Volume 20 Issue 3 July-September 2023

Pediatric Oncall Journal

ORIGINAL ARTICLE

CASE REPORTS

IMAGES IN CLINICAL PRACTICE

TEACHING FILES (GRAND ROUNDS)

ABOUT PEDIATRIC ONCALL JOURNAL

Aims & Scope:

Pediatric Oncall Journal is the official journal of Pediatric Oncall. It is in publication since 2004. From the beginning the emphasis has been on clinical pediatrics and it publishes articles that are useful for pediatricians in day-to-day pracice, The journal publishes editorials, review articles, original articles, case reports, viewer's choice (letter to editor) and scientific correspondence with commentaries on paper in pediatrics. There are also sections such as Teaching Files (Grand Rounds) and Images in Clinical Practice to help clinicians to deal the unusual cases in their clinical practice. The international, peer-reviewed papers cover a wide range of diseases in childhood. The main aim is to enable authors from across the globe to publish their unusual cases and research which changes clinical practice on an international platform. The emphasis of the journal is on the clear, concise presentation of information of direct clinical relevance to both hospital and community-based pediatricians.

Disclaimer

Pediatric Oncall make every effort to ensure the accuracy of all the information contained in our publications. However, Pediatric Oncall, our agents and our licensors make no representations or warranties whatsoever as to the accuracy, completeness or suitability for any purpose of the content. Any opinions and views expressed in this publication are the opinion and views of the authors and are not the views of or endorsed by Pediatric Oncall. The accuracy of the content should not be relied upon and should be independently verified with primary sources of information. Pediatric Oncall shall not be liable for any losses, actions, claims proceedings, demands, costs, expenses, damages and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection within relation to or arising out of the use of the content.

Subscription Information

The Pediatric Oncall Journal is published 4 times a year. Volume 19 (4 issues) will be published in 2022.
ISSN: Print 0973-0966 | Online 0973-0958
For any inforamtion on subscription rates please Contact journal@pediatriconall.com

Office of Publication

Levioza, 1/B, Saguna, 271/B, St. Francis Road, Vile Parle (West), Mumbai 400056. India.
Website: www.pediatriconcall.com/pediatric-journal
Indexed: • Index copernicus • Ulrichsweb • Open-J-Gate • Safety Lit • Locator Plus • Abstract on Hygiene and Communicable Diseases • CAB Abstract • Global Health • Global Health Archive • Tropical Diseases Bulletin • EBSCO

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.3

CASE REPORTS

NEWBORN WITH A RARE CAUSE FOR TESTICULAR ENLARGEMENT

Andre Costa Silva[1], Licinia Lima[2], Bernardete Rodrigues[2], Arnado Rêgo[2], Carla Dias[2], Isabel Soro[2], Dalila Rocha[2]

[1]Department of Pediatrics, Unidade Local de Saúde Alto Minho, Povoa De Varzim, Portugal, [2]ULSAM, Hospital Santa Luzia, Viana Castelo, Viana, Portugal.

ABSTRACT

Background: Meconium peritonitis is a rare condition characterized by sterile chemical peritonitis resulting from intrauterine bowel perforation. An even rarer entity occurs when meconium reaches the paratesticular soft tissue through a patent processus vaginalis, meconium periorchitis.

Case presentation: We hereby report a rare case of meconium periorchitis diagnosed following the investigation for a testicular mass in newborn. The diagnosis was confirmed by laparoscopic surgery. Concurrently alpha-1 antitrypsin deficiency is also determined on the midst the investigation.

Conclusion: When investigating a testicular mass in a newborn, a variety of diagnosis should be considered by clinicians including meconium periorchitis. Ultrasonography represents the gold-standard imaging technique due to its ability to differentiate between the extratesticular and intratesticular masses

ARTICLE HISTORY

Received 12 June 2023

Accepted 20 June 2023

KEYWORDS

Hydrocele, Meconium peritonitis, Meconium periorchitis, Alpha-1 antitrypsin deficiency.

Introduction

Meconium leakage into the peritoneal cavity induces meconium peritonitis (MP), a sterile chemical peritonitis. It is rare condition with a 1 in 30 000 birth incidence rate.[1,2] MP was thought to be a lethal illness between 1950 and 1960, with a death rate of 80% to 90%. Since then, a marked improvement in the survival rate—up to 80%—has been noted. This could arise from advancements in prenatal diagnosis methods and effective early intervention.[2]

Although the etiology of MP is not fully understood, some theories regarding the perforation mechanism have been put forth. According to some writers, a reduction in blood flow to the mesentery artery may produce mucosal necrosis, which may cause bowel obstruction; a further reduction in mesenteric blood flow may result in necrosis and intestinal wall perforation. However, ischemia is not the only factor that contributes to intestinal wall perforation during the fetal stages. In addition to meconium plugs, extramural conditions like hernia, band and volvulus can also elicit gut obstruction, leading to a perforation.[2]

Possible causes of MP[1,2,3] are listed in Table 1.

Meconium ascites develops as a result of meconium leakage into the peritoneal cavity following intestinal perforation. A severe inflammatory response brought on by the extruded meconium results in calcium depositing on the abdominal walls and other intra-abdominal tissues.[3] A fibrous wall may grow around the meconium concentration, establishing a pseudocyst, if the perforation happens early enough, before to delivery and the leakage persists over a significant amount of time. Predisposing factors include infections (mainly cytomegalovirus infection and parvovirus B19 or genetics, with cystic fibrosis accounting for 20-40 % of all cases of MP.[1,2,3]

Table 1. Major causes of MP

Vascular occlusion
Meconium ileus*
Internal hernia
Intussusception
Volvulus
Hirschsprung disease
Intrauterine appendiceal rupture
Meckel diverticulum
Imperforate anus

*Causes of meconium ileus: Cystic fibrosis, ileocecal atresia, functional consequence of prematurity pancreatic duct stenosis and partial pancreatic aplasia.

Meconium periorchitis, or MPO, is a rare condition in which meconium enters the paratesticular soft tissue through a patent processus vaginalis and causes an inflammatory response. It can appear at birth as a soft hydrocele, a scrotal enlargement, or a discoloration incorrectly attributed to birth trauma. As the meconium calcifies, the scrotal mass that develops over the course of weeks or months, becomes harder.[4,5] Scrotal mass at birth presents a broad differential diagnosis as summarized in Table 2.[4,6,7,8]

Address for Correspondance:
Andre Costa Silva, Av Mouzinho de Albuquerque 59 Póvoa de Varzim, Porto, Portugal.
Email: andrecostaesilva1@gmail.com

Table 2. Differential diagnosis of scrotal mass.

With calcifications	Without calcifications
Sertoli tumors	Hydrocele (simple)
Gonadoblastoma	Inguinal hernia
Teratoma	
Volvulus	
Meconium periorchitis	
Metastatic neuroblastoma	
Testicular torsion followed by hemorrhagic infarction	

Regarding MPO diagnosis, imaging by scrotal and abdominal ultrasonography is the gold standard.[7] It has been suggested that calcifications in the scrotum and abdomen are diagnostic. However, the majority of situations in the literature do not list these calcifications in either the scrotum or the abdomen.[8]

Case Report

We hereby present the case of a newborn, born after an uneventful pregnancy, with the exception of the third trimester ultrasound which displayed intrascrotal disperse calcifications, no reference to other findings, specifically abdominal lesions. Clinical examination of the newborn on his first day of life revealed bilateral enlargement of the testicles alongside with a darker coloration of the scrotum. Palpation was "stony" and transillumination test was negative as depicted on Figure 1.

Figure 1. Testicular enlargement and negative transillumination of scrotum.

Ultrasound with doppler confirmed ecogenic and heterogeneous material in both scrotal sacs, including several calcific formations (Figure 2) and no signs of vascular compromise (Figure 3).

Figure 2. Testicular ultrasonography of the newborn showing several small calcific hyperechoic formations (arrows).

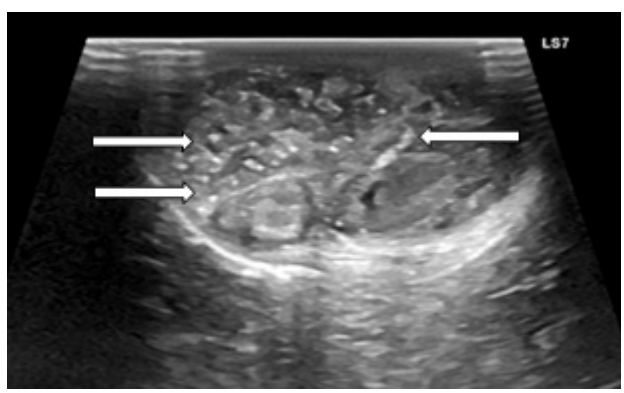
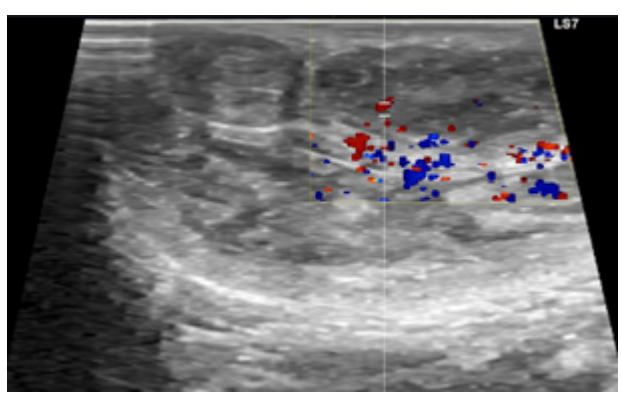


Figure 3. Testicular ultrasonography with doppler of the newborn showing no vascular compromise.



Both testicles had normal size and were symmetrical. Blood tests were performed at day 2. Full blood count, serum C-reactive protein, alpha-fetoprotein levels and b-human chorionic gonadotrophin (b-HCG) were all within age-appropriate age. Total and direct bilirubin were respectively 4.47 and 3.06 mg/dl. The days that followed the newborn was submitted to an abdominal ultrasound and radiography, both suggesting peritoneal calcifications. When combined, these results point out strongly to a diagnostic of meconium periorchitis.[7,8] that is an inflammation on the scrotal sac as a result of a

peritonitis process that crossed the peritoneal-vaginal duct.

Clinically the newborn was found to be more hypoactive and feeding worse on day 4 and 5 after birth. Pediatric Surgery was then consulted and based on clinical and radiographic findings decided to perform an exploratory laparotomy. Multiple meconial concretions and hard meconial pseudocysts were found and removed confirming the diagnosis of meconium periorchitis. Also, a prophylactic appendicectomy was performed. It was decided not to perform bilateral orchidopexy, instead a "wait and see" approach with recurrent evaluations.

Cystic fibrosis was tested, and both metabolic and genetic tests were negative for multiple mutations of CFTR gene. Post-surgically, the new-born evolved with no significant complications but the cholestasis parameters remained high. Infants with meconium ileus alone are at an increased risk of neonatal cholestasis. Further studies showed alpha 1 antitrypsin deficiency (AAT deficiency). Genetic tests followed for alpha 1 antitrypsin deficiency, and SZ phenotype was identified. There is only one case described on literature with both alpha 1 antitrypsin deficiency and meconium ileus, in which, meconium ileus was associated with cystic fibrosis.[8]

Discussion

When bowel wall is perforated, usually in the late fetal or early postnatal period, meconium leakages into the peritoneal cavity, resulting in meconium peritonitis. Table 1 lists the etiologies of MP, including mesenteric vascular insufficiency, volvulus, and meconium ileus. If the perforated gut wall heals, the "why" and "where" of the perforation might not be visible or acknowledgeable. Meconium passing through the patent processus vaginalis can induce MPO, and the mass-like lesion develops as a result of an inflammatory response to the meconium in the scrotal sac. The meconium ileus is the most typical reason for obstruction. According to most statistics, cystic fibrosis accounts for over 80% of cases of meconium ileus, which causes the meconium to thicken even more due to a lack of pancreatic enzymes. Therefore, screening patients for cystic fibrosis in the context of MPO should always be considered. In a recent assessment, up to 9% of MPO patients had cystic fibrosis diagnosed. In contrast, in MP, cystic fibrosis is discovered in up to 20-40% of patients.[8] Regarding the clinical history, it should be remembered that cocaine and non-steroidal anti-inflammatory medicines (NSAIDs) consumption by the mother is known to result in intestinal ischemia and should also be taken into consideration in the differential for a newborn who has signs of in utero intestinal perforation.[4,8] Due to its capacity to distinguish between extratesticular and intratesticular masses, ultrasonography is the imaging method of choice. We know that the majority of extratesticular lesions are benign, whereas the majority of intratesticular lesions are malignant. As to abdominal radiographs, they can be used to identify calcifications and significantly support the theory that meconium periorchitis is present. Simultaneous scrotal and abdominal calcifications virtually make up the diagnosis of MPO. Recent research has connected AAT deficiency to ANCA-associated vasculitis, chronic renal disease, diabetes, and metabolic changes, including lower serum triglyceride levels.[13] Excess of neutrophil elastase determined by alpha 1 antitrypsin deficiency leads to structural damage and consequently emphysema on the lungs. A possible similar mechanism could be responsible for the colonic/ileal perforation and the occurrence of meconium peritonitis/periorchitis. Further studies on this matter are needed.

Learning Points:

- Meconium periorchitis, an uncommon condition, is brought on by meconium leakage into the scrotal sac, which results in sterile inflammation.
- Ultrasonography represents the gold standard imaging technique in testicular enlargement, due to its ability to differentiate between the extratesticular and intratesticular masses.
- Simultaneous scrotal and abdominal calcifications virtually make up the diagnosis of MPO.
- While in asymptomatic neonates, conservative treatment/ surveillance is enough, severely ill patients are in need for urgent surgical intervention.

Compliance with Ethical Standards

Funding None
Conflict of Interest None

References:

1. 1. Shiri Shinar et al, Fetal Meconium Peritonitis - Prenatal Findings and Postnatal Outcome: A Case Series, Systematic Review, and Meta-Analysis, Ultraschall Med, 2020 Jun 23. DOI: 10.1055/a-1194-4363.
2. 2. So Hyun Nam et al, Experience with meconium peritonitis, Journal of Pediatric Surgery, 2007. https://doi.org/10.1016/j.jpedsurg.2007.07.006.
3. 3. Reynolds, E., Douglass, B. & Bleacher, J. Meconium Peritonitis. J Perinatol 20, 193-195 2000. https://doi.org/10.1038/sj.jp.7200287.
4. 4. Pamela Acosta et al, Meconium periorchitis. A case report, Arch Argent Pediatr 2015 http://dx.doi.org/10.5546/aap.2015.e330.
5. 5. Alanbuki AH, Bandi A, Blackford N. Meconium periorchitis: A case report and literature review. Can Urol Assoc J. 2013;7:E495-8. DOI: 10.5489/cuaj.316.
6. 6. Algaba F, Mikuz G, Boccon-Gibod L, et al. Pseudoneoplastic lesions of the testis and paratesticular structures. Virchows Archiv. 2007;451(6):987-997. DOI: 10.1007/s00428-007-0502-8.
7. 7. Regev RH, Markovich O, Arnon S, Bauer S, Dolfin T, Litmanovitz I. Meconium periorchitis: intrauterine diagnosis and neonatal outcome: case reports and review of the literature. J Perinatol. 2009 Aug;29(8):585-7. doi: 10.1038/jp.2009.15. PMID: 19638993.
8. 8. Shapira R, Hadzic N, Francavilla R, Koukulis G, Price JF, Mieli-Vergani G. Retrospective review of cystic fibrosis presenting as infantile liver disease. Arch Dis Child. 1999 Aug;81(2):125-8. doi: 10.1136/adc.81.2.125. PMID: 10490518; PMCID: PMC1718019.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.2

PEDIATRIC ONCALL
CHILD HEALTH CARE

IMAGES IN CLINICAL PRACTICE

NON-OSSIFYING FIBROMA IN A TEENAGER

Ana Luisa Correia, Carolina Castro, Joana Machado Morais, Ana Lurdes Aguiar.
Department of Pediatrics, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Matosinhos, Portugal.

KEYWORDS

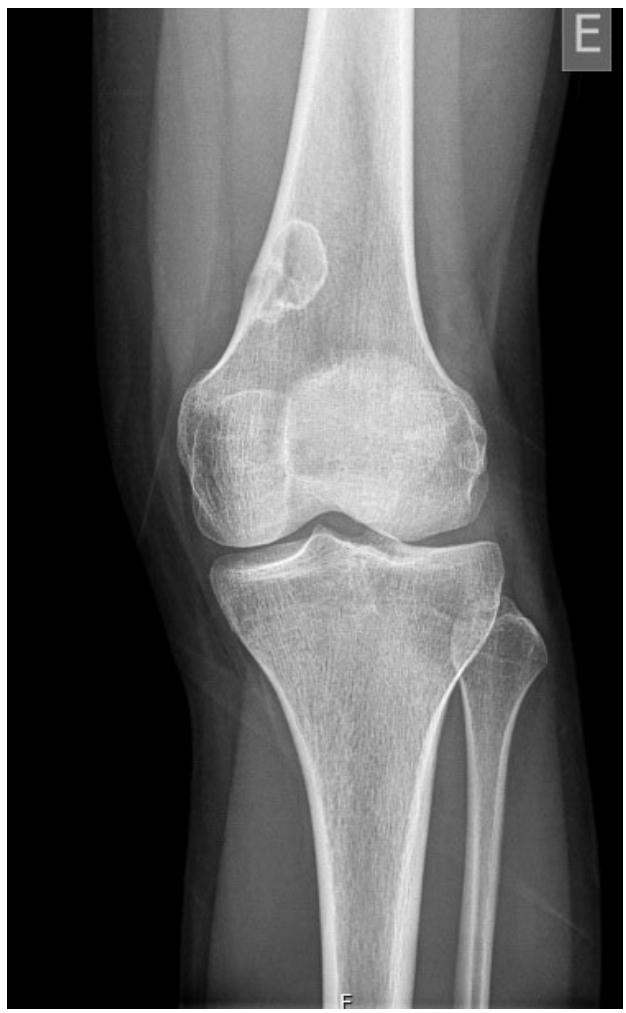
fibroma, teenager, image finding.

ARTICLE HISTORY

Received 28 December 2022
Accepted 29 March 2023

A previously healthy 17-year-old girl presented at the emergency department with acute pain in the left popliteal fossa with 4 hours of evolution, which woke her from sleep. She also mentioned paresthesias in the painful area. Fever, recent injuries, strenuous exercise, consumption of any medication, or tobacco use were denied. On presentation, she was hemodynamically stable and afebrile, walking with a limp. Palpation of the left popliteal fossa revealed tenderness and movement maneuvers showed pain with knee extension and flexion; the remaining physical examination did not reveal any significant abnormality, namely, any cutaneous findings A complementary study showed normal blood count, normal renal and liver function, negative C-reactive protein, normal lactate dehydrogenase, and normal erythrocyte sedimentation rate (9 mm/h). The coagulation profile and D-dimer test were within the reference range. A vascular surgeon performed a doppler ultra-sound and ruled out vascular pathology. She was observed by an orthopedist, who prescribed a left leg X-ray. This exam revealed a radiotransparent multiloculated bone lesion with a sclerotic rim located in the distal femur, without associated periosteal reaction, cortical breach, or associated soft tissue mass (Figures 1 and 2). This lesion was diagnosed as a small non-ossifying fibroma, which was considered an imaging finding, not related to the patient's complaints. Since the physical examination was normal and the complementary study did not reveal abnormal findings, the patient was discharged with symptomatic treatment. To follow the evolution of the non-ossifying fibroma, she was referred to an orthopedic consultation.

Figure 1. Conventional X-ray, anterior view of the left leg.



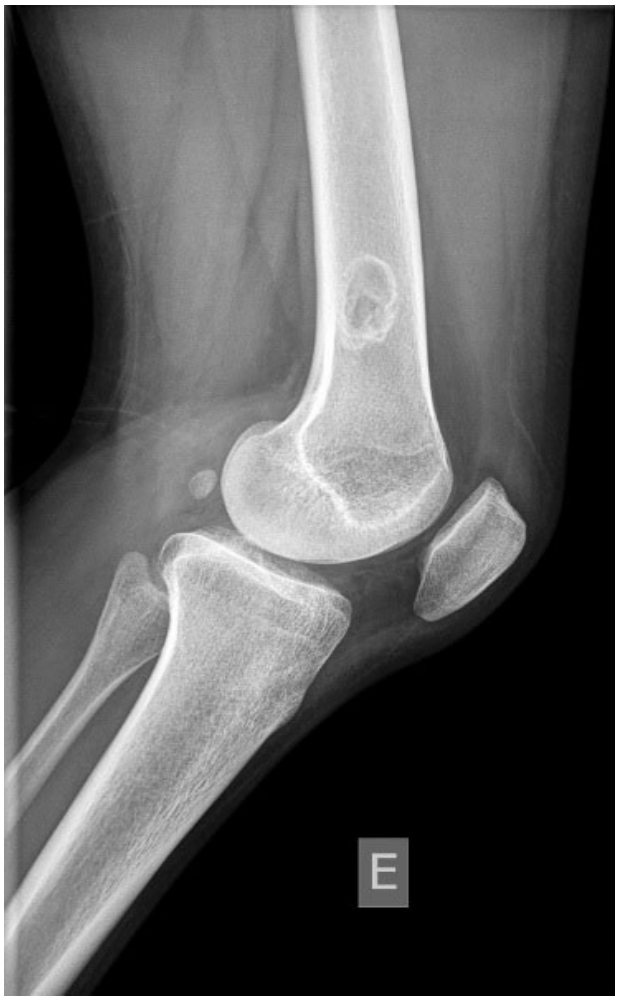
What is the diagnosis?

Benign bone tumors are frequently discovered incidentally. It's fundamental to recognize the characteristic radiographic features of these lesions, avoiding unnecessary advanced imaging and invasive diagnostic studies.[1,2,3,4,5,6] A careful anamnesis can lead us to the correct diagnosis: nonaggressive nonmalignant bone lesions usually are asymptomatic but may cause pain in association with pathologic fracture or neurovascular compression.[1,2,3,4,5,6] On the other hand, malignant bone tumors may be associated with pain that awakens the child from sleep and is more rapidly progressive. Our patient presented with potential warning signs and an abnormal leg X-ray. However, the fibroma was small and was not considered the cause for the patient's complaints; hence the importance of correctly identifying these benign lesions, that do not require treatment. Non-ossifying fibromas are very common in pediatric age (30% of estimated prevalence).[1,2] Most of these are asymptomatic and heal spontaneously with time.

Address for Correspondance: Ana Luisa Correia, Avenida Padre Sá Pereira nº27, lote 8, RC direito, Esposende, 4740-206, Portugal.

Email: analuisacorreia57@gmail.com

Figure 2. Lateral view of the left leg.



Larger lesions may be painful and weaken the bone, predisposing to pathological fractures.[1,2,3,4,5,6] According to Ritschl classification, which distinguishes the four different stages of a non-ossifying fibroma[5], this lesion was a stage B: a lesion with a thin sclerotic border, near the metaphysis; this stage has the highest risk for pathologic fracture[5], thus the need for follow up in this patient. We intend to familiarize clinicians with this condition and its radiographic features, since it can raise a suspicion of malignancy, especially in the presence of confounding symptoms.

Compliance with ethical standards

Funding: None

Conflict of Interest: None

References:

1. 1. Emori, M., Tsuchie H., Teramoto A., Shimizu J., Mizushima E., Murahashi Y., et al. "Non-Ossifying Fibromas and Fibrous Cortical Defects around the Knee - an Epidemiologic Survey in a Japanese Pediatric Population." BMC Musculoskeletal Disorders 2022;volume(23):378-383. https://doi.org/10.1186/s12891-022-05330-9.
2. 2. Sakamoto A., Arai R., Okamoto T., and Matsuda S.. "Non-Ossifying Fibromas: Case Series, Including in Uncommon Upper Extremity Sites." World Journal of Orthopedics 2017;Volume(8), no.7:561-566. https://doi.org/10.5312/wjo.v8.i7.561
3. 3. Bovée, J., Pancras, H. "Non-Ossifying Fibroma: A Ras-Mapk Driven Benign Bone Neoplasm." The Journal of Pathology 2019;volume(248):127-30. https://doi.org/10.1002/path.5259.
4. 4. Bowers, L., Cohen D., Bhattacharyya I., Pettigrew J., and Stavropoulos M. "The Non-Ossifying Fibroma: A Case Report and Review of the Literature." Head and Neck Pathology 2013;volume(7):203-210. https://doi.org/10.1007/s12105-012-0399-7.
5. 5. Herget, G., Mauer D., Krauß T., Tayeh A., Uhl M., et al. "Non-Ossifying Fibroma: Natural History with an Emphasis on a Stage-Related Growth, Fracture Risk and the Need for Follow-Up." BMC Musculoskeletal Disorders 2016;Volume(17):147-153. https://doi.org/10.1186/s12891-016-1004-0.
6. 6. Jashmitha R., Zhang C., Thahir A., and Krkovic M. "Imaging of Non-Ossifying Fibromas: A Case Series." Cureus, 2021;13(3):e14102 https://doi.org/10.7759/cureus.14102.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.1

IMAGES IN CLINICAL PRACTICE

INFANT WITH ASYMMETRIC FACIES WHEN CRYING

Adriana Ferreira, Inês Paiva Ferreira, Eulália Sousa, Cláudia Monteiro.
Pediatrics Department, Centro Hospitalar do Tâmega e Sousa, Penafiel, Portugal.

KEYWORDS

congenital, facial asymmetry, infant.

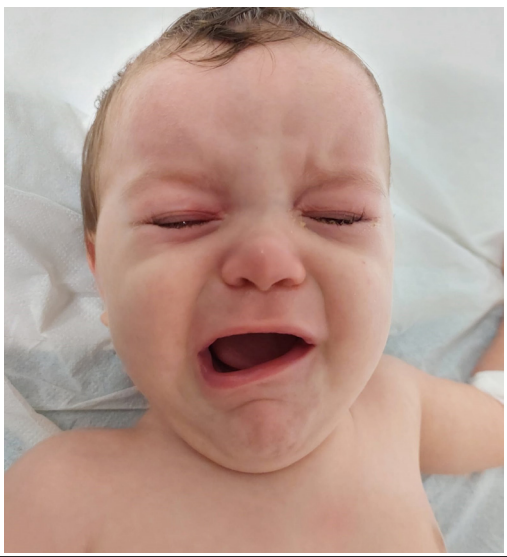
ARTICLE HISTORY

Received 27 December 2022

Accepted 29 March 2023

A seven-month-old male infant presented to the emergency department with mild respiratory symptoms. During the observation, asymmetry of the face with a downward deviation of the right labial commissure was noted when the patient was crying (Figure 1). At rest, the face was symmetric except for a slightly thinner and inward-turned lower left lip (Figure 2). According to the parents, these alterations have been present since the first days of life. The further neurologic assessment was normal. No other major or minor malformations were detected, and cardiac auscultation was normal without murmurs. He presented normal growth and neurodevelopment. There was no history of problems with sucking or drooling and no family history of congenital abnormalities, including facial asymmetry. The patient was a second-born child from nonconsanguineous parents. Pregnancy was uneventful and the patient was born at 38-3/7 weeks gestation by cesarean section because of prolonged labor, with a birth weight of 3270 g, birth length of 51 cm, and head circumference of 35 cm. Apgar scores at 1, 5, and 10 minutes were 7, 8, and 10, respectively.

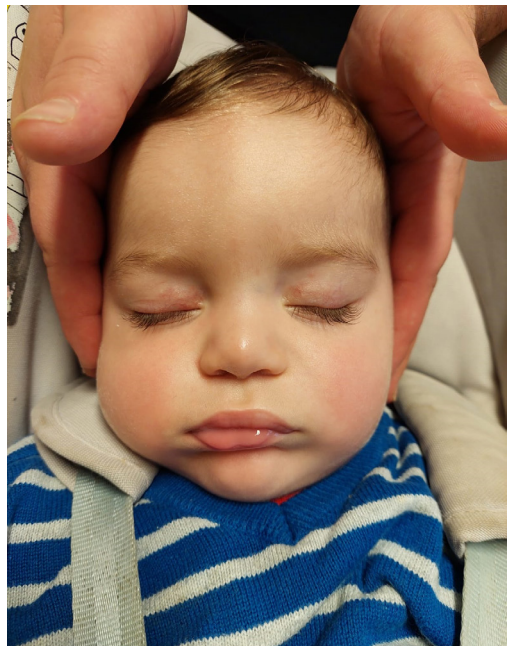
Figure 1. Facial asymmetry observed when crying with the right side of the mouth deviated downward while the left side remained unmoved.



Address for Correspondance: Adriana Ferreira, Avenida do Hospital Padre Américo 210, 4564-007 Guilhufe.

Email: adriana.amf1@gmail.com

Figure 2. Symmetrical facial expression at rest with only the left lower lip slightly thinner and turned inwards.



What is the diagnosis?

Asymmetric crying facies (ACF) was diagnosed and assumed to derive from left depressor anguli oris muscle (DAOM) hypoplasia. ACF is defined by facial asymmetry observed during crying and is characterized by a downward deviation of the unaffected side of the mouth's angle, while the affected side remains unmoved. The facial expression is symmetric at rest, though the lip from the affected side can be slightly thinner and turned inward.[1] ACF has an estimated incidence of 0,31% to 0,82% of live births and is more prevalent in males (M:F ratio of 2:1).[1] The etiology of the asymmetric crying facies can be explained by two theories: the traumatic theory and the faulty development theory. In the first one, ACF is caused by the compression of one of the facial nerve branches in utero or during labor. In the second theory, the cause of the ACF is the hypoplasia or agenesis of the DAOM or the hypoplasia of the depressor labii inferioris muscle.[2] ACF due to nerve compression is typically an isolated abnormality. Potential risk factors include primiparity, multiple births, high birth weight, difficult labor or delivery, forceps delivery, and

uterine tumors.[1,2] Clues in physical examination for this mechanism are the presence of mandibular asymmetry and maxillary-mandibular nonparallelism.[1] On the other hand, the hypoplasia and agenesis of DAOM can be caused by intrauterine viral infections, genetic factors, or a brainstem-level defect.[3] Familial occurrence has been reported, with autosomal dominant inheritance with variable penetrance being suggested.[3] An association with other major and minor congenital malformations has been reported in up to 15% of patients with DAOM hypoplasia.[1] Such anomalies can involve every system, but the most commonly reported are cardiovascular and cervicofacial malformations.[2,3] A well-known association of ACF with congenital heart disease and 22q11 microdeletion has already been described.[2] ACF is a clinical diagnosis and can be differentiated from other entities as true facial paralysis based on the clinical history and physical examination. Typically, sucking, forehead wrinkling, eye closure, nasolabial fold depth, and tearing are preserved and symmetric in ACF.[1] Ultrasonographic and electromyographic testing of the facial muscles can be helpful diagnostic aids if a physical examination is not revealing.[2] Early determination of ACF cause is important since it affects therapeutic management and, thus, the prognosis.[1] In most cases, spontaneous resolution can be expected if the cause is traumatic and no further evaluation is necessary. However, if there is agenesis or hypoplasia of DAOM or DLIM, a careful physical examination is important to exclude associated malformations. And if these are present, performing an echocardiogram and eventually a FISH analysis for 22q11 microdeletion is crucial. If the physical examination is normal, observation only is appropriate.[1,2] As the child grows, risorius and other facial muscle use become more frequent. Smiling appears and dominates the child's facial expression, leading to a less noticeable facial asymmetry.[4] However, surgical intervention may be required to improve cosmetic outcomes.[1] In conclusion, in ACF, physical examination can be sufficient for its diagnosis, for the differential diagnosis with facial palsy, management, and parent reassurance. Despite being a benign condition in most of the cases, clinicians should not dismiss the possibility of association with other clinically significant malformations.[2]

Compliance with ethical standards
Funding: None
Conflict of Interest: None

References:

1. Sapin SO, Miller AA, Bass HN. Neonatal asymmetric crying facies: a new look at an old problem. Clin Pediatr (Phila). 2005 Mar;44(2):109-19. doi:10.1177/000992280504400202.
2. Shapira M, Borochowitz ZU. Asymmetric Crying Facies. NeoReviews. 2009;10:e502-9. doi:10.1542/neo.10-10-e502
3. Liang X, He B. Congenital asymmetric crying facies syndrome: A case report. Medicine (Baltimore). 2018 Aug;97(31):e11403. doi: 10.1097/MD.0000000000011403.
4. Nelson KB, Eng GD. Congenital hypoplasia of the depressor anguli oris muscle: differentiation from congenital facial palsy. J Pediatr. 1972 Jul;81(1):16-20. doi: 10.1016/s0022-3476(72)80367-6.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.17

IMAGES IN CLINICAL PRACTICE

NODULAR SCABIES IN AN INFANT - A CHALLENGING DIAGNOSIS

Laura Leite de Almeida[1], Tomás Ferrão[2], Rita Alvelos[2], Luís Santiago[3], Marisol Pinhal[2].
[1]Department of Pediatrics, Centro Hospitalar Universitário de São João, Porto, Portugal,
[2]Department of Pediatrics, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal,
[3]Department of Dermatology, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal.

KEYWORDS

dermatology, infant, infestation, pediatrics, scabies.

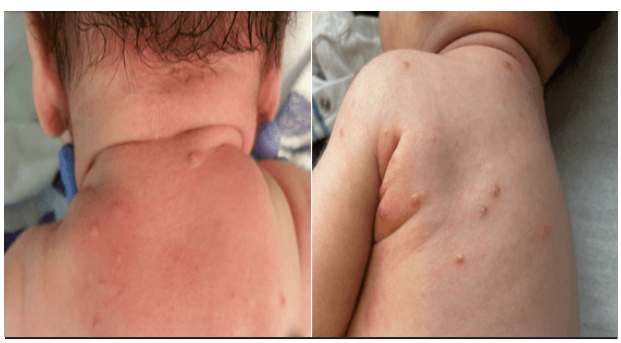
ARTICLE HISTORY

Received 3 July 2023

Accepted 24 July 2023

A 6-week-old male infant was brought to the emergency department with a three-day history of irritability, decreased food intake, and a polymorphic skin eruption. He had no significant medical history, was exclusively breastfed with good weight gain. None of his family members had similar symptoms or lesions. The infant was in good general condition. Skin examination revealed an erythematous base with scattered vesicles, pustules, and papules. The lesions were more prominent on the scalp, back, and abdomen, including the neck, inguinal, and axillary regions (Figure 1). Blood parameters were within reference ranges for age, with no increased inflammatory markers. Nevertheless, due to the exuberance of the lesions, a bacterial infection was suspected, and intravenous flucloxacillin was initiated. The following day, the infant presented with new lesions, and nodular scabies was suspected. The delta-wing jet sign observed on direct dermoscopy confirmed the diagnosis (Figure 2). The patient and his parents were treated with topical 6% sulfur ointment for three consecutive days, repeated after seven days. In the follow-up evaluation four days after completing treatment, the infant presented with additional lesions on his back. His aunt had been taking care of him in the previous days, and neither she nor her family had been treated. The patient and all his close contacts underwent two more cycles of treatment, with complete resolution of the lesions.

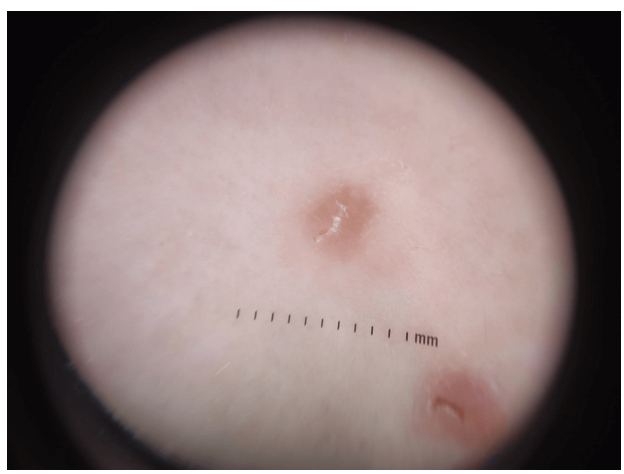
Figure 1A and 1B. Lesions in the torso: scattered vesicles, pustules, papules and nodules in an erythematous base.



