure, mmHg	-0.51	2.20	0.03 ^b	-	0.04	-	0.53	1.30	0.03 ^a	-	-	-
Diastolic blood pressure, mmHg	-0.18	0.16	0.02 ^a	-	0.01	-	-1.47	1.21	-	-	0.08 ^c	-
Girls												
Systolic blood pressure, mmHg	-	-	-	-	-	-	-	-	-	-	-	-
Diastolic blood pressure, mmHg	0.09	-2.20 ^a	0.01 ^c	-	-	-	-2.03	-1.99 ^d	0.01 ^a	-	-	-

^ap ≤ 0.050.

^bp ≤ 0.010.

^cp ≤ 0.001.

- , because the regression coefficient was not significant, it was removed from the final model. Abdominal subcutaneous adipose tissue (SAT) and abdominal visceral adipose tissue (VAT) were included in the same model. Models adjusted for sex (except blood pressure variables), sexual maturity, and height-for-age Z-score. In models, schools and participants' identification were added as random intercepts, and participants' age was added as a random slope.

A, constant; B, regression coefficient. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

Sexual dimorphism in fat distribution has been observed in late and post-puberty, such that males experience larger changes in central adiposity compared to girls³⁷. This may explain in part why VAT changes were not associated with measures of BP among females.

Findings from this study support the measurement of abdominal adiposity using multiple slices (compared to total regions) given that different measurements have a differential effect on specific cardiometabolic indicators. Assessing fat depots using multiple slices could provide more specific assessments of changes in fat distribution during this critical developmental stage³⁸. Most research has been conducted to evaluate abdominal fat at L4-L5; however, VAT estimated at L2-L3 is a more accurate estimation of total VAT volume³⁹. In our study, changes

in VAT at L1-L2 were longitudinally associated with cardiometabolic risk. While total adiposity typically remains constant, the distribution of fat mass experiences rapid and significant changes during puberty, which may provide insights into the metabolic effects of growth over time in specific depots⁴⁰.

To gain insight into the clinical implications of this study, one can examine the differences in cardiometabolic risk factors between individuals with and without coronary artery calcification. In a sample of young adults (mean age: 27 years) from Iowa, the average differences between those with and without coronary artery calcification were 17.4 mg/dL for cholesterol, 15.1 mg/dL for LDL-C, 2.7 mg/dL for HDL, 9.4 mg/dL for triglycerides, and 5.6 mmHg for SBP⁴¹. In our sample, among

Table 5. Multilevel linear regression models having cardiometabolic indicators as outcomes and total body fat as a predictor in a sample of Mexican adolescents

Dependent variables	Constant	Age, yr	TBF, %	Age × TBF
	A	B	B	B
Glucose, mg/dL	-0.03	-1.30 ^d	0.11 ^a	-
Insulin, μU/mL	-11.37 ^c	-0.07	0.48 ^c	-
TC, mg/dL	-9.72	2.16	0.23 ^b	-
LDL-C, mg/dL	-11.23 ^d	1.87	0.29 ^c	-
HDL-C, mg/dL	7.68 ^c	0.07	-0.39 ^c	-
Triglycerides, mg/dL	-37.04 ^c	-8.89	1.79 ^c	-
Boys				
Systolic blood pressure, mmHg	-10.64 ^c	6.18 ^c	0.33 ^c	-
Diastolic blood pressure, mmHg	-5.98 ^b	0.67	0.18 ^c	-
Girls				
Systolic blood pressure, mmHg	-	-	-	-
Diastolic blood pressure, mmHg	-7.46 ^a	-2.31 ^c	0.22 ^b	-

^ap ≤ 0.050.^bp ≤ 0.010.^cp ≤ 0.001.^dp ≤ 0.100.

-, because the regression coefficient was not significant, it was removed from the final model. Models adjusted for sex (except blood pressure variables), sexual maturity, and height-for-age Z-score. In models, schools and participants' identification were added as random intercepts, and participants' age was added as a random slope.

A: constant; B: regression coefficient.

adolescents who experience an increase in VAT at L1-L2, the mean change was 13.78. In the scenario of a rise of 13.78 mm² of VAT in 1-year, the increment in cholesterol would be 1.51 mg/dL, 0.86 mg/dL in LDL-C, and 0.86 mmHg for SBP (see the regression coefficients of the age by VAT interaction in table 3). Although the annual changes could be small, their accumulation over a lifetime can be significant. With respect to cross-sectional associations, adolescents with one standard deviation higher in SAT at L1-L2 (81.3 mm², Table 1) could have a HDL-C level 2.44 mg/dL lower, meanwhile their triglyceride level could be 13.0 mg/dL higher (see the regression coefficients of SAT in Table 3).

The longitudinal design of this study is a strength because it allows for documenting changes in adipose tissue across the pediatric age and pubertal stages³⁷. This study employed accurate imaging techniques among a heterogeneous sample, enabling direct quantification of total and regional fat distribution³⁸. In addition, using multiple slices to assess SAT and VAT allowed for a more specific investigation of the contribution of

these fat depots to cardiometabolic risk⁴². Future studies should examine changes across total and regional fat depots over longer periods of time to further contribute to our understanding of how changes in these fat depots contribute to cardiometabolic risk over time.

The sample size and attrition rate could be the main limitations of our research. The cost of the study was the primary determinant of the number of participants (n = 134 with follow-up) that we recruited and followed. Sample sizes of previous longitudinal studies using MRI to assess fat depots ranged from 16 to 128¹⁴⁻¹⁶. A risk of a small sample size is that an existing association could not be observed. However, we observed significant cross-sectional and longitudinal associations. Another limitation is that while we measured SAT, we could not differentiate between deep and superficial SAT. Another limitation of our research is that we relied solely on standard fasting blood tests to assess metabolic parameters. While these tests offer valuable insights, they may not capture the influence of diurnal variations, and the postprandial state on metabolism may not be fully accounted for in our measurements.

Conclusions

Cross-sectional associations were observed among Mexican adolescents between SAT and TBF and most cardiometabolic risk indicators. Changes in VAT were associated with cardiometabolic risk. This suggests that during puberty, VAT becomes a risk factor for cardiometabolic alterations. Future studies should examine the impact of changes in VAT over extended periods to assess the effects of fat accumulation in this depot on future disease risk. Findings from this study suggest the need for lifestyle interventions that target VAT to prevent cardiometabolic risk among pubers.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study. The ethical approval for this research was granted by the Divisional Council of Biological and Health Sciences of the UAM-Xochimilco (agreement number DCBS.CD.38.15).

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

Supplementary data

Supplementary data are available at DOI: 10.24875/BMHIM.25000061. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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Familial intrahepatic cholestasis: consensus recommendations for healthcare professionals in Latin America

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Abstract

Background: Progressive familial intrahepatic cholestasis (PFIC) is rare genetic liver disorders that often present with early-onset cholestasis, pruritus, and potential progression to severe liver complications. This article outlines consensus recommendations for the diagnosis and management of PFIC tailored to Latin American healthcare providers. **Methods:** A working group of 10 hepatologists across Latin America utilized the Population, Intervention, Comparison, and Outcome (P.I.C.O.) framework to address critical clinical questions related to PFIC's epidemiology, diagnosis, and treatment. A systematic literature review was conducted to understand the disease's heterogeneous nature and its impact on patients' quality of life. **Results:** The consensus emphasizes early referral to specialists, the importance of genetic testing for definitive diagnosis, and individualized treatment approaches with medical therapies including ursodeoxycholic acid and novel ileal bile acid transport inhibitors. Surgical options, including liver transplantation, should be considered based on disease sub-types. The article also highlights challenges unique to Latin America, such as limited access to specialized care and genetic testing. **Conclusions:** Early diagnosis and a comprehensive, individualized management plan are essential for improving outcomes in PFIC patients. This consensus aims to increase awareness and understanding of PFIC among healthcare providers.

Keywords: Progressive familial intrahepatic cholestasis. Consensus. Cholestasis. Genetic diseases. Pediatric hepatology.

Colestasis intrahepática familiar: recomendaciones consensuadas para profesionales en Latinoamérica

Resumen

Introducción: La colestasis intrahepática familiar progresiva (PFIC, por sus siglas en inglés) son un conjunto de enfermedades hepáticas genéticas raras que suele manifestarse con colestasis de inicio temprano, prurito y posible progresión a complicaciones hepáticas graves. Este artículo presenta recomendaciones consensuadas para el diagnóstico y tratamiento

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de la PFIC, adaptadas para los profesionales de la salud en América Latina. **Métodos:** Un grupo de trabajo conformado por diez hepatólogos de distintos países de América Latina utilizó el marco población, intervención, comparación, resultado-outcome (PICO) para abordar preguntas clínicas clave relacionadas con la epidemiología, el diagnóstico y el tratamiento de la PFIC. Se realizó una revisión sistemática de la literatura con el fin de comprender la naturaleza heterogénea de la enfermedad y su impacto en la calidad de vida de los pacientes. **Resultados:** El consenso destaca la necesidad de una remisión temprana a especialistas, la importancia de las pruebas genéticas para un diagnóstico definitivo y enfoques de tratamiento individualizados que incluyan terapias médicas como el ácido ursodesoxicólico y nuevos inhibidores del transporte de ácidos biliares ileales. Las opciones quirúrgicas, incluido el trasplante hepático, deben considerarse según el subtipo de la enfermedad. El artículo también subraya desafíos particulares de América Latina, como el acceso limitado a atención especializada y a pruebas genéticas. **Conclusiones:** El diagnóstico precoz y un plan de tratamiento integral e individualizado son esenciales para mejorar los resultados en pacientes con PFIC. Este consenso busca aumentar la conciencia y comprensión de la enfermedad entre los profesionales de la salud.

Palabras clave: Colestasis intrahepática familiar progresiva. Consenso. Colestasis. Enfermedades genéticas. Hepatología pediátrica.

Introduction

Progressive familial intrahepatic cholestasis (PFIC) comprises a group of rare, heterogeneous genetic liver diseases with autosomal recessive inheritance. The estimated incidence is 1/50,000-100,000^{1,2}. PFIC characterized by early-onset cholestasis in infancy, accompanied by pruritus and malabsorption. The condition may progress to liver failure, portal hypertension, cirrhosis, and hepatocellular carcinoma, ultimately necessitating liver transplantation². PFICs are subcategorized based on genetic defects, clinical presentation, laboratory findings, and liver pathology^{2,3}.

All PFIC types result from defects in bile secretion from hepatocytes to canaliculi, with distinct features observed in each phenotype³. Diagnosis is facilitated by liver function tests, serum bile acid measurements, and imaging studies, which also help exclude other pathologies³. PFIC patients may exhibit elevated serum alkaline phosphatase, variable bilirubin elevation, normal or increased γ -glutamyl transferase (GGT), and increased bile acids³.

Genetic testing can aid in confirming the diagnosis of PFIC. With the advent of advanced diagnostic methods such as next-generation sequencing (NGS) and whole-exome sequencing (WES), the identification of novel causative genes has been eased⁴. Genes implicated in PFIC have also been associated with benign recurrent intrahepatic cholestasis, intrahepatic cholestasis of pregnancy, drug-induced cholestasis, low-phospholipid-associated cholelithiasis, and hepatocellular carcinoma⁴.

Pruritus, the most distressing symptom of cholestasis, is likely caused by the stimulation of non-myelinated sub-epidermal free nerve endings due to increased bile

acids^{3,4}. Severe pruritus can lead to significant skin issues and substantially impact daily activities, resulting in sleep deprivation, irritability, attention deficits, and impaired academic performance^{2,5}. Treatment includes medical and surgical approaches with multiple alternatives³; the most frequently reported are ursodeoxycholic acid (UDCA) or rifampicin¹. A novel mechanism of action was directed at the inhibition of the ileal bile acid transporter (IBAT), which reabsorbs intestinal bile acid for recirculation to the liver and thus relieves pruritus⁶. To date, two IBAT are available⁶⁻⁹, which adequate safety profile and efficacy in pruritus improvement and patient's and family's quality of life^{6,8}. Finally, liver transplant is considered a treatment option in PFIC when medical treatment fails to achieve symptoms relief or end-stage liver disease develops³. The present study aimed to establish a series of recommendations regarding the prevalence, diagnosis, and treatment of patients with PFIC in Latin America.

Methods

Formation of the working group

A working group was established, comprising 10 hepatologists from Latin America (Argentina, Brazil, Chile, Colombia, Mexico, and Peru) with recognized expertise in PFIC and a methodological specialist. A leading expert, G.P., was appointed to oversee the group.

Defining clinical questions

The expert group formulated open clinical questions to address three key areas: (1) epidemiological data, (2) diagnosis, and (3) treatment, utilizing the Patient,

Intervention, Comparator, and Outcome (P.I.C.O) framework (see Appendix A for details).

Systematic literature review

A methodological expert independently conducted a systematic literature review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines¹⁰. The aim was to gather evidence relevant to the three primary topics and their associated research questions. Searches were conducted in July 2024 across PubMed, Cochrane Database of Systematic Reviews, and BVS databases focusing on studies published between 2014 and 2024. Medical Subject Headings and free-text keywords were used to explore each clinical question. Duplicate entries were removed during the screening process. Exclusion criteria included studies with fewer than 10 patients, *in vitro*/animal studies, non-English or Spanish language studies, incomplete studies, non-systematic reviews, and studies unrelated to the research questions (Fig. 1). References from existing guidelines and review articles were also reviewed for supplementary data.

Development and validation of guidance statements

The findings from the systematic review and original articles were distributed to all participants for evaluation and discussion. The methodological and leading clinical expert (G.P.) initially drafted preliminary guidance statements for each clinical question. These drafts were circulated through an open online survey platform (*Google Docs*) to the expert panel for feedback and additional input. Following this, the methodological and clinical expert (G.P.) revised the statements based on the input and distributed them to the expert panel through an online survey for a Delphi voting process^{11,12}. To ensure comprehensive participation, reminders were sent over 10 days. Statements were rated using a Likert scale from one (strongly disagree) to nine (strongly agree) (Appendix B). Statements with a median score above eight or an interquartile range below one were considered agreed upon. Statements not meeting these criteria were subjected to further discussion.

Open debate

An academic meeting was held in Sao Paulo, Brazil, involving the methodological expert and the expert panel. This meeting focused on various methodological

consensus types, as well as the results of the consensus process. All recommendations were discussed in this forum. Panelists were divided into two groups to examine, evaluate, and revise recommendations that did not meet the threshold. Each group presented their revised statements, followed by a discussion to finalize the statements with consensus. The final statements were voted on individually using the same online survey platform and Delphi methodology. During the session, several recommendations were removed – specifically those originally numbered 2, 6, 8, 9, 10, and 17 – while others were consolidated (e.g., 3 and 4; 10 and 11; 12 and 13-15). The session concluded with each expert drafting a summary of the consensus reached.