Address for Correspondance: Laura Leite de Almeida,Department of Pediatrics, Centro Hospitalar Universitário de São João, Alameda Prof. Hernâni Monteiro, 4200-319, Porto, Portugal.

Email: analauramlalmeida@gmail.com

Figure 2. Dermoscopy of the lesions: delta-wing jet sign, a triangular structure at the end of the central S-shaped burrow.



What is the Diagnosis?

Scabies is a global public health concern.[1,2] Its diagnosis is challenging, especially during infancy, as it may present atypically. In adults and older children, it usually involves the hands and feet.[1] In young children, it can manifest as papules and pustules on the head and trunk, as seen in this case.[1,2] Visualization of mites or the delta-wing jet sign in dermoscopy can confirm the diagnosis.[1] Higher organism loads are present in infants, making them highly efficient vectors.[1] Therefore, prompt diagnosis is critical in preventing the spread of mites and avoiding complications. Effective treatment of all close contacts and careful follow-up are important for a positive outcome.

Compliance with ethical standards
Funding: None
Conflict of Interest: None

References:

1. 1. Brockman R, Leitenberger S. Review of Scabies Infestation and Selected Common Cutaneous Infections. Pediatr Rev. 2021;42:21-30.
2. 2. Hill TA, Cohen B. Scabies in babies. Pediatr Dermatol. 2017;34:690-694.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.16

IMAGES IN CLINICAL PRACTICE

DEPRESSED SKULL FRACTURE CONGENITAL

Patrícia Campos[1], Patrícia Gomes Pereira[1], José Gustavo Soares[2], Marta Mesquita[1].
[1]Pediatrics Department, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal,
[2]Neurosurgery Department, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

KEYWORDS

Depressed skull fracture, Ping-pong fracture, Congenital fracture, Spontaneous fracture, Newborn, Neurosurgery.

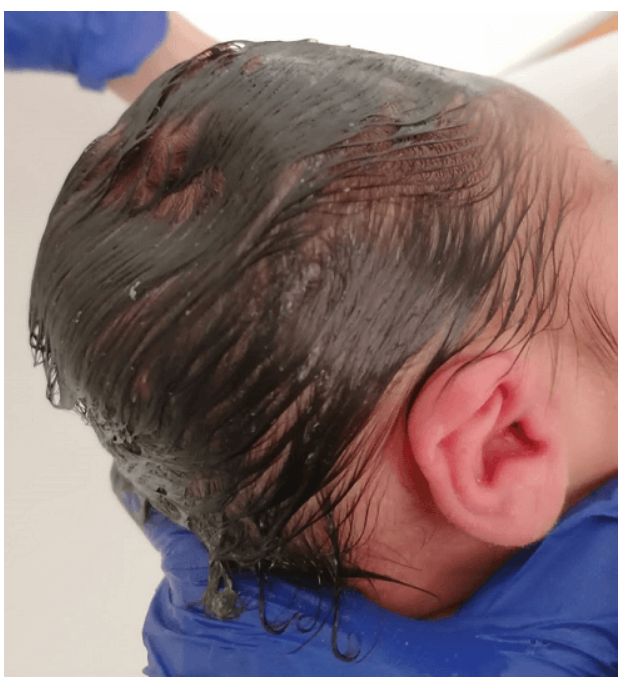
ARTICLE HISTORY

Received 27 May 2023

Accepted 1 June 2023

A male term newborn was delivered at 39 weeks of gestation from a 43-year-old woman by an urgent caesarean for fetal bradycardia. Pregnancy was complicated with gestacional diabetes controlled with metformin. Fetal ultrasounds were normal and there was no history of prenatal maternal trauma. The fetus was difficult to extract but no obstetric instruments were used during delievery. He adapted well with an Apgar score of 9 and 10 at first and fifth minutes, respectively. Somatometry at birth was adequate for gestational age: weight of 3500g (50th percentile), length of 48 cm (15th-50th percentile) and head circumference of 35,5 cm (50th-85th percentile). Postbirth physical examination revealed a depression in the right parietal region measuring 4 x 3 cm with 2 cm depth (Figure 1). No local bruising or soft tissue swelling was evident. His neurological examination was normal and there were no other congenital abnormalities.

Figure 1. Depression in the newborn's right parietal bone (at birth).



What is the diagnosis?

The diagnosis of depressed skull fracture (DSF) was considered and skull radiography confirmed an abnormal concavity in the right parietal bone (Figure 2). Cranial ultrasound showed no intracranial hemorrhages (ICH) or cerebral edema. Given his good clinical condition, the newborn was discharged home after 48 hours of hospitalization with weekly neurosurgery follow-up consultations. After a 3-week period there was no evident spontaneous remodelling of the skull. Given the fracture's dimensions, surgical elevation of the bone was performed after parental consent with a good clinical outcome (Figure 3). No post-operative complications were reported and the child showed an adequate growth and neurodevelopment over the first year of life.

Figure 2. Skull radiography after birth showing a concavity in the right parietal bone (arrows).

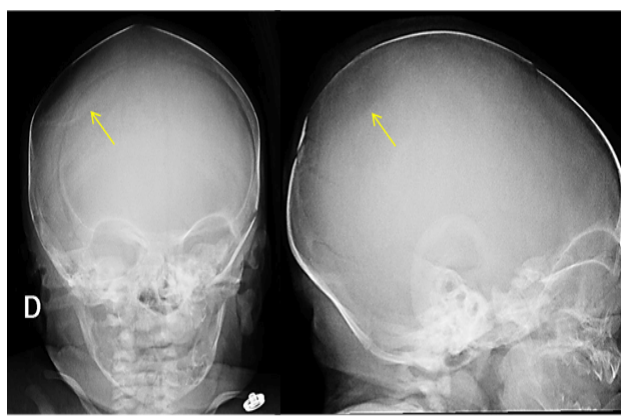
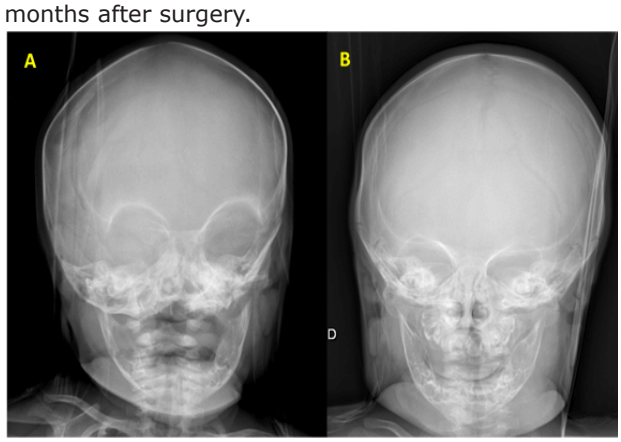


Figure 3. Skull radiography after surgical elevation of the parietal bone. **A.** - One week after surgery. **B** - Two months after surgery.



Address for Correspondance: Patrícia Campos, Av. Artur Ravara 35, 3810-164 Aveiro, Portugal.

Email: appcampos94@gmail.com

DSF, also called *ping-pong* fractures, are a rare condition that occurs in 1-2,5/100.000 neonates. Congenital DSF are commonly associated to birth trauma (instrumentation or maternal bone structures), causing inward buckling of the bones during delivery. Although rare, sometimes they can be observed in newborns following a non-traumatic delivery and are therefore described as spontaneous DSF; these are believed to be caused by prolonged focal pressure on the neonatal skull by structures on the mother's pelvis (ischial bone, sacral promontory, symphysis pubis, uterine fibroid, the fifth lumbar vertebrae, etc.).[1,2,3] Most cases reported in the literature affect the parietal or frontal bones, as it is believed that the location of the fracture correlates with the presentation of the fetal head to the pelvic inlet.[4] A concavity in a newborn's skull should always evoque the diagnosis of DSF. Detailed birth history and postnatal examination for evidence of acute injury are crucial to distinguish between spontaneous and traumatic lesions.

Skull radiography often shows the degree of deformation but no fracture line is seen, as there is undisrupted bone continuity.[5] Cranial ultrasound can identify ICH, hematomas or cerebral edema, that are significantly more frequent in DSF secondary to instrumental delivery. Although a computed tomography scan is a more sensitive exam, given the high radiation exposure it should be performed only if there is diagnostic doubt or associated complications.[1] Some rare but serious complications have been described after compound traumatic DSF, such as cerebral contusions, parenchymal lesions and long-term deficits like epilepsy or brain tumours[6,7,8] In the present case, the parietal area was involved without any intracranial pathology or neurological deficits, and there was no history of trauma or instrument-assisted delivery, although the fetus was difficult to extract. As there was no local bruising or soft tissue swelling, a traumatic etiology seemed less likely.

Management of this condition is still controversial as there is no standard protocol at the current moment. Since the bone progressively remodels into a normal shape, DSF can be managed expectantly, as described in some previous case reports.[2,3,9,10] Other treatment options include non-surgical interventions, such as digital pressure or vacuum extractor, and surgical elevation. The choice is usually based on clinical symptoms, the severity of the fracture and the existence of underlying brain injury or increased intracranial pressure.[3,4]

Spontaneous DSF and those affecting children with a normal neurological examination are associated with a good prognosis and most cases resolve spontaneously within the first six months of life.[3,10] It has been suggested that a depression greater than 5 mm on the neonatal skull could lead to a focal area of tissue hypoperfusion and cerebral edema[11]; however, a critical measurement has not been yet established to indicate the need for intervention. Corrective surgery may be required when no spontaneous remodeling of the skull is observed or in large lesions with a mass effect on brain structures. Further comments and reports on neonates with DSF may be required to enlighten the most adequate treatment approach for each case.

Compliance with ethical standards
Funding: None
Conflict of Interest: None

References:

1. 1. Preston D, Jackson S, Gandhi S. Non-traumatic depressed skull fracture in a neonate or "ping pong" fracture. BMJ Case Rep. 2015;2015: bcr2014207077.
2. 2. Ilhan O, Bor M, Yukkaldiran P. Spontaneous resolution of a 'pingpong' fracture at birth. BMJ Case Rep. 2018;2018: bcr2018226264.
3. 3. Sorar M, Fesli R, Gürer B, Kertmen H, Sekerci Z. Spontaneous elevation of a ping-pong fracture: Case report and review of the literature. Pediatr Neurosurg. 2013;48:324-6.
4. 4. Veeravagu A, Azad TD, Jiang B, Edwards MSB. Spontaneous intrauterine depressed skull fractures: report of 2 cases requiring neurosurgical intervention and literature review. World Neurosurg 2018; 110: 256-262.
5. 5. Lunt CMB, Roth K, Eich G, et al. Neonatal ping pong fracture. Swiss Society of Neonatology, 2006.
6. 6. Dupuis O, Silveira R, Dupont C, et al. Comparison of "instrument-associated" and "spontaneous" obstetric depressed skull fractures in a cohort of 68 neonates. Am J Obstet Gynecol 2005;192: 165-70.
7. 7. Tervilä L, Huhmar EO, Krokfors E. Cerebral birth injury as a cause of epilepsy. Ann Chir Gynaecol Fenn 1975;64: 118-22.
8. 8. Gurney JG, Preston-Martin S, McDaniel AM, et al. Head injury as a risk factor for brain tumors in children: results from a multicenter case-control study. Epidemiology 1996;7:485-9.
9. 9. Basaldella L, Marton E, Bekelis K, et al. Spontaneous resolution of atraumatic intrauterine ping-pong fractures in newborns delivered by cesarean section. J Child Neurol 2011;26:1449-51.
10. 10. Loire M, Barat M, Mangyanda Kinkembo L, Lenhardt F, M'buila C. Spontaneous ping-pong parietal fracture in a newborn. Arch Dis Child Fetal Neonatal Ed. 2017;102: F160-1.
11. 11. Ben-Ari Y, Merlob P, Hirsch M, et al. Congenital depression of the neonatal skull. Eur J Obstet Gynecol Reprod Biol 1986;22: 249-55.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.15

IMAGES IN CLINICAL PRACTICE

PRETERM WITH MILKY URINE

Anshika Taiwade1, Shweta Anand[1], Rashmi Vishwakarma[1], Rajeev Vishwakarma[1], G.C Bhatt[2].
[1]Department of Pediatrics, LN Medical College and JK Hospital, Bhopal, Madhya Pradesh, India,
[2]Department Of Paediatric Nephrology, AIIMS, Bhopal, Madhya Pradesh, India.

KEYWORDS

Preterm, Milky Urine,Benign crystalluria.

ARTICLE HISTORY

Received 19 January 2023

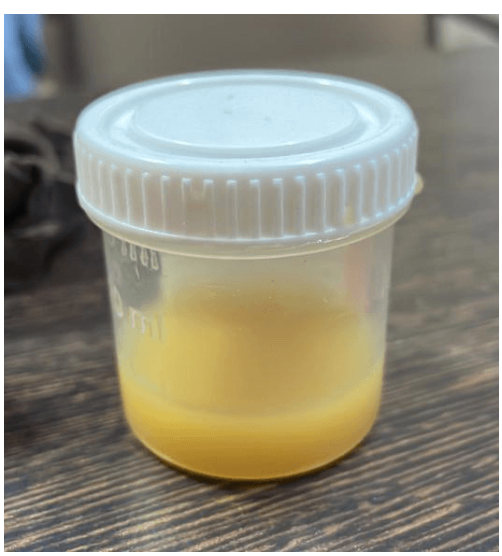
Accepted 27 July 2023

A primigravida mother delivered a preterm (35±2 weeks) male baby by Emergency LSCS (Severe oligohydramnios) with birth weight of 2.28 kg. Baby required no resuscitation and shifted to mother side after routine care.

Baby developed neonatal jaundice on 60 hours of life for which phototherapy started. Neonatal hyperbilirubenemia resolved within 24 hours and baby was discharge on 6th day of life.

On 10th day mother came with complaint of passing turbid urine (Figure 1) and significant weight loss (300 gms).

Figure 1. Showing milky urine.



We hospitalized the baby and started initial management. Initial management of urine revealed amorphous amount of calcium oxalate crystal with no pus cell. septic screening were negative and urine culture showed commensal pathogen. Radioimaging done which was normal, RFT were normal. Urine calcium/ creatinine ratio was high and urine chylomicron was negative.

Figure 2. Breast feeding, Hydration improved.

Figure 3. Urine became clear

Address for Correspondance: Anshika Taiwade, JK hospital, Kolar road, Bhopal, 462042, India.

Email: anshika22.taiwade@gmail.com

What is Benign crystalluria?

Finally we made diagnosis of benign crystalluria. Crystalluria refers to crystals found in urine when performing a urine test. Crystalluria is considered often as a benign condition and may represent Dehydration. Which in newborns can be corrected by encouraging breastfeeding.

Compliance with ethical standards

Funding: None

Conflict of Interest: None

References:

1. 1. Milky urine in a premature infant by Lucia Marseglia &Sara Manti &Gabriella D'Angelo &Ignazio Barberi &Eloisa Gitto IPNA 2013.
2. 2. Yamauchi S (1945) Chyluria: clinical, laboratory and statisti-cal study of 45 personal cases observed in Hawaii. J Urol 54:318-347
3. 3. Diamond E, Schapira HE (1985) Chyluria-a review of the literature.Urology 26:427-431
4. 4. Hemal AK, Gupta NP (2002) Retroperitoneoscopic lymphatic man-agement of intractable chyluria. J Urol 167:2473-2476
5. 5. Koo CG, Van Langenberg A (1969) Chyluria. A clinical study. J RColl Surg Edinb 14:31-41
6. 6. WHO Expert Committee on Filariasis (1992) Lymphatic filariasis:the disease and its control. Fifth report of the WHO expert committeeon Filariasis. WHO Tech Rep Ser 821:1-71
7. 7. Buck AA (2002) Filariasis. In: Strickland GT (ed) Hunterstropical medicine, 7th edn. WB Saunders, Philadelphia, pp713-
8. 8. Stalens JP, Falk M, Howmann-Giles R, Roy LP (1992) «Milky»urine-a child with chyluria. Eur J Pediatr 151:61-62
9. 9. Kittredge RD, Hashim S, Roholt HB, Van Itallie TB, Finby N (1963)Demonstration of lymphatic abnormalities in a patient with chyluria.Am J Roentgenol 90:159-165
10. 10. Punj J, Anand R, Darlong V, Pandey R (2013) Milky urine! A causefor concern? Indian J Anaesth 57:87-88
11.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.44

IMAGES IN CLINICAL PRACTICE

BLACK LINEAR NAIL LESION IN A PRESCHOOLER

Carolina Fraga[1], Alexandra Azevedo[2], Fábio Barroso[3].
[1]Pediatrics Department, Centro Materno-Infantil do Norte, Centro Hospitalar Universitário de Santo António, Porto, Portugal.

[2]Dermatology Department, Centro Hospitalar Universitário de Santo António, Porto, Portugal.

[3]Pediatrics Department, Centro Hospitalar do Tâmega e Sousa, Penafiel, Portugal.

KEYWORDS

melanocytes, child, nail alterations.

ARTICLE HISTORY

Received 4 October 2023

Accepted 9 November 2023

A four-year-old Caucasian female was being observed in emergency department for an unrelated complain (dysuria), when her mother reported the presence of a black linear lesion on her right thumb nail. This was present for two years and there was no history of previous trauma or recent medication when it was initially noted. It kept the same characteristics throughout time despite the nail's growth. Her father displayed a similar lesion.

On physical exam she presented a narrow black linear pigmentation along the entire length of the nail of the first finger of the right hand (Figure 1A). There were no other lesions on the remaining hand and feet nails or in the skin.

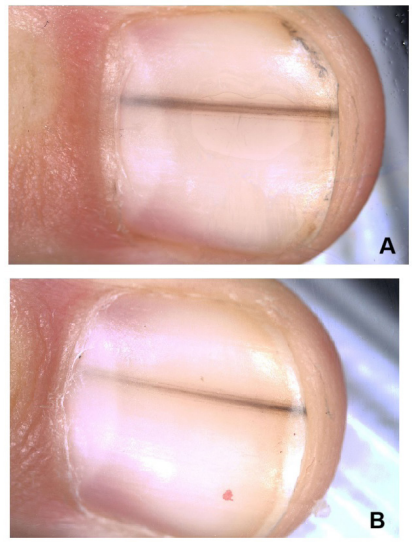
The child was referred to Dermatology where longitudinal melanonychia (LM) was diagnosed. Since the lesion was stable, conservative approach was adopted. Following two years of dermoscopic surveillance, spontaneously partial regression of the lesion was confirmed with lightening of the proximal half. (Figure 1B).

What is the diagnosis?

LM is a dark pigmentation of the nail plate that results from either activation or hyperplasia of melanocytes in the nail matrix. It is more prevalent in darked-skin individuals, mostly in adulthood, being rare in children particularly Caucasian. Familial occurrence with an early age of onset was described only exceptionally.[1]

Although it may rarely be secondary to subungual melanoma, it is typically benign in children. Clinical features that raise concern for melanoma include rapid evolution, changing pigmentation or shape, color heterogenicity, blurred lateral borders, pigment band greater than 3 mm and associated nail dystrophy. Hutchinson sign (periungual pigmentation) is a hallmark for subungual melanoma in adults but in children it may be present in benign melanonychia.[2] Most recent publications support a wait-and-see strategy in pediatric LM with clinical and dermoscopic follow-up. Biopsy is indicated in the presence of concerning signs.[1,3]

Figure 1. Dermatoscopic images: A - Pigmented band along the entire length of the nail of the right thumb without nail dystrophy at diagnosis; B - the same lesion two years later, narrower and lighter proximally.



Compliance with ethical standards
Funding: None
Conflict of Interest: None

References:

1. 1. Leung AKC, Lam JM, Leong KF, Sergi CM. Melanonychia striata: clarifying behind the Black Curtain. A review on clinical evaluation and management of the 21st century. Int J Dermatol. 2019 Nov;58(11):1239-1245. doi: 10.1111/ijd.14464. Epub 2019 Apr 21. PMID: 31006857.
2. 2. Cooper C, Arva NC, Lee C, Yélamos O, Obregon R, Sholl LM, Wagner A, Shen L, Guitart J, Gerami P. A clinical, histopathologic, and outcome study of melanonychia striata in childhood. J Am Acad Dermatol. 2015 May;72(5):773-9. doi: 10.1016/j.jaad.2015.01.010. Epub 2015 Mar 9. PMID: 25766363.
3. 3. Morato IB, Gontijo JRV, Tavares GT, Bittencourt FV. Longitudinal melanonychia in childhood: a great challenge. An Bras Dermatol. 2022 Jul-Aug;97(4):516-519. doi: 10.1016/j.abd.2021.02.012. Epub 2022 Jun 9. PMID: 35691736; PMCID: PMC9263629.

Address for Correspondance: Carolina Fraga, Largo da Maternidade de Júlio Dinis 45, 4050-651 Porto, Portugal.

Email: carolinamoraesfraga@gmail.com

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.43

IMAGES IN CLINICAL PRACTICE

PARAMEATAL CYST IN AN INFANT

Vilma Lopes, Mariana Oliveira, Maria Adriana Rangel.

Department of Pediatrics, Centro Hospitalar Vila Nova de Gaia/Espinho Unidade 1, Vila Nova de Gaia, Portugal.

KEYWORDS

parameatal cyst, urethral meatus, infant.

ARTICLE HISTORY

Received 17 September 2023

Accepted 17 October 2023

A 2-months old male infant presented in the pediatric outpatient clinic with complaints of a cystic bulge on the glans penis observed a few days earlier. There were no other symptoms, such as perception of discomfort, stream distortion, urinary flow disturbance or urinary tract infections. Trauma was denied. The patient was previously healthy and family history was unremarkable. Physical examination showed a well-defined, nontender oval cyst adjacent to the meatal opening, as shown in the image (Figure 1). The patient was seen by a Pediatric Nephrology specialist that recommended a wait-and-see approach. The patient is currently 9-month old and remains asymptomatic. Variations in size have been documented but without dimensional increase.

What is the diagnosis?

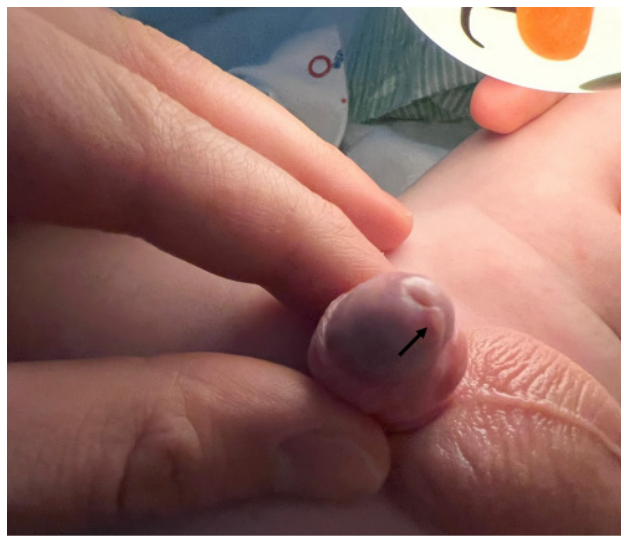
Parameatal cyst is a rare condition, with only near 50 cases described in the literature. It is a benign clinical entity that typically manifests at birth or in early childhood.[1] They commonly appear on the ventral or lateral margin of the urethral meatus, usually measuring less than 1 cm and without urinary disturbances.[2,3] The diagnosis is based on clinical appearance.[4] The etiology and pathogenesis of these cysts remains undetermined.[5] There are no known comorbidities or syndromes associated with this condition.[6] Management of parameatal cysts should be conservative in asymptomatic cases. However, close observation is crucial as the cysts may increase in size and/or lead to urinary flow disturbance, dysuria, urinary retention, as well as cosmetic complaints. In such cases, a comprehensive evaluation of the urinary tract is necessary to assess for obstructive phenomena, and surgical excision should be considered.[4,6,7]

The authors aim to raise awareness for this rare benign finding that can present a diagnostic challenge for pediatricians.

Address for Correspondance: Vilma Neto Santos Lopes, Department of Pediatrics, Unidade 1, Centro Hospitalar Vila Nova de Gaia/ Espinho R. Conceição Fernandes, s/n, 4434-502 Vila Nova de Gaia, Portugal.

Email: vilmanetolopes5@gmail.com

Figure 1. Parameatal uretheral cyst.



Compliance with ethical standards

Funding: None

Conflict of Interest: None

References:

1. 1. S L, Ankur A. Parameatal cyst: a presentation of rare case and review of literature. J Clin Diagn Res. 2013;7(8):1757-8.
2. 2. Kaselas C, Spyridakis I, Patoulias D, Tsioulas P, Patoulias I. Parameatal Urethral Cyst in a Newborn-A Case Report and Review of the Literature. J Clin Diagn Res. 2016;10(1):SD01-2.
3. 3. Tirtayasa PMW, Samuel AG, Lisnawati, Retnowulan A. Parameatal glans cyst: A case report. Urol Case Rep. 2021;39:101802.
4. 4. Shaw SC, Vinod MS, Devgan A. Parameatal urethral cyst. Med J Armed Forces India. 2018;74(1):76-7.
5. 5. Rathod S, Neema S. Parameatal Urethral Cyst. Indian Pediatr. 2022;59(10):819.
6. 6. Christensen CA, Mugarab-Samedi V. Management of large congenital parameatal cyst: Observation or intervention? (Case Report). Int J Surg Case Rep. 2020;69:58-60.
7. 7. Song SH, Kim DS. Neonate with a parameatal urethral cyst. AME Case Rep. 2019;3:16.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.29

IMAGES IN CLINICAL PRACTICE

TINEA CAPITIS- A COMMON LESION WITH AN UNUSUAL PRESENTATION

Caroline Lopes[1], Cristina Amaro[2].
[1]General Pediatric Department, Hospital de Santo André - Centro Hospitalar de Leiria, EPE, Leiria, Portugal, [2]Dermatology Department, Hospital de Egas Moniz - Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal.

KEYWORDS

Tinea capitis, kerion, Tricophyton, Tonsurans.

ARTICLE HISTORY

Received 18 July 2023

Accepted 9 September 2023

A healthy 8-year-old boy was observed in a Dermatology consultation, with a 4-week history of an erythematous patch on the scalp with alopecia measuring approximately 3 cm long axis. Scalp dermoscopy revealed broken hairs, black dots and pustules and the Wood´s lamp examination was negative. There were no local adenopathies. His past medical history was unremarkable. A recent contact with a cat was described. There was no history of fever or a recent travel.

A hair sample was obtained for mycological examination, and he was started on an eight-week course of microsized griseofulvin (15 mg/kg/day orally) and ketoconazole shampoo. Approximately ten days after initiation of therapy, there was a clinical worsening, with transformation into an exudative swelling with purulent discharge, pain and occipital adenopathies (Figure 1). Additional collection of pus for bacteriologic examination was performed. He continued treatment with griseofulvin and was started on topical betamethasone plus gentamicin ointment and clarithromycin (15 mg/kg/day orally), which he completed for seven days. Because of persistent signs of inflammation, despite the negativity of the bacteriological examination, he was switched to amoxicillin plus clavulanic acid (90 mg/kg/day orally), which he continued for another seven days. The inflammation progressively improved, with complete resolution with residual alopecia (Figure 2). Seven weeks after diagnosis, the scalp scraping mycologic examination revealed Trichophyton tonsurans.

What is the diagnosis?

Anthropophilic and zoophilic dermatophytes are the most common causes of tinea capitis, with *Trichophyton spp* and *Microsporum spp* being the most common causes, respectively.[1,2] An increasing number of cases of *Trichophyton tonsurans* have been observed in Europe.[1,2] Kerion is a rare and severe inflammatory form of tinea capitis resulting from an intense immune response to dermatophytes, characterized by tender,

Address for Correspondance: Caroline Lopes, Hospital de Santo André, R. de Santo André, 2410-197 Leiria.

Email: reislopescaroline@hotmail.com

Figure 1. Subcutaneous nodule with purulent discharge.

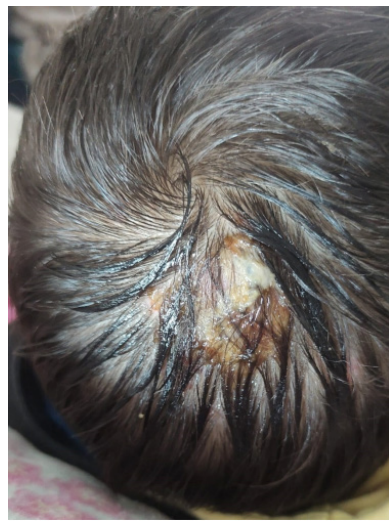
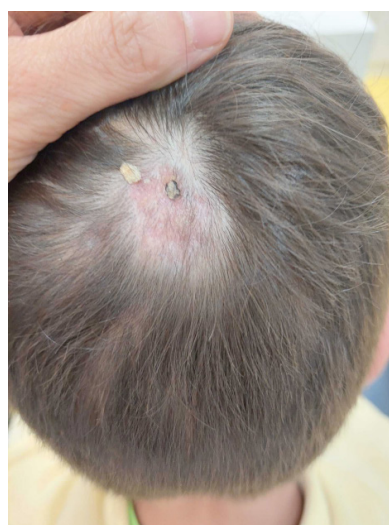


Figure 2. Progressive resolution of the lesion with residual alopecia.



erythematous, purulent swelling with associated alopecia and regional lymphadenopathy.[2,3,4] *Trichophyton tonsurans*, an anthropophilic endothrix dermatophyte, is most commonly found in asymptomatic carriers and causes non-inflammatory tinea capitis, whereas inflammatory tinea capitis usually results from Microsporum canis infection, although one published study described nearly 30% of cases of kerion in patients infected with *Trichophyton tonsurans*.[5] To avoid inappropriate treatment and alopecia, the local fungal epidemiology should be known.[1,2,4] Our patient lived in the Lisbon metropolitan area, where *Microsporum audouinii* and *Trichophyton soudanense* are the main causes of tinea capitis, with *Trichophyton tonsurans* being present in almost 10% of the cases described.[6] Based on the epidemiology, history, and physical examination we decided to treat with griseofulvin, which is a first-line therapy for tinea capitis. Although terbinafine has been reported to be more effective against *Trichophyton tonsurans*, the authors decided to keep griseofulvin considering the adequate clinical response to this therapeutic option.[5,7] The use of corticosteroids remains controversial, but some authors recommend it to minimize the risk of scarring alopecia and to minimize the dermatophyte response.[8] Concomitant topical therapies such as shampoos or fungicidal creams or lotions may help to remove scales and spores.[1]

Conclusion

Tonsurans infection must be considered in the inflammatory course of tinea. Kerion can be misdiagnosed as a bacterial abscess, leading to unnecessary antibiotic or surgical intervention.

Compliance with ethical standards

Funding: None

Conflict of Interest: None

References:

1. Lapergola G, Breda L, Chiesa PL, et al. Kerion celsi caused by Trichophyton tonsurans in a child. Lancet Infect Dis. 2018;18(7):812.
2. Tonin B, Geat D, Girolomoni G. A case of kerion celsi caused by Trichophyton tonsurans. Pediatrics International. 2020;62(8):1007-1008.
3. Yasuda-Sekiguchi F, Kamata A, Hosokawa R, et al. A Case of Kerion Celsi Caused by Trichophyton Tonsurans, a Plate Culture of Which Showed Yellow-Green Fluorescence Under UVA Light.; 2022.
4. Grijsen ML, de Vries HJC. Kerion. CMAJ . 2017;189:E725.
5. Dascalu J, Zaaroura H, Renert-Yuval Y, et al. Pediatric Tinea Capitis: A Retrospective Cohort Study from 2010 to 2021. Journal of Fungi. 2023;9(3):366.
6. Rato M, Costin A, Furtado C, et al. Epidemiologia das infeções fúngicas superficiais em Portugal - revisão de 3 anos (2014-2016). Journal of the Portuguese Society of Dermatology and Venereology. 2018;76(3):269-278.
7. Chen X, Jiang X, Yang M, et al. Systemic antifungal therapy for tinea capitis in children. Cochrane Database of Systematic Reviews. 2016;2016(5).
8. Gómez-Moyano E, Fernández-Sánchez AM, Crespo-Erchiga V, et al. Kerion Celsi caused by Trichophyton tonsurans with dermatophytid reaction. Rev Iberoam Micol. 2021;38(3):151-152

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.22

IMAGES IN CLINICAL PRACTICE

IT LOOKS LIKE A SCRATCH ON THE TOENAIL

Jacinta Mendes, Nuno Vilas Boas, Sara Diogo Santos.
Department of Pediatrics, Centro Hospitalar do Oeste - Caldas da Rainha, Caldas da Rainha, Portugal.

KEYWORDS

children, longitudinal melanonychia, melanonychia striata, nail pigmentation.

ARTICLE HISTORY

Received 13 June 2024

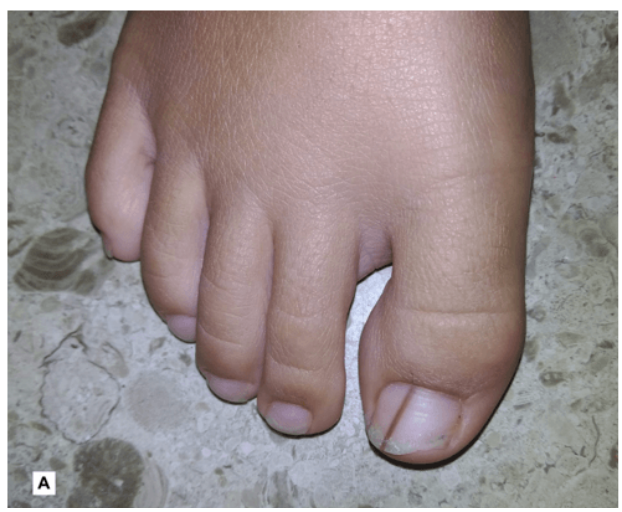
Accepted 30 October 2024

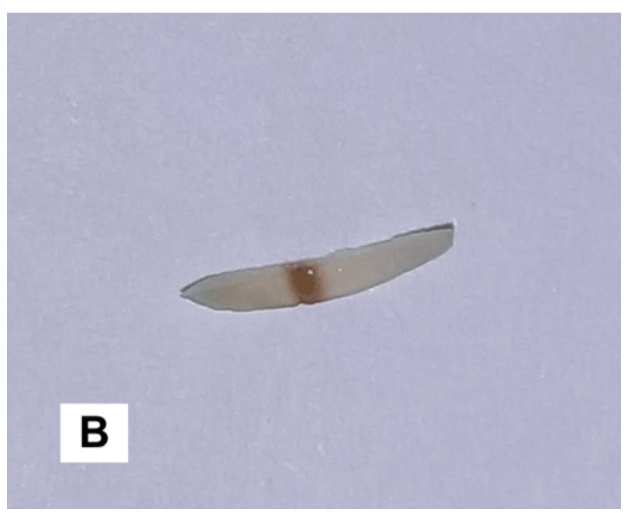
A 6-year-old caucasian boy presented to a Pediatric appointment with a longitudinal and linear brown pigmentation in his right hallux fingernail (Figure 1A). The nail alteration extends from eponiquium to the free edge of the nail plate (Figure 1B). This asymptomatic alteration appeared about ten months before and had not changed in thickness, texture, or pigment intensity. There were no other alterations on physical examination including in the remaining nails. The boy had a history of short stature due to growth hormone deficiency and was under growth hormone therapy since the age of four years. No prior nevus at the affected nail was observed. The child had no history of trauma, irradiation, drugs, or other causes of melanocytic activation. There was no personal or family history of melanoma.

What is the most likely diagnosis?

Longitudinal melanonychia also designated melanonychia striata is a melanin-derived brown or black pigmentation along the nail[1,3] The pigmented streak is caused by a melanin deposition that runs from the proximal nail fold to the distal part of the nail plate.[2,7,9] It looks like a dark band within the nail plate from the proximal boarder up to the distal margin. Longitudinal melanonychia can affect a single nail, as in the clinical case presented, or multiple nails which is less frequent.[2] This alteration is often located on a fingernail, and the thumb is the most common site of occurrence.[3,6,7,8,10] On feet generally, as it is more prone to trauma, the hallux is more frequently affected than the other toes.[7] But it can occur regardless of the existence of trauma, as seen in the clinical case presented. In general, longitudinal melanonychia result from an increased activity of melanocytes in the nail matrix, with subsequent increased synthesis of melanin in the nail matrix, and deposition in the nail plate.[2,7] Causes of longitudinal melanonychia are related to melanocytic activation and include ethnic melanonychia in dark-skinned individuals, pregnancy, chronic local trauma, infections, graft-vs-host disease, hemochromatosis, porphyria, alkaptonuria, Peutz-Jeghers and Laugier-Hunziker syndromes, dermatological disorders, endocrine disorders and certain medications.[6,7] Longitudinal melanonychia can also result from melanocytic hyperplasia, which seems to be more frequent in children due to a melanocytic nevus or lentigo affecting the nail matrix.[4,7,10] In the pediatric population a study of 40 cases showed that benign melanocytic hyperplasia (lentigo or nevus) was the cause of 77.5% of cases of longitudinal melanonychia

Figure 1. (A) Rigth hallux fingernail of a 6-year-old boy with longitudinal nail pigmentation. (B) Fragment of the free edge of the nail plate with a linear pigment deposition.





Address for Correspondance: Jacinta Mendes, Serviço de Pediatria, Centro Hospitalar do Oeste, Rua Diário de Notícias, 2500-176 Caldas da Rainha, Portugal.

Email: jacintamendes@gmail.com

and of 85% of cases in the subset of white patients.[4]

The differential diagnosis includes exogenous discoloration, splinter hemorrhages, longitudinal erythronychia, subungual hematoma, fungal melanonychia, onychomatricoma, transverse orange-brown chromonychia, atypical melanocytic hyperplasia, and melanoma of the nail matrix.[3,6,7] The prevalence of longitudinal melanonychia varies significantly, ranging from 1.4% in fair-skinned populations, where it is rare, to 77% in dark-skinned populations.[1] No differences in sex incidence had been reported.[10] This case is atypical because this condition is rare in caucasian individuals and even more in children.[6,7] So in children diagnosis and management criteria of longitudinal melanonychia are even more poorly defined.[10]

The diagnosis is mainly clinical and usually done by a dermatologist.[7] In the absence of concerning clinical features such as a pigment band wider than 3 mm, rapid growth, increasing darkening of the lesion, pigment variegation, periungual pigmentation (Hutchinson sign), nail plate dystrophy, or a family history of melanoma or dysplastic nevus-biopsy and histopathologic examination should be avoided to prevent the risk of permanent nail dystrophy.[1,3,5,7] For this reason, pediatricians should be familiar with this diagnosis and aware of the importance of referring for evaluation by a dermatologist. In most cases, longitudinal melanonychia is a benign condition, particularly in children, and subungual melanoma is exceptionally rare in this age group.[1,2,4] In a study involving 40 children with melanonychia, no malignant lesions were detected upon histologic examination.[4] Because of its typically indolent and non-aggressive clinical course, nearly all cases can be managed conservatively. Most researchers recommend a watchful waiting approach, as was the case in our situation, which continues to be monitored clinically.[1,3,4,7,8]

Spontaneous regression of longitudinal melanonychia, despite having been described, is rare and unique to children.[2,8,10]

Extended follow-up is recommended once melanoma of the nail apparatus, in adults with a previous history of longitudinal melanonychia beginning in childhood, has been reported.[1,3,4,7,10]

Compliance with ethical standards
Funding: None
Conflict of Interest: None

References:

1. Burleigh A, Lam JM. Pediatric longitudinal melanonychia. CMAJ. 2017; 189:e1093. Doi: 10.1503/cmaj.170256
2. Chu DH, Rubin AI. Diagnosis and management of nail disorders in children. Pediatr Clin North Am. 2014;61(2): 293-308. Doi: 10.1016/j.pcl.2013.11.005
3. Cooper C, Arva NC, Lee C, Yélamos O, Obregon R, Sholl LM, Wagner A, et al. A clinical, histopathologic, and outcome study of melanonychia striata in childhood. J Am Acad Dermatol. 2015;72(5):773-9. doi: 10.1016/j.jaad.2015.01.010
4. Goettmann-Bonvallot S, André J, Belaich S. Longitudinal melanonychia in children: A clinical and histopathologic study of 40 cases. J Am Acad Dermatol. 1999; 41(1):17-22. Doi: 10.1016/s0190-9622(99)70399-3.
5. Gomes S, Lencastre A, Lopes MJP. Alterações ungueais em Pediatria. Nascer e Crescer 2012; 21(1):19-24.
6. Guerrero-Fernández J, García-Ascaso MT, Guerrero Vázquez J. Pigmentación en banda en uña del pie. An Pediatr (Barc) 2004; 61(5):455-6. Doi: 10.1016/S1695-4033(04)78431-3
7. Leung AKC, Lam JM, Leong KF, Sergi CM. Melanonychia striata: clarifying behind the Black Curtain. A review on clinical evaluation and management of the 21st century. Int J Dermatol. 2019; 58(11):1239-1245. Doi: 10.1111/ijd.14464
8. Matsui Y, Sasaki J,Sumiko Takatsuka S, Tatsuya Takenouchi T. Natural course of pediatric longitudinal melanonychia: A retrospective cohort study in Japan. J Am Acad Dermatol 2021; S0190-9622(21):00644-7. Doi:10.1016/j.jaad.2021.03.082
9. Richert B, André J. Nail disorders in children: Diagnosis and management. Am J Clin Dermatol. 2011;12(2):101-12. Doi: 10.2165/11537110-000000000-00000.
10. Starace M, Piraccini BM, Brandi N, Alessandrini A. When the nail appearance plays tricks: a case of longitudinal melanonychia. EMJ 2018; 3(1):106-110.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.22

IMAGES IN CLINICAL PRACTICE

ISOLATED CUTIS MARMORATA TELANGIECTATICA CONGENITA

Joana Victor Lage, Rita Ribeiro Martins, Beatriz Henriques, André Salvada, Teresa Ferreira.
Department of Child and Youth, Hospital Professor Doutor Fernando Fonseca, Lisbon, Portugal.

KEYWORDS

cutis marmorata telangiectatica congenita, CMTC, vascular malformation, newborn.

ARTICLE HISTORY

Received 04 October 2024

Accepted 30 October 2024

A 24-day-old female newborn presented to the pediatric emergency department due to erythematous-violaceous cutaneous lesions in both inferior limbs that did not resolve with local warming. The patient was born full-term at 40 weeks and 4 days, with an APGAR score of 10 at both 1st and 5th minutes and a birth weight of 3145 grams. The patient's parents were unrelated and there were no significant prenatal ou perinatal complications. On physical examination, the infant was hemodynamically stable and well-appearing. The distinct net-like vascular pattern was observed solely on the inferior limbs. The remaining systemic examination was unremarkable. Laboratory investigation, including coagulation profile and platelet count were within normal range. Imaging via transfontanellar ultrasound and ophthalmologic evaluation showed no abnormalities. She maintained regular pediatric follow-up and over the first two years, the cutaneous lesions gradually began to fade.

What is the diagnosis?

Cutis marmorata telangiectatica congenita (CMTC) is a rare, sporadic congenital vascular disorder of unknown etiology characterized by persistent erythematous-to-violaceous, reticulated, net-like or marbled skin lesions and occasionally ulcers.[1] CMTC is usually present at birth however, there are some cases reported in the literature of delayed onset, with skin changes developing after three months. The lesions can be either localized or generalized, with the localized variant more prevalent and affecting approximately 60% of children. The most commonly affected areas are the lower limbs, although it can also occur on other regions, such as upper limbs, torso and, less frequently, on the face and scalp.[2] CMTC remains primarily a clinical diagnosis. Kienast et al. proposed diagnostic criteria that require three major and two minor criteria. The major criteria include congenital marmorated erythema, absence of venectasia by one year of age and lack of response to local warming. Minor criteria include fading of erythema within two years, telangiectasia in the affected area, port-wine stains outside the CMTC area, ulcerations and cutaneous atrophy. However, these criteria have not been validated and histopathological findings in skin biopsies are often nonspecific and inconsistent.[3,4] Although CMTC is often regarded as a benign condition, it can be associated with other anomalies such as limb asymmetry, skeletal anomalies, central nervous system involvement and congenital glaucoma. Individuals with isolated CMTC have no other syndromic features. When suspected, it is essential to conduct a thorough evaluation for associated anomalies, ideally involving a multidisciplinary

Figure 1. Erythematous-violaceous net-like vascular lesions on the right inferior limb.

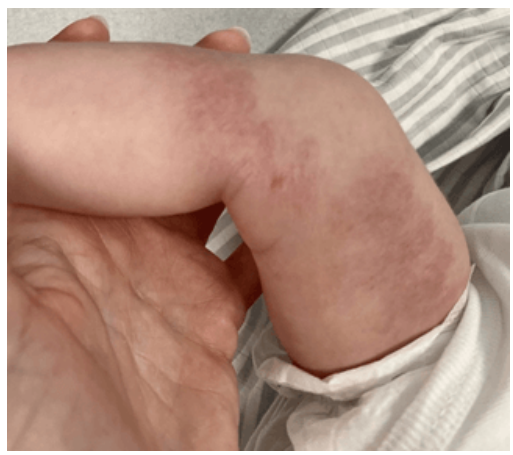
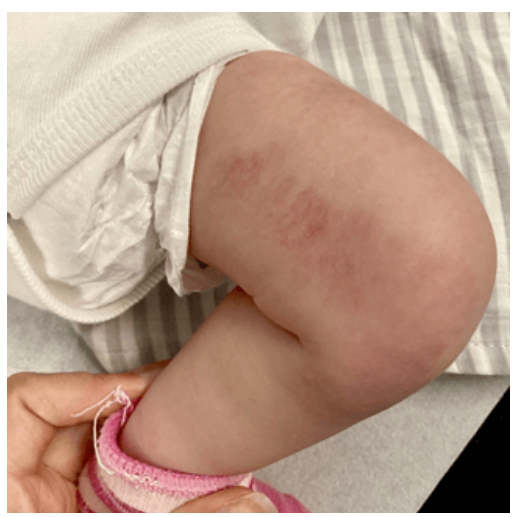


Figure 2. Erythematous-violaceous net-like vascular lesions on the left inferior limb.



Address for Correspondance: Joana Victor Lage, Avenida do Rio de Janeiro 29, 1º direito, 1700-331, Lisboa.

Email: jvclage@gmail.com

team that includes a pediatrician, dermatologist, ophthalmologist and eventually an orthopedic surgeon.[5] CMTC usually does not require any treatment. Typically, the reticular vascular skin pattern improves during the first two years, although complete resolution is rare. Various treatments have been reported including vasodilators, aspirin, pentoxifylline and psoralen plus ultraviolet-A radiation (PUVA), but their efficacy has shown considerable variability. Prognosis is generally good with the majority of patients experiencing improvement of skin lesions.[6]

Compliance with ethical standards

Funding: None

Conflict of Interest: None

References:

1. Matic A, Prcic S, Matic M, Filipovic GV, Ristivojevic A. Cutis marmorata telangiectatica congenita in a preterm newborn - case report and literature review. Iran Red Crescent Med J. 2012;14(9): 578-583.
2. González JB, Martín MMS, Casaño AV. Cutis marmorata telangiectática congenita. Review of 33 cases. An Pediatr. 2008;69(6):557-64.
3. Bui TNPT, Corap A, Bygum A. Cutis marmorata telangiectatica congenita: a literature review. Orphanet J Rare Dis. 2019;14:283.
4. Kienast AK, Hoeger PH. Cutis marmorata telangiectatica congenita: a prospective study of 27 cases and review of the literature with proposal of diagnostic criteria. Clin Exp Dermatol. 2009;34(3):319-23.
5. Moreno-Alfonso JC, Caballero AM, Martínez AP. Infrequent associations of cutis marmorata telangiectatica congenita: a two-case report. Cir Pediatr. 2024;37(1):33-36.
6. Maio C, Pomero G, Delogu A, Briatore E, Bertero M, Gancia P. Cutis marmorata telangiectatica congenita in a preterm female newborn: case report and review of the literatrure. Ped Med Chir. 2014;36:161-166.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.33

IMAGES IN CLINICAL PRACTICE

CUTANEOUS LARVA MIGRANS - AN IMPORTED TROPICAL DISEASE

Rita Ribeiro Martins, Catarina Ferreira Nunes, Francisca Costa, Paula Correia.
Department of Pediatrics, Prof. Dr. Fernando Fonseca Hospital, Amadora, Portugal.

KEYWORDS

Cutaneous larva migrans, Helminth infections, Tropical disease.

ARTICLE HISTORY

Received 08 October 2024

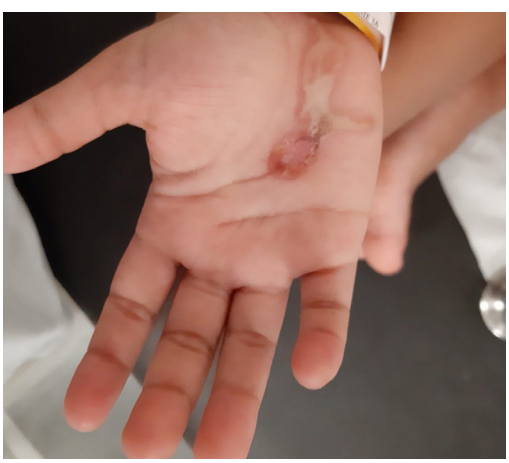
Accepted 30 October 2024

A healthy 4-year-old girl came to the Emergency Department with a 1-week history of an itchy and painful skin rash on the palm of her right hand. Initially, the rash was vesicular and associated with a fever that started 48 hours before. Epidemiological context was relevant for a recent 2 month-visit to Guinea-Bissau, where she had contact with sandy areas. Upon observation, she presented an erythematous, painful lesion, approximately 1 cm wide and 2 cm long, on the palm of her right hand, adjacent to a lesion with whitish relief and a serpentine shape, measuring about 4 cm in length (Figure 1). Blood tests revealed an increase in C-reactive protein (3.72 mg/dL), a normal leukogram (no eosinophilia), negative blood culture, and negative anti-Toxocara spp-Larva Migrans Visceral antibody. The girl was prescribed flucloxacillin and oral antihistamine, and her condition was closely monitored. In the following days, the lesion acquired a migratory nature and increased in size (Figure 2).

What is the diagnosis?

Based on these clinical findings, a diagnosis of cutaneous larva migrans was made. The girl completed a therapeutic cycle of three doses of albendazole and showed complete remission after 15 days (Figure 3). Additionally, a parasitological examination was carried out in the feces, in order to exclude other parasites.

Figure 1. Initial observation of the hand lesion.



Address for Correspondance: Rita Ribeiro Martins, Hospital Prof. Doutor Fernando Fonseca E.P.E., IC 19, 2720-276 Amadora, Portugal.

Email: rita.r.martins@hff.min-saude.pt

Figure 2. The second observation of the hand lesion (one week later).

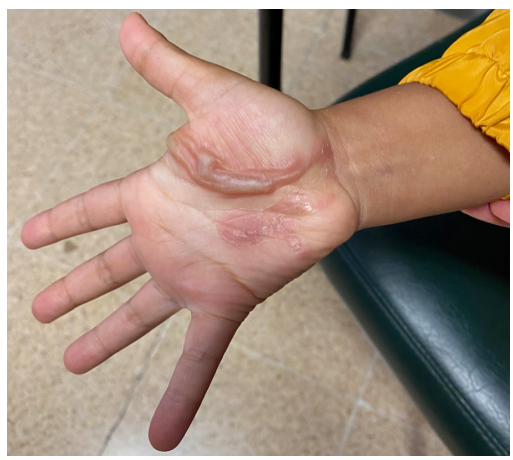
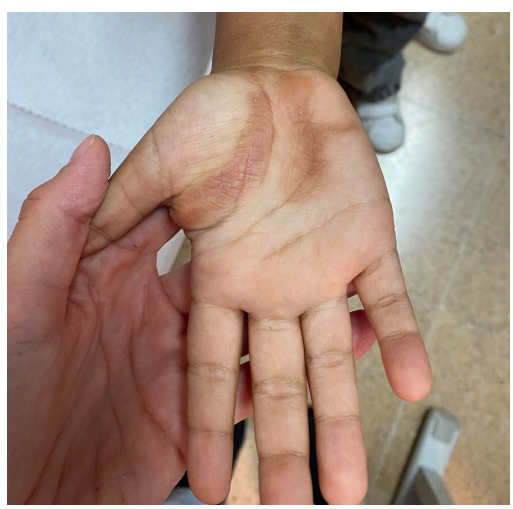


Figure 3. Complete remission after three doses of albendazole.



Cutaneous larva migrans is one of the most frequent helminth infections in travelers returning from tropical or subtropical countries after contact with infested soils.[1] The diagnosis is primarily clinical, based on the observation of a pruritic and migratory lesion on the skin.[2] Although the condition is usually self-limited, treatment helps to reduce the duration of symptoms.[3]

This case highlights the importance of taking a comprehensive clinical history, including recent travel history and exposure to contaminated soils, as well as a close follow-up.

Compliance with ethical standards
Funding: None
Conflict of Interest: None

References:

1. Leung AKC, Barankin B, Hon KLE. Cutaneous Larva Migrans. Recent Pat Inflamm Allergy Drug Discov. 2017;11(1):2-11.
2. Prashanth SN, Kumar KJ, Kumar MGA. Cutaneous larva migrans in a child. Sudanese Journal of Paediatrics. 2017;17(1):66-67
3. Villagrasa-Boli P, Martínez-Cisneros S, Monte-Serrano J. Larva cutánea migrans en viajero. Atencion Primaria. 2022 Jul; 54(7):102287. Spanish.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.63

CASE REPORTS

WHAT LIES BENEATH - CHILD POISONING

Catarina Ferreira Nunes, Andreia Filipa Mota, Catarina Luís, Helena Almeida.

Pediatrics Department in Hospital Professor Doutor Fernando Fonseca, Lisbon, Portugal.

ABSTRACT

A 3-year-old child, diagnosed with chickenpox 24 hours before, was admitted to the emergency room due to drowsiness and generalized hypertonia that had evolved for hours. Upon observation, he was drowsy, feverish, with hypertonia of the upper limbs. Due to suspicion of encephalitis, he underwent analytical evaluation, investigation of toxic substances, cranioencephalic CT scan and lumbar puncture, which showed no alterations. The EEG documented scanty bilateral temporo-occipital epileptiform activity. Empiric therapy with acyclovir was started. A few hours after admission, toxiphilic habits were found in the cohabitants, namely cocaine in the form of crack, and the parent's usual therapy with aripiprazole and trazodone, so biological samples were collected. The patient was asymptomatic 72h later. Repeated EEG in the post-critical phase and cranioencephalic MRI that did not document alterations. Later, the presence of high doses of cocaine and metabolites of aripiprazole and trazodone was confirmed.

ARTICLE HISTORY

Received 30 January 2024

Accepted 26 February 2024

KEYWORDS

cocaine, antipsychotics, trazodone, poisoning, child

Case Report

A previously healthy 3-year old boy, the second of a phratry of three, was brought to the emergency department due to drowsiness and generalized hypertonia evolving in the last few hours. Chickenpox was diagnosed the previous day in the emergency department. Accute medical history was otherwise unremarkable, namely fever, toxic exposure or family members with similar symptoms. He had previously been admitted to the paediatric department, whe he was 2-years old, due to self-limited somnolence and ataxia lasting 48 hours, concomitantly with his 6-year-old sister.

Upon admission, he was feverish (auricular temperature 103ºF), somnolent (Glasgow Coma Scale of 11, responsive only to verbal commands and with inappropriate speech). He presented with generalized body stiffness, with cephalic rotation to the left. Cranial computerized tomography scan and lumbar puncture were normal, and blood analysis showed an increase in creatinine [Cr] (Cr 1,07 mg/dl, Glomerular Filtration Rate [GFR] 52 mL/min/1,73m^2). The toxicology report of the urine sample came back negative for opioids, cannabinoids and cocaine and the blood sample came back negative for benzodiazepines and tricyclic antidepressants.

Albeith the normal liquor results, encephalitis was assumed and the child was admitted and medicated with empiric acyclovir and intravenous fluid therapy.

He remained in anuria for the first 12 hours, but kidney function improved gradually and normalized in 72 hours (Cr 0,7 mg/dL GFR 80 mL/min/1,73m^2). Neurological alterations subsisted less than 24-hours and he was afebrile 48 hours later.

Address for Correspondance:
Catarina Ferreira Nunes, Largo Miguel José Mendes, no 10, cave esquerda, Lisboa, 1500, Portugal.
Email: andrecostaesilva1@gmail.com

During this period further investigation was performed: a Cranial Magnetic Resonance Imaging that showed no alterations; and an Electroencephalogram (EEG), carried out 24 hours after the beginning of the neurological symptoms, that showed bilateral temporo-occipital epileptiform activity, non suggestive of encephalitis. After clinical resolution, another EEG was performed, and it showed no alterations. The urinary ionogram was unaltered. Blood and cephalorachidian liquid microbiology exams came back negative. IgG titers for varicella zoster virus were similar in cephalorachidian liquid and serum, but IgM titers were elevated in serum, excluding intrathecal synthesis. Protein chain reaction for herpes simplex virus 1 and 2, cytomegalovirus, Epstein-Barr virus, varicella zoster virus and human herpesvirus 6 was negative. He completed five days of acyclovir, until encephalitis was excluded.

Around the first 12 hours after he had been admitted, the medical team discovered that the mother used crack cocaine and that she was treated with trazodone and aripiprazole for severe depression. Despite our negative toxicological results, we sent new blood and urine samples, collected at admission, to the National Institute of Forensic Medicine and Forensic Sciences (NIFMFS) for deeper analysis. Weeks later, when the results came back, they were positive for cocaine, aripiprazole, trazodone and m-Chlorophenylpiperazine (mCPP), a trazodone's metabolite.

Due to the inherent risk (cocaine and drugs were within the reach of children or purposely administered to the child), Hospital Support Center for Children and Adolescents at Risk was engaged in order to keep the child and his siblings safe, and the situation was reported to the police investigation department.

Discussion

This case report illustrates a rare case of concomitant intoxication with cocaine, trazodone and an antipsychotic, aripiprazole. There are few reports of

seizures and lethargy in cocaine intoxications in children under 10 years old, although cocaine is associated with excitatory behavior.[2] We believe that the clinical presentation resulted in different side-effects of the drugs: generalized stiffness and the posture of the neck and the head rotation was an extrapyramidal effect of the aripiprazol, whilst the drowsiness was most likely related to the cocaine poisoning[3,4,5] because trazodone in high concentrations loses its sleep-inducing capacity. The acute renal failure was probably caused by dehydration (prerenal etiology) along with direct damage to the kidney (renal etiology).

Drug exposure and accidental ingestion is common in paediatrics, and are a common cause of acute neurological symptoms. In fact, it was one of the primary causes addressed in the emergency department, and a toxic screening was ordered.[1] Although negative, a high index of suspicion remained, strengthened by the previous history of self-limited neurological symptoms, the rapid recovery in less than 24 hours, and by discovery of the maternal toxic habits. Blood and urine were send to NIFMFS, and the intoxication with multiple drugs was proved.

Compared to the forensic tests conducted in the NIFMFS, hospital test have a lower sensitivity, so if there is a high suspicion level, the tests should be done in a more specific laboratory to guarantee reliable results.

Another important aspect to take under consideration is that children accidental poisoning is usually underdiagnosed by parents/caregivers. Toxic aetiology should not the disregarded, and early collection of the appropriate samples is paramount. Family education to prevent reoccurrence is advised. If suspected negligence or intentional poisoning, rapid referral to social services and the police investigation department is mandatory.

Compliance with Ethical Standards
Funding : None
Conflict of Interest : None

References:

1. Lee J, Fan NC, Yao TC, Hsia SH, Lee EP, Huang JL, Wu HP. Clinical spectrum of acute poisoning in children admitted to the pediatric emergency department. Pediatr Neonatol. 2019 Feb;60(1):59-67. doi: 10.1016/j.pedneo.2018.04.001. Epub 2018 Apr 19. PMID: 29748113.
2. de Knegt VE, Breindahl T, Harboe KM, Møller GL, Børresen ML. Gamma-hydroxybutyrate and cocaine intoxication in a Danish child. Clin Case Rep. 2016 Jan 11;4(3):228-31. doi: 10.1002/ccr3.492. PMID: 27014439; PMCID: PMC4771861.
3. Garland JS, Smith DS, Rice TB, Siker D. Accidental cocaine intoxication in a nine-month-old infant: presentation and treatment. Pediatr Emerg Care. 1989 Dec;5(4):245-7. doi: 10.1097/00006565-198912000-00013. PMID: 2602201.
4. Ernst AA, Sanders WM. Unexpected cocaine intoxication presenting as seizures in children. Ann Emerg Med. 1989 Jul;18(7):774-7. doi: 10.1016/s0196-0644(89)80017-4. PMID: 2735598.
5. Mott SH, Packer RJ, Soldin SJ. Neurologic manifestations of cocaine exposure in childhood. Pediatrics. 1994 Apr;93(4):557-60. PMID: 8134208.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.5

CASE REPORTS

MULTI SYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MISC) - AN INCIDENTAL FINDING

Abdul Qadeer[1], Khatidja Ally[1], Hira Waseem[1], Hina Rajani[1], Ashar Masood Khan[2].

[1]National institute of child health, Karachi, Pakistan,

[2]Dr Ziauddin University hospital, Karachi, Pakistan.

ABSTRACT

SARS-Cov-2, commonly known as severe acute respiratory syndrome, is primarily asymptomatic or mild in severity in children, as documented by the COVID-19 spread.1 A unique problem during this worldwide outbreak has been the emergence of "multi-system inflammatory syndrome in children (MIS-C), a rare post-infectious hyper-inflammatory disorder associated with SARS-CoV-2". The patient can present with characteristics such as signs of congestive heart failure, pyrexia, hypotension, and inflammatory conditions. Additionally, this illness has features similar to toxic shock syndrome (TSS), macrophage activation syndrome (MAS), and Kawasaki disease (KD). The purpose of this report is outlining the presenting characteristics, suspected immunopathogenesis, treatment, and prognosis of MIS-C patients.

ARTICLE HISTORY

Received 12 November 2023

Accepted 26 February 2024

KEYWORDS

Introduction

The official term for the SARS-CoV2-caused illness is COVID-19 (Coronavirus disease of 2019). City of wuhan, china was supposidely the center of spread of the disease from were the first case emerged by the end of 2019 and soon after the pandemic started to pose a threat to the entire planet. It has affected around 49 million individuals and more than a million people have died from it, becoming a global health burden and leaving some rare but debilitating consequences on the health of affected individuals.[2] There have been numerous reports in which patients suffering from COVID-19 have developed complications like thromboembolism, including coagulopathy in several organs such as the brain, lungs, spleen, legs and heart. Severe form of this diseases leads to complications like multi organ failure and significant fatality rates. According to available clinical data," Pulmonary embolism (PE) and deep vein thrombosis (DVT) are the most frequently observed thrombotic events in COVID-19". Despite receiving anticoagulation prophylaxis, the probability of developing venous thromboembolism (VTE) is still significant among hospitalized patients.[3]

Case Report

Clinical Presentation:

A 7 year old male child was admitted at the National Institute of Child Health with a complaint of jaundice for 6 days. The child had a fever 10 days back which subsided after 4 days. After that, the parents noted yellowish discoloration of sclera. There was no history of melena, concentrated urine, abdominal distension, pain, vomiting, hematemesis, skin rash, itching, conjunctival hyperemia, or respiratory distress. The family drank tap water and had a poor hygienic lifestyle.

The child has an history of Ventricular septal defect (VSD), Atrial septal defect (ASD), Dextro-Transposition of the Great Arteries (d-TGA) and Severe Pulmonary Stenosis. Significant procedures like Blalock-Taussig (BT) Shunt and Glen shunt were done in 2018 and 2021 respectively.

On presentation, the child was thin and lean with an icterus. The child weighed 16 kg (25^{the} centiles) with a heart rate of 88 beats/min and respiratory rate of 28/min. BP readings were <50^{the} centile while clubbing was grading 3 positive.

On pericardium examination, S1 and S2 heart sounds were audible with holosystolic murmur at the left lower sternal border. On chest examination, 2 scar marks were seen extending from the sternal angle to the xiphoid space process and at the 6th intercostal space from the midclavicular line to the posterior axillary line.

On abdominal palpation, the liver was palpable 5 cm BRCM with a liver span of 16 cm, smooth surface, and regular margins. No splenomegaly was appreciated.

Investigation:

On lab investigation, CBC showed a total leukocyte count of 8900/cm with neutrophils at 60% and lymphocytes at 32%. Reticulocyte counts 3.70, increased total bilirubin of 10.7 with direct bilirubin of 5.3 and SGPT 86.

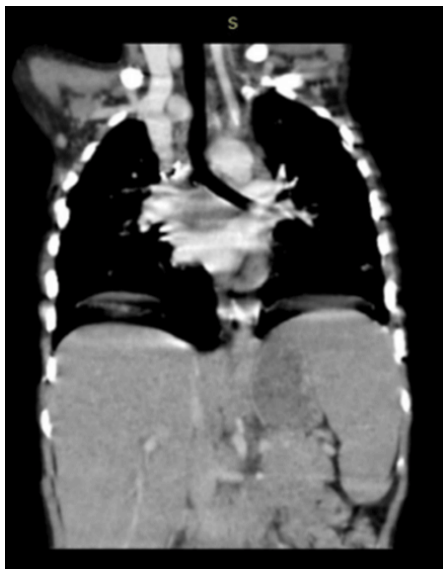
To investigate further the possible cause of hepatitis in this patient, a serological test for viral hepatitis and a test to evaluate possible autoimmune hepatitis were performed. The child showed a positive IgM for hepatitis A while the rest of the tests were negative. The ultrasound of the abdomen was done to look for liver echotexture, which was normal but, the heterogeneous pancreas was seen, however serum amylase and lipase were normal.

Address for Correspondance:
Ashar Masood Khan, SF2 Block 7 Seaview Apartments Dha Phase 5, Karachi - 75500, Pakistan.
Email: asharmasood65@gmail.com

CT abdomen was done which showed hepatomegaly, edematous gallbladder with clinical pericholecystic fluid resulting in periportal tracking and few prominent para-aortic lymph nodes.

An incidental finding was seen at the lower sides of the CT abdomen, revealing filling defects seen in the segmental branches located in pulmonary arteries. CT pulmonary angiography was also done which showed cardiomegaly with filling defects in segmental branches present in pulmonary arteries (Figure 1). These findings were due to pulmonary embolism.

Figure 1. HRCT showing filling defects in segmental branches of the pulmonary arteries.



Echocardiography showed non-function right SP shunt. Large VSD with BD shunt, large ASD II with BD shunt. Severe PS with dilated and hypertrophied right ventricle and normal functioning right ventricle.

Thromboembolic disorder was suspected, plasma protein C (123%) and protein S (96%). Antithrombin III (109%) was in the normal ranges.

Possibility of post COVID thromboembolism was raised and COVID antibodies, COVID PCR, samples of serum ferritin, LDH, and D-Dimer levels were sent. The patient was diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C) because of elevated blood ferritin, LDH, and D-Dimer levels, as well as positive COVID antibodies.

Management:

Initially, the Injection of Enoxaparin 1 mg/kg was given BD subcutaneously and monitored for Respiratory symptoms, the patient's LFTs were repeated and showed improvement with decreasing Total bilirubin and direct bilirubin and SGPT, and HRCT was repeated after 15 days. There was Significant interval reduction of pulmonary emboli (Figure 2).

The Patient was discharged on Tab Rivaroxaban for 6 weeks and follow-up HRCT was repeated, in which no filling defects were seen in the right and left main pulmonary arteries and right segmental branches (Figure 3).

Figure 2. Significant interval reduction of pulmonary arteries with reduction of pulmonary embolism.

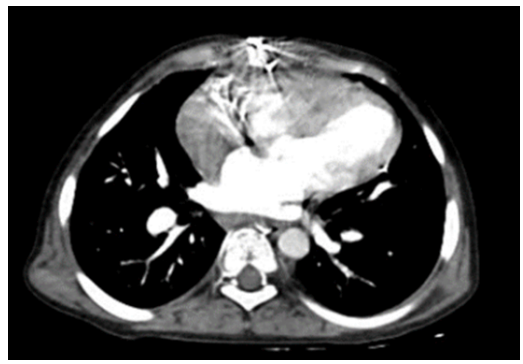
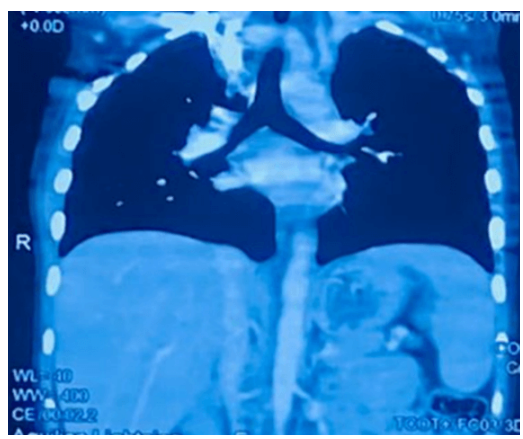


Figure 3. Previously mentioned multiple filling defects not seen in scan.