Ensuring independence

Biopass, the manufacturer of Maralixibat, sponsored the meeting, which was intended to draft the recommendations on an open debate. However, Biopass did not participate in or influence any aspect of the process, including the scope, content, voting, or drafting of statements. An independent expert and a medical writer managed the publication process.

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Recommendations

PATHOPHYSIOLOGY, CLINICAL PRESENTATION, AND EPIDEMIOLOGY

Hepatocytes and cholangiocytes work to produce organic and inorganic compounds that aid in the digestion and excretion of metabolites¹³. Bile is formed by

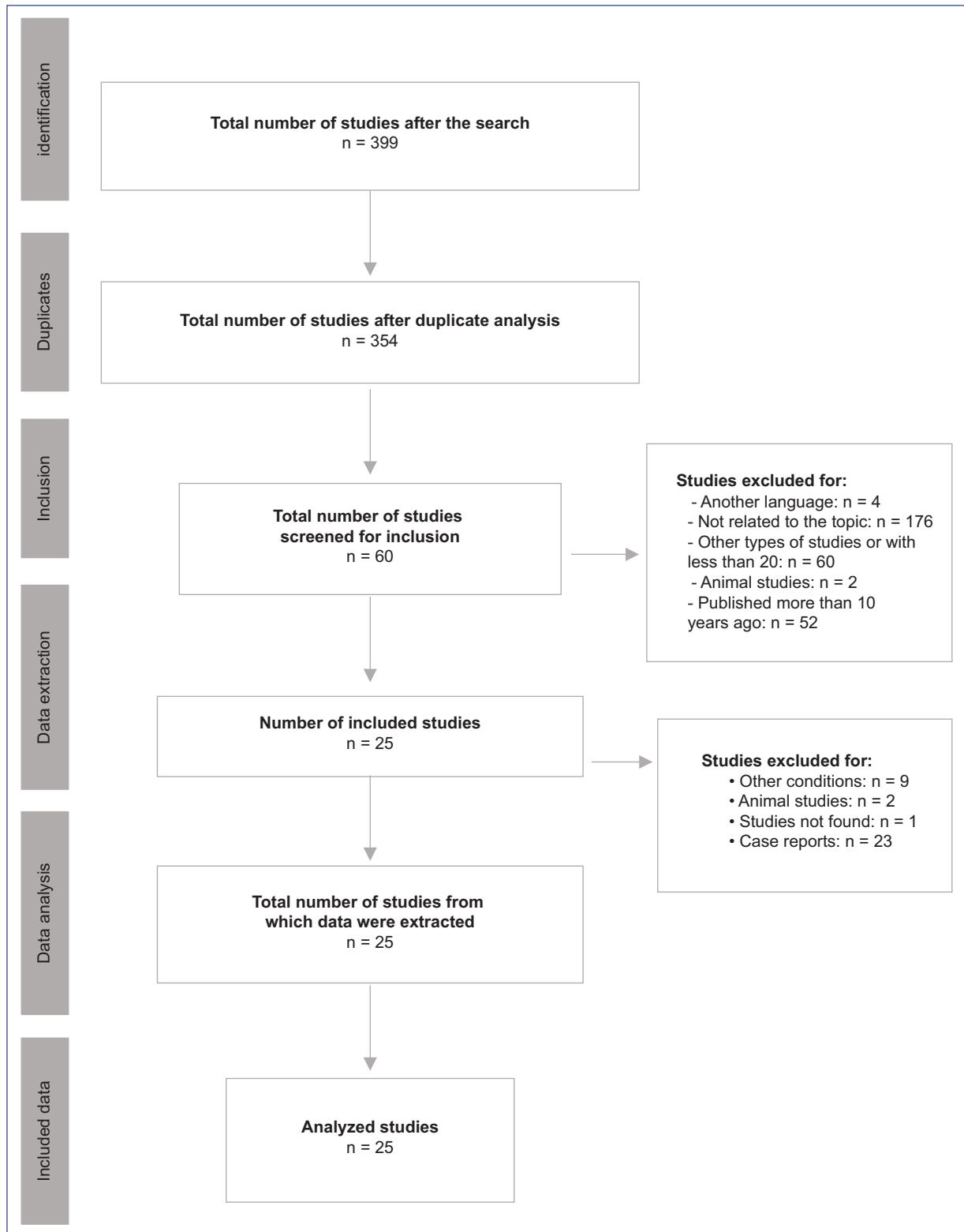


Figure 1. PRISMA flow diagram of study selection process. This flow diagram summarizes the process of study identification, screening, and inclusion. A total of 399 records were initially retrieved, of which 354 remained after removing duplicates. Sixty studies were screened in full, and exclusions were made for language, irrelevance to the topic, inappropriate study design, animal studies, and outdated publications. Ultimately, 25 studies met the inclusion criteria and were analyzed. n: number of studies; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

the formation and conjugation of bile acids by the hepatocytes and the alkalization and dilution by the cholangiocytes; it can be stored in the gallbladder and secreted to the duodenum¹⁴. Gene products in PFIC encode proteins expressed in the hepatocyte canalicular membrane and the secretion of bile salts into the biliary canaliculus (stage III)¹⁴. Conventionally, three forms of PFIC have been documented, with type 1 being the most common, beside types 2 and 3; recently, additional types have also been identified¹. However, different subtypes emerge as genes are identified¹⁵. Patients with PFIC usually present in infancy with cholestasis and associated problems such as pruritus, diarrhea, growth retardation, jaundice, and malabsorption^{14,16}. PFIC can have a devastating impact on the quality of life of the patient and their family with the possibility of developing end-stage liver disease; early diagnosis and appropriate treatment are imperative¹⁵.

In Latin America, the point prevalence of PFIC has yet to be established, and a sub-registry of patients exists due to challenges in diagnosis, insufficient clinical suspicion, and delayed interventions. These issues are further exacerbated by the lack of legislation in some countries regarding screening and treatment, which increases access barriers for affected individuals.

- PFIC is a group of rare diseases whose exact prevalence cannot be established; however, literature estimates a prevalence of 1/50,000-1/100,000 births. It represents 10-15% of neonatal cholestasis cases^{1,2}.
Median: 8
IQR: 1

- PFIC is a heterogeneous group of chronic cholestatic diseases of genetic origin (Table 1). It is clinically suspected when there is jaundice with pruritus, elevated transaminases, and generally low levels of GGT (except for types 3, 6, 8, and 9, where it is elevated), as well as elevated serum bile acids. PFIC should be suspected in patients in whom other causes of cholestasis have been ruled out (Fig. 2).

At present, there are more than 12 described subtypes of PFIC, with a wide clinical variability that shares cholestasis with differences in phenotype, laboratory findings, and evolution (Table 1).

- Median: 9
IQR: 0
- Early referral to a specialist is recommended for patients with intractable or difficult-to-manage pruritus, associated or not with jaundice.

- Median: 9
IQR: 0

DIAGNOSIS

The diagnosis of PFIC has traditionally relied on clinical assessment, which includes evaluating symptoms, family history, laboratory investigations, liver ultrasound, and biopsy¹⁵. Gene sequencing is widely accepted as the gold standard for diagnostic confirmation¹⁷. In addition to standard gene sequencing, genetic diagnosis can employ NGS techniques. These techniques include targeted gene panel analysis, which sequences multiple cholestasis-associated genes in a single test¹⁷⁻¹⁹ as well as WES and whole-genome sequencing for cases with complex phenotypes or when previous genetic diagnoses have been inconclusive²⁰. Despite medical and diagnostic advances, it can be challenging to predict pathogenic variants, and phenotype-genotype correlations are not always consistent in PFIC^{17,19,21,22}.

Given that cholestasis is a frequent finding in neonatal intensive care units, it is important to clarify that not all infants with cholestasis should undergo extensive evaluation for PFIC. The diagnostic approach should be expanded particularly in cases of persistent cholestasis with no identifiable cause after exclusion of common etiologies, low or normal GGT levels in association with intense pruritus, poor response to conventional management, or a positive family history of early liver disease or unexplained sibling death.

In Latin America, the diagnosis of rare diseases is hindered by numerous challenges such as: limited access to specialized medical care and expertise, and lack of awareness among healthcare professionals, which may lead to late diagnosis and inappropriate treatment. In addition, restrictions in the availability of essential genetic diagnostic tools and marginalized populations create new obstacles and further disparities in rare diseases such as PFIC. Therefore, biochemical parameters such as serum bile acids and GGT levels play a crucial role as first-line tools in low-resource settings, guiding clinical suspicion and facilitating appropriate referral even before genetic confirmation.

Although liver biopsy is not diagnostic for PFIC, it is often indicated in cases of cholestasis with inadequate progression or unclear etiology. In such scenarios, typical histological features – such as intracellular and canalicular cholestasis, variable ductular reaction, and, in certain subtypes, pseudoxanthomatous change – may support clinical suspicion and help exclude alternative diagnoses.

- The definitive diagnosis of PFIC is established through molecular studies that identify variants associated with PFIC.

- Median: 9

Table 1. Genetic, clinical, and biochemical features of progressive familial intrahepatic cholestasis (PFIC) subtypes

PFIC	Gene	Locus	Protein	Inheritance	Age of onset	Clinical presentation	Progression	Histology	Laboratory test results				
									Bile acid	BD	GGT	AST/ALT	α fetoprotein
PFIC 1	ATP8B1	18q21-22	FIC1	AR	Early (1 st months of life)	Early jaundice, hepatomegaly, splenomegaly, and intense itching	Moderate	Intrahepatic cholestasis, giant cell transformation, bridging fibrosis, and cirrhosis	High	High	Low or normal	Slightly elevated	Normal
						Short stature, growth failure, diarrhea, pancreatitis, sensorineural hearing loss, urolithiasis, elevated sweat chloride, exocrine pancreatic insufficiency, resistance to parathyroid hormone, pneumonia, and congenital hypothyroidism							
PFIC 2	ABCB11	2q24	BSEP	AR	Early (childhood)	Early jaundice, hepatomegaly, splenomegaly, intense itching, moderate to rapid progression of cholelithiasis, risk of hepatocellular carcinoma, cholangiocarcinoma, and pancreatic adenocarcinoma	Rapid	Giant cell transformation, portal fibrosis, and cirrhosis	Very High	High	Low or normal	Moderate elevation	High
						Short stature, growth failure, diarrhea, lipid, and vitamin malabsorption							
PFIC 3	ABCB4	7q21	MDR3	AR	Late (childhood or adolescence)	Jaundice, hepatomegaly, splenomegaly, and itching, which may be	Variable	Proliferation, portal fibrosis, and cirrhosis	High	High	High	Slightly elevated	Normal

(Continues)

Table 1. Genetic, clinical, and biochemical features of progressive familial intrahepatic cholestasis (PFIC) subtypes (continued)

PFIC	Gene	Locus	Protein	Inheritance	Age of onset	Clinical presentation	Progression	Histology	Laboratory test results				
									Bile acid	BD	GGT	AST/ALT	α fetoprotein
PFIC 4	TJP2	9q21.11	ZO-2	AR	Early (early childhood)	triggered by medications, risk of cholangiocarcinoma and hepatocellular carcinoma	Rapid	Tight and elongated junctions between hepatocytes and bile canaliculi	High	-	Normal or mildly elevated	Elevated	High
						Diarrhea, lipid and vitamin malabsorption, and delayed puberty							
PFIC 5	NRIH4	12q23.1	FXR	AR	Early or late (before 2 months, some reports up to 2 years of life)	Vitamin K-independent coagulopathy, sensorineural hearing loss, neurological symptoms, and respiratory disease	Very rapid	Ductal reaction, intrahepatic cholestasis, transformation, hepatocyte bulging, hepatic fibrosis, and cirrhosis	High	-	Normal	Moderate elevation	High
						Neonatal cholestasis with rapid progression to liver failure, jaundice, and hepatomegaly Growth failure, a patient with hydrops							

(Continues)

Table 1. Genetic, clinical, and biochemical features of progressive familial intrahepatic cholestasis (PFIC) subtypes (*continued*)

PFIC	Gene	Locus	Protein	Inheritance	Age of onset	Clinical presentation		Progression	Histology	Laboratory test results			
										Bile acid	BD	GGT	AST/ALT
PFIC 6	<i>SLC51A</i>	3q29	O86UW1	AR	-	Onset > 2 years, jaundice, hepatomegaly, and itching Diarrhea, lipid, and vitamin malabsorption	-	Cholestasis, portal and periportal fibrosis	High	-	High	Mild or moderate elevation	Normal
PFIC 7	<i>USP53</i>	4q26	Q70EK8	AR	Early or Late (mostly in childhood, some reported in adolescence)	Jaundice, hepatomegaly, some have splenomegaly, and portal hypertension Sensorineural hearing loss and diarrhea	Slow or non-progressive	Hepatocellular cholestasis, canalicular, giant cells, and fibrosis	-	High	Normal	High	-
PFIC 8	<i>KIF12</i>	9q32	Q96FN5	AR	-	Jaundice, hepatomegaly, splenomegaly, and portal hypertension Hyper-echoic pancreas	-	Bile duct proliferation, hepatic fibrosis, and sclerosing cholangitis	High	High	High	High	High
PFIC 9	<i>ZFYVE19</i>	15q15.1	Q96K21	AR	-	Jaundice, hepatomegaly, itching, splenomegaly, portal hypertension Gastrointestinal bleeding, diarrhea	-	Periductal fibrosis, ductal reaction, proliferation of bile ducts, poor ductal plate formation, micro-nodular cirrhosis, and sclerosing cholangiopathy	High	High	High	High	-
PFIC 10	<i>MYO5B</i>	18q21.1	Myosin VB	AR	Early or late (typically late childhood or early in the 2 nd year of life)	Jaundice, hepatomegaly, and itching Chronic diarrhea (some patients with	Slow	Hepatocellular cholestasis, giant cell transformation, and fibrosis	High	High	Normal	High	-

(Continues)

Table 1. Genetic, clinical, and biochemical features of progressive familial intrahepatic cholestasis (PFIC) subtypes (continued)

PFIC	Gene	Locus	Protein	Inheritance	Age of onset	Clinical presentation	Progression	Histology	Laboratory test results				
									Bile acid	BD	GGT	AST/ALT	α fetoprotein
PFIC 11	SEMA7A	15q24.1	O75326	AR	-	microvillus atrophy), neurological symptoms	-	Intrahepatic cholestasis, and enlarged liver	High	Normal	Normal	High	-
PFIC 12	VPS33B	15q26.1	Q9H267	AR	-	Jaundice, hepatomegaly, splenomegaly, and intractable itching Dextro-scoliosis (1 patient)	-	Giant cell transformation	Slightly elevated	slightly elevated	Normal	Slightly elevated	-

Laboratory values reflect typical trends observed in PFIC patients but may vary depending on disease stage, associated comorbidities, and genetic modifiers. ALT: alanine aminotransferase; AR: autosomal recessive; AST: aspartate aminotransferase; BD: direct bilirubin; GGT: γ -glutamyl transferase.