Discussion

Children with corona virus have been accounted for to be asymptomatic or with mild symptoms clinically contrasted with adults. As of late, cases of more older school-aged children and teenagers have been reported with prolonged fever, shock, pain in the abdomen, and cardiac issues after the virus that can mimic Kawasaki Disease (KD). It appears to be a hyper inflammatory illness involving several organs. The CDC (Centers for Disease Control and Prevention) has named the condition MIS-C related to corona virus and developed an example case for this disease.[4,5]

A young adult of age less than 21 years who claims to have had a fever for more than 24 hours, >38.0°C; laboratory reports suggesting inflammation, such as an elevated CRP (C-reactive protein), ESR (erythrocyte sedimentation rate), fibrinogen, procalcitonin, d-dimer, ferritin, LDH (lactic acid dehydrogenase), or IL-6 (interleukin 6); raised neutrophils, decreased lymphocytes, and reduced albumin; and proof of serious disease clinically that makes hospitalization necessary, with more than 2 organs involved, which can be one of the following: heart, kidney, lungs, blood and lymph nodes, gastrointestinal tract, skin, or brain and spinal cord; and no alternative conceivable diagnosis.[6]

The goal is to attain an anti-Xa activity level after a 4-hour dose of 0.2 to less than 0.5 U/mL. The most suitable choice in children admitted because of illness

linked with COVID-19, including MIS-C, is subcutaneous low-dose low-molecular-weight heparin given two times a day for anticoagulant thromboprophylaxis in clinically stable patients without significant kidney dysfunction and without any contraindications. Unfractionated heparin should be constantly pumped intravenously in patients with severe kidney impairment, with a target to attain anti-Xa activity levels between 0.1 and less than 0.35 U/ml.[7,8]

Platelet count of less than 20,000 to 50-000/µL, hypofibrinogenemia (such as fibrinogen activity less than 100 mg/dL by Clauss method), an event of significant bleeding, and the consumption of aspirin at a dose higher than 5 mg/kg/d are all warning signs that the patient might have a massive bleeding risk when taken with thromboprophylaxis of anticoagulation. However, in scenarios where there are no other bleeding risk variables, low-dose thromboprophylaxis anticoagulation therapy aspirin given at doses less than or equal to 5 mg/kg/d due to heart-related abnormalities or features associated with Kawasaki-like illness is not linked to any major bleeding risk in MIS-C.[7]

Conclusion

MIS-C, which is occasionally observed in the younger population, has also been noticed in patients suffering from Corona virus. Further investigation is required for the association between MIS-C and the SARS-Cov-2 infection. As knowledge and cases regarding COVID-19 in children are emerging, reporting these cases is essential to helping health care professionals identify the MISc symptoms better. This is crucial for the initiation of timely and appropriate treatment for this disease.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Nikolopoulou GB, Maltezou HC. COVID-19 in Children: Where do we Stand? Arch Med Res. 2022 Jan;53(1):1-8. doi: 10.1016/j.arcmed.2021.07.002. Epub 2021 Jul 6. PMID: 34311990; PMCID: PMC8257427.
2. Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Ann Intern Med. 2020;173(4):268-277. doi:10.7326/M20-2003.
3. Ali MAM, Spinler SA. COVID-19 and thrombosis: From bench to bedside. Trends Cardiovasc Med. 2021 Apr;31(3):143-160. doi: 10.1016/j.tcm.2020.12.004. Epub 2020 Dec 16. PMID: 33338635; PMCID: PMC7836332.
4. Yasuhara J, Kuno T, Takagi H, Sumitomo N: Clinical characteristics of COVID-19 in children: a systematic review. Pediatr Pulmonol. 2020, 55:2565-2575. 10.1002/ppul.24991.
5. https://www.cdc.gov/kawasaki/index.html
6. Radia T, Williams N, Agrawal P, Harman K, Weale J, Cook J, Gupta A. Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation. Paediatr Respir Rev. 2021 Jun;38:51-57. doi: 10.1016/j.prrv.2020.08.001. Epub 2020 Aug 11. PMID: 32891582; PMCID: PMC7417920.
7. Goldenberg NA, Sochet A, Albisetti M, et al. Consensus-based clinical recommendations and research priorities for anticoagulant thromboprophylaxis in children hospitalized for COVID-19-related illness. J Thromb Haemost. 2020;18(11):3099-3105. doi:10.1111/jth.15073.
8. Schmitz AH, Wood KE, BurghardtEL, et al. Thromboprophylaxis for children hospitalized with COVID-19 and MIS-C. Res Pract Thromb Haemost. 2022;6:e12780. doi: 10.1002/rth2.12780.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.62

CASE REPORTS

BARTONELLA HENSELAE NEURORETINITIS IN A HEALTHY TEENAGE BOY

Joana Brígida Capela[1], Inês Almeida[1], Mariana Reis[1], Erica Guerreiro[2], Carla Mendonça[3], Maria João Virtuoso[1].

[1]Pediatrics Service, Hospital de Faro, Centro Hospitalar Universitário do Algarve, Faro, Portugal,

[2]Ophtalmology Service, Hospital de Faro, Centro Hospitalar Universitário do Algarve, Faro, Portugal,

[3]Neuropediatrics and Development Center, Hospital de Faro, Centro Hospitalar Universitário do Algarve, Faro, Portugal.

ABSTRACT

Introduction: Cat Scratch Disease (CSD) is a zoonotic infectious disease, typically caused by Bartonella henselae. The disease usually has a benign course, but systemic involvement may occur. CSD is the most common cause of neuroretinitis.

Case Report: We present a case of a 16-year-old male, with a positive family history of neurodegenerative diseases, frequent contact with stray cats and four-week visual symptoms. Serologies for Bartonella henselae were positive for both IgM and IgG. The fundoscopy showed a macular star, that is typical of neuroretinitis by Bartonella henselae. He was started on corticosteroid and antibiotic treatment for six weeks, with full recover after six months.

Discussion: We report a rare case presentation, where the clinical history was essential to guide the investigation. In the face of a suspicion of severe neuroretinitis due to Bartonella henselae, early treatment should be initiated. Mild cases usually have spontaneous remission.

ARTICLE HISTORY

Received 12 January 2024

Accepted 16 February 2024

KEYWORDS

neuroretinitis, Bartonella henselae, teenager

Introduction

Cat Scratch Disease (CSD) is a zoonotic infectious disease, typically caused by *Bartonella henselae* (BH), an intracellular gram-negative bacterium.[1] Cats are the natural reservoir of these bacteria and may infect humans through scratches, bites or licks near the conjunctiva.1 Most cases occur in children and adolescents and in immunocompromised individuals.[2] The disease usually has a benign course, but systemic involvement may occur, even in immunocompetent patients.[3]

The most common presentation of CSD is a cutaneous lesion (nontender erythematous pustules or papules) at the sight of inoculation, that lasts for 3-10 days, and associated self-limited regional lymphadenopathy.[2,4] These may be combined with systemic symptoms such as fever, malaise, fatigue, anorexia, nausea, vomiting, weight loss, headache, night sweats, rash or arthralgia.[1,3] In some cases, atypical presentations, like cutaneous, hepatosplenic, cardiac, renal, pulmonary, ophthalmological, neurological, hematologic and musculoskeletal manifestations may occur, but they are rare among immunocompetent patients (5-14%).[3,5]

Neuroretinitis is characterized by unilateral optic neuropathy, with inflammation of the peripapillary retina and optic nerve, resulting from a variety of bacterial, viral, fungal, parasitic, and inflammatory etiologies.5 CSD is the most common cause of neuroretinitis, although it is rare (1-2% of the patients), and might affect immunocompetent children.[6,7]

Neuroretinitis can present with unilateral reduced visual acuity, afferent pupillary defect, visual field defect (including central scotoma) and dyschromatopsia.[2,4] Ocular symptoms manifest 2-3 weeks after the onset of systemic symptoms, although they can appear in their absence.[4] The referred pain on extraocular movements is not often described.[7] On ophthalmology examination, fundoscopy findings are usually consistent with a swollen optic nerve and a macular star.[3] Optic disc oedema decreases within two weeks, but complete resolution may take up to three months.[1] OCT shows flattening of the fovea, a thickened neurosensory retina, and subretinal fluid accumulation.[7] The differential diagnosis includes other infectious diseases, inflammatory optic neuropathies, demyelinating, autoimmune, compressive and toxic conditions (Table 1).[1,2,5,7]

Diagnosis of BH neuroretinitis includes clinical findings of young age and history of contact with cats, signs and symptoms of typical neuroretinitis (including positive fundoscopy and OCT findings), systemic symptoms and positive serology (IgG and IgM).[1] IgM positivity for BH indicates acute or very recent infection and confirms the CSD diagnosis.[1] If IgM is negative, the diagnosis is controversial, despite a positive IgG measurement.[2] IgG level of 1:64 or less suggests absent active infection, while levels of 1:256 and above confirms acute infection.[4] Nonetheless, levels between 1:64 and 1:256 suggest possible CSD, and retesting after 10-14 days is mandatory.[4] Blood culture, skin testing, lymph node biopsy and PCR are also among the

Address for Correspondance:
Joana Brígida Capela, Rua Leão Penedo, 8000-386, Faro, Portugal.
Email: joanabccapela94@gmail.com

Table 1. Differential diagnosis of acute visual loss accompanied by optic disc swelling[6]

Neurological or Ophthalmological conditions	Malignancies or systemic conditions	Infectious diseases
Optic neuritis/ neuropathy	Intracranial malignancies	Cat scratch disease
Leber hereditary optic neuropathy	Paraneoplastic disorders	Lyme disease
Intracranial hypertension	Orbital tumors	Syphilis
Optic disc drusen	Nutricional and toxic optic neuropathy	Tuberculosis
Retinal artery/ vein occlusion	Sarcoidosis	Salmollenosis
Uveitis/ chorioretinitis	Behçet disease	Leptospirosis
Diabetic papillopathy	Severe high blood pressure	Toxocariasis
		Toxoplasmosis
		Histoplasmosis
		Viral diseases (mumps, varicella, rubella, measles, Epstain-Barr, Cytomegalovirus, Herpes simplex virus and Hepatitis B virus)

confirmatory tests in patients with suspected CSD.[2] The sensitivity of a PCR test in blood is low, so a negative result does not exclude the diagnosis.[8]

The treatment of atypical presentations of CSD is controversial. While mild cases can resolve spontaneously, antibiotic therapy may prevent serious complications and shorten the duration of symptoms in severe cases.[3] Standardized treatment recommendations do not exist, so antibiotic recommendations differ for each clinical presentation.[3] Neuroretinitis is typically a self-resolving condition, although treatment should be considered for high-risk patients (like immunocompromised children), or in patients with profound vision loss.[5] The mainstay treatment normally includes steroids and antibiotic therapy, in most case reports with rifampicin in combination with doxycycline, for at least 2-6 weeks. Full recovery is usually achieved.[3,7,8]

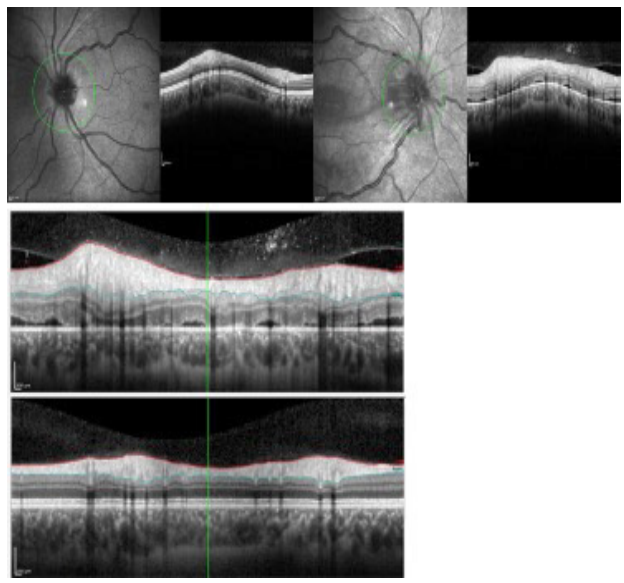
Case Report

We present a case study of a 16-year-old male with a positive family history of glaucoma and neurodegenerative diseases, who lived in a rural area and had regular contact with farm animals, dogs and stray cats. The patient came to the emergency department with a four-week visual acuity loss in the right eye (RE), accompanied by retrobulbar pain, color vision distortion and a scotoma in the center of the visual field.

A few days prior to the onset of visual changes, he had flu-like symptoms, with myalgia and arthralgia. He referred having been in occasions scratched by cats. He denied having had fever, headache, vomiting, weight loss, night sweats, cough or other neurological symptoms.

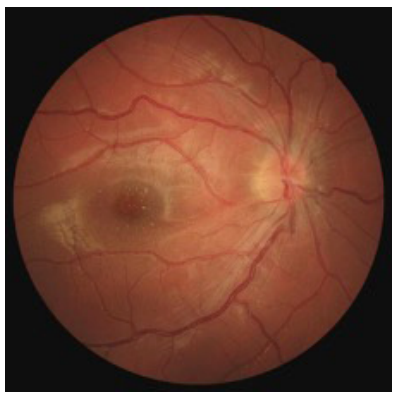
On observation, he had a visual acuity of the RE 0,3 and subnormal color vision. Fundoscopy of the RE revealed papillary oedema and optic disc engorgement. No adenopathies or skin lesions were noted and the neurologic examination was normal. The computerized optical tomography (OCT) showed optic nerve changes (Figure 1) and maculopathy of the RE (Figure 2). He was admitted for further investigation and was started on methylprednisolone 30 mg/kg/day for five days, with only slight relief of the symptoms.

Figure 1. A. Right eye OCT (on the right) and left eye OCT (on the left), on admission. Right eye OCT shows disc edema, subretinal fluid accumulation and retinal thickening. B. Right eye OCT (upper figure) and left eye OCT (down figure), on admission. Right eye OCT reveals maculopathy, with retinal thickening and subretinal fluid.



The white blood count, renal and hepatic function, C-reactive protein or sedimentation rate were unremarkable. Serologies for Bartonella henselae were positive for both IgM and IgG (IgM >32 and IgG >128). All the other serologies tested were negative (Mycoplasma pneumoniae, Cytomegalovirus (CMV), Human Immunodeficiency Virus (HIV) 1 and 2, Ebstein-

Figure 2. Fundoscopy with a macular star, characteristic of neuroretinitis by Bartonella henselae.



Barr (EBV), Borrelia burgdorferi, Herpes simplex virus (HSV) 1 and 2, Varicella zoster virus (VZV) and Treponema pallidum). Mantoux, IGRA test, anti-MOG and anti-aquaporin-4 antibodies were also negative. For the cerebrospinal fluid (CSF), the cytochemical exam was normal and polymerase chain reaction (PCR) for neurotropic agents and bacteriologic culture were negative. CSF immunoelectrophoresis revealed bands with polyclonal IgG distribution (considered normal). The magnetic resonance imaging (MRI) of the brain, orbits and spinal cord did not show any relevant changes. Clinical aspects and positive serologies for Batonella henselae motivated antibiotic treatment with doxycycline 100 mg 12/12 hours and rifampicin 300 mg 12/12 hours.

Infection with *Bartonella henselae* was confirmed in a second sample taken two weeks later, with IgM 1:512 and IgG 1:4096. The ophthalmology exam was also repeated two weeks later, and the fundoscopy showed a macular star, that is typical of neuroretinitis by *Bartonella henselae* (Figure 2). CSD with neuroretinitis was therefore confirmed, and antibiotic therapy was continued for 6 weeks.

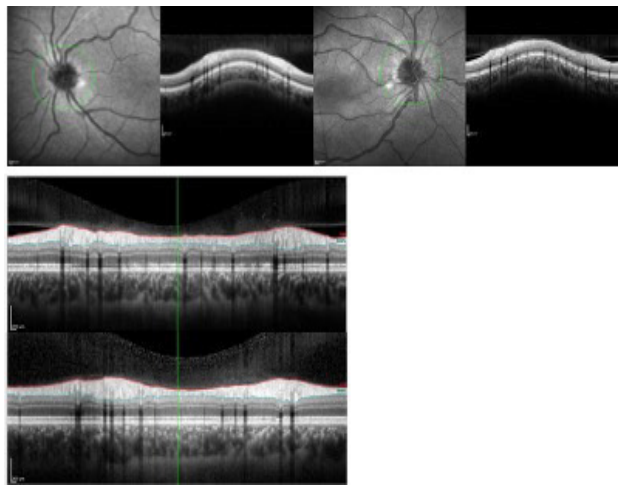
He was discharged with steroid therapy in a weaning regime. On fundoscopy, the macular star disappeared after two months and there was no papilledema or optic disc engorgement after three months. The OCT was normal after five months (Figure 3). Complete recovery of visual acuity, with normal visual field and color vision in the RE was achieved after six months.

Discussion

We report a rare case presentation, where the clinical history was essential to guide the investigation. In our case report, the boy had three of the referred manifestations for neuroretinitis and he referred flu-like symptoms a few days before visual symptoms started. The macular star may be absent early in the disease, developing within 2 weeks, as in our case report, and may last for up to one year; it is caused by leakage of lipid-rich exsudates due to increased permeability of the optic nerve capillaries.[1,2,6]

In the face of a suspicion of severe neuroretinitis due to *Bartonella henselae*, early treatment should be initiated, although there is not enough evidence that delay in starting therapy leads to incomplete remission or sequelae. Mild cases usually have spontaneous remission. In a retrospective multicenter

Figure 3. A. Right eye OCT (on the right) and left eye OCT (on the left), five months later after admission. Right eye OCT shows full recovery. B. Right eye OCT (upper figure) and left eye OCT (down figure), five months after admission. Right eye OCT shows nearly complete resolution of maculopathy.



study involving 86 patients, the outcomes appear to have been worse in the group that received antibiotic therapy alone compared to the group that received antibiotics and corticosteroids.[9] The choice of antibiotic for *Bartonella henselae* infection depends on the site of infection, with doxycycline, rifampin, azithromycin, ciprofloxacin, trimethoprim-sulfamethoxazole, and gentamicin being effective options.[10] When there is central nervous system involvement, the combination of doxycycline and rifampin appears to be the most appropriate regimen, with good results and complete recovery, and appropriate susceptibility without described resistances. However, the use of antibiotics is not universally agreed upon, as in other retrospective studies, the use of antibiotic therapy, with or without corticosteroids, did not seem to alter the prognosis.[11] Empirical treatment with doxycycline 100 mg every 12 hours (2.2 mg/kg if <45 kg) and rifampin 10 mg/kg every 12 hours appears appropriate in immunocompromised or immunocompetent patients with moderate to severe systemic disease or significant vision loss.[9] Doxycycline can be replaced with azithromycin in children under eight years of age (due to the risk of irreversible dental discoloration with prolonged doxycycline treatment), at a dose of 500 mg every 24 hours, and then 250 mg every 24 hours (if <45.5 kg, 10 mg/kg every 24 hours, and then 5 mg/kg every 24 hours), and ciprofloxacin or trimethoprim-sulfamethoxazole are options in case of allergy.[9] In the case of suspected infectious neuroretinitis without an identified cause, some authors recommend starting treatment with doxycycline and rifampin for four to six weeks, with coverage for *Bartonella henselae*, Lyme disease, Rocky Mountain spotted fever, leptospirosis, and possible benefit in syphilis, in addition to good tolerance and good penetration into the central nervous system.[9] Regarding corticosteroids, studies also do not concur on their benefit in vision recovery. Considering the morbidity associated with corticosteroids and the limited robust evidence for their use in neuroretinitis,

routine systemic corticosteroid use is not recommended. However, due to their potent anti-inflammatory effect, they may theoretically offer benefit in severe cases with vision loss, fulminant optic disc edema, or significant intraocular inflammation, in combination with antibiotic therapy over six weeks with gradual tapering.[9,11] We chose the therapy described with good results and complete resolution of the clinical condition.

Regarding the ophthalmological follow-up, although follow-up protocols for cases of neuroretinitis caused by *Bartonella henselae* have not been identified in the literature, the authors consider it relevant to have regular assessments of visual acuity, fundoscopy, and OCT every two or three weeks, to monitor the resolution of optic disc edema and macular star. Long-term considerations include monitoring visual function and early identification of any secondary complications, such as the development of corticosteroid-induced cataracts or disease recurrence every three months, until completing an 18-month period. After this period, annual ophthalmological evaluation may be recommended. Considering the family history of the teenager in question and the fact that some neurodegenerative diseases manifest with retrobulbar neuritis, it is crucial to have regular follow-up, with particular attention to acute vision changes.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Ksiaa, I. et al. Update on Bartonella neuroretinitis. J. Curr. Ophthalmol. 31, 254-261 (2019).
2. Karti, O., Ataş, F. & Saatci, A. O. Posterior Segment Manifestations of Cat-scratch Disease: A Mini-review of the Clinical and Multi-modal Imaging Features. Neuro-Ophthalmology 45, 361-371 (2021).
3. Lemos, A. P., Domingues, R., Gouveia, C., de Sousa, R. & Brito, M. J. Atypical bartonellosis in children: What do we know? J. Paediatr. Child Health 57, 653-658 (2021).
4. Conde, E., Antueno, E., Palmieri, F. & Cheistwer, A. Neurorretinitis por Bartonella henselae en un adolescente. Arch. Argent. Pediatr. 119, 616-620 (2021).
5. Nikolic, B. et al. Child Neurology: Bartonella henselae Neuroretinitis in 2 Patients. Neurology 98, 896-900 (2022).
6. Jurja, S. et al. brain sciences The Clinical Profile of Cat-Scratch Disease's Neuro-Ophthalmological Effects. (2022).
7. Sykes, D. A. W., Joseph, S. L., Williams, S. P. & Das, S. U. A 13-Year-Old Girl With Unilateral Visual Changes. 0-3 (2023) doi:10.1177/23247096221150635.
8. Alonso Montejo, M. del M. & Muñoz Vilches, M. J. Bartonella henselae neuroretinitis: a case report. Med. Clin. (Barc). 157, 199-200 (2021).
9. Fairbanks, A. M., Starr, M. R., Chen, J. J. & Bhatti, M. T. Treatment Strategies for Neuroretinitis : Current Options and Emerging Therapies. (2019) doi:10.1007/s11940-019-0579-9.
10. Raihan, A. R., Zunaina, E., Wan-Hazabbah, W. H., Adil, H. & Lakana-Kumar, T. Neuroretinitis in ocular bartonellosis: A case series. Clin. Ophthalmol. 8, 1459-1466 (2014).
11. Cirone, D., Mandarà, E., de Simone, L., Pellegrini, F. & Cimino, L. Ophthalmic manifestations of cat scratch disease. Ann. Eye Sci. 6, 0-1 (2021).

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.62

CASE REPORTS

ATYPICAL PREDOMINANCE OF VERTEBRAL FRACTURES AS THE FIRST SIGN OF COL1A2-RELATED OSTEOGENESIS IMPERFECTA

Carolina Fraga[1], Inês Aires Martins[2], Telma Barbosa[3], Célia Azevedo Soares[4,5,6,7], Anabela Bandeira[8].

[1]Pediatrics Department, Centro Materno-Infantil do Norte, Centro Hospitalar Universitário de Santo António (CMIN-CHUdSA), Porto, Portugal,

[2]Pediatrics Department, CMIN-CHUdSA, Porto, Portugal,

[3]Pediatric Pneumology Department, CMIN-CHUdSA, Porto, Portugal,

[4]Serviço de Genética Médica, Centro de Genética Médica Jacinto Magalhães, CHUdSA, Porto, Portugal,

5Unit for Multidisciplinary Research in Biomedicine, Instituto de Ciências Biomédicas Abel Salazar/ Universidade do Porto, Porto, Portugal,

[6]Departamento de Ciências Médicas, Universidade de Aveiro, Aveiro, Portugal,

[7]Institute for Investigation and Innovation in Health (i3S), University of Porto, Porto, Portugal,

[8]Reference Center for Inherited Disorders of Metabolism, CMIN-CHUdSA, Porto, PortugalFaro, Portugal.

ABSTRACT

Although fractures are common in children, vertebral fractures are exceptional and should raise the suspicion for the presence of osteoporosis. This can be primary, particularly in the presence of positive family history, or secondary to chronic illnesses, endocrine disorders or to some drugs.

We report on a 10-year-old boy with asthma controlled with prolonged inhaled corticosteroids who presented with spontaneous vertebral fractures and decreased bone density. There was positive family history for early-onset osteoporosis. A deleterious variant in gene COL1A2 was identified, diagnosing osteogenesis imperfecta. Bone Mineral Density improved with intravenous bisphosphonates with no further fractures during follow-up period.

Presentation with vertebral fractures is uncommon in COL1A2 Osteogenesis imperfecta. Since there are therapeutic options available that might enhance quality of life, further investigation for primary and secondary causes is imperative in the case of osteoporosis in children.

ARTICLE HISTORY

Received 31 October 2023

Accepted 13 February 2024

KEYWORDS

osteoporosis, spinal fracture, adolescent, pathological fracture.

Abbreviations

- BMD - bone mineral density
- BP – bisphosphonates
- DEXA – dual energy X-ray absorptiometry
- ICS – inhaled corticosteroids
- OI - Osteogenesis imperfecta

Introduction

Vertebral fractures in pediatric age are extremely rare, particularly in an otherwise healthy child. Estimated incidence for traumatic vertebral fractures in pediatric age is of 66:1,000,000, though true global incidence is unknow.[1] Genetic forms of bone fragility, such as osteogenesis imperfecta (OI), can play a role in increasing the susceptibility to vertebral fractures. OI is a connective tissue disorder primarily, with an incidence between 1:13,500 and 1:9,700, caused by deleterious variants in either *COL1A1* or *COL1A2* genes. Another form of OI, resulting from deleterious variants in the *PLS3* gene, is characterized by a predominance of vertebral fractures and follows an X-linked inheritance pattern.[2,3]

OI exhibits a wide range of phenotypic variations, including mild to severe and even lethal forms, often involving multiple systems. It is associated with significant morbidity, negatively affected life quality and decreased life expectancy.[3]

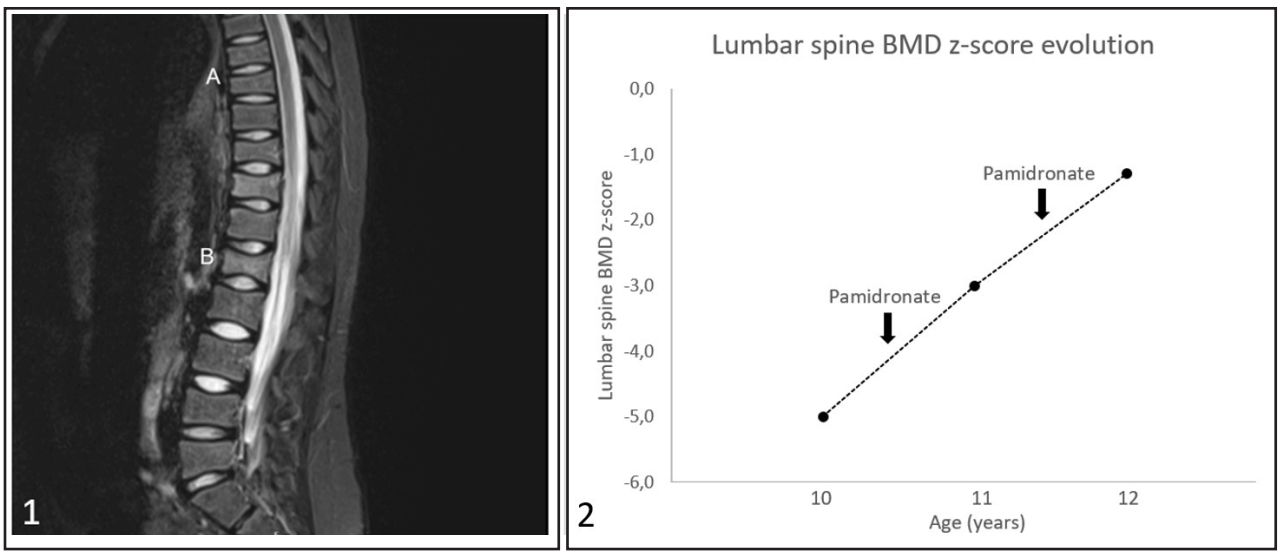
Address for Correspondance:
Carolina Fraga, Largo Prof. Abel Salazar 45, 4099-001 Porto, Portugal.
Email: carolinamoraesfraga@gmail.com

Case Report

A 10-year-old boy was referred to Inherited Metabolic Diseases Consultation due to severe spine osteoporosis. He had allergic asthma, diagnosed when he was 6 years-old, controlled with inhaled low dose corticosteroid during the fall and winter months. He practiced swimming and karate without history of fractures. Family history indicated a pattern of early onset osteoporosis: the mother was diagnosed at 36 years-old and the maternal grandmother at 40 years.

Following a weight gain as a result of sedentary lifestyle, he reported experiencing low back pain without any known trauma. X-ray revealed the presence of two vertebral fractures at the T11 and L1 levels, along with a significant decrease in bone density. Magnetic resonance imaging (MRI) confirmed the presence of the two recent fractures, showing a 40% loss of vertebral height ratio (Figure 1) and, additionally, revealed vertebral wedging in T6-T9, indicating the likely occurrence of previous fractures.

Figure 1. 1 - Spinal Magnetic Resonance: **A.** Wedging of vertebral bodies T6, T7, T8 e T9 in relation to chronic fractures. **B.** Shorting of vertebral height of L1 body in approximately 40%, in relation to recent fracture. 2 – Graph of Bone mineral density z-score evolution with pamidronate administration timings.



He denied other symptoms and the consumption of other drugs. On physical examination, discrete blue sclera was noted, dentition and muscle strength were normal and no other skeletal deformities were apparent. Height was in the 75th percentile and body mass index was 21 Kg/m^2 (95th percentile).

Bone Density Scan confirmed very low bone mineral density (0.304 g/cm^2), with Z-score of -5.0 for lumbar density (Figure 1). Secondary causes of osteoporosis were excluded through lab results. Skeletal X-ray did not document other fractures. He was started on vitamin D and calcium oral supplementation and contact sports were advised against.

Due to the notable predominance of spine fractures and the observed inheritance pattern from the matrilineal lineage, a high suspicion was raised for a genetic form of bone fragility. In order to investigate genes linked to bone fragility, a skeletal dysplasia gene panel analysis was conducted. Subsequently, a heterozygous variant, c.757G>T p. (Gly253Cys), in the *COL1A2* gene was identified. After co-segregation with the phenotype within the family, this variant was classified as likely pathogenic.

After two cycles of intravenous pamidronate, with six months interval, the Bone Density Scan improved to a density (0.566 g/cm^2), with Z-score -1.3 for lumbar density (Figure 1). No other fractures were reported in the following two years of follow-up.

Discussion

While fractures are very frequent in childhood, vertebral fractures are uncommon in an otherwise healthy child.[1] The reported child had no previous history of fractures or of major trauma, but presented multiple vertebral fractures with evidence of osteopenia. In such cases, both primary and secondary causes should be considered. The approach of osteoporosis includes a routine measurement of bone metabolism and the assessment of bone mass by dual energy X-ray absorptiometry (DEXA). Secondary causes are evaluated by clinical history, physical examination, and laboratory investigations. Genetic studies should be considered in the presence of clinically significant fracture history and in the absence of a secondary cause.[5] This child was active, without symptoms of chronic inflammatory disease or consumption of potentially osteotoxic drugs, apart from low-dose inhaled corticosteroids (ICS) which, unlike high dose long-term ICS, have no influence on BMD.[6] The family history of middle-aged onset of osteoporosis raised the suspicion of a primary cause.

A likely pathogenic variant in heterozygosity in the *COL1A2* gene was identified which segregated in the mother and grandmother, both having documented osteoporosis of undetermined etiology. *COL1A2* may present as different clinical types and with variable severity.[3]

Management of osteoporosis aims to improve function, mobility and pain, and prevent further fractures, requiring a multidisciplinary approach. High impact physical activities and contact sports should be avoided. Oral supplementation with vitamin D and calcium may be necessary.[5] Pharmacological treatment in OI is based on bisphosphonates (BP) which improve BMD, reduce fracture incidence and in children, may have a role in reshaping of fractured vertebrae. Intravenous BP are better tolerated than oral, intravenous pamidronate being the most widely used in children. In the reported case, treatment with BP resulted in 85.9% improvement of BMD and no fractures. Genetic counselling should be offered to affected families.

In conclusion, the presence of a vertebral fracture in a child always requires further investigation. Bisphosphonates in OI increase BMD and reduce the incidence of fractures, and therefore a timely diagnosis is crucial to start the proper treatment.

Compliance with Ethical Standards

Funding None

Conflict of Interest None

References:

1. Clark EM. The epidemiology of fractures in otherwise healthy children. Curr Osteoporos Rep. 2014 Sep;12(3):272-8. doi: 10.1007/s11914-014-0227-y.
2. Yang L, Liu B, Dong X, Wu J, Sun C, Xi L, et al. Clinical severity prediction in children with osteogenesis imperfecta caused by COL1A1/2 defects. Osteoporos Int. 2022 Jun;33(6):1373-1384. doi: 10.1007/s00198-021-06263-0. Epub 2022 Jan 19.
3. Tauer JT, Robinson ME, Rauch F. Osteogenesis Imperfecta: New Perspectives From Clinical and Translational Research. JBMR Plus. 2019 Feb 20;3(8):e10174. doi: 10.1002/jbm4.10174.
4. Saraff V, Högler W. ENDOCRINOLOGY AND ADOLESCENCE: Osteoporosis in children: diagnosis and management. Eur J Endocrinol. 2015 Dec;173(6):R185-97. doi: 10.1530/EJE-14-0865.
5. Ciancia S, van Rijn RR, Högler W, Appelman-Dijkstra NM, Boot AM, Sas TCJ, et al. Osteoporosis in children and adolescents: when to suspect and how to diagnose it. Eur J Pediatr. 2022 Jul;181(7):2549-2561. doi: 10.1007/s00431-022-04455-2. Epub 2022 Apr 6.
6. Kwda A, Gldc P, Baui B, Kasr K, Us H, S W, et al. Effect of long term inhaled corticosteroid therapy on adrenal suppression, growth and bone health in children with asthma. BMC Pediatr. 2019 Nov 5;19(1):411. doi: 10.1186/s12887-019-1760-8.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.61

CASE REPORTS

UNUSUAL EARLY SKELETAL MANIFESTATIONS IN A NEONATE WITH CONGENITAL SYPHILIS

Tehsin Patel, Sruthi Nair, Prashanth RR, Anitha Haribalakrishna.

Department of Neonatology, Seth G.S. Medical College and King Edward Memorial Hospital, Mumbai, India.

ABSTRACT

Congenital syphilis is a preventable infection caused by Treponema Pallidum usually involving multiple system. We report a case of a neonate born to mother with latent syphilis, presenting with bone changes on radiography without any clinical signs or symptoms of congenital syphilis. In this case, it is demonstrated that isolated long bone fractures can be the initial presenting sign of congenital syphilis with other classical findings possibly appearing later and early treatment for the same. We have highlighted the importance of radiological survey in asymptomatic neonates with positive serology.

ARTICLE HISTORY

Received : 26 November 2023

Accepted 07 February 2024

KEYWORDS

congenital syphilis, fracture, metaphysitis.

Introduction

Congenital syphilis (CS) is an infection caused by Treponema Pallidum usually involving the liver, bone, and brain. Even though the disease prevalence has remained latent over the years, there has been a resurgence reported by Centre for Disease Control(CDC) in the year 2017.[1,2]

Among the babies born to untreated mothers, 40% are either stillborn or manifest with immediate complications like hydrops fetalis, preterm birth, low birth weight or may be asymptomatic at birth.[3] Among those symptomatic, various clinical features include severe anemia, jaundice, hepatosplenomegaly, snuffles, mucocutaneous lesions, pneumonia, osteochondritis, periostitis and pseudo paralysis. These symptoms may manifest at birth or within 4 to 8 weeks of life.[4]

Bone involvement secondary to syphilis in neonates is an unusual presentation and those presenting as a fracture is even more rare. In a large case series reporting 60-80% of infants with CS presenting with skeletal manifestations including symmetric osteoperiostitis of long bones there were no fractures reported.[5] We report a case of CS with metaphysistis of bilateral tibia and femur with left clavicular fracture and have described the importance of early identification in a resource limited setting and management for a better outcome.

Case Report

A male neonate born by vaginal delivery at 39 weeks of gestation to a 30 years old mother by spontaneous conception, with previous two uncomplicated pregnancies, with a birth weight of 3098 grams (50-90 centile) and head circumference of 35 cm (50-90 centile). Neonate required no resuscitation at birth, APGAR scores of 9 at both 1 and 5 minutes with no difficulty in extraction and was hemodynamically stable with normal physical and systemic examination including no pallor, skin lesions, hepatosplenomegaly or paucity of limb movements.

In the antenatal period, on routine evaluation, the mother was detected to be VDRL positive (Titres 1:16) and TPHA positive. She was asymptomatic and was diagnosed to have latent syphilis. She was treated with intramuscular penicillin as per CDC protocol and she was compliant with the treatment. Serological markers for HIV and HBsAg were negative. The husband also tested RPR and TPHA positive and was also treated for latent syphilis. No other family members were tested.

In the delivery room, universal precautions were followed and placental gross examination was normal and neonate was roomed with the mother in the postnatal ward and was initiated on breastfeeding. In view of the maternal history of latent syphilis, the neonate was evaluated with qualitative RPR and TPHA both of which were positive. A diagnosis of confirmed congenital syphilis was made and further evaluated and managed as per CDC guidelines.