Table 1. Genetic, clinical, and biochemical features of progressive familial intrahepatic cholestasis (PFIC) subtypes (continued)

PFIC	Gene	Locus	Protein	Inheritance	Age of onset	Clinical presentation	Progression	Histology	Laboratory test results				
									Bile acid	BD	GGT	AST/ALT	α fetoprotein
PFIC 11	SEMA7A	15q24.1	O75326	AR	-	microvillus atrophy), neurological symptoms	-	Intrahepatic cholestasis, and enlarged liver	High	Normal	Normal	High	-
PFIC 12	VPS33B	15q26.1	Q9H267	AR	-	Jaundice, hepatomegaly, splenomegaly, and intractable itching Dextro-scoliosis (1 patient)	-	Giant cell transformation	Slightly elevated	slightly elevated	Normal	Slightly elevated	-

Laboratory values reflect typical trends observed in PFIC patients but may vary depending on disease stage, associated comorbidities, and genetic modifiers. ALT: alanine aminotransferase; AR: autosomal recessive; AST: aspartate aminotransferase; BD: direct bilirubin; GGT: γ -glutamyl transferase.

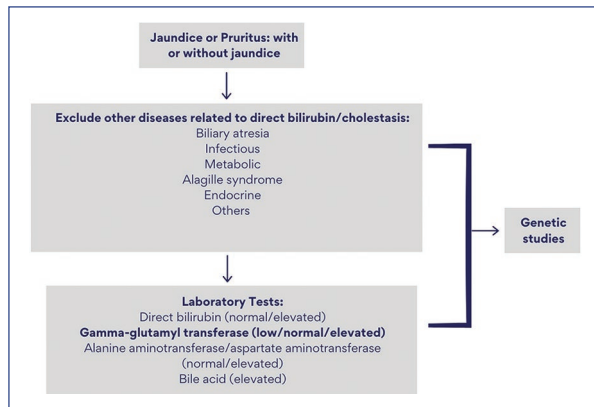


Figure 2. Diagnostic algorithm for clinical suspicion of progressive familial intrahepatic cholestasis (PFIC). This flowchart outlines the diagnostic approach to PFIC in patients presenting with jaundice or pruritus. The first step requires exclusion of other causes of direct hyperbilirubinemia/cholestasis, including biliary atresia, infectious, metabolic, endocrine, and syndromic conditions such as Alagille syndrome. Once these are ruled out, laboratory investigations – direct bilirubin, γ -glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bile acids – help guide the evaluation. Abnormal findings, particularly low/normal GGT in the context of cholestasis, support the suspicion of PFIC. Confirmatory diagnosis requires genetic testing to identify specific PFIC subtypes. GGT: γ -glutamyl transferase; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

IQR: 0

- Patients with suspected PFIC should be referred to a pediatric hepatologist.

Median: 9

IQR: 0

- The main barriers to diagnosing PFIC patients in Latin America are the lack of awareness of the disease, limitations in access to specialists, difficulties in referring patients, and the high cost of genetic testing.

Median: 9

IQR: 0

- A relevant genetic test includes the genes implicated and described in the literature to date for PFIC. However, it is possible to find patients with a high clinical suspicion of PFIC for whom genetic testing yields negative results, which may be due to intronic variants, microdeletions, undescribed variants, or genes not yet identified as causing the phenotype; similarly, this can be due to limitations in the number of genes assessed by a specific panel, which limits the results.

Median: 9

IQR: 0

Table 2. Recommended daily requirements of fat-soluble vitamins in pediatric patients

Vitamin	Requirement/kg/day
Vitamin A	1,000 IU/kg/day
Vitamin E	22-90 mg/kg/day as D α -tocopherol
	if water -soluble: 15-25 mg/kg/day
Vitamin K	2,5-5 mg/dose
Vitamin D	Normal levels are above 30 ng/mL
	Maintain levels 20-60 ng/mL
	2,000 IU/day of cholecalciferol (D3), increase by 2,000 IU according to level; if severe deficiency < 20 ng/mL, consider 50,000-100,000 IU per week

Values represent general pediatric reference ranges and should be adjusted according to age, clinical condition, and laboratory monitoring.

TREATMENT

Medical treatment, combined with dietary supplementation of fat-soluble vitamins, typically serves as the first line of therapy for all subtypes of PFIC. UDCA is commonly used to enhance hepatobiliary secretion and reduce bile toxicity²³⁻²⁵, and it is utilized off-label in PFIC to manage pruritus. Cholestyramine, which sequesters bile acids in a resin complex for excretion, is specifically approved for adults with cholestatic pruritus²³. Rifampicin has been noted to significantly improve pruritus, although its mechanism of action remains unclear²⁶. Additional treatment options include antihistamines^{23,24} and opioid antagonists²⁷. Emerging pharmacological interventions targeting enterohepatic bile acid circulation are known as IBAT inhibitors. IBATs offer a non-surgical approach to disrupt the enterohepatic circulation of bile acids¹⁵ and have been approved explicitly for PFIC by showing normalization of serum bile acids, reduction of pruritus severity, and improvement in quality of life^{6-9,28,29}. Nevertheless, patient's refractory to medical management of pruritus may benefit from surgical interventions such as liver transplants. This can ultimately be indicated in cases with severe pruritus, progression to cirrhosis, or hepatocarcinoma^{26,30,31}.

In Latin America, patients face significant barriers not only in diagnosis, as previously described, but also in accessing treatment. These challenges stem from health-care systems' lack of coverage for specific therapeutic agents and the limited availability of these treatments. This dual obstacle complicates the management of

Table 3. Pharmacological management of PFIC: commonly used medications, doses, and side effects

Medication	Class	Dose	Side effects
Ursodeoxycholic acid	Choleretic	10-30 mg/kg/day	Diarrhea, abdominal pain, and vomiting
Cholestyramine	Bile acid sequestrant	240 mg/kg/day in 3 doses (Max 16 g/day)	Poor palatability, increased malabsorption, constipation, and abdominal pain
Hydroxyzine	Antihistamine	1-2 mg/kg in two doses	Drowsiness
Odevixibat	IBAT	40 micrograms/kg/day	Diarrhea, abdominal pain, vomiting, and weight loss
Maralixibat	IBAT	380 micrograms/kg/day (initially 190 micrograms/kg/day)	Diarrhea, abdominal pain, and nausea
Naltrexone	Opioid	0.25-0.5 mg/kg/day	Irritability and withdrawal symptoms
Ondansetron	Serotonin 5-HT3 receptor antagonist	0.15 mg/kg/day	Headache, constipation, and drowsiness
Rifampicin	Hepatic hydroxylation	10 mg/kg/day in 2 doses	Hepatitis, hypersensitivity, and choloria
Sertraline	SSRI	1.4 mg/kg/day (Max 100 mg/day)	Agitation, gastrointestinal discomfort

IBAT: ileal bile acid transporter inhibitor; SSRI: selective serotonin reuptake inhibitor; 5-HT3: 5-hydroxytryptamine type 3 receptor.

conditions such as PFIC, ultimately impacting patient outcomes and quality of life.

– There are multiple management options for PFIC patients that should be individualized according to the specialist’s criteria and local regulations, including:

- Management of cholestatic patients:
 - Nutritional support: Fat-soluble vitamin supplements and medium-chain triglycerides with doses adjusted to age (Table 2).
 - Pruritus management: Antihistamines (e.g., Hydroxyzine), UDCA, cholestyramine, IBAT (Maralixibat and odevixibat), naltrexone, ondansetron, rifampicin, and sertraline (Table 3).
- Surgical management:
 - Biliary diversion
 - Liver transplantation

Median: 9
IQR: 0

– Biliary diversion has been reported in PFIC types 1 and 2; it is contraindicated in patients with cirrhosis, advanced fibrosis, hepatocellular carcinoma, or PFIC2 without residual protein activity³².

Median: 9
IQR: 1

– Liver transplantation is indicated for PFIC patients who present with intractable pruritus, hepatocellular carcinoma, or terminal liver disease^{30,33}. In some patients with PFIC type 2, disease recurrence may

occur in the graft. In patients with PFIC type 1, diarrhea may worsen, and severe steatosis may develop in types 1 and 5³⁴⁻³⁶. PFIC type 1 with diarrhea can be a contraindication for a liver transplant.

Median: 9
IQR: 1

– The initiation of the previously described supportive treatment in patients with PFIC should be immediate.

Median: 9
IQR: 0

– A specialist should indicate more specialized treatments, such as IBAT (Maralixibat and odevixibat), according to clinical manifestations and molecular studies. It is advisable to have baseline bile acid levels for patients starting treatment with IBAT.

Median: 9
IQR: 0

– IBATs are a treatment option for patients with certain types of PFIC and cholestatic pruritus^{6-9,28,29}.

Median: 9
IQR: 1

Discussion

PFIC is a rare, heterogeneous group of chronic cholestasis diseases^{14,16}. Our findings highlight that PFIC typically presents in infancy, with symptoms such as jaundice and pruritus emerging early in life². The phenotypic differences can present challenges for diagnosis

and prognosis³⁷. The high clinical suspicion of PFIC, especially when other causes of cholestasis have been excluded, is essential for guiding timely diagnosis and treatment. This is particularly relevant in resource-limited settings, where lack of access to specialists and diagnostic tools complicates early intervention.

Genetic testing is considered the gold standard for diagnosis⁴. However, barriers to genetic testing – such as high costs, limited access, and complex cases – can hinder genotype-phenotype correlation and delay diagnosis³⁸; posing additional challenges in Latin America. Despite these complexities and local barriers, genetic testing should be prioritized in children with early-onset unexplained cholestasis.

As observed in our study, patients with PFIC in Latin America often face delayed diagnoses, which can result in irreversible liver damage and increased morbidity. Moreover, the absence of screening programs and healthcare policies supporting the identification of rare diseases creates significant barriers to early detection and intervention. Therefore, healthcare systems in Latin America must invest in increasing awareness of rare diseases such as PFIC, improving access to specialized care, and supporting the integration of genetic testing into routine clinical practice.

At present, the management of PFIC is primarily supportive, focusing on symptom control and nutritional support. Our study also highlights the emerging role of novel pharmacological treatments, such as IBATs, which have been shown to improve both serum bile acid levels and pruritus, offering a promising non-surgical option for PFIC patients. However, the availability and affordability of these newer treatments remain significant obstacles in many regions, particularly in Latin America, where access to specialized care and medications is limited.

Conclusions

The consensus is directed at healthcare professionals as a guide for the evaluation of a rare disease that manifests as chronic cholestatic hepatopathy. This group of diseases, known as PFIC, accounts for approximately one in 10 cases of cholestasis and encompasses a wide range of genetic disorders associated with severe pruritus. The classification of these conditions is based on the findings of genetic studies, which are essential for establishing an accurate diagnosis and providing appropriate genetic counseling. While conventional treatments to alleviate itching and prevent disease progression may be insufficient in many cases, new

therapeutic options have been developed, such as IBATs, which have shown efficacy in certain types of PFICs. These alternatives not only improve symptoms and the quality of life for patients and their caregivers but also offer the possibility of better progression of liver disease, even in cases where liver transplantation has been considered. Early detection, based on the association between direct bilirubin levels and GGT with itching, is crucial for properly managing these patients.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Ethical considerations

Protection of humans and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

Supplementary data

Supplementary data are available at DOI: 0.24875/BMHIM.25000067. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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Associated comorbidities in pediatric patients with alopecia areata

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Abstract

Background: Alopecia areata (AA) in children is associated with comorbidities such as atopy, vitiligo, psoriasis, and thyroid disease, but reported data are lacking. Our objective is to estimate the frequency of comorbidities present in children with AA, as well as their relationship with age of onset, specific subtype, and treatment efficacy. **Methods:** We retrospectively reviewed clinical records of patients treated at the National Institute of Pediatrics between 2008 and 2018. Patients were categorized into subgroups: localized versus non-localized AA, onset in preschool age (< 7 years) versus school age (≥ 7 years), and treatment response as good ($\geq 50\%$ regrowth) versus suboptimal (< 50%). Comorbidities were classified as autoimmune, inflammatory/reactive, congenital, psychological, infectious, and neoplastic. **Results:** We included 105 patients diagnosed with AA. The most prevalent subtype was localized in 78 (74.3%) patients. Ninety-five (90%) patients had comorbidities, with allergic rhinitis ($n = 12$, 11.4%) and atopic dermatitis ($n = 11$, 10.4%) being the most frequent. Autoimmune comorbidities occurred in 16 patients (15.2%), with autoimmune thyroid disease being the most prevalent in 8 patients (76%). Localized AA was associated with better outcomes, shorter duration, fewer relapses, and fewer treatments, as well as inflammatory and congenital diseases. **Conclusions:** The association of AA with atopic, autoimmune, and psychiatric comorbidities is consistent with literature reports. Our findings support intentionally seeking associated diseases in pediatric patients with AA to identify them and treat them timely.

Keywords: Alopecia areata. Comorbidity. Pediatrics. Autoimmune disease.

Comorbilidades asociadas en pacientes pediátricos con alopecia areata

Resumen

Introducción: La alopecia areata (AA) en niños se asocia a comorbilidades como atopia, vitiligo y enfermedad tiroidea. Nuestro objetivo es estimar la frecuencia de comorbilidades presentes en niños con AA, así como su asociación con edad de inicio, subtipo específico y la eficacia del tratamiento. **Métodos:** Se realizó un estudio retrospectivo de pacientes menores de 18 años atendidos en el Instituto Nacional de Pediatría entre 2008 y 2018. Se categorizó a los pacientes en subgrupos: AA localizada vs. no localizada, inicio en edad preescolar vs. edad escolar, y respuesta al tratamiento buena ($\geq 50\%$ de recrecimiento) vs. subóptima (< 50%). Las comorbilidades se clasificaron como autoinmunes, inflamatorias, congénitas, psiquiátricas, infecciosas y neoplásicas. Se analizaron diferencias entre grupos utilizando estadística analítica, considerando un valor de $p \leq 0.05$ como estadísticamente significativo. **Resultados:** Se incluyeron 105 pacientes con AA. El subtipo más prevalente fue el localizado en el 74.3% de los pacientes. El 90% de los pacientes presen-

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taban comorbilidades, las más frecuentes fueron la rinitis alérgica (11.4%) y la dermatitis atópica (10.4%). Se encontraron comorbilidades autoinmunes en 16 pacientes (15.2%), siendo la enfermedad tiroidea autoinmune la más prevalente en 8 pacientes (7.6%). La AA localizada se asoció a mejores resultados, menor duración, menos recaídas y menos tratamientos; al igual que las enfermedades inflamatorias y congénitas. **Conclusiones:** La asociación de AA con comorbilidades atópicas, autoinmunes y psiquiátricas concuerda con los informes de la literatura. Nuestros hallazgos apoyan la búsqueda intencionada de enfermedades asociadas en pacientes pediátricos con AA para identificarlas y tratarlas a tiempo.

Palabras clave: Alopecia areata. Comorbilidad. Pediatría. Autoinmunidad.

Introduction

Alopecia areata (AA) is a chronic autoimmune disease that affects hair follicles, leading to hair loss that occurs on the scalp or affect all hair-bearing sites on the body. It affects approximately 2% of the general population, with about 20% of all AA cases appearing in childhood¹.

In adults, AA is linked to an increased prevalence of vitiligo, thyroid disease, atopy (particularly atopic dermatitis [AD]), and psychiatric diseases^{2,3}. Limited data exists for children, but studies indicate AD as the most common comorbidity with a frequency ranging from 17.4% to 34.4%^{1,4,5}. Other frequently associated diseases in this age group include vitiligo, psoriasis, and thyroid disease⁴. There is scarce data about differences in clinical characteristics or associated diseases according to subtype and clinical course. Our objective was to assess the frequency of comorbidities in pediatric patients with AA as well as their association with age at onset, specific subtypes, and treatment outcomes. Due to the descriptive nature of the study, it was not feasible to determine risk factors for the onset of AA.

Methods

In this retrospective study, we reviewed medical records of patients at the National Institute of Pediatrics (INP) in Mexico City between 2008 and 2018 (IRB registration no. GA/003/2020). Inclusion criteria comprised patients of both sexes, aged 0-18 years, with a diagnosis of AA (ICD-10 L63), who attended the outpatient dermatology clinic at the INP between January 01, 2008, and December 31, 2018. As well, exclusion criteria included medical records with < 70% of the data required for the study and patients who did not attend at least one follow-up visit. We classified patients into the following

categories: extension of hair loss was divided into localized or patchy subtype versus non-localized AA (universalis, totalis, ophiasis, sisaipho subtypes). This clinical classification was considered as it is universally accepted in the literature, and also because using more precise scores (e.g., SALT) would have excluded a considerable number of records that do not mention this information. Onset of disease was categorized as pre-school age (< 7 years) versus school age (\geq 7 years), and response to treatment as good (\geq 50% regrowth) versus suboptimal (< 50% regrowth). Comorbid diseases were categorized as autoimmune, inflammatory/reactive, congenital, and mental health disease. Statistical analysis using non-parametric U Mann-Whitney test for continuous variables and χ^2 or Fisher's exact test for categorical variables was performed; a $p < 0.05$ considered statistically significant.

Results

We found 147 patients with a diagnosis of AA, of which, 105 met inclusion criteria and 42 were excluded (nineteen patients did not have at least one follow-up visit, 17 patients' medical records did not have sufficient data, and six patients' final diagnosis was not AA). With regard to sex, 59 patients (56.2%) were girls (Table 1); mean age at onset was 7.1 years (SD \pm 3.9), and duration of disease was 14.09 months (SD \pm 19.56). Fifty-six (53.3%) patients had disease onset at pre-school age. The most frequent subtype was localized disease in 78 (74.3%) patients, the rest had non-localized presenting as AA universalis in 17 (16.2%), ophiasis in 7 (6.7%), and totalis in 3 (2.9%). Patients received on average 2.58 (SD \pm 2.06) treatment modalities, 82 (78%) patients used topical steroids, 35 (33.3%) applied minoxidil, and 10 (9.5%) received systemic treatment with immunosuppressants or corticosteroids (of these, 9 had non-localized disease).

Table 1. Demographic and clinical data of patients with AA (n = 105)

Demographic and clinical characteristics	n (%)
Female sex	59 (56.2)
Pre-school age (< 7 years) at onset	56 (53.3)
Treatment modalities mean (\pm SD)	2.58 (\pm 2.06)
Required systemic treatment	10 (9.5)
Relapsed	31 (29.5)
Disease duration in months mean (\pm SD)	14.09 (\pm 19.56)
Subtypes	
Localized or patchy	78 (74.3)
Non-localized	27 (25.7)
Universalis	17 (16.2)
Totalis	3 (2.9)
Ophiasis	7 (6.7)
Associated conditions	95 (90)
Inflammatory/reactive	47 (44.7)
Atopy*	24 (22.9)
Allergic rhinitis	12 (11.4)
Eczema	11 (10.4)
Asthma	4 (3.8)
Allergic conjunctivitis	3 (2.8)
Food allergy	2 (1.9)
Congenital*	36 (34.2)
Down syndrome	10 (9.5)
Silver Russell syndrome	2 (1.9)
Craniosynostosis	2 (1.9)
Psychiatric/psychological disease	28 (26.6)
Anxiety	16 (15.2)
Depression	7 (6.6)
Adjustment disorder	4 (3.8)
Attention-Deficit/Hyperactivity Disorder	2 (1.9)
Autoimmune	16 (15.2)
Autoimmune thyroid disease	8 (7.6)
Vitiligo	5 (4.7)
Lupus erythematosus (systemic/cutaneous)	3 (2.8)
Psoriasis	1 (0.9)

*Other congenital comorbidities occurred in one patient each.

Ninety-five (90%) patients had associated comorbidities (Table 1). The most frequent were inflammatory/reactive (n = 47, 44.7%), and atopy accounted for half of these. Congenital diseases occurred next in frequency in 36 patients (34.2%); Down syndrome affected 9.5% (n = 10). Mental health disease was present in 26.6% (n = 28) of patients, the most common being anxiety (n = 16, 15.2%) and depression (n = 7, 6.6%). Autoimmune comorbidities were present in 16 patients (15.2%), most frequently autoimmune thyroid disease in 8 (7.6%).

Patients with localized disease had good regrowth more frequently compared to non-localized AA (73.3%

vs. 6.6%, $p < 0.0001$), as well as a shorter mean duration of disease (13.41 vs. 40.66 months, $p = 0.02$), less frequently relapsed (20.5% vs. 55.5%, $p = 0.001$), and received on average less therapeutic modalities (1.6 compared to 5.33, $p < 0.001$) (Table 2). Patients who experienced good regrowth used on average less treatments (1.82 vs. 4.46, $p < 0.0001$) and relapsed with less frequency (18.6% vs. 56.6%, $p < 0.0001$). Patients whose disease started at pre-school age were more frequently women (64.2% vs. 46.9%, $p < 0.001$) and had increased disease relapses (70.9% vs. 45.9%, $p = 0.01$). Inflammatory and congenital diseases were associated with localized AA (51%, $p = 0.02$ and 42%, $p < 0.01$; respectively) and good regrowth (50%, $p = 0.05$ and 42%, $p < 0.01$; respectively).

Discussion

In this study, there was an almost even sex distribution (H:M = 1:1.2) in studied patients, which corresponds to other studies, as sex is not a predisposing factor for the onset of AA. Mean age at onset of the disease was 7.1 years, similar to reported ages of 5.9-9 years^{1,6}. These findings of higher frequency at early ages could reflect an interaction between genetic predisposition, immunological immaturity, and environmental factors. Pre-school age girls were affected more frequently and relapsed more often, which has not been previously described in the literature. These findings do not appear to be associated with a higher proportion of women in the study and could instead be associated with greater disease severity in young girls.

Remission rates of localized AA in the literature vary between 30% and 50% within 6-12 months of disease onset, while in this study mean duration was 1 year⁷. The rest of the subtypes had a statistically significant longer duration, the longest being ophiasis mean duration of 72 months. Patients with AA totalis had no resolution of their condition in the observed period. These observations show that the more extensive the subtype, the more difficult it is to treat.

Our study aligns with previous research, highlighting that AD is one of the most common comorbidities among pediatric AA patients⁴⁻⁶. Notably, allergic rhinitis has not been associated as frequently as we found in our study. We believe this association exists due to a combination of shared immune dysregulation and

Table 2. Clinical characteristics and associated diseases by alopecia areata (AA) subtype, hair regrowth and age of onset categories

Characteristics and associations	Localized AA (n = 78) (%)	Non-localized AA (n = 27) (%)	p	> 50% regrowth (n = 75) (%)	≤ 50% regrowth (n = 30) (%)	p	Pre-school age at onset (n = 56) (%)	School age at onset (n = 49) (%)	p
Patient characteristics									
Age at diagnosis (mean ± SD)	7.53 ± 4.13	6.18 ± 3.30	0.16	7.44 ± 4.06	6.56 ± 3.68	0.34	4.21 ± 1.47	10.59 ± 3.06	-
Disease duration (mean ± SD)	13.41 ± 18.45	40.66 ± 30.66	0.02	14.56 ± 19.56	* 4.46 ± 2.30	<0.001	18.64 ± 24.17	10.11 ± 11.67	0.30
No. treatments (mean ± SD)	1.6 ± 1.13	5.33 ± 1.52	<0.001	1.82 ± 1.37	17 (56)	<0.001	1.72 ± 1.46	1.79 ± 1.27	0.59
Relapse	16 (20)	15 (55)	<0.001	14 (18)	18 (60)	0.39	22 (39)	9 (18)	0.01
Female sex	42 (53)	17 (62)	0.27	41 (54)			36 (64)	23 (46)	0.05
Associated diseases									
Autoimmune	14 (17)	2 (7)	0.18	13 (17)	3 (10)	0.34	7 (12)	9 (18)	0.40
Inflammatory or reactive	40 (51)	7 (25)	0.02	38 (50)	9 (30)	0.05	22 (39)	25 (51)	0.22
Mental health	19 (24)	9 (33)	0.36	18 (24)	11 (36)	0.14	15 (26)	13 (26)	0.97
Congenital	33 (42)	3 (11)	<0.001	32 (42)	4 (13)	<0.001	25 (44)	11 (22)	0.01

Statistically significant p values in bold.
*These cases did not show resolution in the period studied.

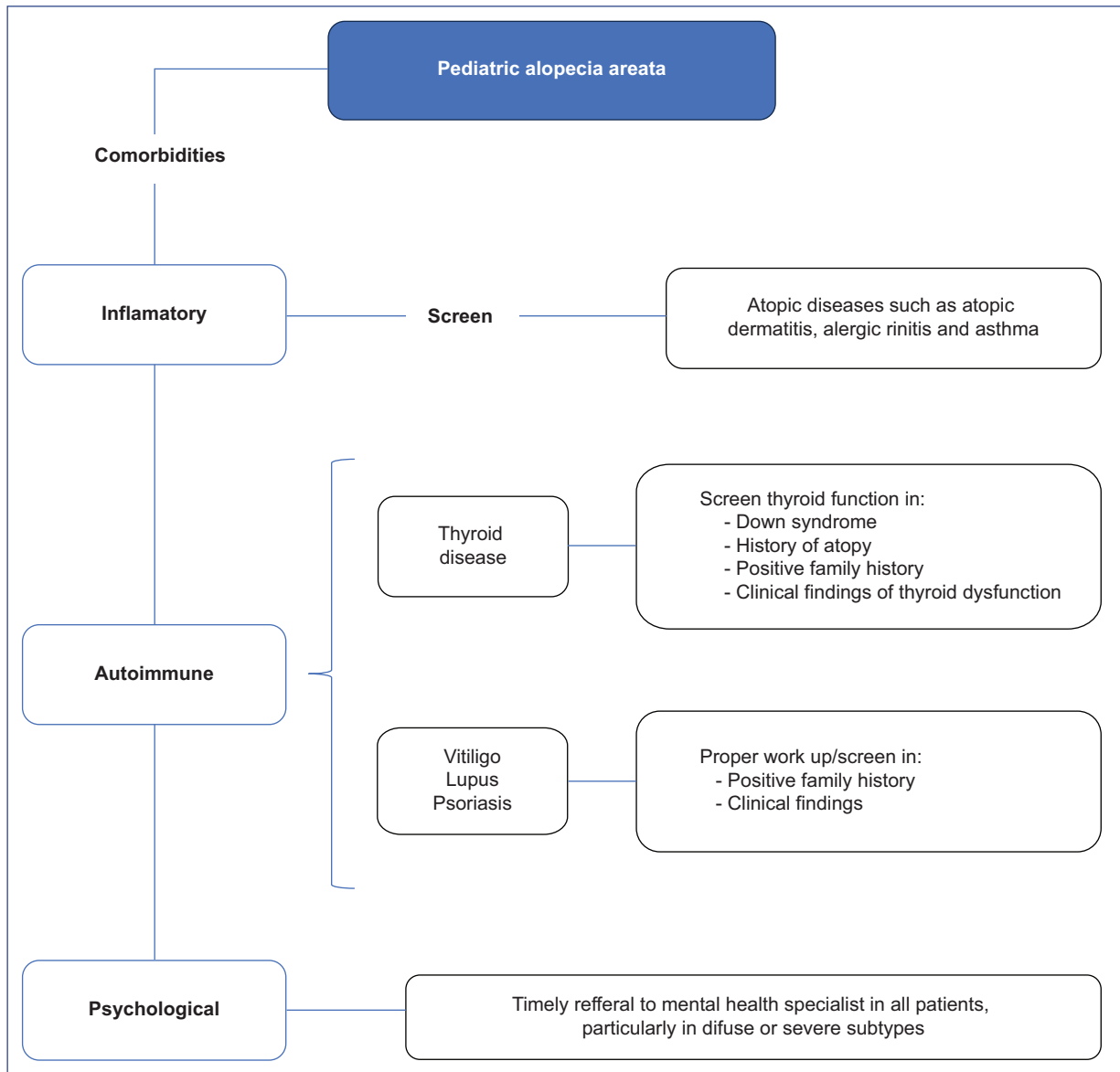


Figure 1. Clinical screening pathway for comorbidities in pediatric patients with alopecia areata.

antigenic exposure caused by the barrier defects characteristic of AD. Patients with inflammatory conditions had significantly higher rates of localized AA with good hair regrowth. This could reflect the high frequency of inflammatory conditions in children and localized AA being the most common disease subtype; additionally, prior studies suggest that comorbidities in AA often precede the diagnosis³, so this apparent better response could be due to prior steroid or immunosuppressive drug use.

Congenital diseases were second in frequency, associated with localized AA, good regrowth, and earlier disease onset ($p < 0.001$). Patients with Down syndrome

were the most frequent, composing 9.5% of the sample. The majority had localized disease ($n = 8$, 80%), the rest ($n = 2$, 20%) presented ophiasis subtype. Information about the most prevalent subtype in these patients is lacking, additional research is needed. This condition is also highly associated with thyroid disease⁸, present in 40% of our patients.