A skeletal survey done was suggestive of changes of bilateral metaphysitis with cortical thickening at diaphysis and localized destruction of the medial portion of the proximal tibial and distal femur. (Figure 1A) There was fracture of the left clavicle at the junction of medial two-thirds and lateral one-third of the bone. (Figure 1B)

Neonate was also evaluated with a hemogram, liver function test, cerebrospinal fluid (CSF) analysis, ophthalmic evaluation, and neurosonogram, all of which were normal. Due to non-availability of aqueous or procaine penicillin G, Inj. Ceftriaxone (75mg/kg/day OD IV and was given for 10 days).

Multidisciplinary care involving neonatologist, microbiologist, radiologist, orthopedician and clinical psychologist was provided. The fracture was managed conservatively with a figure of eight bandage and neonate was discharged on day of life 11. Family counselling regarding the need for timely follow-up was

Address for Correspondance:
Sruthi Nair, Department of Neonatology, 10th floor, MSB, KEM hospital, Parel, Mumbai 400012, India.
Email: sruthis.doc@gmail.com

Figure 1A. Radiolucency at the proximal and distal metaphysis of femur, tibia, with periosteal reaction, metaphyseal serration as shown by arrow, suggestive of congenital syphilis.

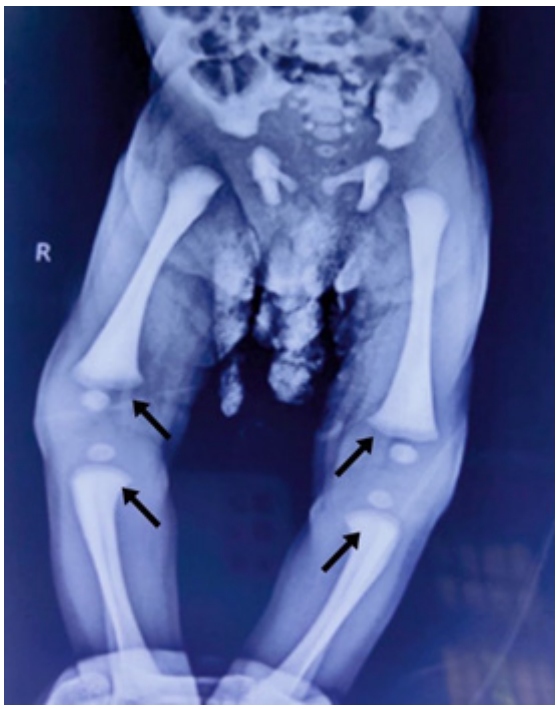
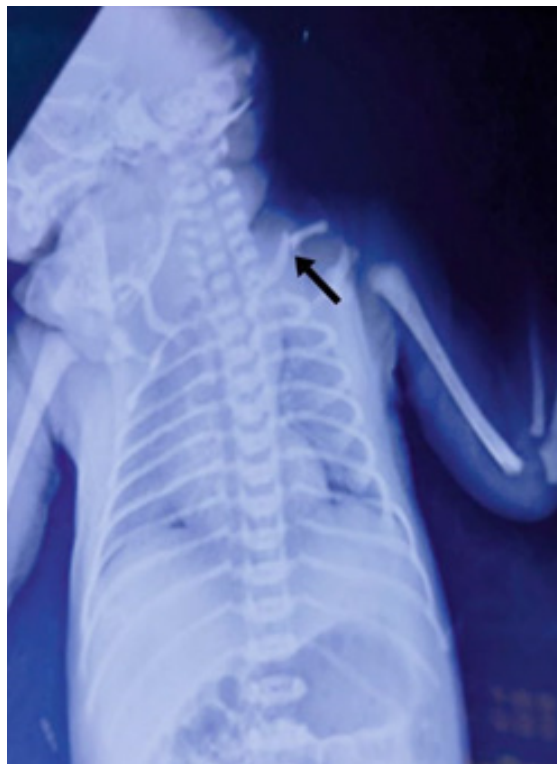


Figure 1B. Fracture of left clavicle as indicated by arrow.



done. The repeat X-ray of long bones done on follow-up revealed resolution of bony manifestations of syphilis and fracture. Hearing assessment, neurodevelopment assessment and repeat serological testing has been planned every 2-3 monthly until the non-treponemal tests are negative.

Discussion

Congenital syphilis occurs as a result of vertical transmission of treponema pallidum with the severity being determined by the stage of syphilis in the mother and the duration of fetal exposure in the uterus.[6] Congenital syphilis can be diagnosed using treponemal and non-treponemal tests. However, interpretation is difficult as both maternal treponemal and non- treponemal IgG antibodies can be transferred through the placenta to the fetus. Thus, RPR and TPHA can show false positive results in uninfected infants of seropositive mothers.[7] In our index case, mother was VDRL and TPHA positive and neonate was RPR and TPHA positive.

The majority of infants born to mothers with untreated syphilis appear normal and have no clinical or laboratory evidence of infection at birth, but may develop manifestations of disease months to years later if left untreated. Early congenital syphilis refers to those clinical manifestations that appear in the first 2 years of age and clinical disease that occurs after 2 years of age is designated as late congenital syphilis. The most specific sign for late congenital syphilis is Hutchinson's triad which consists of Hutchinson's teeth, eighth cranial nerve deafness, and interstitial keratitis.[6] Bone lesions in congenital syphilis mainly involve tibia and other long bones which is generally multiple and symmetrical. Cremin and Fisher in 1970, in their report of 102 cases of CS from South Africa, considered their skeletal findings not due to an active inflammation of the bones but dystrophic in nature instead.[8] They classified their findings into three different groups: Group I: Metaphyseal dystrophy, Group II: Osteitis-like dystrophy and Group III: Periosteal dystrophy.[9] As per this classification of Cremin and Fisher, the index neonate's bone changes are classified as group II. In addition to periosteal reaction and metaphysistis in the long bones, the presence of clavicular fracture makes it important to look for these fractures carefully in other bones without dystrophic changes. Clavicular fracture has been commonly reported occurring as a result of birth trauma, osteogenesis imperfecta and other bone diseases associated with increased bone fragility[10] however those in neonates with CS has very limited reporting.

CDC and ACOG recommends universal first trimester screening for syphilis and additional third trimester screening for pregnant women with high risk behavior for syphilis.[11] Diagnosis and management of syphilis during pregnancy and in neonatal period have been clearly defined by CDC. Non-uniformity in this practice as seen in the index case including late diagnosis during pregnancy, non-availability of titres of VDRL, RPR and also the non-availability of penicillin has been an issue in certain resource-limited settings. The use of a skeletal survey and early diagnosis of metaphysistis and fracture, along with the qualitative tests as in our case might aid in accurate early diagnosis of CS and initiation of treatment. This might also lead to an earlier resolution of the skeletal changes as seen in this case.

In neonates with congenital syphilis, serology (treponemal and non-treponemal) needs to be repeated

at 1, 2, 4, 6 and 12 months.[11] At 6 months if non treponemal specific test (NTST) is non reactive and infant remains asymptomatic, no further evaluation or treatment is required. The non treponemal titre is expected to be negative by 12 months after treatment in appropriately treated cases.[11] Children with positive titres on follow up are to be considered for the second course of treatment. Long term outcomes in symptomatic CS include increased risk of growth restriction, developmental delay and microcephaly.[12]

Conclusion

Despite universal screening during pregnancy and treatment of latent syphilis in the antenatal period, congenital syphilis can present as only radiological manifestations of metaphysistis which re emphasizes the need for a detailed skeletal survey. Other bone fractures including clavicular fracture need to be carefully identified and treated early for better outcome and reduced morbidity.

Compliance with Ethical Standards

Funding None

Conflict of Interest None

References:

1. Tao, YT., Gao, TY., Li, HY. et al. Global, regional, and national trends of syphilis from 1990 to 2019: the 2019 global burden of disease study. BMC Public Health 23, 754 (2023). https://doi.org/10.1186/s12889-023-15510-4.
2. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2017. Atlanta, GA: US Department of Health and Human Services; 2018.
3. American Academy of Pediatrics. Syphilis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red Book: 2018 Report of the Committee on Infectious Diseases. Grove Village, IL: American Academy of Pediatrics; 2018. p. 773-88.
4. Dobson SR. Congenital syphilis: clinical features and diagnosis. In: Kaplan SL, Weisman LE section eds. UpToDate. 2021. Congenital syphilis: clinical features and diagnosis - UpToDate . Accessed 1 Nov 2021.
5. Cooper JM, Sánchez PJ. Congenital syphilis. Semin Perinatol. 2018;42(3): 176-184.
6. Singhal P, Patel P, Marfatia YS. A case of congenital syphilis with Hutchinson's triad. Indian J Sex Transm Dis AIDS. 2011 Jan;32(1):34-6. doi: 10.4103/0253-7184.81252. PMID: 21799574; PMCID: PMC3139286.
7. Dai Y, Zhai G, Zhang S, Chen C, Li Z, Shi W. The Clinical Characteristics and Serological Outcomes of Infants With Confirmed or Suspected Congenital Syphilis in Shanghai, China: A Hospital-Based Study. Front Pediatr. 2022 Feb 23;10:802071. doi: 10.3389/fped.2022.802071. PMID: 35281239; PMCID: PMC8904424.
8. Cremin BJ, Fisher RM. The lesions of congenital syphilis. Br J Radiol. 1970;43(509):333-41.
9. Pg Mohammad Hussein PMN, Kew ST, Nang KM, et al. Skeletal manifestations of congenital syphilis: Rare but clinically relevant. Radiol Case Rep. 2021 Oct 1;16(12):3635-3637. doi: 10.1016/j.radcr.2021.09.004. PMID: 34630789; PMCID: PMC8495030.
10. Jenny C, Committee on Child Abuse and Neglect. Evaluating infants and young children with multiple fractures. Pediatrics. 2006;118(3):1299-303.
11. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64(RR):1-137.
12. Lago EG, Vaccari A, Fiori RM. Clinical features and follow-up of congenital syphilis. Sex Transm Dis. 2013;40(2): 85-94.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.66

CASE REPORTS

CHOLESTATIC JAUNDICE IN PEDIATRIC COVID-19: TWO CASE REPORTS

Karen Janice Moras, Suneel C Mundkur, Rochelle Anne Periera.

Department of Pediatrics, Kasturba Medical College, MAHE, Manipal University, Manipal, India.

ABSTRACT

Hepatic involvement in COVID-19 in children is typically characterized by elevation in Alanine transaminase (ALT) and Aspartate aminotransferase (AST) with preserved liver synthetic function.1 Severe hepatic involvement in COVID-19 is seen in COVID Multisystem Inflammatory Syndrome in Children (MIS-C), which typically occurs several weeks to months after the initial SARS-CoV-2 infection rather than during acute infection.(2, 3) However, there is a paucity of literature describing Paediatric cases of cholestatic jaundice as a primary manifestation of acute SARS-CoV-2 infection. We report two cases of cholestatic jaundice as the primary manifestation of COVID-19.

ARTICLE HISTORY

Received : 26 November 2023

Accepted 07 February 2024

KEYWORDS

Pediatric COVID-19, cholestasis, jaundice, SARS-CoV-2 infection.

Case Report

Case 1

An 8 year old male child presented with fever since one week, with generalised urticaria. The rash started in the trunk progressed to involve the upper limbs and lower limbs and face. Eyes showed conjunctival congestion. Genitalia and oral cavity were normal. No history of rhinitis, cough, difficulty in breathing. No history of allergy, atopy. No history of travel or drug intake. Growth and development were normal. His vaccination was age appropriate. On day 3 of admission, he developed jaundice with itching. There was no past history or family history of jaundice. History of atopic dermatitis at 4 years of age which resolved on medication.

On examination, child was febrile and toxic. His vitals were stable. Generalised urticaria was present. Systemic examination showed soft tender hepatomegaly, liver span 11 cms.

His blood investigations showed - Haemoglobin: 12.6 g/dl; Haematocrit: 38.3 %; Platelet Count: 417.0 X 10^3/µl; RBC Count: 4.83 X 10×6/µl; Total WBC: 16.2 X 10^3/µl; ESR: 6 mm/hr; Peripheral smear: Normocytic normochromic RBCs with anisocytosis

Total Bilirubin (Serum): 4.83 mg/dl; Direct Bilirubin 4.33 mg/dl; Alanine Transaminase: 535.0 IU/L; Aspartate Transaminase: 286 IU/L; Alkaline Phosphatase :455 U/L; Total Protein (Serum): 6.80 G/dl; Albumin (Serum): 3.30 g/dl; Globulin: 3.50 g/dl; Prothrombin Time: 13.4 Sec; INR: 1.20 LDH- 100IU/dL

Hepatitis-B Surface Antigen: Negative; Antibodies to Hepatitis C Virus: Non-Reactive; Anti IgM Hepatitis A Virus- Negative. Hepatitis E- negative. Antibodies to Leptospira (IgM): Negative; Standard agglutination test for Brucellosis: Negative; OX K: Negative; OX 19: Negative; OX 2: Negative; Scrub typhus IgM: Negative; Widal test: Negative; Anti-Dengue IgM: Negative Dengue Ns1Ag: Negative.

Blood culture was sterile. Serum Ceruloplasmin: 40 mg/dl. No KF ring,

G6PD- 28 IU/l (normal-8-18IU/L)

Covid-19 RTPCR- nasopharyngeal and oropharyngeal swab – Positive. SARS-CoV-2-Antibodies-negative

Ultrasound abdomen showed normal echotexture of liver. Autoimmune hepatitis panel (anti-nuclear antibody, anti-smooth muscle antibody, anti-liver kidney microsomal antibody) was negative.

Patient was treated with intravenous fluids and multivitamins and choleretics. Hepatic Transaminases, ALT and AST showed peak increase around day 11 and gradual decline over 8 weeks (Figure 1) Serum ALP was only marginally elevated in comparison to the rise in Bilirubin and showed gradual decline over 8 weeks. Serum total bilirubin and conjugated bilirubin also decreased over a span of 8 weeks. (Figure 2)

Case 2

A 16-year-old female presented with fever for 8 days and rash for 3 days. At presentation she looked toxic with generalised urticaria. The rash started with face and progressed to involve the trunk, upper and lower limbs with sparing of genetalia and oral cavity. No history suggestive of upper or lower respiratory tract infection. No history of drug intake or travel. COVID vaccine was not given. On day 4 of admission, she developed jaundice with pruritis. Past history of atopic dermatitis 4 years back. No similar history of jaundice in the past. No family history of jaundice.

On examination she appeared toxic. She was hemodynamically stable. She had generalized urticaria scratch marks. Systemic examination showed soft, tender hepatomegaly, with liver span 13 cms.

Her blood investigations showed, Haemoglobin: 11 g/dl; Haematocrit:32.8 %; Platelet Count :1.54.0 X 10^3/µl;RBC Count:3.98 X 10 × 6/µl; Total WBC: 5.9 X 10^3/µl; ESR: 32mm/hr; Peripheral smear: Normocytic normochromic RBCs with anisocytosis

Address for Correspondance:

Karen Janice Moras, Associate Professor, Department of Pediatrics, Kasturba Medical College, MAHE, Manipal University, Manipal-576104, India.

Email: drkarenmoras87@gmail.com

Figure 1. Patient 1-Trend of Hepatic enzymes X axis- AST (BLUE) ALT(ORANGE) ALP(GREY) Y axis- AST, ALT and ALP IU/L.

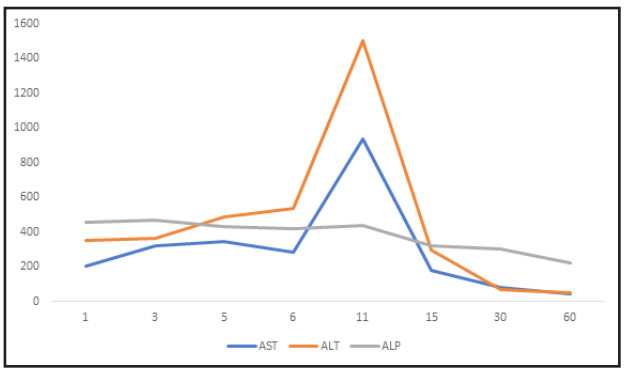


Figure 2. Patient 1-Trend of Serum Bilirubin Xaxis- Conjugated bilirubin(orange) total Bilirubin(blue) Y axis- Bilirubin in mg/dl.

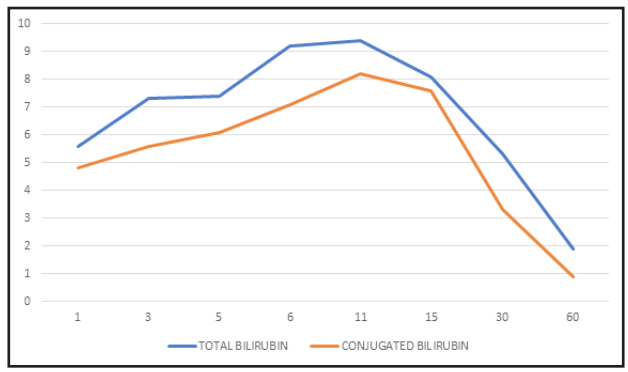


Figure 3. Patient 2-Trend of Hepatic enzymes X axis- AST (BLUE) ALT(ORANGE) ALP (GREY) Y axis - AST, ALT, and ALP IU/L.

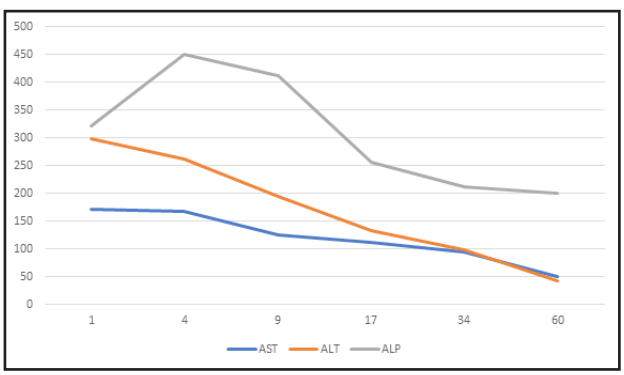
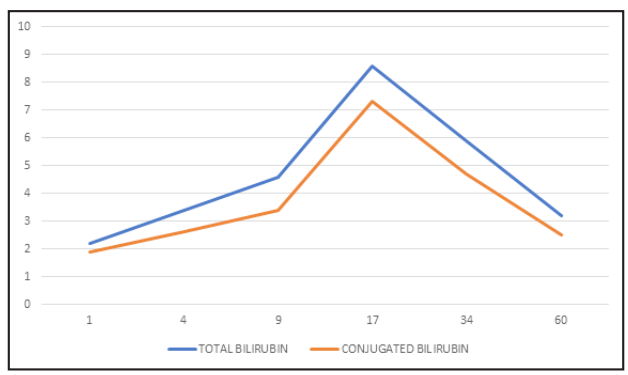


Figure 4. Patient 2 -Trend of Serum Bilirubin, Conjugated bilirubin(orange) total Bilirubin(blue) Y axis- Bilirubin in mg/dl.



Total Bilirubin (Serum): 5.22 mg/dl; Direct Bilirubin: 4.16 mg/dl; Alanine Transaminase: 298.0 IU/L; Aspartate Transaminase: 172 IU/L; Alkaline Phosphatase: 412 U/L; Total Protein (Serum): 1 g/dl; Albumin (Serum): 3.50 g/dl; Globulin: 4.60 g/dl; Prothrombin Time: 12.4 Sec; INR: 1.10 LDH- 100 IU/dL

Hepatitis-B Surface Antigen: Negative; Antibodies to Hepatitis C Virus: Non-Reactive; Anti IgM Hepatitis A Virus- Negative. Hepatitis e- negative. Antibodies to Leptospira (IgM): Negative; Standard agglutination test for Brucellosis: Negative; OX K: Negative; OX 19:Negative; OX 2: Negative; Scrub typhus IgM: Negative; Widal test: Negative; Anti-Dengue IgM: Negative; Dengue Ns1Ag: Negative. Autoimmune hepatitis panel (anti-nuclear antibody, anti-smooth muscle antibody, anti-liver kidney microsomal antibody) was negative.

Serum Ceruloplasmin: 50mg/dl. No KF ring, G6PD-42IU/l.

Ultrasound abdomen showed normal echotexture of liver. Blood culture was sterile.

COVID-19 RTPCR- nasopharyngeal and oropharyngeal swab - Positive.

SARS-CoV-2-Antibodies-negative

Patient was treated with intravenous fluids and multivitamins and Ursodeoxycholic acid. Transaminases, ALT, and AST showed peak increase around day 9, gradual decline over 8 weeks (Figure 3). Alkaline phosphatase showed gradual decline over 8 weeks. Serum total bilirubin and conjugated bilirubin, peaked around 2 weeks, with gradual decline over a span of 8 weeks (Figure 4).

Discussion

Liver involvement in the absence of pulmonary involvement in SARS-COV2 infection is very rarely reported in children. Hepatic involvement in the form of mild elevation of transaminases with normal synthetic function has been reported in Paediatric population.[4] Severe hepatic disease with pulmonary involvement is seen in children with COVID -MISC or in severe SARS-COV2 infection with multiorgan involvement.[1,3] Different mechanisms for liver injury in COVID-19 have been proposed including direct viral cytotoxic effect, mitochondrial protein interaction, endothelial dysfunction, and systemic inflammatory in response to the virus.[5]

COVID-19 virus causing cholestatic jaundice as the primary manifestation of SARS-COV2 infection is not yet reported in Paediatric population.

In both our patients COVID-19 RTPCR was positive, with serum negative for covid antibodies. They did not fulfill the criteria for COVID- MISC (fever for over 24 hours, elevated inflammatory markers, multisystem organ involvement, no alternative diagnoses, and past history of SARS-CoV-2 infection).[6,7] The extensive blood investigations for all causes of primary liver disease

were negative.

Hepatic involvement in both patients showed moderate elevation of transaminases with peak around 11th day and gradual decline over 8 weeks. Serum ALP, marker of cholestasis, was moderately raised in comparison with serum Bilirubin and declined in a similar pattern as transaminases. Serum bilirubin, both total and conjugated, showed similar gradual decline over 8 weeks. In other case series, severe elevation of hepatic enzymes has been reported and improvement was observed at 2 months. 8 Both the patients in the present case report, had normal coagulation profile with normal albumin indicating that synthetic liver function was not affected. In other case series[8], synthetic liver function was affected with multiorgan involvement.

It is important to note that both the patients presented with fever and rash and had past history of atopic dermatitis. Other causes of endemic viral exanthems like Dengue, Scrub typhus were ruled out. None of the patients were on any medication. Whether past history of atopy predisposes to severe cholestatic hepatitis in COVID-19 is yet to be proved.

Both the patients were treated with supportive measures, choleretics, and fat-soluble vitamins. Both the patients were discharged after 3 weeks of admission.

What we know

- COVID-MISC or Severe SARS-CoV-2 infection with respiratory involvement can cause severe liver dysfunction

What is new?

- SARS-CoV-2 infection can cause severe cholestatic jaundice.
- Past history of atopic dermatitis can be a predisposing factor for cholestatic jaundice in COVID-19. However, further studies are required to prove this correlation.
- Complete resolution of liver biochemistry can take about 8 weeks in SARS-CoV-2 infection.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Perez A, Cantor A, Rudolph B, Miller J, Kogan-Liberman D, Gao Q, Da Silva B, Margolis KG, Ovchinsky N, Martinez M. Liver involvement in children with SARS-COV-2 infection: Two distinct clinical phenotypes caused by the same virus. Liver Int. 2021 Sep;41(9):2068-2075. doi: 10.1111/liv.14887. Epub 2021 Apr 22. PMID: 33826804; PMCID: PMC8251417.
2. Saviano, A., Wrensch, F., Ghany, M.G. and Baumert, T.F. (2021), Liver Disease and Coronavirus Disease 2019: From Pathogenesis to Clinical Care. Hepatology, 74: 1088-1100. https://doi.org/10.1002/hep.31684.
3. Cantor A, Miller J, Zachariah P, DaSilva B, Margolis K, Martinez M. Acute Hepatitis Is a Prominent Presentation of the Multisystem Inflammatory Syndrome in Children: A Single-Center Report. Hepatology. 2020 Nov;72(5):1522-1527. doi: 10.1002/hep.31526. Epub 2020 Oct 27. PMID: 32810894; PMCID: PMC7655704.
4. Bloom PP, Meyerowitz EA, Reinus Z, Daidone M, Gustafson J, Kim AY, Schaefer E, Chung RT. Liver Biochemistries in Hospitalized Patients With COVID-19. Hepatology. 2021 Mar;73(3):890-900. doi: 10.1002/hep.31326. Epub 2020 Nov 4. PMID: 32415860.
5. Sultan S, Altayar O, Siddique SM, Davitkov P, Feuerstein JD, Lim JK, Falck-Ytter Y, El-Serag HB; AGA Institute. Electronic address: ewilson@gastro.org. AGA Institute Rapid Review of the Gastrointestinal and Liver Manifestations of COVID-19, Meta-Analysis of International Data, and Recommendations for the Consultative Management of Patients with COVID-19. Gastroenterology. 2020 Jul;159(1):320-334.e27. doi: 10.1053/j.gastro.2020.05.001. Epub 2020 May 11. PMID: 32407808; PMCID: PMC7212965.
6. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. JAMA. 2021;325(11):1074-1087. doi:10.1001/jama.2021.2091.
7. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007 Feb;48(2):124-31. doi: 10.1002/pbc.21039. PMID: 16937360.
8. Antala S, Diamond T, Kociolek LK, Shah AA, Chapin CA. Severe Hepatitis in Pediatric Coronavirus Disease 2019. J Pediatr Gastroenterol Nutr. 2022 May 1;74(5):631-635. doi: 10.1097/MPG.0000000000003404. PMID: 35149651; PMCID: PMC9117453.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.66

CASE REPORTS

PROTEIN-LOSING ENTEROPATHY AS A RARE COMPLICATION OF GIARDIASIS IN CHILDREN

Filipa Sutre, Margarida Caldeira, Alexandra Gavino, Aldina Lopes.
Paediatric Department, Hospital de Santarém, Santarém, Portugal.

ABSTRACT

Giardiasis, caused by Giardia lamblia, is an intestinal infection that presents various clinical manifestations. While malabsorption is a recognized complication, protein-losing enteropathy (PLE) is infrequent. This report describes a 17-month-old healthy girl who presented to the emergency department exhibiting generalized edema attributed to hypoalbuminemia, which resulted from gastrointestinal protein loss. Subsequent investigations identified giardiasis as the underlying etiology. After appropriate treatment, the patient fully recovered. With this case, the intention is to highlight the importance of considering giardiasis in patients with hypoproteinemia of unknown origin to prevent severe comorbidities, particularly in children.

ARTICLE HISTORY

Received : 24 January 2024

Accepted : 27 March 2024

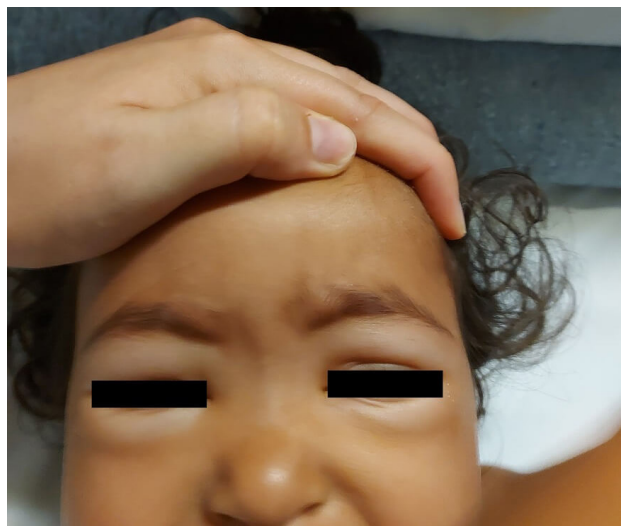
KEYWORDS

Hypoalbuminemia; Giardiasis; Protein-Losing Enteropathy.

Case Report

A 17-month-old healthy girl of Indian descent, following a vegetarian diet and maintaining adequate nourishment, experienced a mild febrile illness with watery diarrhea and vomiting two weeks before seeking admission to the emergency department. One week later, she developed facial edema, as shown in Figure 1, hands and feet, without other associated symptoms. The physical examination revealed the patient to be afebrile with stable vital signs; however, she exhibited pallor in the skin, diffuse pitting edema, and abdominal distention, with no signs of organomegaly. The chest X-ray displayed no abnormalities, and the abdominal ultrasound indicated a small quantity of free intraperitoneal fluid in the subhepatic and perisplenic regions. Laboratory findings revealed anemia (hemoglobin 10.8 g/dL), hypoproteinemia (2.9 g/dL), and hypoalbuminemia (1.4 g/dL). Serum biochemical parameters for liver and kidney function were within the normal range. Urinalysis and a 12-hour urinary protein excretion test excluded the presence of proteinuria. Additionally, ferritin, calcium, vitamin D, and serum levels of immunoglobulin G were found to be low. Celiac disease was eliminated from the diagnostic considerations. Despite stool cultures failing to identify pathogenic organisms, the stool analyses for *Giardia lamblia* antigen consistently yielded positive results in three samples. She underwent management with fluid restriction and a high-protein diet supplemented with iron, calcium, and vitamin D. Following a five-day albendazole treatment, there was a remarkable improvement in signs, symptoms, and laboratory findings. One month after being discharged, during her follow-up visit, she remained asymptomatic; the physical examination was completely normal, and her serum levels of total protein, albumin, and immunoglobulins were within the normal range.

Figure 1. Facial edema.



Discussion

Giardiasis, caused by the extracellular protozoan parasite *Giardia lamblia*, is a worldwide intestinal infection.[1] The symptoms of giardiasis can manifest across a spectrum of severity, encompassing asymptomatic instances to more pronounced presentations, which may involve acute or chronic diarrhea, nausea, bloating, abdominal pain, and weight loss.[2] While malabsorption is an acknowledged complication of Giardia infection, selective protein-losing enteropathy (PLE) is uncommon. In instances of severe hypoproteinemia, symptoms may involve edema, ascites, pericardial or pleural effusion, or a combination, and may also be linked to an elevated susceptibility to infections.[3] Our patient exhibited generalized pitting edema with ascites but without pleural or pericardial effusion.

PLE is characterized by the pronounced loss of proteins through the gastrointestinal tract, occurring when the losses into the gastrointestinal system surpass

Address for Correspondance:
Filipa Sutre, Pediatric Department, Hospital de Santarém, Avenida Bernardo, Santareno 3737B, 2005-177 Santarém, Portugal.
Email: filipasutre@gmail.com

the liver's production capacity.[3,4] The leakage of serum proteins into the gastrointestinal tract occurs independently of molecular weight. Consequently, the serum proteins most affected by this disrupted equilibrium are those with extended half-lives, such as immunoglobulin A (IgA), IgG, IgM, albumin, fibrinogen, and ceruloplasmin.[4] In our patient, there was evidence of hypoalbuminemia and reduced levels of serum IgG.

The consideration of PLE in patients presenting with hypoproteinemia is warranted after excluding other potential causes, such as insufficient dietary intake, significant proteinuria, impaired protein synthesis due to liver disease, obstruction in the lymphatic system, and extensive inflammation of the vasculature (as seen in sepsis).[3] PLE was suspected in this patient due to the simultaneous presence of gastrointestinal signs and symptoms without the occurrence of proteinuria or clinical and laboratory evidence of liver disease. The patient›s vegetarian diet could contribute to an inadequate dietary intake of protein and energy. However, isolated vegetarianism is rarely associated with such low albumin levels, as observed in our patient.

Despite significant advancements in recent decades in elucidating the pathogenesis of giardiasis, the pathophysiology of this disease remains a subject of ongoing investigation.[5] It is hypothesized that *Giardia lamblia* colonizes the upper part of the small intestine, specifically the duodenum and jejunum, without invading the tissues. This colonization can result in damage to the intestinal mucosa, compromising the barrier function of enterocytes by disrupting the epithelial brush border and tight junctions.[2,5] This leads to malabsorption, resulting in clinical manifestations such as anorexia, abdominal pain, diarrhea, and weight loss. Consequently, patients may experience various deficiencies in minerals and vitamins, including iron, folic acid, vitamin B12, vitamin A, and thiamine, leading to anemia.[5] The deficiency in iron is a widely acknowledged complication associated with giardiasis, in line with the existing literature.[6] Our patient manifested abdominal distention and edema, indicative of malabsorption. Additionally, she exhibited anemia, low serum ferritin levels, vitamin D deficiency, and low calcium levels. These conditions might be linked to insufficient dietary intake, malabsorption, or a combination of both, requiring supplementation.

Regarding the diagnosis, molecular tests utilizing enzyme-linked immunosorbent assay (ELISA) to detect *Giardia lamblia* antigens demonstrate high specificity and sensitivity, making them a recommended choice for initial diagnostic testing.[3] In a comparative analysis, the effectiveness of microscopic examination of stool samples for parasites was reported as 83%, while stool antigen tests showed a higher sensitivity at 95%.[7] In our patient, even though stool cultures did not identify pathogenic organisms, ELISA for detecting *Giardia lamblia* antigen consistently yielded positive results in three samples.

Giardia lamblia can induce illness both during the acute phase of the infection and in the post-infectious period. Evidence from a prospective longitudinal cohort study indicates that giardiasis in early life was identified as a risk factor for stunted growth at two years of age.[2,8] Therefore, despite PLE being considered a rare manifestation of giardiasis, its identification is crucial, and eradicating the infection leads to rapid recovery, as evidenced in our patient.

In conclusion, giardiasis is a treatable cause of PLE, potentially linked to severe comorbidities. Conducting an epidemiological investigation and promptly recognizing and treating Giardia infection in PLE cases contribute to swift clinical and laboratory recovery. This approach is crucial for preventing malnutrition, particularly in growing children.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Feng, Y., & Xiao, L. (2011). Zoonotic potential and molecular epidemiology of Giardia species and giardiasis. Clinical microbiology reviews, 24(1), 110-140. https://doi.org/10.1128/CMR.00033-10.
2. Allain, T., & Buret, A. G. (2020). Pathogenesis and post-infectious complications in giardiasis. Advances in parasitology, 107, 173-199. https://doi.org/10.1016/bs.apar.2019.12.001.
3. Akkelle, B. S., Tutar, E., Sengul, O. K., et al. (2018). A Rare Complication of Giardiasis in Children: Protein-losing Enteropathy. The Pediatric infectious disease journal, 37(12), e345-e347. https://doi.org/10.1097/INF.0000000000002025.
4. Takeda, H., Ishihama, K., Fukui, T., et al. (2003). Significance of rapid turnover proteins in protein-losing gastroenteropathy. Hepato-gastroenterology, 50(54), 1963-1965.
5. Allain, T., Amat, C. B., Motta, J. P., et al. (2017). Interactions of Giardia sp. with the intestinal barrier: Epithelium, mucus, and microbiota. Tissue barriers, 5(1), e1274354. https://doi.org/10.1080/21688370.2016.1274354.
6. De Vizia, B., Poggi, V., Vajro, P., et al. (1985). Iron malabsorption in giardiasis. The Journal of Pediatrics, 107(1), 75-78. https://doi.org/10.1016/s0022-3476(85)80618-1.
7. Addiss, D. G., Mathews, H. M., Stewart, J. M., et al. (1991). Evaluation of a commercially available enzyme-linked immunosorbent assay for Giardia lamblia antigen in stool. Journal of Clinical Microbiology, 29(6), 1137-1142. https://doi.org/10.1128/jcm.29.6.1137-1142.1991.
8. Donowitz, J.R., Alam, M., Kabir, M., et al. (2016). A Prospective Longitudinal Cohort to Investigate the Effects of Early Life Giardiasis on Growth and All Cause Diarrhea. Clin Infect Dis. 15;63(6):792-7. doi: 10.1093/cid/ciw391.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.64

CASE REPORTS

THE EFFICACY AND SAFETY OF IMATINIB THERAPY IN A CASE OF NON-FAMILIAL CHERUBISM

Sarah M. Alfaqaih[1], Mohamed Bashaga[2,3,] Yaser Omar Howayw[4].