We found a slightly higher frequency of lupus erythematosus and a lower frequency of psoriasis than previously reported², reflecting our specific population as a referral hospital.

Regarding psychological comorbidities, 28 patients (26.6%) were affected. This association has been well

described previously with a prevalence from 25% to 78%⁹. The association is more prominent in severe subtypes, underlining the psychological impact. Evidence about the role of mental health diseases in the precipitation of autoimmune disorders has triggered debates on whether AA should be considered a psychosomatic disease; further randomized studies are required to generate conclusions. We did not find an association between psychological disease and subtype, clinical course, and age at onset of AA.

Study limitations include the retrospective methodology with the associated risks of bias, such as information bias related to the medical records retrieved, and the possible changes in treatment protocols in the studied period. Furthermore, the lack of control over possible confounding variables in the statistical test performed should also be mentioned. Finally, the study population comes from a single reference hospital, which may limit generalizability as patients might have more severe associated diseases.

Conclusions

In pediatric AA, associated inflammatory, autoimmune, and psychiatric comorbidities are frequent, confirming the importance of adequately referring to specialists to confirm and manage concurrent diagnoses. In line with the study objectives and findings, we propose a clinical screening pathway for comorbidities in pediatric patients with AA so to aid on the diagnostic workup of these patients (Fig. 1).

Noteworthy observations include a higher frequency of inflammatory and congenital diseases in children with localized AA and consequently good regrowth rates; and earlier age of onset more frequently associated to congenital diseases. Moreover, patients with earlier onset, non-localized AA, and suboptimal regrowth exhibit significantly higher relapse rates. Finally, onset at pre-school age was more common in girls and linked to higher relapse rates. Larger studies at a population level are required to confirm further these associations and enhance care for children with AA.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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Luxación congénita de rodilla: tratamiento conservador de una serie de casos

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Resumen

Introducción: La luxación congénita de rodilla (LCR) es una anomalía musculoesquelética poco frecuente, caracterizada por hiperextensión de la rodilla al nacimiento. Sus posibles causas incluyen factores mecánicos, como el oligoamnios o la presentación podálica, así como alteraciones genéticas o neuromusculares. El objetivo fue describir la incidencia, características clínicas, tratamiento y resultados de los casos de LCR diagnosticados en una unidad neonatal del norte de España durante un periodo de 20 años. **Métodos:** Se llevó a cabo un estudio observacional, descriptivo y retrospectivo de casos de LCR diagnosticados entre 2005 y 2024 (43,500 nacimientos). Se analizaron variables demográficas, obstétricas, clínicas, terapéuticas y de complicaciones, obtenidas de los historiales clínicos e imágenes diagnósticas. **Resultados:** Se identificaron ocho pacientes (11 rodillas afectadas), con una incidencia del 0.02%. La edad gestacional media fue de 37 semanas y el peso medio al nacer de 2,435 gramos. El 75% de los casos correspondieron a niñas, con afectación bilateral en el 37.5% y predominio de la rodilla izquierda. Se observó oligoamnios en el 25% y presentación podálica en el 37.5% de los casos. La displasia del desarrollo de cadera fue la comorbilidad más frecuente (37.5%). Todos los pacientes fueron tratados de forma conservadora mediante yesos seriados, con resultados favorables en seis de ellos. Un caso requirió tratamiento ortopédico prolongado por malformaciones complejas y otro presentó una leve discrepancia en la longitud de las extremidades. **Conclusiones:** El diagnóstico precoz, habitualmente mediante exploración física, es esencial para un pronóstico favorable. El tratamiento conservador resulta eficaz en la mayoría de los casos, reservándose la cirugía para situaciones refractarias. La incidencia observada fue superior a la descrita clásicamente, lo que podría reflejar variaciones metodológicas o poblacionales. La evaluación integral de los pacientes es fundamental para identificar anomalías asociadas y prevenir complicaciones a largo plazo.

Palabras clave: Luxación de rodilla. Oligohidramnios. Presentación de nalgas. Displasia del desarrollo de la cadera. Ortopedia pediátrica. Infante. Recién nacido.

Congenital knee dislocation: conservative management of a series of cases

Abstract

Background: Congenital knee dislocation (CKD) is a rare musculoskeletal anomaly characterized by hyperextension of the knee at birth. Its possible etiologies include mechanical factors, such as oligohydramnios or breech presentation, as well as genetic or neuromuscular abnormalities. The objective was to describe the incidence, clinical characteristics, management, and outcomes of CKD cases diagnosed in a neonatal unit in northern Spain over a 20-year period. **Methods:** We conducted

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an observational, descriptive, and retrospective study including all cases of congenital knee dislocation diagnosed between 2005 and 2024 (43,500 live births). Demographic, obstetric, clinical, therapeutic, and complication variables were analyzed based on medical records and diagnostic imaging. Results: Eight patients (11 affected knees) were identified, with an incidence of 0.02%. The mean gestational age was 37 weeks, and the mean birth weight was 2,435 grams. Seventy-five percent of patients were female, with bilateral involvement in 37.5% and a predominance of left-sided dislocation. Oligohydramnios was observed in 25% of cases and breech presentation in 37.5%. Developmental dysplasia of the hip was the most frequent comorbidity (37.5%). All patients were treated conservatively with serial casting, achieving favorable outcomes in six. One patient required prolonged orthotic management due to complex malformations, and another presented a mild limb-length discrepancy. Conclusions: Early diagnosis, typically through physical examination, is essential for a favorable prognosis. Conservative treatment is effective in most cases, while surgery should be reserved for refractory situations. The incidence observed was higher than previously reported, which may reflect methodological or population-based differences. Comprehensive patient evaluation is crucial to identify associated anomalies and prevent long-term complications.

Keywords: Congenital knee dislocation. Oligohydramnios. Breech presentation. Developmental dysplasia of the hip. Pediatric orthopedics. Infant. Newborn.

Introducción

La luxación congénita de rodilla (LCR) es una anomalía rara caracterizada por una deformidad en hiperextensión de la rodilla al nacimiento. Su incidencia se estima en aproximadamente un caso por cada 100,000 nacimientos vivos, lo que la hace mucho menos frecuente que la luxación congénita de cadera, cuya incidencia es alrededor de 100 veces mayor. Aunque la causa exacta de la LCR no se comprende completamente, se han propuesto diversos factores contribuyentes, entre ellos el oligoamnios, la presentación podálica, las anomalías del ligamento cruzado anterior y alteraciones genéticas que afectan los sistemas neuromuscular y osteotendinoso. Asimismo, se ha descrito su asociación con otras malformaciones musculoesqueléticas, como la displasia del desarrollo de cadera y el pie equinovaro, así como con síndromes como Turner, Down, Larsen, la secuencia de Pierre Robin y la artrogriposis congénita^{1,2}.

El diagnóstico de la LCR puede realizarse en etapa prenatal o en las primeras horas tras el nacimiento mediante la evaluación clínica. Las radiografías son útiles para valorar la gravedad del defecto y detectar posibles anomalías óseas asociadas^{3,4}. Se considera que las formas graves se relacionan con alteraciones mesenquimatosas durante el desarrollo fetal y suelen asociarse con síndromes u otras condiciones congénitas. Por su parte, los casos más leves se atribuyen a una malposición intrauterina, por lo que se recomienda una evaluación dirigida a descartar afecciones concomitantes, como la luxación congénita de cadera.

A pesar de su llamativa presentación clínica, el pronóstico suele ser favorable cuando el tratamiento se inicia tempranamente. La mayoría responden a la

inmovilización progresiva en flexión durante 4-8 semanas, y el tratamiento quirúrgico se reserva para los casos refractarios⁵⁻⁷. Aunque se trata de una entidad poco frecuente, la mayoría de los resultados descritos en la literatura son satisfactorios; sin embargo, se han reportado casos con desenlaces desfavorables y repercusiones funcionales a mediano y largo plazo^{8,9}. Por consiguiente, resulta necesario realizar un estudio exhaustivo que permita establecer un diagnóstico preciso y detectar posibles síndromes asociados.

Métodos

Se realizó un estudio observacional, descriptivo y retrospectivo de pacientes diagnosticados con LCR en un hospital de tercer nivel del norte de España, centro de referencia regional con una unidad neonatal de nivel III-B. Los casos se identificaron por medio de los registros de diagnósticos de alta hospitalaria entre enero de 2005 y diciembre de 2024, periodo durante el cual se registraron 43,500 nacimientos. Se revisaron las historias clínicas de los pacientes a estudio y se analizaron distintas variables, tales como demográficas (sexo y edad), miembro afectado, enfermedades y deformidades asociadas, tipo de tratamiento recibido, la evolución funcional y complicaciones objetivadas.

El análisis estadístico se realizó mediante el programa IBM SPSS Statistics 24[®], expresando las variables categóricas como frecuencias absolutas y porcentajes, y las variables continuas mediante medianas e intervalos intercuartílicos (IQR). El estudio fue aprobado por el comité de ética e investigación del centro y se garantizó la confidencialidad de los datos conforme a la normativa vigente.

Resultados

Se analizaron un total de 8 pacientes (11 rodillas), con una edad gestacional media de 37 semanas (IQR: 33.7-39.7) y un peso medio de 2,435 g (IQR: 1,963-2,885). Predominaron las pacientes femeninas (6 casos, 75%). Se presentan descripciones detalladas de los casos en la [tabla 1](#), con una imagen representativa en la [figura 1](#).

La luxación bilateral ocurrió en tres pacientes (37.5%), con la rodilla izquierda afectada en el 80% de los casos (4 casos). Las ecografías prenatales mostraron resultados normales en la mayoría de los casos, exceptuando dos casos con oligoamnios y uno con sospecha de malformación distal de las extremidades. El parto fue vaginal en cuatro casos, instrumental en dos y por cesárea en dos. La presentación podálica ocurrió en tres casos (37.5%), mientras que los cinco restantes (62.5%) fueron cefálicos. Ninguno de los pacientes requirió reanimación neonatal avanzada.

La malformación musculoesquelética asociada más frecuente fue la displasia de cadera, observada en tres pacientes (37.5%), dos de ellos tratados con arnés de Pavlik y uno con cirugía. Un paciente presentó pie equinovaro asociado a un síndrome malformativo de las extremidades (con sospecha en ecografía prenatal de artrogriposis).

Todos los pacientes recibieron tratamiento conservador: siete con yesos seriados y uno con medidas físicas (flexión de rodilla y aproximación). La duración media del yeso corrector fue de 3.5 semanas (IQR: 3-4). En un caso no se evaluó la duración del tratamiento debido a que se encontraba en manejo ortopédico. Ninguno de los pacientes requirió corrección quirúrgica para la luxación de rodilla, aunque dos requirieron cirugía para otras condiciones (corrección de pie equinovaro y displasia de cadera).

Los resultados funcionales no estuvieron disponibles para un paciente con un síndrome malformativo complejo que requirió ortesis rígidas para la marcha y presentaba luxación bilateral de cadera, pie equinovaro y neuropatía axonal ciática. Entre los otros siete pacientes, seis tuvieron buenos resultados con movilidad normal al alta. En el paciente restante, se observó una ligera discrepancia en la longitud de las piernas (acortamiento de la extremidad inferior derecha en comparación con la izquierda), junto con un déficit en la flexión y rotación de la cadera izquierda. Se prescribió un plan de fisioterapia, aunque no se puede descartar una intervención quirúrgica futura para la cadera y la rodilla.



Figura 1. Imagen de la luxación congénita de rodilla de un paciente de la serie (*imagen clínica propia, consentimiento informado obtenido*).

Discusión

En esta serie de casos, la LCR fue una entidad infrecuente pero clínicamente relevante, con una incidencia superior a la descrita clásicamente¹. Este hallazgo podría explicarse por características poblacionales, una mayor capacidad diagnóstica o diferencias metodológicas respecto a otros reportes, más que por un verdadero aumento en la frecuencia de la enfermedad.

La LCR se caracteriza por el desplazamiento anterior de la tibia respecto al fémur, lo que puede ser causado por diversos factores y estar asociado con condiciones subyacentes. La asociación con displasia del desarrollo de cadera observada en el 37.5% de los casos refuerza la necesidad de realizar una evaluación sistemática de ambas articulaciones, dado que ambas malformaciones comparten posibles mecanismos mecánicos intrauterinos y alteraciones en la maduración del tejido conectivo. Es obligatorio realizar una ecografía de cadera sistemática en estos

Tabla 1. Características de la muestra estudiada

Caso	Sexo	Parto	Presentación	Edad gestacional	Afectación	Displasia cadera	Síndrome asociado	Tratamiento conservador	Complicaciones
1	Mujer	Cesárea	Cefálica	38	Derecha	No	No	Yesos correctores	No
2	Mujer	Cesárea	Nalgas	33	Bilateral	Sí	No	Yesos correctores + arnés Pavlick	Sí*
3	Mujer	Fórceps	Cefálica	36	Izquierda	No	No	Yesos correctores	No
4	Mujer	Eutócico	Nalgas	36	Bilateral	No	No	Yesos correctores	No
5	Varón	Ventosa	-	39	Izquierda	Sí	No	Yesos correctores	No
6	Mujer	Eutócico	Nalgas	40	Bilateral	Sí	Sí	Yesos correctores + arnés Pavlick + arnés Frejka + ortesis	Sí†
7	Varón	Eutócico	-	32	Izquierda	No	No	Medidas posturales	No
8	Mujer	Eutócico	Cefálica	41	Izquierda	No	No	Yesos correctores	No

*Mínima disimetría (hipometría) del miembro inferior derecho respecto al izquierdo. Déficit de la flexión y rotaciones de cadera izquierda y de abducción. Cadera derecha normal. No inestabilidad de rodillas.

†Neuropatía axonal bilateral de ambos ciáticos. Portador de ortesis dinámica de tobillo y pie.

Fuente: elaboración propia a partir de los registros clínicos institucionales.

neonatos debido a la alta incidencia de ambas condiciones¹⁰.

En cuanto a los factores predisponentes, se identificaron casos con oligoamnios y presentación podálica, lo que apoya la hipótesis de una causa multifactorial, donde factores mecánicos y posiblemente genéticos podrían intervenir en el desarrollo de la LCR. La detección precoz mediante exploración física neonatal sigue siendo la herramienta diagnóstica más importante¹¹⁻¹³, complementada con estudios radiográficos que permiten clasificar la gravedad y descartar otras anomalías óseas^{14,15}.

El tratamiento debe iniciarse rápidamente dentro de las primeras 24-48 h para optimizar los resultados. Las estrategias de tratamiento varían según la gravedad, pero generalmente incluyen medidas conservadoras para los casos leves y cirugía para los casos graves o refractarios. La comparación con la literatura es limitada debido al pequeño tamaño de las muestras y la variabilidad en las clasificaciones y tratamientos. La [figura 2](#) muestra la opción de tratamiento propuesta por Rampal et al.⁹ En los casos en que coexisten otras anomalías musculoesqueléticas, la mayoría de los autores recomienda tratar primero la rodilla, ya que una correcta posición de la rodilla es crucial para mantener una correcta posición de la cadera o el pie equinovaro.

Si no se hace así, o no se hace correctamente, pueden producirse secuelas a largo plazo¹².

Todos los casos en nuestra serie fueron leves y solo requirieron tratamiento conservador, sin necesidad de corrección quirúrgica para la LCR. La displasia de cadera asociada se manejó con tratamiento mediante arnés de Pavlik. Factores como la posición intrauterina y la predisposición genética pueden haber contribuido al desarrollo de la LCR en nuestros pacientes. Cinco de los casos presentaron antecedentes de oligoamnios, gestación múltiple o presentación podálica. En otro caso se sospechó una alteración genética del sistema neuromuscular que pudo haber sido la causa de las malformaciones en las extremidades observadas al nacer. En los dos casos restantes no se encontraron factores de riesgo adicionales más allá del sexo femenino. Todos los casos progresaron bien sin recurrencias.

Este estudio presenta limitaciones inherentes a su diseño retrospectivo, dependiente de la calidad y completitud de los registros médicos. Además, el tamaño muestral reducido limita la extrapolación de los resultados y la comparación estadística con otras series. La falta de seguimiento a largo plazo en algunos casos impide valorar de forma completa las secuelas funcionales en la edad adulta.

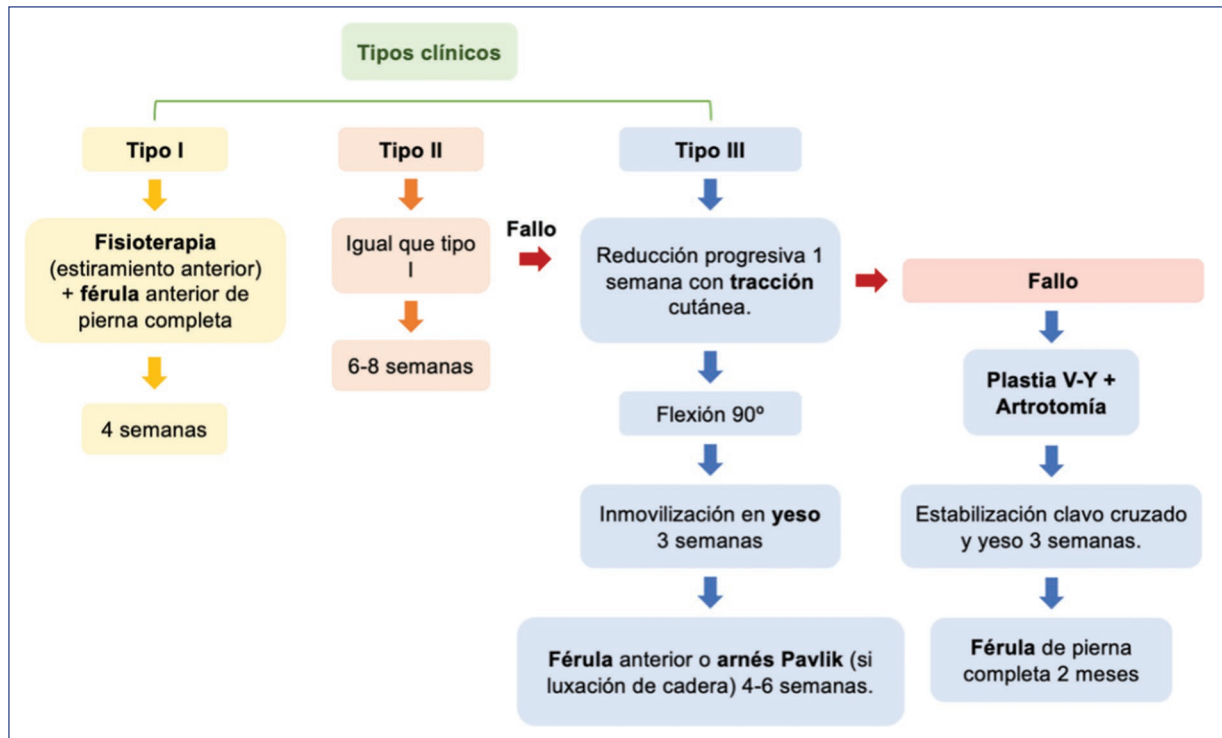


Figura 2. Tratamiento de las luxaciones congénitas de rodilla según Rampal (adaptada de Rampal et al.⁹).

Conclusiones

En conclusión, en nuestra serie, la LCR es una condición poco frecuente pero potencialmente manejable, con un pronóstico favorable cuando se detectó y trató de manera precoz. La mayoría de los pacientes respondió satisfactoriamente al tratamiento conservador mediante yesos seriados, reservándose la cirugía para los casos complejos o refractarios. La incidencia observada fue superior a la reportada en la literatura, lo que podría explicarse por diferencias metodológicas, poblacionales o en los criterios diagnósticos empleados. Estos hallazgos destacan la importancia del diagnóstico precoz y de una evaluación integral para identificar anomalías asociadas y optimizar el pronóstico funcional.

Financiamiento

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. No aplica (investigación sin experimentación).

Confidencialidad, consentimiento informado y aprobación ética. Los autores han obtenido la aprobación del Comité de Ética para el análisis de datos clínicos obtenidos de forma rutinaria y anonimizados. Debido a la naturaleza del estudio, no fue necesario el consentimiento informado individual. Se han seguido las recomendaciones éticas pertinentes.

Declaración sobre el uso de inteligencia artificial (IA). Los autores declaran que no se utilizó ningún tipo de inteligencia artificial generativa para la redacción ni la creación de contenido de este manuscrito.

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Malformación pulmonar congénita híbrida: reporte de caso

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Resumen

Introducción: Una causa poco frecuente de morbilidad en el recién nacido son las malformaciones congénitas del tracto respiratorio. Muchas de ellas pueden tener un origen común, es por ello que existe la posibilidad de que se presenten en conjunto, lo que se conoce como malformación pulmonar híbrida. La aparición conjunta de secuestro pulmonar y malformación adenomatoidea quística se ha descrito en muy pocos casos, aproximadamente 40-60 pacientes desde el primer caso reportado en 1949. Secuestro pulmonar se define como tejido quístico pulmonar ectópico no funcionante, con vascularización arterial propia de origen sistémico. Es una enfermedad congénita infrecuente, de presentación clínica variable, que puede ser intralobar o extralobar, y se puede acompañar de otras malformaciones, como en el caso de la enfermedad adenomatosa congénita. En la mayoría de los casos el tratamiento es quirúrgico y consiste en resecciones lobares por medio de videotoracoscopía. **Caso clínico:** Paciente de 7 días de vida que al nacer inicia con dificultad respiratoria grave, requiriendo ventilación mecánica invasiva. Identifican derrame pleural y neumotórax izquierdo, por lo que colocan tubo de toracostomía, sin embargo, no resuelve completamente. Parte la sospecha clínica de malformación congénita pulmonar, la cual se confirma por medio de tomografía computarizada pulmonar y angiotomografía pulmonar, la cual evidencia vaso accesorio de origen aórtico, por lo que se realiza tratamiento quirúrgico. **Conclusiones:** La resección temprana puede ser beneficiosa para el crecimiento pulmonar.

Palabras clave: Malformaciones adenomatoides quísticas congénitas. Secuestro pulmonar. Malformación torácica congénita.

Hybrid congenital lung malformation: case report

Abstract

Background: A rare cause of morbidity in the newborn is congenital malformations of the respiratory tract. Many of them can have a common origin, which is why there is the possibility of presenting them together, known as hybrid pulmonary malformation. The joint appearance of pulmonary sequestration and cystic adenomatoid malformation has been described in very few cases, approximately 40-60 patients since the first case reported in 1949. Pulmonary sequestration is defined as ectopic nonfunctioning pulmonary cystic tissue, with its own arterial vascularization of systemic origin. It is a rare congenital disease, with variable clinical presentation, which can be intralobar or extralobar, and may be accompanied by other malformations as in the case of congenital adenomatous disease. In most cases the treatment is surgical, consisting of lobar resections through video thoracoscopy. **Clinical case:** Seven-day-old patient who at birth begins with severe respiratory diffi-

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culty requiring invasive mechanical ventilation. Left pleural effusion and pneumothorax are identified, so a thoracostomy tube is placed, however, it does not completely resolve, the clinical suspicion of congenital pulmonary malformation arises, which is confirmed by means of pulmonary computed tomography and pulmonary angiography, which shows accessory vessel of aortic origin for which surgical treatment is performed. **Conclusions:** Early resection may be beneficial for lung growth.

Keywords: Congenital cystic adenomatoid malformations. Pulmonary sequestration. Congenital thoracic malformation.

Introducción

Las malformaciones congénitas de las vías respiratorias bajas son poco comunes. Se estima que ocurren entre 30 y 42 casos por cada 100,000 habitantes, lo que equivale al 0.6-2.2% de todos los pacientes hospitalizados. El uso del ultrasonido prenatal facilita la detección temprana, identificando la malformación en un 10% de los casos al nacer, mientras que el 14% se diagnostican durante la adolescencia, a menudo debido a hallazgos radiológicos o síntomas crónicos en las vías respiratorias inferiores. El secuestro pulmonar se refiere a un área anormal de tejido broncopulmonar irrigada por una arteria sistémica anómala¹. La malformación congénita de la vía aérea pulmonar (MCVAP), conocida anteriormente como malformación adenomatoidea quística (MAQ), es una alteración del desarrollo pulmonar que involucra la formación de quistes en lugar de las pequeñas vías respiratorias y el tejido pulmonar. La coexistencia de ambas malformaciones es poco frecuente, habiéndose reportado aproximadamente 60 casos en la literatura internacional. Los secuestros pulmonares se dividen en dos tipos principales: intralobulares y extralobulares. Aproximadamente el 60% de estos se encuentran en el hemitórax izquierdo y tienen su propia envoltura pleural. En estos casos, la irrigación arterial proviene de la circulación sistémica y el drenaje venoso difiere de los secuestros intralobulares al dirigirse hacia la circulación general²⁻⁴. La MCVAP es una anomalía poco común del desarrollo pulmonar de tipo hamartomatoso, caracterizada por la proliferación y dilatación anormal de las estructuras respiratorias terminales, lo cual resulta en la formación de quistes de diversos tamaños y ubicaciones. Representa aproximadamente el 25% de todas las malformaciones congénitas del pulmón. La mayoría de los casos (85%) se diagnostican durante los primeros dos años de vida debido a síntomas como dificultades respiratorias o infecciones recurrentes. La presentación en la edad adulta es poco frecuente y generalmente se detecta como hallazgos en imágenes, como lesiones cavitadas en radiografías de tórax o en relación con infecciones pulmonares recurrentes⁵.

Caso clínico

Paciente de sexo masculino de 7 días de vida referido de hospital regional departamental; producto de cuarta gestación, padres jóvenes, no consanguíneos, sanos; embarazo normoevolutivo, 40 semanas de edad gestacional, nace por cesárea transperitoneal por desproporción cefalopélvica, bañado en líquido amniótico meconial, APGAR 7-9^{1,5}. Se proporciona cuidados de recién nacido y posteriormente este inicia con dificultad respiratoria y se decide colocar tubo endotraqueal. Se toman rayos X de tórax y se evidencia derrame pleural izquierdo, por lo que se coloca tubo de toracostomía, el cual drena aproximadamente 280 cc de líquido seroso en 24 h. Se decide traslado a hospital de cuarto nivel para tratamiento especializado. Al examen físico, tórax simétrico, murmullo vesicular disminuido en campo pulmonar izquierdo, sin uso de músculos accesorios de la respiración. Se inicia investigación de caso y se toman distintos paraclínicos, en los cuales se obtienen los siguientes resultados: tiempo de protrombina 13.1 s, tiempo de tromboplastina parcial 28.5 s, ratio internacional normalizado 1.18, fibrinógeno 380 mg/dl, hemoglobina 16.1 g/dl, hematocrito 47%, leucocitos 15.52 K/ul, neutrófilos 57%, linfocitos 32.6%, monocitos 9.3%, eosinófilos 1%, eritrocitos 5.03 M/microl, plaquetas 253 K/ul, proteína C reactiva 0.18 mg/dl (0.050 mg/dl). Realizan rayos X de tórax, en los cuales se observa tubo de toracostomía izquierdo, silueta cardiaca desplazada hacia hemitórax derecho, área hiperluciente izquierda (Fig. 1). Se toma muestra de drenaje de toracostomía con líquido serosanguinolento para análisis citoquímico, el cual reporta proteínas totales 0.83 g/dl, deshidrogenasa láctica 192 U/l, triglicéridos 9 mg/dl, albúmina 0.52 g/dl, colesterol total 10.7 mg/dl, criterios de Light positivo para trasudado, se descarta quilotórax. Se realiza tomografía computarizada (TC) pulmonar (Fig. 1), en la cual se observa imagen hiperdensa lobulada en la ventana pulmonar corte coronal y axial en hemitórax izquierdo, con aparente hilio vascular, por lo que se realiza angiografía, con la cual se confirma diagnóstico de secuestro pulmonar por hallazgo de arteria nutricia originada de aorta descendente (Fig. 2). Se presenta

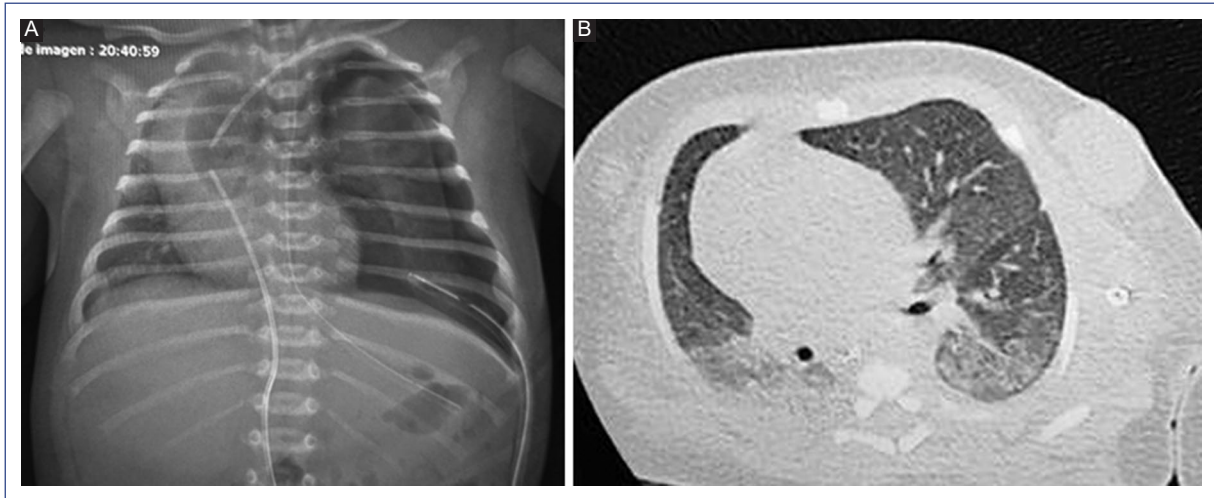


Figura 1. A: radiografía de tórax con tubo de toracostomía izquierdo y persistencia de neumotórax, catéter umbilical central, catéter subclavio izquierdo central. **B:** tomografía de tórax corte axial, imagen hiperdensa lobulada basal izquierda.