[1]Pediatric Oncology Department, National Cancer Institute, Misurata, Libya,

[2]Faculty of Medicine, University of Misurata, Libya,

[3]Diagnostic Radiology department, National cancer institute, Misurata, Libya,

[4]Oral and Maxillofacial Department, Misurata Medical Center, Misurata, Libya.

ABSTRACT

Background: Cherubism is a rare autosomal dominant inherited disorder, caused by a mutation in the SH3BP2 gene. imatinib has been effectively reported as an option of treatment. imatinib, a tyrosine kinase inhibitor (TKI), has been established to promote osteoblast differentiation. According to our knowledge, this is the first reported case of cherubism in Libya that suggest effectivity of imatinib.

Case presentation: We present the case of a 4-year-old boy was diagnosed with cherubism. The child was consistently administered a daily oral dosage of imatinib (300 mg/m2) for three months. Throughout the treatment, the patient was closely monitored every two weeks for potential side effects and signs of clinical improvement.

Conclusion: The observed therapeutic potential of imatinib for cherubism in this case study suggests a promising avenue for future exploration. However, further research is needed to establish a safe and effective protocol for imatinib treatment in pediatric cherubism.

ARTICLE HISTORY

Received : 31 December 2023

Accepted : 20 March 2024

KEYWORDS

Tyrosine kinase inhibitor, cherubism, imatinib, non-familial cherubism, SH3BP2 gene.

Introduction

Cherubism (Online Mendelian Inheritance in Man, "OMIM #118400") is a rare genetic disorder inherited in an autosomal dominant manner. It is caused by a mutation in the SH3BP2 gene, which leads to painless enlargement of the mandibular bones. This enlargement is due to a fibrous granuloma containing multinucleated giant cells that can express and differentiate into activated osteoclast giant cells, dependent on or independent of RANK.[1,2] The condition was first identified by Jones in 1933[3] and typically presents in childhood, gradually growing until puberty and then slowly regressing until around the age of 30.[4] Treatment options have been described, including observation, reconstructive surgery, and pharmacological therapy.[5] Kueper, et al.[6], from a systemic review of published literature, analyze data including 92 individuals from 34 families diagnosed with cherubism. Only 15% of the included individuals have no family history of cherubism, which mostly became clinically evident between 5 and 9 years of age. The surgical approach to treatment was mostly followed for cases receiving lesion curettage and recontouring; some cases showed no sign of recurrence during one year of follow-up, while on the other hand, some cases showed aggressive signs of disease progression.

In our case, we report the results of imatinib for cherubism regarding efficacy and safety. To the best of our knowledge, only three patients have been treated with imatinib, as reported in the literature.[7]

Address for Correspondance:
Sarah M. Alfaqaih, Almahjoub, Misurata, Libya.
(Postal code: Onwan.ly 3555004).
Email: elfagieh@yahoo.com

Case Report

In October 2022, a 4-year-old boy with no family history of the disease presented with bilateral ear discomfort and cheek fullness over a three-month duration. He was referred for further evaluation. Physically, he has bilateral painless swelling of the cheekbones, no palpable lymph nodes, and a pre-pubertal tanner stage. His height (106 cm, 75^{the} percentile), weight (17.8 kg, 75^{the} percentile), and body mass index (15.8/m^2, 50^{the} percentile) met normal developmental milestones and he was fully vaccinated under the national vaccination program.

The baseline laboratory normal, including complete blood count and bone profile, is shown in Table 1. An imaging computerized tomography scan showed symmetric bilateral mandibular bone expansible lytic lesions with internal trabeculations, giving the soap bubble appearance, involving the mandibular bodies, and rami, sparing the condyles (Figure 1). Cherubim Grade-I, according to the Seward and Hankey grading system.[8]

We diagnosed the child with cherubism upon clinical and detailed radiological evaluation. The parents have been counseled about the natural history of the disease and treatment options and trials, including waiting and follow-up, surgical intervention, and drugs (imatinib). His family wished to start noninvasive treatment.

This study approved by the National Cancer Institute Misurata's ethical Committee (No. 02-133/2023). We

Table 1. Baseline and follow-up laboratory profile.

Variant	Initial	Week 6	Week 12	Post treatment
Hb g/dl	11.2	10.9	11.3	10.7
WBC × 103	7.7	5.5	7.8	7.8
Lymphocyte %	38	54	39.4	40.4
Granulocyte %	45	31	53.4	51.3
Mix %	16	15	7.6	8.3
Platelet ×103	266	361	100	236
ALT U/l	8	13	11	10.7
AST U/l	25	35	35	22.1
? GT U/l	-	10	10	
Bilirubin (T/D) mg/dl	0.1/-	0.8/0.1	0.3/0.1	0.24/0.1
Lipase U/l	20	96	19	
Amylase U/l	105	22	119	
Alk. Ph U/l	150	114	141	
LDH U/l	273	347	227	239
Total protein g/l	6.1	6.2	6.8	
Serum albumin g/l	4.1	3.7	3.8	
PTH	27.9			
Vitamin D	28			35

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ? GT: gamma-glutamyl transferase, Alk. Ph: alkaline phosphatase, LDH: lactate dehydrogenase, PTH: parathyroid hormone

Figure 1. A, 3D reconstruction; B, axial CT scan shows bilateral mandibular bone expansible lytic with internal trabeculations at presentation.

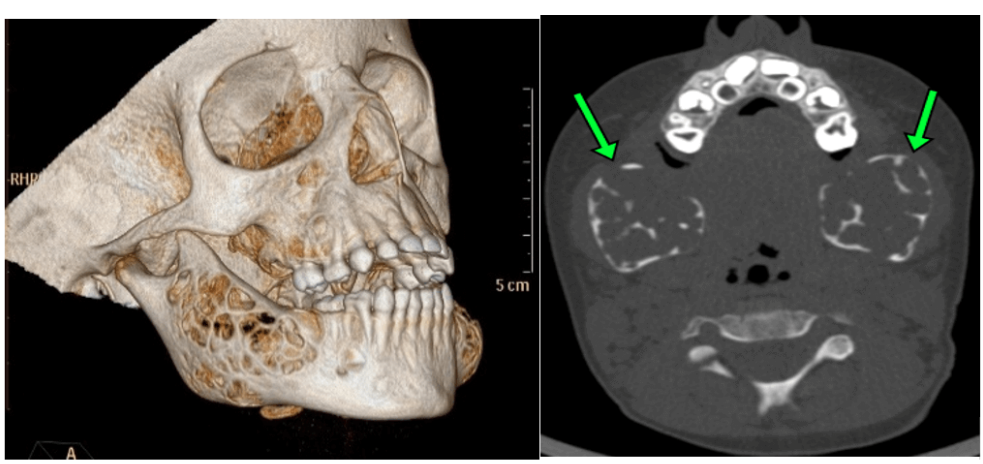
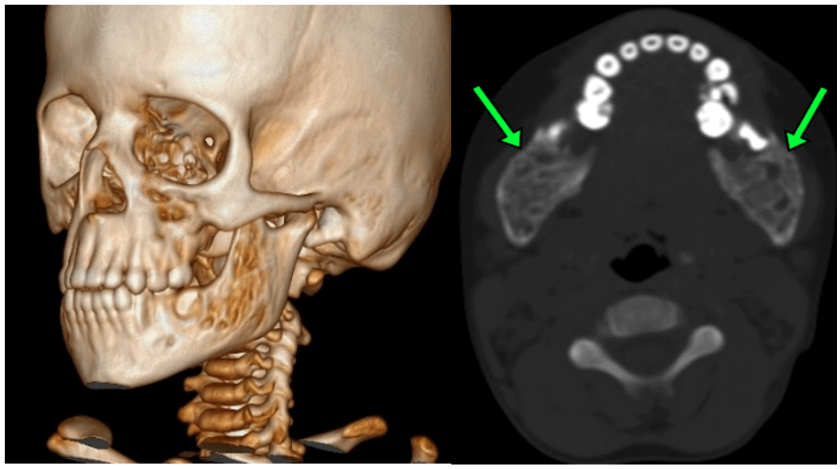
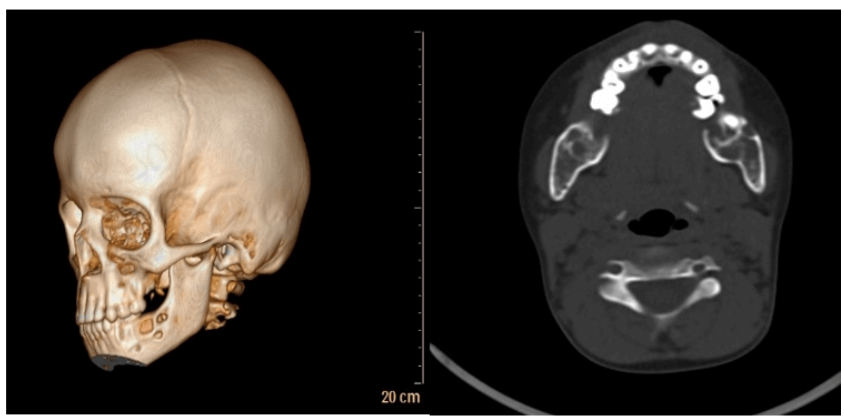


Figure 2. A, 3D reconstruction; B, axial CT scan shows the regressive course of the lesion 3 months post imatinib treatment.



A B

Figure 3. A, 3D reconstruction; B, axial CT scan shows the regressive course of the lesion 8 months post imatinib treatment.



A B

obtained parents' written consent for treatment and for publishing the pictures and treatment results. Imatinib, 300 mg/m^2 by mouth daily (rounded to the nearest tablet), was 200 mg daily. The patient was treated consistently for three months without interruption. He followed up every two weeks to closely monitor side effects and signs of clinical improvement. The patient tolerates treatment well apart from occasional nausea, which oral ondansetron controls. By week 10 of the treatment course, complete blood counts showed thrombocytopenia (platelet count 100-103), which recovered spontaneously without modification of dosage. The comparative imaging study pre- and post-introduction of imatinib showed the mandibular thickness measured 1.7 cm» as compared to 3.0 cm» in the previous study, with still a few trabeculations and a response rate of 43% (Figure 2 A, B). The follow-up imaging scan eight months post treatment showed a further response although cessation of imatinib treatment with response > 60% compared with initial scans (Figure 3 A, B).

The patient's growth curves have been unaffected over eight months of follow-up. At the last follow-up, he did not show any sign of recurrence.

Discussion

The treatment options for cherubism raise several dilemmas for the treating physician, as expected of self-limiting and usually involuntary consequences of treatment effects.[9,10] On the other hand, the early aggressive course of the disease and the major disfigurement and functional complications indicate a search for a minimally invasive modality of treatment.[7,11,12,13] The surgical intervention is the typically reported first-line module of treatment for symptomatic and plastic surgery.[4,14,15] For severe cases, the timing of intervention and surgical approach remain the most challenging parts for surgeons.[15]

As a consequence, several pharmacological treatment trials (for instance, imatinib, denosumab, calcitonin, tacrolimus, alodronate, and adalimumab) have been reported for the limited number of cases, but no established guidelines for treatment have been reached.[12,13,16,17,18,19,20]

We report a case of cherubism in a prepubertal age, in which imatinib was administered as a therapeutic intervention. The rationale for prescribing imatinib is grounded in its demonstrated capacity to promote

osteoblastogenesis by inhibiting platelet-derived growth factor.[21] The definite mechanism of action is not well established.[22,23] The administration of imatinib was chosen due to the parents› unwillingness to make alternative therapeutic choices. Parents and physician were aware of minor and serious side effects reported. Imatinib has demonstrated favorable results in several cases pertaining to the management of cherubism and clinically similar occurrences of Central Giant Cell Granuloma of the Jaw (CGCGJ).[7,24]

Imatinib, a tyrosine kinase inhibitor (TKI), has been effective in treating many childhood disorders, including chronic myelogenous leukemia (CML) and acute lymphoblastic lymphoma (Ph+ ALL, Philadelphia chromosome positive). This provides a solid foundation for its ongoing utilization. Children often exhibit good tolerance to the therapy, which can last from 24 to 60 months. Nevertheless, there have been documented instances of adverse effects, including bone marrow suppression, nausea, muscular cramps, diarrhea, edema, hepatotoxicity, dermatitis, and growth inhibition in prepubescent children.[25] It is important to mention that the inhibition of growth often resolves with puberty.[26] Several reports on its effects on male and female fertility.[27]

In this report, a three-month treatment with imatinib resulted in a significant reduction of the lesion with new bony ossification of osteolytic lesions. The patient reported a minor side effects includes an occasional nausea with initiation of imatinib which effectively controlled with ondansteron and thrombocytopenia which require no dose modification. Ricalde et al.[7], report three cases ("case 1," a 6-year-old boy; "case 2," a 6-year-old boy; "case 3," a 4-year-old girl) that have been treated with imatinib for at least 6 months of consistent treatment for a severe form of cherubism. Two cases underwent surgical debulking and tumor relapse before the initiation of treatment. They had treatment responses of 65%, 22%, and 75%, respectively, with reductions in tumor volume, no significant side effects reported except for nausea, and no reported effect on linear growth. Although they comment on partial compliance and difficult follow-up for treated cases, these results indicate that imatinib may have therapeutic potential for cherubism.

Denosumab is an inhibitor of the RANK ligand, which significantly suppresses the differentiation, proliferation, and activation of osteoclasts.[28] Denosumab has been reported in the literature as a possible pharmacological therapy for cherubism. Four cases («Case 1,» a 9-year-old boy; «Case 2,» a 19-year-old female; «Case 3,» a 15-year-old female; and «Case 4,» a 5-year-old female) from three published studies have been treated with denosumab.[13,29,30] Duration of treatment ranges from 6-12 months in which the response of treatment ranges from the dramatic clinical and radiographic response for pre-pubertal "cases 1, 4" and radiographic response without clinical effect on older ages "case 2, 3". In addition, significant toxicity associated with denosumab in the form of hypocalcemia may be asymptomatic " case 1"[13], or high-grade hypocalcemia requires hospitalization and modified subsequent doses and spacing e.g. "case 4".[30] An acute renal injury with hyperkalemia has been reported in patients treated with denosumab.[31] Also as a consequence of denosumab toxicity on the growth rate, it showed a decreased effect on growth for pre-pubertal age "case 1: after initiation of treatment and after 5 months from the end of therapy.[13] There were no significant adverse events reported for "case 2, 3".[29]

It has been reported that calcitonin is a feasible option for treatment for a severe form of central giant cell granuloma (CGCG). The rationale for administration is that it inhibits the osteoclastic activity of the giant cells and theoretically should have an effect on cherubism as the lesions are histologically indistinguishable from those in central giant cell granuloma, and the bone resorption by the multinucleate cells of cherubism is reduced by calcitonin in vitro.[32] There is limited data regarding calcitonin therapy for cherubism. Etoza et al.[11] And Lange et al.[33], two cases of cherubism ("case 1," a 14-year-old boy; "case 2," a 10-year-old boy) treated with salmon calcitonin nasal administration 200 IU for 30 months and 15 months, respectively, post-surgical reconstructive approach for both cases. A significant radiographic response has been reported for "case 1". In the second case, the lesions were stable and showed no regression for the first 12 months. After 15 months, an initial regression was noticed, and the therapy was terminated. The control CT scan, three months after cessation of therapy, showed a considerable regression of the lesions and a restoration of the normal contour of the mandible. There were no considerable side effects reported in either case.

Kadlub et al.[18] reported a 2-year-old with severe progressive cherubism with complete obstructive nostrils, enlarged mandibular lymph nodes, and orbital compression. Initially, a multiple decompression surgical approach was performed. Tacrolimus was introduced at the age of 4 years in two oral doses (0.15 mg/kg/day). After 12 months of initiation of treatment, a clinical improvement was documented by regression of lymph node enlargement, eruption of permanent teeth, and stabilization of tumor growth.

Bradley et al.[16] have presented a 12-year-old boy treated with oral alendronic acid 70 mg weekly as an adjuvant treatment to surgical debulking for severe cherubism. The duration of treatment initially continued for six months. After 24 months of evaluation, there was a slight progression of the maxillary lesion and a restart of treatment with alendronate for another 12 months, with no final result reported. No significant side effects of treatment were reported during the course of therapy (Table 2).

Anti-tumor necrosis factor (TNF-α antagonist) treatment in cherubism has been reported in the literature by Hero et al.[12] Two children, a 7.3-year-old boy and a 4.8-year-old girl, were treated for 2.5 years duration with adalimumab. After a course of treatment, reported cases did not respond to adalimumab. TNF-α antagonists may alter the formation of pathogenic giant cells but do not affect active cherubism.[12]

Conclusion

The observed therapeutic potential of imatinib for cherubism in this case study suggests a promising avenue for future exploration. However, further research is needed to establish a safe and effective

Table 2. Literature review on cherubism pharmacological therapy.

Author name/ country	No. of cases	Age (year)	Gender	Treatment protocol	Follow-up (months)	Results
Bradley, et al. (2020), UK.16	1	3	M	Alendronic acid, 70 mg PO weekly (*)	36	Limiting the need for more radical surgery
Kawamura, et al. (2020), Japan.13	1	9	M	Denosumab. s/c (120 mg/dose) at days 0, 7, and 28, and then every 4 weeks thereafter for 6 months	12	Maybe a therapeutic option for extensive and aggressive cherubism
Droma, et al. (2020), Israel.29	2	19,15	F	Denosumab, administered subcutaneously in 120 mg doses on days 1, 8, 15, and 28 and then every 28 days	15	A response to treatment was evident within 3 months
Ricalde, et al. (2019), USA.7	3	6,8,4	(1,2) M (3) F	Imatinib, 300 mg/ m2, PO daily dose (*)	24, 5, 10 respectively	Significant reduction of size by 75,22,65% respectively
Upfill-Brown, et al. (2019), USA.30	1	12	F	Denosumab, administered subcutaneously in 120 mg doses monthly doses	24	The therapy results in significant clinical and radiographic improvement for pediatric patients.
Kadlub, et al. (2014), France.18	1	4	M	Tacrolimus, two oral daily doses (0.15 mg/kg/day) with target trough level was 5 ng/ mL (*)	12	Showed enhanced bone formation by stimulating osteogenesis
Hero, et al. (2012), Finland.12	2	(1) 7.3 (2) 4.8	(1) M (2) F	Adalimumab, 40 mg s/c every 2 weeks, for 2 years and 3 months (Patient 1) and 2 years and 7 months (Patient 2)	30	Does not appear to provide sufficient amelioration for patients
Etoz, et al. (2011), Turkey.11	1	14	M	Salmon calcitonin, using a nasal spray of 200 IU	30	Significant radiographic improvement was observed
Lange, et al. (2007), Netherlands.33	1	11	M	Salmon calcitonin, using a nasal spray of 200 IU	36	After 15 months, an initial regression reported

s/c: subcutaneously, (*): adjuvant therapy with surgical debulking , F=female, M=male.

protocol for imatinib treatment in pediatric cherubism.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Ueki Y, Lin CY, Senoo M, Ebihara T, Agata N, Onji M, Saheki Y, Kawai T, Mukherjee PM, Reichenberger E et al: Increased myeloid cell responses to M-CSF and RANKL cause bone loss and inflammation in SH3BP2 "cherubism" mice. Cell 2007, 128(1):71-83.
2. Kittaka M, Yoshimoto T, Hoffman H, Levitan ME, Ueki Y: RANKL-independent osteoclastogenesis in the SH3BP2 cherubism mice. Bone Rep 2020, 12:100258.
3. Jones WA: Familial Multilocular Cystic Disease of the Jaws. American Journal of Cancer 1933, 17:946-950.
4. Papadaki ME, Lietman SA, Levine MA, Olsen BR, Kaban LB, Reichenberger EJ: Cherubism: best clinical practice. Orphanet J Rare Dis 2012, 7 Suppl 1(Suppl 1):S6.
5. Ahmadzadeh K, Vanoppen M, Rose CD, Matthys P, Wouters CH: Multinucleated Giant Cells: Current Insights in Phenotype, Biological Activities, and Mechanism of Formation. Front Cell Dev Biol 2022, 10:873226.
6. Kueper J, Tsimbal C, Olsen BR, Kaban L, Liao EC: SH3BP2-related fibro-osseous disorders of the maxilla and mandible: A systematic review. Int J Oral Maxillofac Surg 2022, 51(1):54-61.
7. P R, I A, ST S: A Paradigm Shift in the Management of Cherubism? A Preliminary Report Using Imatinib. In., vol. 77. United States; 2019: 1278.e1271-1278.e1277.
8. Seward GR, Hankey GT: Cherubism. Oral Surg Oral Med Oral Pathol 1957, 10(9):952-974.
9. J K, C T, BR O, L K, EC L: SH3BP2-related fibro-osseous disorders of the maxilla and mandible: A systematic review. International journal of oral and maxillofacial surgery 2022, 51(1):54-61.
10. CH K, NM S, JD E, SG K, ME W: The surgical and orthodontic management of cherubism in a growing child. In., vol. 40. Scotland; 2012: 229-233.
11. OA E, D D, O G: Treatment of cherubism with salmon calcitonin: a case report. European journal of dentistry 2011, 5(4):486-491.
12. M H, A S, J H, P S, R K, H A, S A, S T-S, P L, O M: Anti-tumor necrosis factor treatment in cherubism--clinical, radiological and histological findings in two children. In., vol. 52. United States; 2013: 347-353.
13. H K, S W, T I, I A, H M, S D: Efficacy and safety of denosumab treatment in a prepubertal patient with cherubism. In., vol. 33. Germany; 2020: 963-966.
14. Erratum: Severe Cherubism Treated with Curettage, Osteotomy, and Bony Repositioning: A Case Series of Three Patients-Erratum, vol. 10. United States; 2022.
15. S J, J S, A S, P S: Surgical Treatment of Cherubism With the Use of ThreeDimensional Virtual Planning and CAD-CAM Resection Guides: A Case Report and Systematic Literature Review. In., vol. 33. United States; 2022: 1502-1506.
16. D B, V P, C H, M M: Adjuvant Alendronic Acid in the Management of Severe Cherubism: A Case Report and Literature Review. In., vol. 79. United States; 2021: 598-607.
17. SI L, I CH, L A: Denosumab Therapy in Cherubism. The Cleft palate-craniofacial journal : official publication of the American Cleft Palate-Craniofacial Association 2022:10556656221113891.
18. N K, MP V, L G, AC LH, L D, T U, B F, I P, C B, S M et al: The calcineurin inhibitor tacrolimus as a new therapy in severe cherubism. In., vol. 30. United States; 2015: 878-885.
19. M FG, L FdBPF, CM H, F AC, M CA: Clinical and surgical management of an aggressive cherubism treated with autogenous bone graft and calcitonin. In., vol. 2011. Egypt; 2011: 340960.
20. I P, G S, M M, T G, L P, R C: Ineffectiveness of tumor necrosis factor-alpha inhibition in association with bisphosphonates for the treatment of cherubism. In., vol. 29. Italy; 2011: 147.
21. Yoshitaka T, Ishida S, Mukai T, Kittaka M, Reichenberger EJ, Ueki Y: Etanercept administration to neonatal SH3BP2 knock-in cherubism mice prevents TNF-α-induced inflammation and bone loss. J Bone Miner Res 2014, 29(5):1170-1182.
22. VM C, PF P, FR A, PE dS, L DM, RS G: Novel mutations in the SH3BP2 gene associated with sporadic central giant cell lesions and cherubism. Oral diseases 2009, 15(1):106-110.
23. Bader-Meunier B, Van Nieuwenhove E, Breton S, Wouters C: Bone involvement in monogenic autoinflammatory syndromes. Rheumatology (Oxford) 2018, 57(4):606-618.
24. B T, RJ P, C M, AKM F, Z F, J B: Response of Central Giant Cell Granuloma of the Jaw to Imatinib. Journal of pediatric hematology/oncology 2022.
25. Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP, Baccarani M, Deininger MW, Cervantes F, Fujihara S et al: Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. N Engl J Med 2017, 376(10):917-927.
26. Marcucci G, Perrotti D, Caligiuri MA: Understanding the molecular basis of imatinib mesylate therapy in chronic myelogenous leukemia and the related mechanisms of resistance. Commentary re: A. N. Mohamed et al., The effect of imatinib mesylate on patients with Philadelphia chromosome-positive chronic myeloid leukemia with secondary chromosomal aberrations. Clin. Cancer Res., 9: 1333-1337, 2003. Clin Cancer Res 2003, 9(4):1248-1252.
27. Rambhatla A, Strug MR, De Paredes JG, Cordoba Munoz MI, Thakur M: Fertility considerations in targeted biologic therapy with tyrosine kinase inhibitors: a review. J Assist Reprod Genet 2021, 38(8):1897-1908.
28. Baron R, Ferrari S, Russell RG: Denosumab and bisphosphonates: different mechanisms of action and effects. Bone 2011, 48(4):677-692.
29. E BD, G B-R, A I, Y F, C A-D, N L, N G: Positive Outcomes of Denosumab Treatment in 2 Patients With Cherubism. In., vol. 78. United States; 2020: 2226-2234.
30. A U-B, S B, NM B, AL F, SD N, A S, K W-P, FC E, NC F: Use of Denosumab in Children With Osteoclast Bone Dysplasias: Report of Three Cases. JBMR plus 2019, 3(10):e10210.
31. Uday S, Gaston CL, Rogers L, Parry M, Joffe J, Pearson J, Sutton D, Grimer R, Högler W: Osteonecrosis of the Jaw and Rebound Hypercalcemia in Young People Treated With Denosumab for Giant Cell Tumor of Bone. J Clin Endocrinol Metab 2018, 103(2):596-603.
32. R B, AM M, A C: [A diagnostic protocol in cherubism]. In., vol. 47. Italy; 1998: 447-451.
33. J dL, HP vdA, M S: Cherubism treated with calcitonin: report of a case. In., vol. 65. United States; 2007: 1665-1667.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.20

CASE REPORTS

A RARE CASE OF AICARDI-GOUTIÈRES SYNDROME WITH NOVEL RNASEH2C GENE MUTATION: A COMPREHENSIVE CLINICAL AND MOLECULAR ANALYSIS

Deepak Mulchandani, Vaishali Singh, Omkar Shelke.

Department of Paediatrics, Bombay Hospital, Mumbai.

ABSTRACT

Aicardi-Goutières syndrome (AGS) is a rare autosomal recessive disorder characterized by early-onset encephalopathy, intracranial calcifications, white matter disease, and elevated interferon-alpha levels in cerebrospinal fluid. This case report presents the clinical and molecular details of a 9-month-old male infant with AGS, harboring mutations in the RNASEH2C gene. The patient exhibited global developmental delay, hearing impairment, and a family history of similar presentations. Whole exome sequencing identified two pathogenic variants in RNASEH2C. This report provides insights into the varied phenotypic features of AGS and emphasizes the importance of genetic testing for accurate diagnosis.

ARTICLE HISTORY

Received : 01 November 2023

Accepted : 11 March 2024

KEYWORDS

Aicardi-Goutières syndrome, RNASEH2C gene, whole exome sequencing, encephalopathy.

Introduction

Aicardi-Goutières syndrome (AGS) is a rare inherited encephalopathy, known for its clinical heterogeneity and genetic basis. It is characterized by intracranial calcifications, white matter abnormalities, and elevated levels of interferon-alpha in the cerebrospinal fluid.[1] Chilblain lesions on the hands, feet and intermittent sterile pyrexias have been reported and can be clues for the diagnosis of AGS.[2] AGS is associated with mutations in several genes, including RNASEH2C. Here, we present a case of AGS with RNASEH2C gene mutations in an infant with a complex clinical history.

Case Report

A 9-month-old male infant, born to non-consanguineous parents, was evaluated for global developmental delay and bilateral sensorineural hearing loss. The child's birth history revealed a term, intrauterine growth-restricted baby with low birth weight. Early life was marked by recurrent, unexplained fevers and developmental regression starting at 3 months of age, reminiscent of AGS characteristics. Interestingly, two elder male siblings also exhibited similar clinical features and died in early adolescence. In contrast, a 3-year-old female sibling was neurologically normal. Clinical examination of the infant revealed microcephaly, light coloured hair, no response to sound and spastic quadriparesis. Routine blood investigations along with thyroid profile, serum lactate and serum ammonia were normal. Urine gas chromatography and Tandem mass spectrometry was also normal. Fundus examination showed left gaze preference with mildly hypopigmented fundus showing inadequate response to bright light. BERA was suggestive of retrocochlear involvement affecting both auditory pathways at upper and lower brain stem level with increased hearing threshold. VEP revealed positive replicable response but no fixation and no response to bright light. TORCH titres were negative and EEG was normal. Magnetic resonance imaging (MRI) was suggestive of cerebral atrophy and intracranial calcifications. CSF studies were unremarkable. Genetic analysis through whole exome sequencing identified two heterozygous variants in RNASEH2C: a novel variant (c.178G>T, p.Glu60) and a known pathogenic variant (c.205C>T, p.Arg69Trp).

Discussion

Aicardi-Goutières syndrome is a rare disease which is transmitted through autosomal recessive mode of inheritance. It has a prevalence of 1-5 in 10,000 newly live births.[3] The disease should not be confused with Aicardi Syndrome which is a rare genetic malformation syndrome characterized by the partial or complete absence of a key structure in the brain called the corpus callosum, the presence of retinal lacunes, and epileptic seizures in the form of infantile spasmsand is almost exclusively seen in females suggesting a X-Linked dominant disorder.[4] In contrast, Aicardi Goutieres Syndrome presents with variable clinical features often resembling cerebral palsy and congenital intrauterine infections like TORCH group of infections. RNASEH2C (Ribonuclease H2 Subunit C) is a protein coding gene which encodes a ribonuclease H subunit that can cleave ribonucleotides from RNA:DNA duplexes. Mutations in this gene cause Aicardi-Goutieres syndrome type 3. Genetic testing such as whole exome sequencing, plays a crucial role in accurate diagnosis. We identified 2 types of RNASEH2C variants, a novel likely pathogenic variant and a pathogenic variant which were consistent with AGS type 3. These variants lead to impaired RNASEH2C function and have been previously associated with AGS. The patient on whole exome testing had one copy (heterozygous) of a non-sense variant, Variant 1 (c.178G>T; p.Glu60) in RNASEH2C gene which is predicted to cause premature truncation of the protein. The variant has been reported in dbSNP database with an identification number: rs941076637.[5] This variant seems to be novel as it has not been previously reported in literature. Since, this variant is predicted to produce a

Address for Correspondance:

Deepak Mulchandani, Room no 1103, MRC wing, Bombay Hospital, 12, new marine lines, Mumbai - 400042.

Email: elfagieh@yahoo.com

truncated protein which might result in loss-of-function and other truncating variants in this gene are also known to cause similar phenotype, therefore, this variant was labelled as Likely Pathogenic. Another mutation in RNASEH2C gene labelled as Variant 2 (c.205C>T; p.Arg69Trp) which affects the protein function was also detected. The variant has been reported in dbSNP database with an identification number: rs78635798 and in the Genome Aggregation Database (gnomAD) with a rare allele frequency of 0.009169%. Also, ClinVar database reports the clinical significance of this variant as 'pathogenic' (VCV000001260.31). The identified variant has been previously identified in patients affected with Aicardi-Goutieres syndrome 3 in heterozygous state.[6] However, the parents did not give consent for further carrier testing.

Conclusion

This case report highlights the clinical and molecular aspects of Aicardi-Goutières syndrome, emphasizing the importance of genetic testing in diagnosing this rare disorder. The clinical variability and novel mutations observed in this case further underscores the challenge of distinguishing AGS from other conditions. Increasing awareness of AGS and its genetic underpinnings can aid in early diagnosis and management.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Aicardi J, Goutières F. A progressive familial encephalopathy in infancy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. Ann Neurol 1984;15:49-54.
2. Rice G, Patrick T, Parmar R, Taylor CF, Aeby A, Aicardi J, et al. Clinical and molecular phenotype of Aicardi-Goutières syndrome. Am J Hum Genet 2007;81:713-25.
3. Viguera-Elías D, de la Iglesia-Nagore I, Toledo-Gotor C, Domínguez-Garrido E, Poch-Olivé ML. Aicardi-Goutières syndrome: a family case due to alteration of the RNASEH2B gene. Rev Neurol 2021;72 (11):407-409.
4. Rosser T. Aicardi Syndrome. Arch Neurol. 2003;60(10):1471-1473.
5. https://www.ncbi.nlm.nih.gov/gene/84153
6. Hebbar M, Kanthi A, Shrikiran A, Patil S, Muranjan M, Francis F, Bhat B V, Girisha KM, Shukla A. p.Arg69Trp in RNASEH2C is a founder variant in three Indian families with Aicardi-Goutières syndrome. Am J Med Genet A. 2018 Jan;176(1):156-160. doi: 10.1002/ajmg.a.38522. Epub 2017 Nov 17.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.19

CASE REPORTS

AN UNEXPECTED CAUSE OF RIGHT UPPER QUADRANT ABDOMINAL PAIN IN A TEENAGER

Marta Pelicano[1], Mariana Eiras Dias[1], Ana Lança[2], Rita Belo Morais[1]

[1]Pediatrics Department, Hospital de São Francisco Xavier, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal,

[2]Pediatrics Department, Hospital Beatriz Ângelo, Lisbon, Portugal.

ABSTRACT

A previously healthy, sexually active 17-year-old female was admitted to our hospital with a 4-day history of right upper quadrant abdominal pain associated with high fever, vomiting and diarrhea. On examination there was tenderness in right hypochondrium. Gynecological exam revealed sparse vaginal bleeding and pain on deep palpation and mobilization of the cervix and adnexa. Abdominal computed tomography scan showed signs of inflammation of the pelvic adipose tissue. While other etiologies were excluded, identification of Neisseria gonorrhoeae using the PCR method in the urine lead to the diagnosis of Fitz-Hugh-Curtis syndrome. Fitz-Hugh-Curtis syndrome is an association between pelvic inflammatory disease and peri-hepatitis, and usually manifests as pain in the right hypochondrium. Right hypochondrium pain has an extensive differential diagnosis, however this syndrome should be considered in sexually active adolescents, which is essential for a targeted treatment and prevention of complications.

ARTICLE HISTORY

Received : 13 December 2023

Accepted : 11 March 2024

KEYWORDS

Fitz-Hugh-Curtis syndrome; Pelvic inflammatory disease; Perihepatitis; Neisseria gonorrhoeae.

Case Report

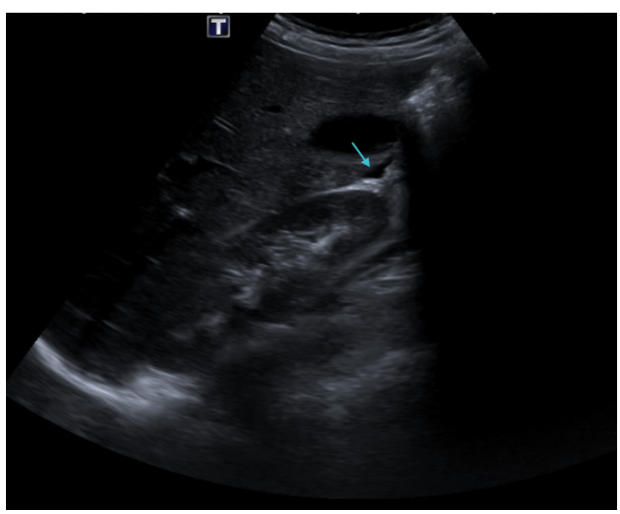
A previously healthy, 17-year-old female, presented to the emergency department with intense right upper quadrant abdominal pain. Four days before admission she noticed a persistent right upper quadrant abdominal pain, along with high fever, vomiting and diarrhea. She had started vaginal bleeding day before admission.