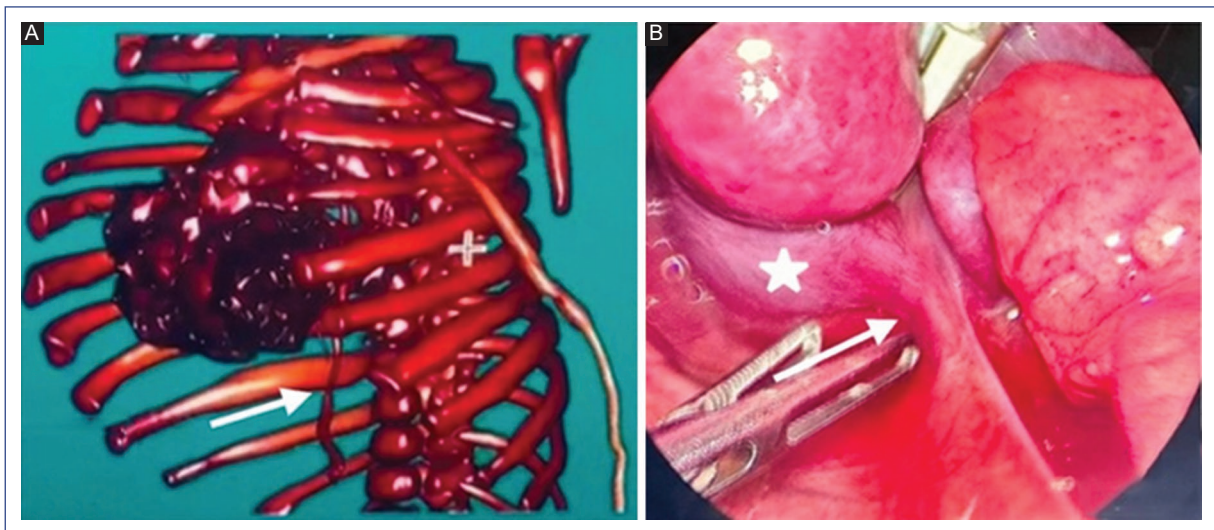


Figura 2. A: angiotomografía con presencia de vaso nutricio originado de aorta descendente (flecha). **B:** toracoscopia con identificación de secuestro pulmonar (estrella) y arteria nutricia (flecha).

el caso a cirugía pediátrica, quienes realizan toracoscopia. Como hallazgos operatorios se describe secuestro pulmonar extralobar supradiagmático basal izquierdo con arteria única desde aorta descendente (Fig. 2), se realiza lobectomía inferior izquierda y se envía pieza quirúrgica a patología, reportando MAQ tipo II. Por lo tanto, se hace diagnóstico de malformación pulmonar congénita híbrida. El paciente tuvo adecuada recuperación clínica posterior cirugía. Se da egreso sin uso de oxígeno.

Discusión

Las anomalías congénitas pulmonares son producto del proceso de formación anómalo que pueden tener distintas manifestaciones y pronóstico; son alteraciones muy poco frecuentes, con una incidencia de 1 cada 10,000 a 35,000 embarazos⁶. Dentro de estas se encuentran las MCVAP, antes conocidas como MAQ, quiste broncogénito, secuestro pulmonar, atresia bronquial, hiperinsuflación lobar congénita y lesiones híbridas^{2,6}.

Tabla 1. Caracterización clínica y pronóstico de algunos pacientes diagnosticados con MCVAP sometidos a tratamiento quirúrgico

Edad al diagnóstico	Sexo	Tipo de malformación	Tratamiento quirúrgico	Pronóstico
9 meses ⁷	Femenino	Híbrida (MCVAP tipo II+secuestro pulmonar) derecha	VATS	Favorable
Al nacimiento ⁸	Femenino	MCVAP tipo III izquierda asociado a atresia esofágica tipo C	Cirugía invasiva	Egresó a los 24 días de vida
2 meses ⁹	Masculino	MCVAP tipo IV derecha	Cirugía invasiva	Favorable, seguimiento por 2 años
4 años ¹⁰	Femenino	MCVAP tipo I derecha (sobreinfectada)	Cirugía invasiva	Favorable
Adolescencia ¹¹	Femenino	MCVAP tipo I derecha	VATS	Favorable, seguimiento por 3 años
11 años ¹²	Masculino	Secuestro pulmonar extralobar torsionado asociado a enfisema lobar congénito izquierdo	VATS	Favorable, seguimiento regular
26 años ¹³	Masculino	Secuestro pulmonar intralobar izquierdo	Cirugía invasiva	Favorable
9 años ¹⁴	Femenino	Secuestro pulmonar bilateral	VATS	Favorable

MCVAP: malformaciones congénitas pulmonares de la vía aérea; VATS: *video-assisted thoracoscopic surgery*.

Anteriormente se conocía la clasificación de Stocker et al., que describe las MAQ en tres tipos según histología (tipos I, II y III); según evolución clínica y aspecto, y posteriormente se ha expandido su uso para incluir también variantes y subtipos⁶. Actualmente ha cambiado su nombre a MCVAP, incluyendo todas las partes del árbol traqueobronquial^{5,6}.

La mayoría de los pacientes son asintomáticos al nacer; sin embargo, existe una pequeña proporción de ellos en los que el defecto aumenta de tamaño durante el último trimestre y es potencialmente mortal⁶. Tienen una sobrevida del ~95% aproximadamente, hasta el 68% de secuestros pulmonares presentan regresión previa a nacimiento y el 15% de MCVAP⁶. La sobrevida se ve afectada por el tamaño del defecto, su asociación con otras malformaciones y el menor grado de desarrollo pulmonar^{2,6}.

Existen teorías en cuanto a su origen, Langston propuso la principal, que describe obstrucción de la vía aérea y alteración de la dicotomización del árbol respiratorio⁶.

El diagnóstico puede realizarse durante el periodo prenatal mediante ecografía y valorar el uso de resonancia magnética si el anterior no es concluyente⁶. En la mayoría de los casos, al nacimiento, la sospecha clínica parte de la realización de rayos X. La TC

representa el método diagnóstico de elección, acompañado de angiografía para un diagnóstico más preciso. El diagnóstico definitivo se realiza por medio análisis de patología^{5,6}.

En el tratamiento prenatal se ha considerado el uso de esteroides sistémicos, con el fin de reducir la producción de líquido y beneficiar su reabsorción; esto se ha observado en lesiones microquísticas, no comprobado en macrocísticas, por lo tanto, actualmente no se recomienda su uso sistemático⁶. La cirugía fetal debe considerarse en pacientes con mal pronóstico intraútero, con el objetivo de realizar una lobectomía a través de histerotomía y laparotomía materna, las indicaciones son las siguientes:

- Malformación sólida micro- o macroquística.
- Hidrops que no responde a esteroide.
- Disfunción cardíaca.
- Ausencia de otras alteraciones no asociadas a malformación pulmonar.
- Cariotipo normal.
- Embarazo de menos de 32 semanas.

El tratamiento posnatal depende de la aparición o ausencia de síntomas al nacer. Los pacientes sintomáticos deben estabilizarse y planificar la cirugía una vez confirmado el diagnóstico; el abordaje quirúrgico puede ser por medio de toracoscopia o toracotomía. En los

pacientes asintomáticos el abordaje quirúrgico aún es controversial. Deben considerarse aspectos como la posible resolución espontánea de la malformación, aunque esta no está descrita por completo y se ha asociado preferentemente a lesiones microquísticas. Deben evitarse las posibles complicaciones asociadas a las malformaciones, siendo la más importante la infección. Hay que considerar la posibilidad de neoplasias asociadas como el blastoma pleuropulmonar (hasta en un 5%) y el carcinoma bronquio-alveolar (en un 1% de pacientes), que pueden valorarse inicialmente por TC. El crecimiento pulmonar puede beneficiarse de una resección temprana⁶.

Actualmente existe la posibilidad de realizar un procedimiento mínimamente invasivo (toracoscopia) en la mayoría de los pacientes, lo que conlleva menos complicaciones posquirúrgicas. Debe tomarse la decisión de realizar lobectomía o segmentectomía tomando en cuenta el tipo de malformación y su localización (unilateral o bilateral)^{2,6}.

Conclusiones

El caso clínico presentado corresponde a un recién nacido que inicia con dificultad respiratoria secundaria a una malformación pulmonar congénita híbrida, hallazgo muy poco frecuente que combina características de secuestro pulmonar extralobar y MCVAP tipo II. Esta presentación clínica es coherente con la literatura descrita, donde las malformaciones congénitas de la vía aérea pueden manifestarse desde el nacimiento con síntomas respiratorios graves, aunque la mayoría son asintomáticos. El diagnóstico se confirmó mediante estudios de imagen y angiotomografía, siendo estos métodos clave según la evidencia actual para la identificación precisa de estas anomalías. La intervención quirúrgica oportuna mediante toracoscopia permitió la resección del tejido malformado, con adecuada recuperación posterior, de acuerdo con las recomendaciones actuales de tratamiento en pacientes sintomáticos al nacimiento, destacando la importancia de un abordaje multidisciplinario y precoz en el pronóstico favorable (Tabla 1).

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. No aplica (investigación sin experimentación).




Confidencialidad, consentimiento informado y aprobación ética. El estudio no involucra datos personales, historias clínicas ni muestras biológicas humanas, por lo que no requiere aprobación ética. No se aplican las guías SAGER.

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Abdominal mass secondary to fetus-in-fetu in a neonate: case report and literature review

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Abstract

Background: Among the various etiologies related to the presence of abdominal masses in newborns, the diagnosis of fetus in fetu (FIF), a term used to describe a congenital condition in which one fetus parasitizes the body, should be considered. **Clinical case:** We present the case of a male newborn who was found to have an abdominal mass during perinatal evaluation, leading to termination of pregnancy by cesarean section. After a thorough evaluation, a protocol was established that resulted in surgical intervention and the diagnosis of FIF. **Conclusions:** FIF is an exceptionally rare entity characterized by the presence of a “parasitic twin.” Its pathophysiology and risk factors remain poorly understood, but it must be considered in the differential diagnosis of neonatal abdominal masses. Owing to its rarity, standardized follow-up protocols have not been established. Nevertheless, with current advances in pediatric surgery, the prognosis after complete excision is favorable.

Keywords: Fetus. Newborn. Congenital Abnormalities.

Masa abdominal secundaria a fetus-in-fetu en un neonato: reporte de caso y revisión de la literatura

Resumen

Introducción: Dentro de las múltiples causas asociadas a la presencia de masas abdominales en el neonato debe considerarse entre las posibilidades diagnósticas el fetus-in-fetu (FIF), término utilizado para describir una condición congénita caracterizada por la presencia de un feto parasitado dentro del cuerpo de su gemelo. **Caso clínico:** Corresponde reportar el caso de un recién nacido de sexo masculino, en quien se detectó la presencia de una masa abdominal durante la evaluación perinatal, por lo que se decidió el nacimiento de dicho producto por vía abdominal. Se le evaluó y protocolizó de manera integral, realizando abordaje quirúrgico y obteniendo como diagnóstico FIF. **Conclusiones:** El FIF es una condición poco común, caracterizada por la presencia de un «gemelo fantasma», cuya explicación fisiopatológica y/o factores de riesgo aún no se encuentran del todo dilucidados, pero que tiene que considerarse como una posibilidad diagnóstica dentro del espectro de las masas abdominales del recién nacido. Por esta infrecuencia, aún no existen protocolos descritos para el seguimiento de estos pacientes. Afortunadamente, gracias al desarrollo de las técnicas quirúrgicas en pediatría, el pronóstico y sobrevida de estos pacientes una vez resuelto el condicionante inicial es bastante favorable.

Palabras clave: Feto. Recién nacido. Malformaciones congénitas.

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Introduction

Abdominal masses in the newborn encompass a broad spectrum of pathologies whose prognosis has improved considerably in recent decades, largely due to advances in prenatal imaging, and the implementation of comprehensive neonatal care protocols. The etiology of these masses is heterogeneous and may involve genetic, molecular, or environmental factors during intra-uterine life. Clinical presentation also varies widely, and in many cases these lesions are asymptomatic, representing a significant diagnostic challenge. Statistically, the most frequent etiologies include organomegaly and non-surgical pathologies, malignant neoplasms, and less commonly, congenital malformations¹⁻³.

Fetus-in-fetu (FIF) is a rare congenital abnormality characterized by the presence of a malformed parasitic twin within the body of its host. Fewer than 200 cases have been reported globally, with an estimated incidence of 1/500,000 live births. The condition is more frequently observed in males, with a male-to-female ratio of approximately 2:1. The most common clinical manifestation is an abdominal mass, typically detected in the neonatal period; prenatal diagnosis is unusual, and detection in adulthood is exceedingly rare. In approximately 80% of cases, the mass is located in the retroperitoneum; however, extraperitoneal locations, such as intracranial, intrahepatic, intrathoracic, adrenal, scrotal, ovarian, and oropharyngeal regions have also been described⁴⁻¹¹.

The embryological origin of FIF remains controversial. It is commonly attributed to aberrant cleavage of totipotent cells during blastocyst development in a monozygotic, monochorionic, and diamniotic pregnancy. It is theorized that during gastrulation and ventral folding of the trilaminar disc, one embryo becomes incorporated into its twin, most often within the abdominal cavity, ultimately leading to the formation of FIF. *In utero*, the growth between the host and parasitic twin undergoes atrophy secondary to vascular insufficiency and structural restriction⁸⁻¹³.

Histopathological confirmation is essential to distinguish FIF from teratomas, as both share many macroscopic features. However, FIF is typically benign and is characterized histologically by the presence of highly differentiated, organized fetiform tissues, such as vertebral column (91%), extremities (82.5%), ribs (82.5%), central nervous system (55.8%), gastrointestinal tract (45%), and genitourinary tract (26.5%). Macroscopically, FIF is usually encapsulated, partially or fully covered by skin, associated with an amniotic sac, and connected by a

vascular pedicle. Complete surgical excision is the treatment of choice, and prognosis is excellent in up to 97% of reported cases⁴⁻¹⁹. Given the rarity of this condition and the diagnostic challenges it poses, we present the case of a neonate with FIF to contribute to the existing literature.

Case report

A 23-year-old primigravida at 39 weeks of gestation, with no relevant medical or family history and no consanguinity with her partner, presented for a routine follow-up. She had received adequate prenatal care. On clinical examination, no uterine contractions were detected and there was no evidence of fetal distress. A third-trimester ultrasound revealed a fetal intra-abdominal mass with a heterogeneous echogenicity, a cyst component with anechoic content, and multiple calcifications (Fig. 1A). Giving the presence of a term pregnancy and the imminent onset of labor, the decision was made to proceed with delivery by cesarean section.

A male neonate was delivered at 37 weeks of gestational age by Capurro assessment. He adapted well to the extrauterine environment, breathing and crying spontaneously at birth. Initial physical examination revealed a palpable firm mass in the hypogastric region, measuring approximately 4 × 4 cm, adherent to deep planes. No additional congenital malformations were identified. The patient was admitted for evaluation by pediatric surgery. During hospitalization, early oliguria was noted (< 0.5 mL/kg/h) without other significant clinical findings.

Computed tomography (CT) demonstrated a hypodense mass, with liquid content, estimated at 125 mL, surrounded by a thickened wall (3 mm) and containing hyperdense calcifications (Fig. 1B). The mass produced a rightward displacement of abdominal structures, causing renal ectasia. Based on these findings an Exploratory Laparotomy was indicated, and realized on day 9 of life.

Intraoperatively, a cystic mass measuring approximately 9 cm in diameter was identified, adherent to the sigmoid colon, with no apparent communication with retroperitoneal or intra-abdominal organs. Blunt dissection revealed a cystic structure containing fluid and a solid cartilaginous mass with multiple calcifications (Fig. 1C). Complete resection of the mass was achieved, and the specimen was sent for histopathologic analysis. In the immediate post-operative period, urine output

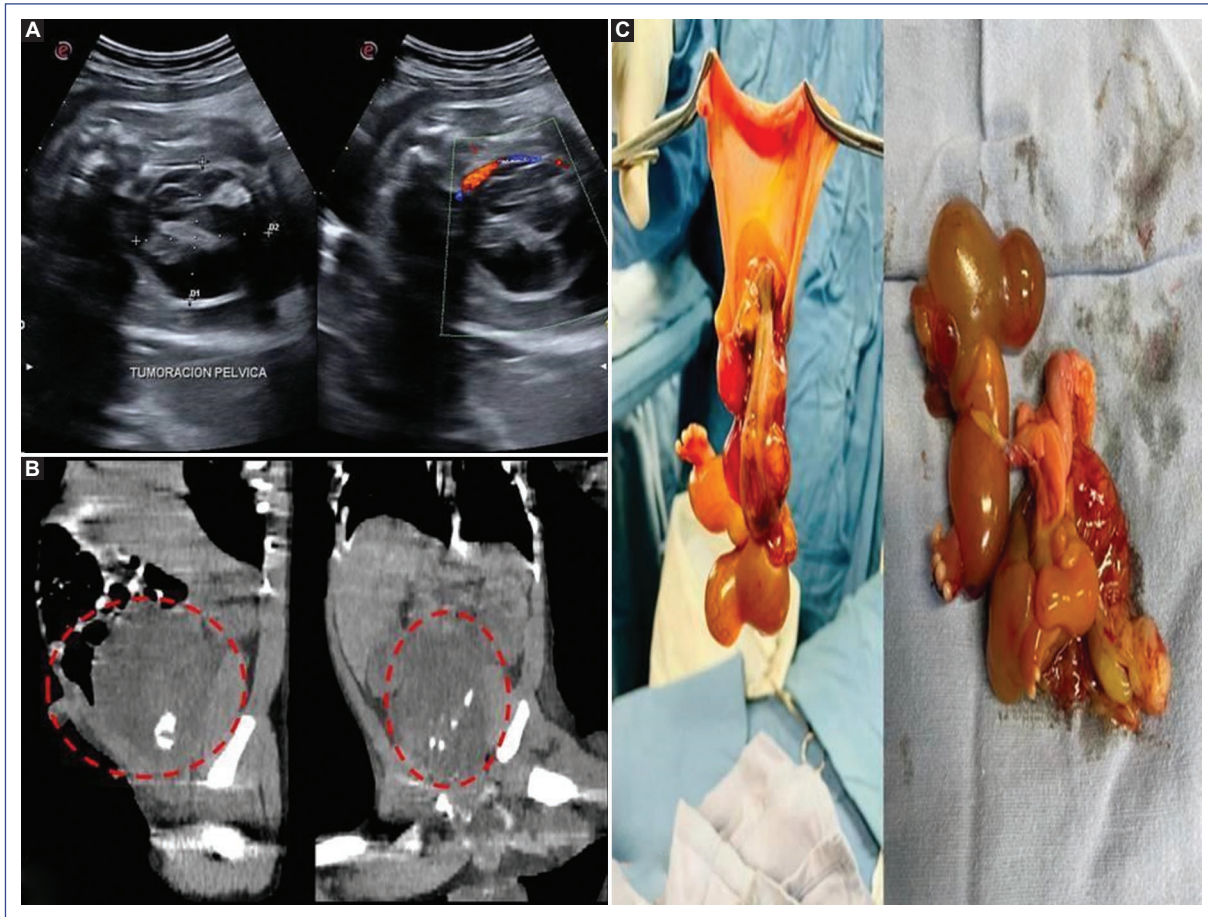


Figure 1. A: prenatal ultrasound performed one day before birth, where an abdominopelvic mass was initially identified, with both diameters of approximately 5 cm, without identifying any other significant alteration or obvious changes in vascularity. **B:** computed tomography, where a mass with cystic characteristics is observed, with the presence of hyperdense images, potentially calcifications, encapsulated, and that exert a mass effect on the abdominal organs fetus-in-fetu surgical specimen obtained during resection of the intra-abdominal mass. **C:** complex structures, such as limbs, umbilical cord, rudimentary head, digestive tract, and capsule (amniotic sac) are visualized.

normalized. During late recovery, the patient required re-intervention for abdominal eventration and developed late-onset neonatal sepsis, both of which resolved. The patient was discharged at 37 days of life (28 days post-operatively). Histopathological examination revealed embryonic tissues, including bone, nerve, dermal and cartilaginous structures, confirming the diagnosis of Fetus in Fetu (Fig. 2). At discharge, the patient was referred to the early stimulation service and was followed in our unit until 6 months of age, during which he maintained adequate nutritional status according to CDC/WHO standards and showed no apparent neurodevelopmental impairments. At present, the child is 15 months old, in good health, and meeting expected neurodevelopmental milestones.

Discussion

FIF is an exceptionally rare congenital anomaly defined by the presence of a fetiform mass composed of well-differentiated tissues enclosed within its genetically identical host. First described by Johann Friedrich Meckel in the late 18th century, its pathogenesis and associated risk factors remain subjects of debate^{4,9,12,13}.

Under 200 case reports have been published since the first description of this pathology in 1808. In the *Boletín Médico del Hospital Infantil de México*, only one publication, authored by Corona-Reyes et al. more than 40 years ago, reported the case of an infant male in whom a parasitic twin was identified at the testicular level. In subsequent decades, additional sporadic reports have been published, such as those by Quero

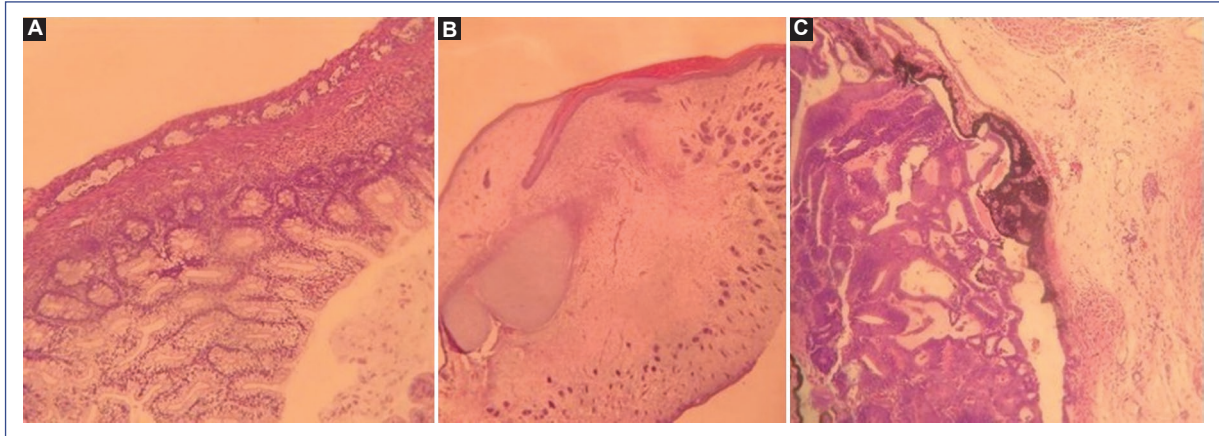


Figure 2. Microscopy of Fetus-in-Fetu. Histologically mature but poorly conformed structures can be seen. **A:** colon tissue **B:** limb-like appendage with cartilage in the central portion and surrounded by skin with cutaneous attachments **C:** outline of eye with neuroepithelium and a layer of cells with melanin pigment (retina).

Hernández et al., in which the diagnosis was established at approximately 2 months of age. A similar experience to the one presented in our unit was described by García Vázquez et al., who opted for an early surgical approach based on findings identified during the prenatal stage²⁰⁻²². Consistent with prior reports, our case occurred in the absence of familial congenital anomalies or prenatal risk factors. The mother's pregnancy was otherwise uncomplicated and no teratogenic exposures were identified²³.

Radiographic diagnosis of FIF is challenging. Ultrasound and CT typically reveal a complex cystic mass with mixed solid and liquid components and internal calcifications. Therefore, the identification on imaging studies of an abdominal mass not arising from adjacent anatomical structures, and demonstrating the aforementioned features, may assist the clinician in distinguishing FIF from other entities, such as adrenal neuroblastoma or teratoma, which more commonly occurs in the sacrococcygeal region or along the midline. Moreover, in the case of teratoma, the literature characterizes these tumors as irregular and predominantly solid rather than cystic, findings that may support a presumptive differential diagnosis on imaging^{13,16}. The presence of a discernible axial skeleton, considered a hallmark of FIF, is only visualized in approximately 9% of the cases²⁴⁻²⁷. In a review of 187 cases of FIF, prenatal detection occurred in only 1 of every 9²⁸. Similarly, in a 20-year cohort, only two cases were diagnosed prenatally by ultrasound²⁹. Ruffo et al. described early prenatal diagnosis following ultrasonographic detection of an abdominal mass³⁰. In our case,

the diagnosis was not suspected prenatally, and the mass was initially interpreted as a probable teratoma or neuroblastoma, necessitating laparotomy for both diagnosis and treatment^{9,11,13,16,23,29}.

Most FIF cases (72-91%) arise in the retroperitoneum. In our case, however, the mass was located in the bowel region, representing an unusual presentation. Although a male predominance (2:1) has been reported, some authors argue that sex distribution is equal. Our case, consistent with the majority, occurred in a male neonate^{23,31-34}.

Prognosis following complete surgical excision and in the context of an early diagnosis is excellent, with reported cure rates exceeding 97%. Recurrence, unlike with teratomas, is rare^{16,18,34,35}. Our patient has had no recurrence or FIF-related complications to date.

A systematic review of 153 cases described FIF as a fetiform mass, encapsulated within an amniotic sac separated from the host, partially or completely covered by skin, pedunculated, and often containing a vertebral axis. However, absence of a spinal column does not preclude the diagnosis, as some cases exhibit only ribs or long bones. In fact, 9% lack a vertebral column altogether. Organs, such as the heart, liver, and spleen, are rarely present. In our patient, multiple classic features were observed: fetiform morphology, encapsulation, vascular stalk, partial skin covering, and skeletal tissue^{27,36-38}.

In a review of 87 cases, most diagnoses (87%) occurred within the first 18 months of life; fewer were identified beyond the first decade. Approximately 76.6% of the cases were presented as abdominal masses; half were diagnosed within the first postnatal month, while

only 7% were identified *in utero*. The youngest reported case involved a 25-week pre-term fetus diagnosed by MRI, and the oldest was a 47-year-old adult. FIF typically presents as a solitary abdominal mass (88-89% of the cases); multiple parasitic fetuses are exceedingly rare. Differential diagnoses most often include teratoma and meconium pseudocyst, due to their similarity in imaging studies. As reported in other studies, our patient presented with a solitary abdominal mass during the neonatal period, with teratoma as the leading pre-operative differential^{16,19,28,30,36-39}.

Conclusions

FIF is an extremely rare congenital anomaly that must be considered in the differential diagnosis of abdominal masses in both the prenatal and neonatal periods. Despite the absence of national guidelines or standardized protocols in Mexico for the management of FIF, any abdominal mass identified during the prenatal period should be approached through a specific diagnostic protocol. The refinement of physician expertise in interpreting various imaging modalities, along with medical education focused on the differential diagnosis of abdominal masses – including FIF – could facilitate earlier diagnostic suspicion during pregnancy and, consequently, enable the development of a definitive surgical plan. Although serum tumor markers (e.g., beta-human chorionic gonadotropin, alpha-fetoprotein, carcinoembryonic antigen) have been proposed as adjuncts in the differential diagnosis, they were not utilized in this case. Nevertheless, their incorporation into future diagnostic protocols, along with the implementation of strategies involving multidisciplinary management, may prove valuable in ensuring favorable clinical outcomes for affected patients.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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CORRIGENDUM

Infección por COVID-19 y actividad física intensa en la parálisis periódica hipopotasémica

F. R. Cammarata-Scalisi, E. San Martín, A. Cárdenas-Tadich, M. Araya-Castillo, C. Peralta Aros, V. Olivares Faúndez, E. Bertini, C. E. Willoughby, M. Callea.

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El Consejo Editorial y el autor correspondiente notifican una corrección en la variante genética identificada en el gen *CACNA1S* del paciente, debido a un error de transcripción en el manuscrito original.

DONDE DICE:

“El estudio genético identificó una variación patogénica en heterocigosis en el gen CACNA1S (c.2700G-A; p.Arg900Ser) en el paciente...”

DEBE DECIR:

“El estudio genético identificó una variación patogénica en heterocigosis en el gen CACNA1S (c.2700G-T; p.Arg900Ser) en el paciente...”

El artículo ha sido actualizado con esta corrección en su versión electrónica.

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