Her menarche was at 11 years of age, and she had started unprotected sexual activity 6 months before this observation. She took no medication and had never experienced similar symptoms.

On palpation, there was tenderness in right hypochondrium. A gynecological exam revealed sparse vaginal bleeding and pain on deep palpation and mobilization of the cervix and adnexa. Blood analyses revealed hemoglobin of 11.8 g/dL, mild leukocytosis (16.9 x 10^9/L) and neutrophilia (87.5%; 14.79 x 10^9/L) and an elevated C-reactive protein of 259 mg/L, with a normal amylase, lipase, and renal and liver function tests. Urinalysis revealed countless erythrocytes, rare leukocytes and no nitrites. Endocervical culture was negative and Neisseria gonorrhoeae was isolated using the PCR method in the urine sample. The chest X-ray was normal. Abdominal and pelvic computed tomography (CT) scan, was suggestive of signs of inflammation of the pelvic adipose tissue. Pelvic inflammatory disease (PID) was suspected so the patient was started on intravenous ceftriaxone and metronidazole plus oral doxycycline. During hospitalization, a repeated pelvic and abdominal ultrasound revealed mild hepatomegaly and perihepatic fluid (Figure 1). Serologies performed for other sexually transmitted diseases were negative (HIV, syphilis, B and C hepatitis). Considering the clinical presentation, laboratory and imaging findings, the patient was diagnosed with a PID complicated with peri-hepatitis, hence Fitz-Hugh-Curtis Syndrome (FHCS).

She had a gradual clinical and laboratory improvement and was discharged after 5 days, with a 14-day course of oral doxycycline and metronidazole. Advice was given on treating previous sexual partners. Two months later, on follow-up consultations the patient was asymptomatic and had a negative endocervical PCR test for *Neisseria gonorrhea* and *Chlamydia trachomatis*.

Figure 1. Abdominal ultrasound showing peri-hepatic fluid in hepatorenal recess (blue arrow).



Address for Correspondance:
Marta Pelicano, Estrada Forte do Alto Duque, 1449-005, Lisboa, Portugal.
Email: mblpelicano@gmail.com

Discussion

FHCS is an association between PID and perihepatitis, occurring in about 10-30% of PID cases. Classically it manifests as right hypochondrium pain, worsening during deep breathing. Patients may also complain of lower abdominal, pelvic, or back pain with varying degrees of severity. Other symptoms include fever, chills, vaginal discharge and dyspareunia.[1,2,3,4,5,6]

Differential diagnosis is wide and includes cholecystitis, peptic ulcer, appendicitis, pancreatitis, urinary tract infection, renal colic and pneumonia.[2,3,4,5,6,7] Although the diagnosis is clinical, some exams are helpful to exclude other diseases, namely imaging exams, and to identify the pathogen. In this syndrome there is perihepatitis without involvement of the hepatic parenchyma, so there is an absent or discreet elevation of liver transaminases.[1,2,3] White blood cells count and inflammatory parameters may also be elevated. Initially it was associated mostly with Neisseria gonorrhoeae infection, but currently Chlamydia trachomatis is considered its main agent.[2,3] Cultures are widely used for pathogen identification, but use of polymerase chain reaction (PCR) tests is increasing due to their high sensitivity and specificity (including vaginal swab, cervical swab and urine samples).[1] Laparoscopy is the gold-standard exam for diagnosis, but it is seldom used for its invasiveness. It allows identification of the characteristic "violin-string adhesions" between the liver and the diaphragm or the anterior wall of the abdomen, as well as the presence of edema, exudate or fluid collections.[2,3] Abdominal and pelvic ultrasounds are the most frequently used exams, making it possible to exclude other diagnosis and identify signs of PID and its complications, including fluid in the subcapsular/hepatorenal space, compatible with FHCS.[1] Abdominal and pelvic CT may also be useful in the differential diagnosis and the visualization of findings suggestive of FHCS – thickening of the hepatic capsule and fluid in the subcapsular/hepatorenal space.[3,4,5,6,7,8]

FHCS treatment consists of antibiotic therapy for PID. Mechanical lysis of the adhesions may be performed laparoscopically if conservative treatment fails.[1,2] Patients should be advised on the importance of safe sex practices to avoid PID and once the diagnosis is made, sexual partners should be treated to halt disease transmission.[7,9,10]

In our case, Neisseria gonorrhoeae was identified in the urine sample by PCR test, which lead to the diagnosis. Despite the isolation of Neisseria gonorrhoeae, the treatment is targeted at most likely pathogens, since isolation of all agents is unlikely. Therefore, due to the clinical severity, with need for hospitalization, she was started on intravenous antibiotic therapy with ceftriaxone and metronidazole plus oral doxycycline, switching for oral antibiotic therapy 5 days later, completing a 14-day course of oral doxycycline and metronidazole, in accordance with the Centers for Disease Control and Prevention guidelines.[9,10] A favorable clinical response was observed, with complete symptomatic resolution and on follow-up, she remained well and had a negative vaginal PCR for Neisseria gonorrhoeae and Chlamydia trachomatis.

The nonspecific presentation of FHCS as a complication of PID makes it a challenging diagnosis, delaying treatment initiation, which can lead to long-term complications, including chronic pelvic pain, ectopic pregnancy and infertility.[1,9] Clinicians should consider this syndrome in the differential diagnosis of right upper quadrant pain in the sexually active adolescent, as in the described case.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Peter N, Clark L, Jaeger J. Fitz-Hugh-Curtis syndrome: A diagnosis to consider in women with right upper quadrant pain. Cleveland Clinic Journal of Medicine. March 2004. Volume 71, number 3. Pages 233-239.
2. Theofanakis CP, Kyriakidis AV. Fitz-Hugh-Curtis syndrome. Gynecological Surgery. 2010. Volume 8. Pages 129-134.
3. Wang PY, Zhang L, Wang X et al. Fitz-Hugh-Curtis syndrome: clinical diagnostic value of dynamic enhanced MSCT. The Journal of Physical Therapy Science. 2015. Volume 27. Pages 1641-1644.
4. Weström L. Incidence, prevalence and trends of acute pelvic inflammatory disease and its consequences in industrialized countries. American Journal of Obstetrics Gynecology. December 1980. Volume 138. Pages 880-892.
5. Kreisel K, Torrone E, Bernstein K et al. Prevalence of Pelvic Inflammatory Disease in Sexually Experienced Women of Reproductive Age - United States, 2013-2014. Morbidity and Mortality Weekly Report. January 2017. Volume 66. Pages 80-83.
6. Shikino K, Ikusaka M. Fitz-Hugh-Curtis syndrome. BMJ case report. 2019. Volume 12.
7. Basit H, Pop A, Malik A et al. Fitz-Hugh-Curtis Syndrome. National Center for Biotechnology Information. January 2022.
8. Pires V, Sucena M, Basso S. Fitz-Hugh-Curtis syndrome: a case of perihepatitis in 'mosaic' pattern. BMJ Case Report. March 2022. Volume 15.
9. Jennings L, Krywko D. Pelvic Inflammatory Disease. National Library of Medicine. January 2022.
10. Workowsk K, Bachmann L, Chan P et al. Sexually Transmitted Infections Treatment Guidelines, 2021. Centers for Disease Control and Prevention. July 2021.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.18

CASE REPORTS

INFERIOR VENA CAVA AND COMMON ILIAC THROMBOSIS IN A NEWBORN TWIN

Gabriela Etzel Gomes de Sa[1], Miguel Machado Carlos Lopes[2], Raquel Alexandra Barbosa de Nunes Gouveia Lopes[2], Isabel Sampaio[2], Maria da Graça Rocha Oliveira[2], Rita Espírito Santo[2], Maria João Palaré[2]

[1]Faculdades Pequeno Príncipe, Curitiba, PR, Brasil,

[2]Departamento de Pediatria do Centro Hospitalar Universitário Lisboa Norte, EPE, Lisboa, Portugal.

ABSTRACT

Introduction: Neonatal thrombosis affects approximately 3 to 5 out of every 100,000 newborns, with a mortality rate of 2 to 4%. Its occurrence may be associated with conditions involving the mother and the fetus/newborn and/or related to the medical assistance.

Case description: A full-term newborn (NB) of biamniotic bicorionic twin pregnancy, with excellent adaptation to extrauterine life, presented sudden hematuria at 28 hours of life, evolving with the need for invasive ventilation and hemodynamic support. Abdominal ultrasound revealed extensive venous thrombosis affecting the infrahepatic inferior vena cava and common iliac veins. The anatomopathological study of the placenta revealed the presence of an intervillous thrombus measuring 1.5 centimeters. The thrombotic condition was managed by the use of subcutaneous Enoxaparin and hospital discharge occurred after 45 days of hospitalization.

Discussion: The thrombus found in the intervillous space of the placenta suggests that it was the result of a maternal coagulative response as a result of a disturbance in maternal-fetal blood flow. Therefore, we believe that the thrombus found in the NB has the same origin as the thrombus found in the placenta, suggesting that the placental intervillous coagulation product has migrated to the fetal circulation. It is recommended to start the investigation of neonatal venous thrombosis through Doppler ultrasound. With regard to treatment, the agents of choice are low molecular weight heparins (LMWH), especially subcutaneous Enoxaparin sodium. It is understood that the mother-fetus binomial faced hemodynamic disorders, however, etiopathogenic clarifications are still lacking to define the triggering factor of the coagulation dysfunction.

ARTICLE HISTORY

Received : 12 December 2023

Accepted : 04 March 2024

KEYWORDS

Venous thrombosis, newborn, enoxaparin

Introduction

Neonatal thrombosis is defined by the occurrence of a thrombus occluding a blood vessel, being it a vein or an artery in a newborn (NB).[1] In recent years, the incidence of thrombotic events in NBs has been increasing as a result of diagnostic advances. of this pathological condition in this period.[2] Excluding the occurrence of Cerebral Vascular Accident (CVA), it is estimated that the incidence of thrombosis in neonates is around 2.5 to 15 per 1000 babies admitted to neonatal intensive care units (NICU), and 3 to 5 NBs per 100,000 births. Furthermore, it is estimated that 2 to 4% of these NBs die directly as a result of the thrombosis.[1,3,4]

Its occurrence in NBs may be associated with the immaturity of the coagulation system of these babies, as they have reduced levels of anticoagulants, as well as lower levels of fibrinolytic components. In addition, the occurrence of neonatal thrombosis is associated with risk factors inherent to the baby, as well as maternal risk factors, related to childbirth and the care process of health care for newborns.[2,3,5]

The main risk factors associated with the development of neonatal thrombosis include maternal factors such as primiparity, infertility, thrombophilia and autoimmune diseases, placental thrombosis, comorbidities (diabetes mellitus, dyslipidemia, preeclampsia), intrauterine growth restriction (IUGR), prolonged rupture and/or premature birth of ovular membranes and placental abruption, as well as neonatal factors, being the main ones the use of central catheters, sepsis, perinatal asphyxia, medications (e.g. corticosteroids), comorbidities (liver dysfunction, kidney disease, congenital heart disease, polycythemia, thrombophilia), among others. In addition, risk factors related to childbirth are also highlighted, such as emergency cesarean section, shoulder dystocia, changes in fetal heart rate and instrumented delivery.[1,2,3,4,5]

Case Report

Male newborn, son of a 32-year-old mother, with two previous pregnancies and history of infertility. The current pregnancy resulted from the implantation of two previously frozen embryos. No comorbidities were mentioned. During the gestational period, the mother was using acetylsalicylic acid (ASA), iodine and folic acid. Prenatal records showed immunity to

Address for Correspondance:
Gabriela Etzel Gomes de Sá, : Rua Ângelo Nabosne, 75, ap 803.
Email: gabrielaegsa@hotmail.com

Figure 1. Doppler flow interruption in the inferior vena cava due to a thrombus.

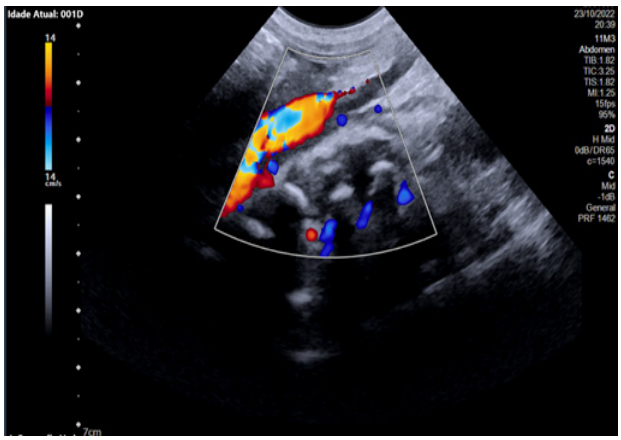
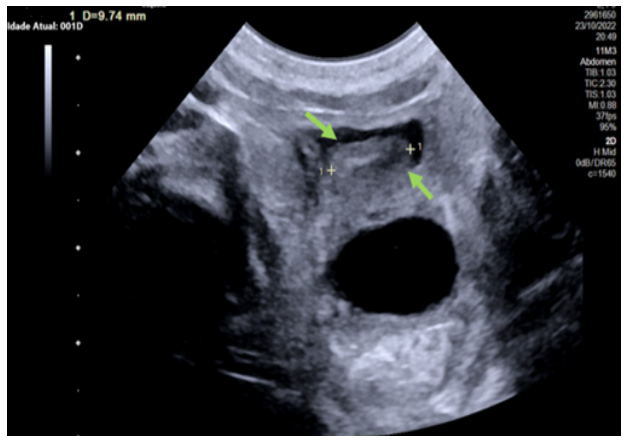


Figure 2. Visible thrombus inside the inferior vena cava measuring nine millimeters.



toxoplasmosis and cytomegalovirus, other serologies and infectious screening were negative. Screening for gestational diabetes mellitus was also negative. Paternal age of 36 years old, without comorbidities. There is no history of consanguinity or morbid family history relevant to the case.

First twin of biamniotic bicorionic twin gestation, born by elective cesarean delivery, with gestational age of 37 weeks and 1 day. The NB's anthropometric measurements were adequate for the gestational age. The apgar score was 10 in the first minute of life and 10 in the fifth minute, with excellent spontaneous adaptation to extrauterine life. The physical examination showed no alterations. No macroscopic changes were noted in the placenta or umbilical cord. The placenta was sent for anatomopathological study.

At 28 hours of life (D2 of life), the NB presented macroscopic hematuria with the presence of clots associated with paleness, jaundice, tachypnea, signs of poor peripheral perfusion and abdomen without palpable masses. He was referred to the Neonatal Intensive Care Unit (NICU), with significant hemodynamic deterioration requiring cardiorespiratory support with invasive ventilation and vasoactive drugs.

Laboratory tests revealed the presence of anemia, lactic acidosis, thrombocytopenia, elevated inflammatory activity tests and compromised renal function. Chest X-rays and transfontanellar ultrasound were performed, which showed no alterations. Abdominal ultrasound confirmed the presence of echogenic content in the lumen of the infrahepatic inferior vena cava and both common iliac veins, with no color Doppler signal at these levels, suggestive of extensive venous thrombosis (Figures 1 and 2).

Therapy with subcutaneous enoxaparin was started on the same day. In the view of positive infectious parameters and multisystemic involvement, ampicillin and cefotaxime were started. At 42 hours of life (D3), the clinical picture worsened with severe metabolic acidosis with hyperlactatemia, acute kidney injury, anemia and thrombocytopenia. The blood culture was negative.

The control abdominal ultrasound revealed the persistence of signs of extensive thrombosis of the IVC and bilateral common iliac veins and probable caudal extension to the right internal iliac vein and superior portion of the right external iliac vein, with involvement of the bilateral renal veins, umbilical vein thrombosis and hepatosplenomegaly On D7, there was clinical and laboratory improvement. On D21 of life, a new abdominal ultrasound showed a reduction in the dimensions of the thrombus in the IVC and in the renal veins, as well as resolution of the hepatosplenomegaly. The diagnostic investigation was complemented with metabolic screening, chromatography of organic acids in urine and aminoacids in blood and urine, study of prothrombotic factors in the mother and baby, which did not reveal abnormalities relevant to the case. The NB remained hospitalized up to 45 days of life until reaching significant weight gain.

The anatomopathological study of the placenta revealed the presence of an intervillous thrombus measuring 1.5 centimeters in its longest axis, with no other alterations. In the placenta of the other twin, which did not show thrombotic clinical manifestations, a hemorrhagic area was identified adjacent to the insertion of the membranes of the fetal face, as well as a hematoma on the maternal face. No other alterations were described in the examination report.

Discussion

It is suggested that venous thromboembolism in pediatric patients is mainly caused by the association of at least two prothrombotic risk factors and result in longer hospitalization, manipulation of central catheters and increased risk of bleeding due to the institution of anticoagulant therapy.[2,6] The reported case describes a male NB, born at term without intercurrences, resulting from in vitro fertilization (IVF) of frozen embryos from a mother with a history of infertility, however, without any other aspects that suggest the etiopathology of thrombosis.

Later in the investigation, the study of the placenta revealed the presence of an intervillous thrombus with 1.5 cm, with no other alterations. The intervillous space is occupied by maternal blood and ensures adequate fetal gas exchange. In this sense, disturbances of this blood flow result in a maternal coagulative response.[7,8] Given the above, we believe that the thrombus found in the NB has the same origin as the thrombus found in the placenta, suggesting that the

placental intravillous coagulation product has migrated to the fetal circulation of the affected twin.

A single-center retrospective cohort study conducted in the United States demonstrated that acute and chronic placental injuries often accompany neonatal thrombotic conditions, with 90% of neonatal stroke cases having at least one placental abnormality. The study reinforces that inflammatory conditions of the placenta, mainly fetal asphyxia and maternal infection, contribute to the formation of a placental embolus that subsequently reaches the fetal circulation.[9]

Regarding the pathophysiology of thrombosis, Virchow's triad describes three important components of thrombus formation – hypercoagulability, endothelial injury, and abnormal blood flow.[8] In order to determine whether placental changes occur as a result of thrombus formation, an American experimental study carried out with mice suggested that damage to the placental vasculature after exposure to intrauterine inflammatory conditions may result in blood flow stagnation and, consequently, vascular damage. Thus, in addition to hypercoagulability, translated by the gestational period itself, changes in blood flow resulting from the intrauterine inflammatory environment and possible endothelial damage represent the second and third pillars of Virchow›s triad.[10,11]

Regarding the diagnostic approach, it is recommended to start the investigation of babies with venous thrombosis through Doppler ultrasound, which is the first-line imaging exam, in addition to the anatomopathological study of the placenta and minimally invasive laboratory tests, such as blood count, coagulogram (PT, TT, a PTT, fibrinogen and D-dimer), protein C, protein S, antithrombin, lupus anticoagulant, anti-cardiolipin antibodies, anti-beta 2-glycoprotein 1 antibodies, factor V Leiden, prothrombin G20210A genetic mutations and Von Willebrand factor (vWF) research.[2,3]

With the aim of preventing the development of embolism and restoring blood flow interrupted by thrombosis, the agents of choice for treatment are low molecular weight heparins (LMWH), especially Enoxaparin sodium, which should be administered at a dose of 1.5 to 1.7 mg/kg, subcutaneously, every twelve hours, for 6 weeks to three to six months, according to the 2022 Neonatal Thrombosis Consensus of the Portuguese Society of Neonatology, still under public discussion. Monitoring should be performed with measurement of anti-Xa levels approximately four hours after administration of the second dose of LMWH and weekly thereafter. Unfractionated heparin (UFH) is an alternative when LMWH is unavailable, but it can only be used in cases where antithrombin levels are adequate, in addition to having a short half-life and variable bioavailability. A major advantage of using LMWH compared to UFH is the reduction in platelet factor IV and osteoblasts, reducing the risk of heparin-induced thrombocytopenia and osteopenia.[2]

Despite its rare occurrence and, mainly, its little-described presentation regarding risk factors and etiologies, fortunately, the described case was successfully managed through high clinical suspicion and the use of effective and efficient diagnostic methods, such as ultrasonography, as well as through subcutaneous therapy with Enoxaparin. There are still etiopathogenic clarifications to be made in order to define the triggering factor of coagulation dysfunction in the placenta and in the affected twin. It is hoped that sharing the experience acquired with the management of this case will serve as a subsidy for new perspectives and research on neonatal thrombosis. The importance of disseminating information on rare cases of neonatal thrombosis is also highlighted, so that more studies on this pathological condition can be directed, mainly regarding etiological investigation and prevention. The hypothesis arises that there may be conditions or situations that lead to the occurrence of thrombosis in newborns that are still unknown by the scientific community.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Robinson V, Achey MA, Nag UP, et al. Thrombosis in infants in the neonatal intensive care unit: Analysis of a large national database. J Thromb Haemost. 2021;19(2):400-7.
2. Makatsariya A, Bitsadze V, Khizroeva J, et al. Neonatal thrombosis. J Matern Neonatal Med. 2022;35(6):1169-77. Available from: https://doi.org/10.1080/14767058.2020.1743668.
3. Sociedade Portuguesa de Neonatologia. Consenso clínico "Trombose Neonatal". Portugal, 2022.
4. Bhatt MD and Chan AKC. Venous thrombosis in neonates. Faculty Reviews 2021 10:(20). Available from: https://doi.org/10.12703/r/10-20.
5. Kenet G, Cohen O, Bajorat T, et al. Insights into neonatal thrombosis. Thromb Res [Internet]. 2019; 181(March):S33-6. Available from: https://doi.org/10.1016/S0049-3848(19)30364-0.
6. Bhat R, Kumar R, Kwon S, et al. Risk Factors for Neonatal Venous and Arterial Thromboembolism in the Neonatal Intensive Care Unit-A Case Control Study. J Pediatr [Internet]. 2018; 195:28-32. Available from: https://doi.org/10.1016/j.jpeds.2017.12.015.
7. Sukhanova M, Mithal LB, Otero S, et al. Maternal vs Fetal Origin of Placental Intervillous Thrombi. Am J Clin Pathol. 2022; 157(3):365-73.
8. Arêas ALBG, Neto ARB. Patologia Geral. Capítulo 10: Patologia Feto Placentária. Sociedade Brasileira de Patologia. São Paulo - SP, 2022.
9. Leon RL, Kalvacherla V, Andrews MM, et al. Placental pathologic lesions associated with stroke in term neonates. Front Endocrinol (Lausanne). 2022; 13 (September): 1-9.
10. Lowe GDO. Virchow's Triad Revisited. 2004;109 (February): 213-5.
11. Eloundou SN, Lee JY, Wu D, et al. Placental malperfusion in response to intrauterine inflammation and its connection to fetal sequelae. PLoS One. 2019; 14(4):1-15.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.69

CASE REPORTS

SUPRACARDIAC TAPVC WITH COMPLETE HEARTBLOCK : AN UNCOMMON ASSOCIATION

Saurabhi Das[1], Deepali Bangalia[2], Siddhartha Jayantkumar Joshi[2]

[1]Department of Fetal And Paediatric cardiology, Health City Hospital, Guwahati,

[2]Department of Paediatric cardiology, The Mission Hospital, Durgapur.

ABSTRACT

Supracardiac total anomalous pulmonary venous connection (TAPVC) associated with complete heart block is an uncommon association. We present a case of a 5 month old baby with isolated Supracardiac TAPVC and complete heart block. The patient underwent rerouting of pulmonary veins and an epicardial pacemaker implantation and is doing well on follow up.

ARTICLE HISTORY

Received : 13 July 2024

Accepted : 11 September 2024

KEYWORDS

Supracardiac TAPVC, complete heart block, epicardial pacemaker

Introduction

Congenital complete heart block (CHB) is well described in a number of structural heart defects. Corrected transposition of great artery, heterotaxy syndromes are well known association of CHB.[1] Totally anomalous pulmonary venous return (TAPVR) can be isolated or associated with other major heart defects. The commonly described association of TAPVR are Tetralogy of fallot, double outlet right ventricle, ventricular septal defect and patent

ductus arteriosus. Association of CHB and TAPVR in a non heterotaxy background has not been described before. We present a case of a 5 month old baby who presented to us with such an association and was successfully treated with pulmonary venous rerouting to the left atrium and epicardial permanent pacemaker implantation.

Case Report

A five month old baby girl weighing 4.5 kg was brought to our attention with a murmur incidentally diagnosed at vaccination. She had an uneventful birth history and had no significant past or family history. On detailed evaluation she had tachypnea and desaturation (SpO2-91%).

She was noted to have a slow heart rate and a split second sound and hepatomegaly. Chest Xray (Figure 1), showed features of right sided volume overload with plethoric lung fields. 12 lead ECG (Figure 2) revealed Complete heart block with ventricular rate of 65/minute.

On further evaluation by echocardiogram, she was found to have a Supracardiac TAPVR (Figure 3, 4). All the pulmonary veins formed a common confluence which was draining into the right superior vena cava (RSVC) via ascending vertical vein and left innominate vein. There was stenosis at the point of joining of the vertical vein to the left Innominate vein. RSVC drained into right atrium (RA) with an ostium secundum atrial septal defect (ASD) allowing mixture between the right and left atria. (LA) There was also a significant size patent arterial duct.

Address for Correspondance:
105 Boys Hostel, The mission hospital, Durgapur, 713201.
Email: Dr.siddharthajoshi@gmail.com

Figure 1. Chest Xray showing dilated right atrium and prominent right. Superior vena cava with plethoric lung fields.

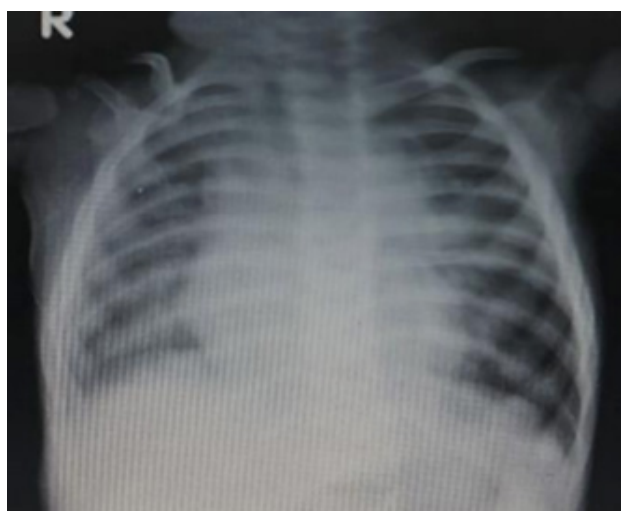


Figure 2. 12 lead ECG showing Complete heart block.

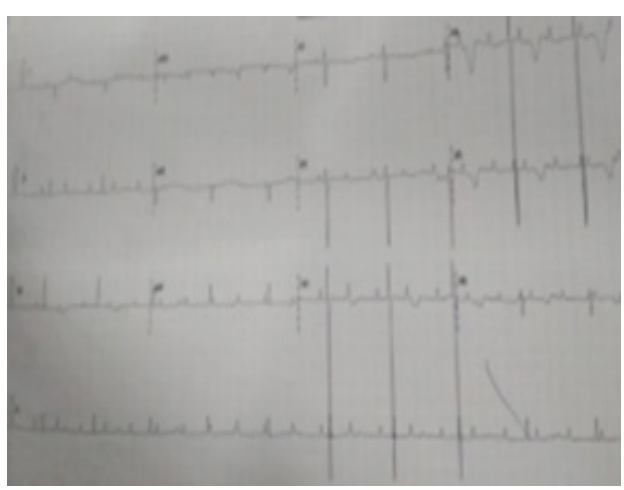


Figure 3. Four-chambered view showing a pulmonary venous confluence behind LA.

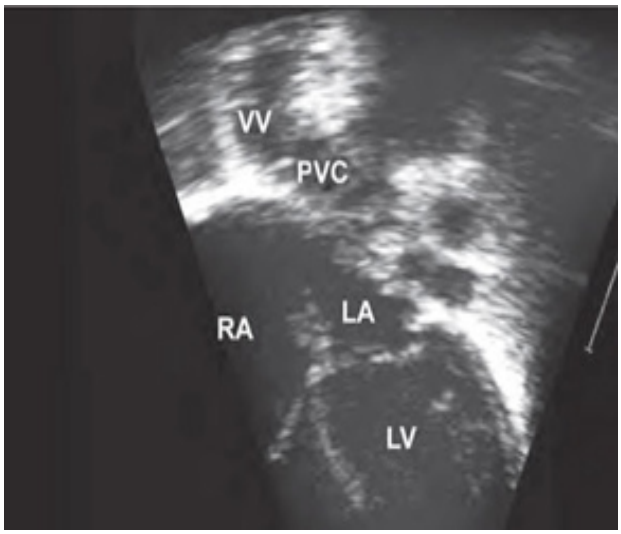
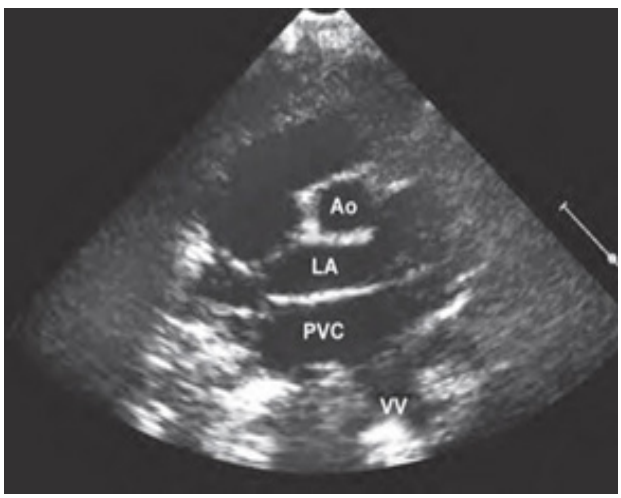


Figure 4. Parasternal long axis view on echocardiography showing all pulmonary veins forming a common confluence behind LA.



The baby underwent corrective surgery with anastomosis of common pulmonary venous chamber to LA, ligation of vertical vein, duct ligation and closure of ASD.. A single chamber epicardial pacemaker was implanted. She had difficult postoperative course complicated by low cardiac output state which was managed by temporary A-V sequential pacing and inotropes. The patient was successfully discharged home on 15th postoperative day and is doing well on follow up.

Discussion

Supracardiac TAPVR with complete heart block is a rare association. To the best of our knowledge this association in a non-heterotaxy setting has not been described before in literature. CHB is well known to occur with heterotaxy specifically left atrial isomerism along with pulmonary venous anomaly (reference). Arrhythmias, usually supraventricular, have been amply recorded in asymptomatic patients after anatomically successful repair of total anomalous pulmonary venous connections, and rarely complete heart block results.[1] Our patient had no lateralization defect as documented by X-ray chest and abdomen and echocardiogram. We implanted an epicardial single chamber pacemaker. In the post-operative period the patient went into low cardiac output state due to ventricular dysfunction for which she was kept on dual chamber temporary pacing. Permanent ventricular pacing was instituted after 5 days. We would like to highlight two important facts in this case; first she presented with yet undescribed but a very important association of TAPVR. Secondly the single chamber epicardial pacing which was placed during primary TAPVR repair was insufficient to maintain cardiac output in the immediate post operative period because of loss of atrial influence on ventricular ejection which was overcome by temporary A-V sequential pacing.

Conclusion

TAPVC and complete heart block is a rare association in a normally differentiated heart. It is necessary that all cases should be evaluated preoperatively for rhythm disturbances before the repair.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Saxena A, Fong LV, Lamb RK et al. Cardiac arrhythmias after surgical correction of total anomalous pulmonary venous connection: late follow-up. PediatrCardiol1991; 12: 89-91.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.68

CASE REPORTS

PROBABLE EPSTEIN-BARR VIRUS ENCEPHALITIS PRESENTING WITH STATUS EPILEPTICUS IN AN 8-YEAR-OLD

André Salvada[1], Mariana Fidalgo Silva[1], Andreia Filipa Mota[1], Francisca Costa[1], Susana Rocha[2], Luís Rito Cruz[3], Paula Correia[1], Catarina Luís[1]

[1]Child and Youth Department, Unidade Local de Saúde de Amadora/Sintra, Amadora, Portugal,

[2]Pediatrics Department, Unidade Local de Saúde do Arco Ribeirinho, Barreiro, Portugal,

[3]Neuroradiology Department, Unidade Local de Saúde de Amadora/Sintra, Amadora, Portugal.

ABSTRACT

Epstein-Barr virus (EBV) infection can lead to complications such as encephalitis, even in immunocompetent individuals.

A previously healthy eight-year-old girl presented with a prodrome of fever, headache, and vomiting. After two days she had a tonic-clonic seizure that evolved to status epilepticus, which resolved with propofol. A diagnosis of probable EBV encephalitis was assumed after detection of EBV DNA in cerebrospinal fluid. Rising copies of EBV DNA were detected in the plasma. Neuroimaging showed focal cortical involvement of the posterior region of the left frontal lobe and of the inferior pole of the ipsilateral temporal lobe. She was treated with acyclovir and showed a full recovery.

EBV encephalitis is a challenging diagnosis due to non-specific clinical manifestations that may significantly overlap with other central nervous system infections

ARTICLE HISTORY

Received : 12 December 2023

Accepted : 04 March 2024

KEYWORDS

Human Herpesvirus 4, Epstein-Barr Virus, Encephalitis, Status Epilepticus, Child

Case Report

A previously healthy eight-year-old girl was admitted to the emergency room due to a short afebrile generalized tonic-clonic seizure on the day of admission (under five minutes). One week prior to admission she had a self-limited episode of fever and headache that lasted for three days. Two days before admission fever, headache and vomiting developed. The parents did not recall any symptoms of altered mental status before the day of admission. She had been in contact with several other children with respiratory symptoms at school, in the previous two weeks. Her twin sister also had a self-limited episode of fever and headache the week before admission.

Whilst she was in the emergency room, she had another afebrile generalized tonic-clonic seizure, with upward eye deviation. Pupils were isochoric and photoreactive. After the first 0.5 mg/kg dose of rectal diazepam, the patient developed respiratory depression necessitating invasive mechanical ventilation. She progressed to status epilepticus, leading to the sequential administration of 0.2 mg/kg of midazolam and 40 mg/kg of levetiracetam, without clinical response. The seizures only ceased after starting a propofol infusion at 2 mg/kg/hour. Additionally, ceftriaxone and acyclovir were empirically administered. She was started on levetiracetam 20 mg/kg/day.

Blood analysis on the day of admission showed leukocytosis with neutrophilia and a C-reactive protein (CRP) of 1.81 mg/dL (Table 1). Brain computerized tomography (CT) and chest x-ray post-intubation were unremarkable.

Cerebrospinal fluid (CSF) testing on admission showed a WBC count of 86/mm^3 (67% mononuclear cells), rare red blood cells/mm^3, glucose 74 mg/dL (serum glucose of 98 mg/dL; CSF/serum glucose ratio of 0.75) and protein of 38.26 mg/dL (Table 1).

Serial electroencephalograms (EEG) starting on day one of admittance showed frontal intermittent rhythmic delta activity (FIRDA) and diffuse brain dysfunction.

Brain magnetic resonance imaging (MRI) on the 3rd day of admittance showed predominantly cortical left frontal posterior and ipsilateral inferior temporal polar small T2/FLAIR hyperintensities, with no other abnormalities reported (Figure 1).

Epstein-Barr virus (EBV) polymerase chain reaction (PCR) in CSF was positive for EBV DNA (250 EBV copies/mL, on the day of admittance). Plasma EBV PCR was also positive, with a rising number of copies throughout the inpatient stay (79 EBV copies/mL, two days after admission; 315 EBV copies/mL, 12 days after admission). EBV plasma serology performed two and 12 days after admission showed, on both occasions, positive anti-EBV viral capsid antigen (VCA) IgG, negative anti-EBV VCA IgM, and positive anti-EBV nuclear antigen (EBNA) IgG.

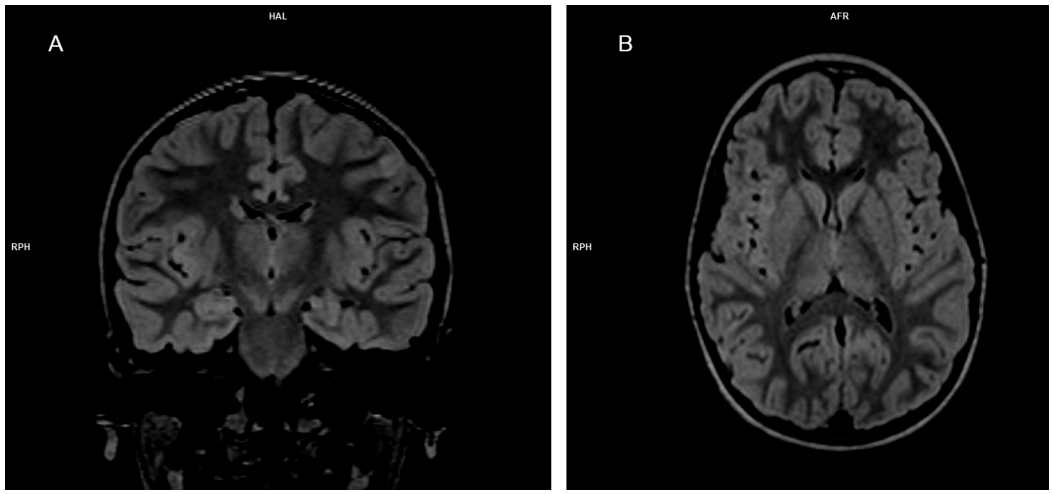
A multiplex PCR CSF meningoencephalitis panel and CSF culture were negative (Table 1). *Mycoplasma pneumonia* plasma serology was IgM positive and IgG negative. *Mycoplasma pneumonia* PCR in CSF was negative. Cytomegalovirus (CMV) plasma serology was IgG positive and IgM negative. HIV serology

Address for Correspondance:
André Salvada, Hospital Professor Doutor Fernando Fonseca, IC 19 276, 2720-276, Amadora, Portugal.
Email: andre.salvada@hff.min-saude.pt

Table 1. Laboratory workup.

Blood analysis on admission	
Hemoglobin	12.0 g/dL
White blood cell count	14.9 x 109/L
Neutrophil count	12.8 x 109/L
Lymphocyte count	1.07 x 109/L
Platelet count	305,000 /µL
C-reactive protein	1.81 mg/dL
Cerebrospinal fluid (CSF) analysis	
White blood cells	86 /mm3
Red blood cells	rare /mm3
Glucose	74 mg/dL
Serum glucose	98 mg/dL
CSF/serum glucose ratio	0.75
Protein	38.26 mg/dL
Multiplex PCR CSF meningoencephalitis panel	
Escherichia coli K1	Negative
Escherichia coli K1	Negative
Haemophilus influenzae	Negative
Listeria monocytogenes	Negative
Neisseria meningitidis	Negative
Streptococcus agalactiae	Negative
Streptococcus pneumoniae	Negative
Herpes simplex virus 1, 2 and 6	Negative
Human parechovirus	Negative
Varicella zoster virus	Negative
Cryptococcus neoformans	Negative
Cryptococcus gattii	Negative
Mycoplasma pneumoniae PCR in CSF	Negative
Epstein-Barr virus PCR in CSF	Positive
CSF culture	Negative
Plasma serologies	
Mycoplasma pneumoniae	IgM positive / IgG negative
Cytomegalovirus	IgM negative / IgG positive
Borrelia burgdorferi	Negative
Parvovirus B19	Negative
Human immunodeficiency virus I/II	Negative
Hepatitis B virus	Negative
Hepatitis C virus	Negative
anti-Epstein-Barr virus viral capsid antigen	IgM negative / IgG positive
anti-Epstein-Barr virus nuclear antigen	IgG positive
Epstein-Barr virus PCR in plasma	Positive
Nasopharyngeal PCR panel	
SARS-CoV-2	Negative
Influenza A and B	Negative
Respiratory Syncytial Virus	Negative
Autoimmunity plasma screen	
Antinuclear antibodies (ANA)	Positive, anti-nucleolar homogeneous pattern (AC-8, titer of 1:160)
Antiganglioside antibodies (AGA) IgM	Weakly positive for GM3 and GQ1b
Antiganglioside antibodies (AGA) IgG	Negative
Rheumatoid factor	Negative
Anticardiolipin antibodies	Negative

Figure 1. Brain magnetic resonance fluid-attenuated inversion-recovery (FLAIR) images. (A) Coronal view showing a cortical left frontal posterior hyperintense lesion. (B) Axial view showing unaffected basal ganglia.



was negative. The remaining plasma serologies and a nasopharyngeal multiplex PCR panel were negative (Table 1).

An autoimmunity plasma screen was positive for antinuclear antibodies (ANA) with an anti-nucleolar homogeneous pattern (AC-8, titer of 1:160). Plasma antiganglioside antibodies (AGA) were IgM weakly positive for GM3 and GQ1b and IgG negative. Rheumatoid factor and anti-cardiolipin IgG and IgM antibodies were not detected (Table 1).

On the second day after admission the EEG showed diffuse brain dysfunction with no epileptic activity. The patient was uneventfully extubated. She had a gradual clinical improvement, with no seizures observed since extubation. Fever resolved by day two of admittance and no further episodes of vomiting were noted since admission.

The patient developed post dural puncture headache, which resolved by the fifth day after admission. On the fourth day after admission, blood analysis showed hepatic cytolysis and cholestasis (increased serum transaminases, alkaline phosphatase and gamma-glutamyl transpeptidase), requiring a switch from ceftriaxone to cefotaxime. Subsequently, there was a gradual analytical improvement with no other complications observed during the inpatient stay.

Cefotaxime was discontinued after negative cultural results. A presumptive diagnosis of EBV viral encephalitis was made and treatment with acyclovir was maintained for 14 days. Blood counts and CRP were within normal values prior to discharge. The last EEG, performed on day 10 of admittance, presented a slight improvement since admission, compatible with mild diffuse brain dysfunction.

The patient was discharged home seizure-free, 12 days after admission, on levetiracetam. On a follow-up appointment at nine months post-discharge, she had a normal brain MRI as well as an EEG with normal background activity and no epileptiform discharges, having recovered her premorbid function in activity and school performance. In this appointment, levetiracetam started to be weaned off.

Discussion

Encephalitis is defined as inflammation of the brain parenchyma and can be caused by infection or autoimmunity.[1] The most common etiology is viral and is most frequently due to infection by HSV-1 and HSV-2, non-polio enteroviruses, and arboviruses.[1] EBV is also a causative agent and can affect immunocompetent individuals.[2] The prevalence of EBV encephalitis/meningoencephalitis ranges across studies, from 2 to 31%.[3]

EBV is usually associated with infectious mononucleosis (IM), a disease most commonly affecting teenagers, which presents with fever, pharyngitis, headache, lymphadenopathy, splenomegaly, and leukocytosis with atypical lymphocytes.[4] In young children most primary EBV infections are asymptomatic, although they can also lead to various neurological complications, such as encephalitis or meningitis.[4] The clinical presentation of EBV encephalitis tends to be nonspecific and has been associated with a prodrome of fever and headache instead of the constellation of infectious mononucleosis symptoms.[3,5] This may be due to the pathogenesis of EBV related-CNS diseases, which can be associated with latent viral reactivation or an antibody-mediated post-inflammatory response, possibly leading to a clinical picture that is different from IM.[3] We should thus consider EBV as one of the causative agents of acute encephalitis in young children, regardless of presenting symptoms or immune status.

In our patient, the prodrome of fever, headache and vomiting followed by tonic-clonic seizures evolving to status epilepticus associated with the plasma, CSF, neuroimaging, and EEG findings reported are consistent with an acute viral encephalitis. She had positive EBV PCR in CSF and increasing EBV copies in plasma PCR during her inpatient stay, which is now preferred as a diagnostic tool over viral culture or serological diagnosis.[6] On the other hand, she had a positive plasma serology for anti-EBV VCA IgG and anti-EBNA and a negative plasma serology for anti-EBV VCA IgM. These findings may be associated with an EBV reactivation, which has been reported both in immunocompetent and immunodeficient patients.[7] It is, however, debatable whether positive EBV DNA in

CSF detected by quantitative PCR indicates active lytic infection versus only latent genome, as EBV may be subclinically reactivated due to other pathological CNS conditions.[7,8] As a limitation to our case, we did not perform CSF or plasma anti-EBV early antigen (EA) serology, which could have helped in establishing a diagnosis of EBV reactivation in our patient, as it rises with primary infection and reactivation.[9] Moreover, we did not calculate the EBV-antibody index in the CSF, which could have helped to elucidate pathophysiology, namely the extent to which a possible immune response might be at play in her condition.[10]

Other infectious causes were largely excluded by multiplex PCR CSF and nasopharyngeal panels, CSF culture, as well as serological plasma testing. The positive IgM Mycoplasma pneumoniae plasma serology could point to an acute infection caused by this pathogen but was more likely due to cross-reactivity with an acute EBV infection or to the low-specificity associated with this test.[11] This hypothesis is also supported by the negativity of Mycoplasma pneumoniae PCR in CSF.

We did not perform CSF testing for autoimmune etiologies as clinical suspicion was low for autoimmune encephalitis (AE). Nonetheless, it is of note that anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, the most common form of antibody-mediated AE, can often begin with a viral prodrome, which may consist of fever, headache, and gastrointestinal symptoms, as seen in our patient.[12] After the prodrome, initial manifestations of disease, especially in young children, often include neurological symptoms, such as seizures, as opposed to predominantly psychiatric symptoms, as is commonly seen in adults. However, irrespective of initial presentation, 90% of children will progress to at least three symptoms, including psychiatric features, memory disturbance, seizures, dyskinesias, change in the level of consciousness or autonomic dysfunction, in the first month after onset.[12] This did not occur in our patient, who recovered to premorbid status less than three months after presentation. Anti-NMDAR encephalitis has been linked to EBV reactivation, in a case report where this diagnosis was concurrent with positive CSF anti-EBV EA IgG in three patients.[13] All the patients in the report presented with both psychiatric and neurologic symptoms, and EBV encephalitis was unconfirmed due to the lack of EBV PCR in CSF. We did not perform CSF anti-EBV EA serologies but did find a positive EBV PCR in CSF, as discussed above.

The incidence of AGAs has not been sufficiently studied in healthy individuals, but appears to range from 1 to 9% in healthy control groups in AGA studies.[14] Of potential interest for follow-up, anti-GM3 and anti-GQ1b AGAs, which in our patient were IgM weakly positive, have both been associated with primary multiple sclerosis, among other diseases.14 Anti-GQ1b AGA has also been linked to Guillain-Barré Syndrome (GBS), and GBS to previous EBV and other infections, although this has not yet been confirmed in the pediatric population.[15,16] Also of note, decreased immune control of chronic EBV infection has been found to contribute to the development of Systemic Lupus Erythematosus, which could be relevant in our patient as she had a positive ANA.[17]

Brain MRI showed mainly focal cortical involvement, which has previously been associated with a good prognosis.[18] Bilateral T2 hyperintense lesions of the basal ganglia and thalami have been associated with EBV encephalitis but were not present in our patient.[19] EEG changes in viral encephalitis are usually nonspecific and have been reported to include generalized or focal brain disfunction, epileptiform discharges, status epilepticus and FIRDA, some of which were present in our patient.[4,20]

There are currently no standard guidelines for the treatment of EBV encephalitis, though many authors opt for a therapeutic cycle of 14 to 21 days of acyclovir or ganciclovir.[3,21] Corticosteroids may be beneficial in the setting of immune-mediated EBV-associated neurologic involvement. The prognosis of EBV encephalitis tends to be good, as was the case for our patient at nine months' follow-up.[20] EBV encephalitis-associated status epilepticus has, however, been reported to be associated with a worse prognosis, including prolonged intensive care stay and death.[4,22,23]

In conclusion, EBV encephalitis should be considered in any child who presents with possible viral encephalitis features. Its diagnosis remains challenging and should be guided by clinical manifestations, laboratory, CSF, neuroimaging, and EEG findings. CSF PCR is the preferred method for establishing the diagnosis. Treatment with antiviral agents is generally recommended and prognosis is good overall.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Costa BK da, Sato DK. Viral encephalitis: a practical review on diagnostic approach and treatment. J Pediatr (Rio J). 2020;96(Suppl 1):12. doi:10.1016/J.JPED.2019.07.006.
2. Carneiro VC de S, Pereira JG, de Paula VS. Family Herpesviridae and neuroinfections: current status and research in progress. Mem Inst Oswaldo Cruz. 2022;117. doi:10.1590/0074-02760220200.
3. Pangprasertkul S, Sanguansermsri C, Sudjaritruk T. Epstein-Barr virus meningoencephalitis in a young immunocompetent child: A case report. Heliyon. 2022;8(10):e11150. doi:10.1016/J.HELIYON.2022.E11150.
4. Doja A, Bitnun A, Ford Jones EL, et al. Pediatric Epstein-Barr virus-associated encephalitis: 10-year review. J Child Neurol. 2006;21(5):384-391. doi:10.1177/08830738060210051101.
5. Kneen R, Michael BD, Menson E, et al. Management of suspected viral encephalitis in children - Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group National Guidelines. Journal of Infection. 2012;64(5):449-477. doi:10.1016/J.JINF.2011.11.013/ATTACHMENT/E7F1BBFE-3A0E-4902-A652-CFBC8C2FE927/MMC2.PDF.
6. Autore G, Bernardi L, Perrone S, et al. Update on Viral Infections Involving the Central Nervous System in Pediatric Patients. Children (Basel). 2021;8(9). doi:10.3390/CHILDREN8090782.
7. Sanefuji M, Ohga S, Kira R, et al. Epstein-Barr virus-

associated meningoencephalomyelitis: intrathecal reactivation of the virus in an immunocompetent child. J Child Neurol. 2008;23(9):1072-1077. doi:10.1177/0883073808315414.

8. Sundén B, Larsson M, Falkeborn T, et al. Real-time PCR detection of human herpesvirus 1-5 in patients lacking clinical signs of a viral CNS infection. BMC Infect Dis. 2011;11. doi:10.1186/1471-2334-11-220.
9. Gulley ML. Molecular diagnosis of Epstein-Barr virus-related diseases. J Mol Diagn. 2001;3(1):1-10. doi:10.1016/S1525-1578(10)60642-3.
10. Kleines M, Schiefer J, Stienen A, et al. Expanding the spectrum of neurological disease associated with Epstein-Barr virus activity. European Journal of Clinical Microbiology and Infectious Diseases. 2011;30(12):1561-1569. doi:10.1007/S10096-011-1261-7/METRICS.
11. MacDonald B, Diamond Y, McCloskey K, et al. Probable acute Epstein-Barr virus encephalitis in a 6-year-old girl. J Paediatr Child Health. 2017;53(12):1233-1235. doi:10.1111/JPC.13642.
12. Hardy D. Autoimmune Encephalitis in Children. Pediatr Neurol. 2022;132:56-66. doi:10.1016/J.PEDIATRNEUROL.2022.05.004.
13. Hou R, Wu J, He D, et al. Anti-N-methyl-D-aspartate receptor encephalitis associated with reactivated Epstein-Barr virus infection in pediatric patients: Three case reports. Medicine. 2019;98(20). doi:10.1097/MD.0000000000015726.
14. Cutillo G, Saariaho AH, Meri S. Physiology of gangliosides and the role of antiganglioside antibodies in human diseases. Cellular & Molecular Immunology 2020 17:4. 2020;17(4):313-322. doi:10.1038/s41423-020-0388-9.
15. Rodríguez Y, Rojas M, Pacheco Y, et al. Guillain-Barré syndrome, transverse myelitis and infectious diseases. Cell Mol Immunol. 2018;15(6):547-562. doi:10.1038/CMI.2017.142.
16. Lubarski K, Mania A, Michalak S, et al. The Clinical Spectrum of Autoimmune-Mediated Neurological Diseases in Paediatric Population. Brain Sci. 2022;12(5). doi:10.3390/BRAINSCI12050584.
17. Houen G, Trier NH. Epstein-Barr Virus and Systemic Autoimmune Diseases. Front Immunol. 2021;11. doi:10.3389/FIMMU.2020.587380.
18. Abul-Kasim K, Palm L, Maly P, et al. The neuroanatomic localization of Epstein-Barr virus encephalitis may be a predictive factor for its clinical outcome: a case report and review of 100 cases in 28 reports. J Child Neurol. 2009;24(6):720-726. doi:10.1177/0883073808327842.
19. Yang CWR, Mason M, Parizel PM, et al. Magnetic resonance imaging patterns of paediatric brain infections: a pictorial review based on the Western Australian experience. doi:10.1186/s13244-022-01298-1.
20. Cheng H, Chen D, Peng X, et al. Clinical characteristics of Epstein-Barr virus infection in the pediatric nervous system. BMC Infect Dis. 2020;20(1). doi:10.1186/S12879-020-05623-1.
21. Matthews E, Beckham JD, Piquet AL, et al. Herpesvirus-Associated Encephalitis: an Update. Curr Trop Med Rep. 2022;9(3):92-100. doi:10.1007/S40475-022-00255-8.
22. Rodrigo-Armenteros P, Kapetanovic-García S, Antón-Méndez L, et al. Akinetic mutism and status epilepticus due to Epstein Barr virus encephalitis. Clin Neurol Neurosurg. 2019;185:105492. doi:10.1016/J.CLINEURO.2019.105492.
23. Mathew AG, Parvez Y. Fulminant Epstein Barr virus encephalitis. Indian Pediatr. 2013;50(4):418-419. doi:10.1007/S13312-013-0101-5.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.67

CASE REPORTS

T-CELL LYMPHOMA COMPLICATING BRUCELLOSIS: A UNIQUE CLINICAL SCENARIO

Nimrah Fatima[1], Khatidja Ally[1], Hira waseem[1], Hina Rajani[1], Ashar Masood Khan[2]

[1]National institute of child health, Karachi, Pakistan,

[2]Dr Ziauddin University hospital, Karachi, Pakistan.

ABSTRACT

Brucellosis is an important but neglected cause of febrile illness in children in areas with high exposure to animals or unpasteurized milk and dairy products. Pyrexia of unknown origin has multiple causes and underlying conditions in paediatric population including multiple infectious, autoimmune, and malignant conditions. Although closely mimicking but some of these conditions can co-exist in a single patient as in our case and a second diagnosis should always be kept in mind in initially improved but then deteriorating patients. Our patient was an eight years old male child who presented with a systemic illness involving lymphadenopathy, hepatospleenomegaly and signs of CNS involvement. He came out to be positive for B.Melitensis and APLA antibodies. He was treated with combination therapy of rifampicin, doxycycline and oral steroids. Even though his initial workup was negative for any malignancy and he responded to the initial treatment but the recurrence of symptoms and deterioration in his general condition led us to repeat some of his investigation which later on came out to be positive for non-Hodgkin's T cell Lymphoma (peripheral T cell Lymphoma).

ARTICLE HISTORY

Received : 14 June 2024

Accepted : 01 August 2024

KEYWORDS

Brucellosis, brucella, T-cell Lymphoma

Introduction

The genus Brucella is responsible for human brucellosis, which continues to be a global public health concern. As unintentional hosts, humans get this disease from consuming animal products or coming in close contact with diseased animals like cattle, goats, pigs, camels and sheep. Consuming unpasteurised dairy products or cheese from sick sheep or goats is the primary cause of most infections. The four main Brucella species that may infect humans and cause disease are B. abortus, B. melitensis, B. canis, and B. suis.[1] Brucella The most common species that causes brucellosis in humans is Melitensis. Brucella is considered endemic in South Asian countries in livestock animals[1] but number of cases of distinguish brucellosis in Pakistan is very limited which could be due to lack of awareness, failure to obtain thorough history and detailed examination.

Risk of anti thrombotic syndrome has been associated with an autoimmune disorder called antiphospholipid syndrome (APS). The paediatric APS refers to diagnosis of APLA in population less than 18 years old. Sapporo classification is used for diagnosis of APLA in adults but due to limited number of cases in paediatric population no proper scale or criteria has been allotted to paediatric population.[2]

The rare and severe form of non-Hodgkin lymphoma (NHL) types is peripheral T-cell lymphomas (PTCLs) which form in adult white blood cells known as "T cells" and "natural killer (NK) cells.'' The WHO classification of Lymphoma has been widely used for classifying the Peripheral T cell lymphoma, which has divided the broader term into multiple categories. [3] PTCLs are among the rare disorder which are associated with poorer prognosis as compared to their B cell origin counterparts and show poor response to conventional therapies along with frequent relapses. The prevalence rate of PTCL is low in children and its heterogeneity pose significant obstacles to properly identify and manage PTCL. Their response to treatment, remissions and relapses are understudied phenomena in paediatric population which has led to difficulty in the management. Regardless of the recent advancements, the treatment for PTCL still comprise of vincristine ,doxorubicin, cyclophosphamide and prednisone (CHOP) or CHOP-like combination chemotherapy[4], whereas studies related to High dose combination chemotherapy and stem cell transplant has shown promising results.[5,6,7]

Case Report

An 8-year-old male boy weighing 20 kg, resident of urban area, presented through emergency department with complains of fever for 3 months, lower limb pain for 1 month and inability to walk for 15 days. The fever was reported as high grade in intensity (axillary temperature 102°F), not associated with rigors and chills, intermittent more at night. Patient developed complain of lower limb pain starting from his ankle joints and progressed to his thighs, pain's intensity increased with progression of time and patient became unable to walk 15 days back. He was prescribed oral antibiotics, paracetamol, and multivitamins by local GP but to no avail.

Medical examination at the time of presentation

Address for Correspondance:
Ashar Masood Khan, SF2 Block 7 Seaview Apartments DHA Phase 5, Karachi - 75500, Pakistan.
Email: asharmasood65@gmail.com

showed fever of 102°F with heart rate of 115 beats/min, sub vitally patient was found to be moderately anaemic with grade 2 clubbing and posterior cervical lymphadenopathy was also observed. His abdominal examination revealed hepatosplenomegaly and his CNS examination showed increased tone in lower limbs with power of 3/5, his plantar reflex was mute bilaterally. No joint swelling, erythema, skin rash ulcers were noticed during examination. Rest of the systemic examination was found to be unremarkable.

Laboratory results showed normocytic normochromic anaemia with Hb levels of 8 g/dl, leukopenia ($4*10^9$/L) with predominant neutropenia 15% and lymphocytes 80% and thrombocytopenia (98,000). His biochemistry (UCEs and LFTs) was normal. Blood and urine culture showed no growth and workup for tuberculosis, Malaria parasite and ICT malaria also came out to be negative. Patient was admitted for further workup and fever documentation and he was started on 3rd generation cephalosporins and paracetamol.Bone marrow biopsy was done with impression of myeloproliferative disorder which showed reactive lymphocytosis. His workup for HLH was negative and lymph node biopsy showed reactive hyperplasia. CT scan chest and abdomen revealed involvement of multiple levels of lymph nodes and hepatosplenomegaly.

Patients MRI brain showed cortical thickening with abnormal signal intensity involving bilateral mesial temporal lobes along with cingulate and hippocampal gyri.

MRI spine was normal. On the basis of his MRI findings autoimmune workup was sent including ANA, Anti DsDNA, ENA profile, Anti CCP and poly specific coombs test came out to be negative. As patient's initial autoimmune and malignancy associated workup was negative and he was not responding to conventional treatment his serology for brucellosis was sent which showed 2 folds increase in antibodies against Brucella Melitensis. He was started on combination therapy of rifampicin 15 mg/kg/day and doxycycline 4 mg/kg/day. As patient's condition improved so he was discharged.

On follow up visit after 1 week patient was found to have high grade fever, livedo reticularis and ulcer on his left foot. Patient was readmitted, baseline investigations were repeated which showed normocytic normochromic anaemia and thrombocytopenia, ultrasound doppler of both legs was done which was normal, his d-Dimer levels were 1.4 mg/L. APLA profile showed positive anticadiolipin IgM and IgG (10.6 and 10.98 respectively). His Lupus Anticoagulant was also positive. Patient was started on oral steroids which showed visible improvement in patient's condition and patient was discharged on 3rd day of starting steroids.

On follow up visit after 3 weeks patient was found to have high grade fever, livedo reticularis ulcer on his left foot with decreased appetite and appeared to be mildly jaundiced. Patient was readmitted, baseline investigations were repeated which showed normocytic normochromic anaemia, severe neutropenia with ANC of 300 and thrombocytopenia, LFTs showed 2 folds increase in SGPT. Ultrasound Abdomen showed increase in the size of liver and spleen. Ultrasound doppler of both legs was done which was normal, his d-Dimer levels were slightly raised 1.4 mg/L. APLA profile showed positive anticardiolipin IgM and IgG (10.6 and 10.98 respectively). His Lupus Anticoagulant was also positive. As patient was deteriorating and his blood workup showed persistent pancytopenia despite treatment and intervention, so his bone marrow trephine biopsy was repeated which this time around showed an extensive interstitial infiltration with small mature T lymphocytes. The abnormal lymphoid cells were positive for CD 3, CD 8, and CD 45 on flow cytometry. Patient was diagnosed as a case of Peripheral T Cell Lymphoma NOS variety. Patient was than referred to oncology department for further treatment and management.

Discussion

There are many causes of pyrexia of unknown origin in paediatric population which include common and rare disorders. Brucellosis is a zoonotic disease, fairly common in areas with exposure of animals and unpasteurized milk, but its diagnosis can easily be missed out in patient with no history of direst exposure to animals. Childhood Brucellosis accounts for 20-30% cases worldwide[1] and could present as multisystem involvement which makes it difficult to differentiate from multiple other illnesses common in this age group. Symptoms can be cute or insidious in nature and usually non-specific. Fever is the most common symptom.[8] Physical examination may reveal hepatospleenomegaly, arthritis or arthralgia, lymphadenopathy and weight loss. Multisystem involvement including musculoskeletal, gastrointestinal, respiratory and Central nervous system has also been reported in literature.[1] Neurobrucellosis has been reported in adolescent and adult population in literature over the course of past few years, but data related to children is very limited and less studied. The diagnosis of brucellosis is generally based on positive serology, blood cultures, bone marrow cultures and antibody titers.[1] There are 2 effective treatment regimens for different age groups. For children over 8 years old, oral doxycycline (4 mg/kg/day) and rifampicin (20 mg/kg/day) are typically prescribed, and for children under 8 years old, oral trimethoprim TMP (6-8 mg/kg/day), sulphamethoxazole SMX (30-40 mg/kg/day), and rifampicin (20 mg/kg/day) are typically prescribed. Both are prescribed for 6-8 weeks.[1] Complications and relapses are usually treated with 3 drug regime adding an aminoglycoside in the treatment.

Brucella has been linked to autoimmune haemolytic anaemia, neutropenia and thrombocytopenia in literature as found in our case. Pargini V. et al reported a case of a boy presenting as SLE but ultimately was diagnosed as Brucellosis[9], another case associated it with haemolytic anaemia[10] but it has never been associated with APLA in past which makes our case a unique presentation.

APLA itself is a less understood and studied entity in paediatric population due to lesser number of cases, vague presentation, its association with pregnancy related complications and lack of any formal criteria for its diagnosis in paediatric population. The updated Sapporo criteria has been used for diagnosis of APS.[11] Clinically, the occurrences that meet the criteria include specific forms of pregnancy morbidity and confirmed vascular thrombosis in arteries, veins, or small

vessels. A positive lupus anticoagulant (a functional test that screens for APLA), anticardiolipin IgG or IgM in medium or high titer, or anti-beta-2 glycoprotein I (β2GPI) IgG or IgM in high titer might satisfy the laboratory requirements. However, since the modified Sapporo criteria is designed for adult population and go beyond thrombosis and the parameters, they are not very useful for the paediatric population. While some children with APS may have positive antibody tests but no clinical symptoms, other children with the condition may exhibit other "non-criteria" indications such as haematologic and neurologic problems.[11] Peripheral T cell lymphomas (PTCL) have a poorer prognosis after conventional treatment than do high-grade B cell lymphomas, so the treatment of PTCL remains clinically difficult. The response rate to first-line treatment for PTCL is low, and the current 5-year overall survival is only 10–30%.[12] Their response to treatment, remissions and relapses are understudied phenomena in paediatric population which has led to difficulty in the management. To date, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like combination chemotherapy still represents the standard approach to the treatment of most PTCLs[4], whereas studies related to High dose combination chemotherapy and stem cell transplant has shown promising results.[5,6,7]

Combination chemotherapy with anthracycline-based regimens both in the United States and in the UK have been established as the standard therapy for these neoplasms. One study conducted in Japan has shown the 5-year overall survival rate after stem cell transplantation to be 62.96%. Although the 5-year event-free survival was 55.56%.[7]

Multiple studies conducted on adult population has shown Positive APLA antibodies result in patients with Non Hodgkin's Lymphoma and its association with adverse outcomes[13,14] but no such studies has been done for paediatric population.

Compliance with Ethical Standards

Funding None

Conflict of Interest None

References:

1. Bukhari EE. Pediatric brucellosis. An update review for the new millennium. Saudi Med J. 2018 Apr;39(4):336-341. doi: 10.15537/smj.2018.4.21896. PMID: 29619483; PMCID: PMC5938645.
2. Madison JA, Zuo Y, Knight JS. Pediatric antiphospholipid syndrome. Eur J Rheumatol. 2019 Dec 3;7(Suppl 1):1-10. doi: 10.5152/eurjrheum.2019.19160. Epub ahead of print. PMID: 31804173; PMCID: PMC7004270.
3. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues: International agency for research on cancer Lyon; 2008.
4. Armitage JO. The aggressive peripheral T-cell lymphomas: 2017. 2017;92(7):706-15.
5. Blystad A, Enblad G, Kvaløy S, Berglund Å, Delabie J, Holte H, et al. High-dose therapy with autologous stem cell transplantation in patients with peripheral T cell lymphomas. 2001;27(7):711-6.
6. Prochazka V, Faber E, Raida L, Papajik T, Vondrakova J, Rusinakova Z, et al. Long-term outcome of patients with peripheral T-cell lymphoma treated with first-line intensive chemotherapy followed by autologous stem cell transplantation. Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia. 2011;155(1):63-9.
7. Kobayashi R, Fujita N, Mitsui T, Iwasaki F, Suzumiya J, Kuroda H, et al. Stem cell transplantation for paediatric patients with non-anaplastic peripheral T-cell lymphoma in J apan. 2012;159(1):88-93.
8. Al Shaalan M, Memish ZA, Al Mahmoud S, Alomari A, Khan MY, Almuneef M, Alalola S. Brucellosis in children: clinical observations in 115 cases. International journal of infectious diseases. 2002 Sep 1;6(3):182-6.
9. Paganelli, V., Marrani, E., Brambilla, A. et al. "Brucellupus" in a boy: challenging sle diagnosis in childhood. Pediatr Rheumatol 12 (Suppl 1), P314 (2014). https://doi.org/10.1186/1546-0096-12-S1-P314.
10. Meena DS, Sonwal VS, Rohila AK, Meena V. Acute Brucellosis Presenting as an Autoimmune Hemolytic Anemia. Case Reports in Infectious Diseases. 2018 ;2018:1030382. DOI: 10.1155/2018/1030382. PMID: 30498608; PMCID: PMC6222226.
11. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS) J Thromb Haemost. 2006;4:295-306. doi: 10.1111/j.1538-7836.2006.01753.x.
12. Zhang P, Zhang M. Epigenetic alterations and advancement of treatment in peripheral T-cell lymphoma. Clinical Epigenetics. 2020;12(1):169.
13. Bairey O, Blickstein D, Monselise Y, Lahav J, Stark P, Prokocimer M, et al. Antiphospholipid antibodies may be a new prognostic parameter in aggressive non-Hodgkin's lymphoma. 2006;76(5):384-91.
14. Gebhart J, Lechner K, Skrabs C, Sliwa T, Müldür E, Ludwig H, et al. Lupus anticoagulant and thrombosis in splenic marginal zone lymphoma. 2014;134(5):980-4.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.32

CASE REPORTS

A RARE FINDING IN A PRETERM INFANT

João Sousa Marques[1], Sara Geitoeira[1], Joana Oliveira[2], Sandra Costa[3,4], Ana Vilan[3,4]

[1]Department of Pediatrics, Centro Hospitalar Tondela-Viseu, Viseu, Portugal,

[2]Department of Pediatrics, Centro Hospitalar de Trás-Os-Montes E Alto Douro, Vila Real, Portugal,

[3]Department of Neonatology, Centro Hospitalar Universitário de São João, Porto, Portugal,

[4]Faculty of Medicine, University of Porto, Porto, Portugal.

ABSTRACT

Neonatal acute parotitis is a rare condition, where high clinical suspicion is necessary to establish a timely diagnosis. The authors aim to describe a case report of a 10-day-old preterm newborn with clinical signs of acute parotitis confirmed by ultrasound and with isolation of a Staphylococcus aureus in a blood culture.

There was clinical improvement after a 10-day course of vancomycin, with no further complications or recurrences.

ARTICLE HISTORY

Received : 11 February 2024

Accepted : 22 July 2024

KEYWORDS

acute parotitis, preterm infant, staphylococcus aureus.

Case Report

A preterm newborn girl of 33 weeks and 2 days is delivered by emergent caesarean section due to bleeding per *vaginum*. The pregnancy was complicated with hospitalization at 32 weeks and 5 days due to blood loss in the context of placenta praevia, previously diagnosed at 21 weeks. Peripartum serologies were negative and lung maturation was completed with a full course of corticosteroid therapy two days before birth. The newborn weighing 2040 g required one cycle of positive pressure ventilation due to low heart rate, with good recovery and an Apgar score of 6 at 1 minute, 9 at 5 minutes, and 9 at 10 minutes. She was adapted to nasal continuous positive airway pressure (*nCPAP*) from 2 minutes of life with 0.4 maximum FiO2. Given the worsening signs of respiratory distress nasotracheal intubation was required at 25 minutes of life.

The newborn showed good evolution having been extubated to *nCPAP* 4 hours after admission to the Neonatal Intensive Care Unit (NICU) and remained in spontaneous ventilation since day two of life with no need for supplemental oxygen therapy. The laboratory blood test on admission revealed a white blood count (WBC) of 14.3x10^9/L cells (40.7% neutrophils, 49.6% lymphocytes), hemoglobin 15.6 g/dL and platelet count of 417 x 10^9/L. Serial C-reactive protein (CRP) monitoring and the blood culture obtained were negative. She remained clinically stable, under parenteral nutrition from day one of life. Partial enteric nutrition was started through a nasogastric tube on day two, which was fully completed on day five of life, with full feeding autonomy acquired from the 12th day of life. She also developed jaundice requiring intensive phototherapy, from day two to day seven of hospitalization, during which an increase in serum sodium was observed (maximum 146 meq/L on day 3) despite normal urine output and a maximum weight loss of 6.5%.

On the 10th day of hospitalization, fever (37.9ºC) and hypoactivity was noticed, as well as the appearance of a right preauricular and ear-jaw articulation swelling, with effacement of the mandibular angle, accompanied by erythema and pain/discomfort on palpation (Figure 1). No history of trauma, maternal skin infection, or mastitis was registered.

The remaining physical exam was unremarkable, including the oral cavity.

The laboratory blood test revealed a WBC of 29.2x10^9/L cells (79.1% neutrophils, 9.7% lymphocytes), platelet count of 846 x 10^9/L, CRP 14.5 mg/L (normal range values <3 mg/L). A blood culture was obtained with an aftergrowth for *Meticillin-Sensitive Staphylococcus aureus* (MSSA). Empirical antibiotic therapy was started with intravenous vancomycin (15 mg/Kg/dose q12h) plus amikacin (15 mg/Kg/dose q36h), later adjusted to monotherapy with vancomycin.

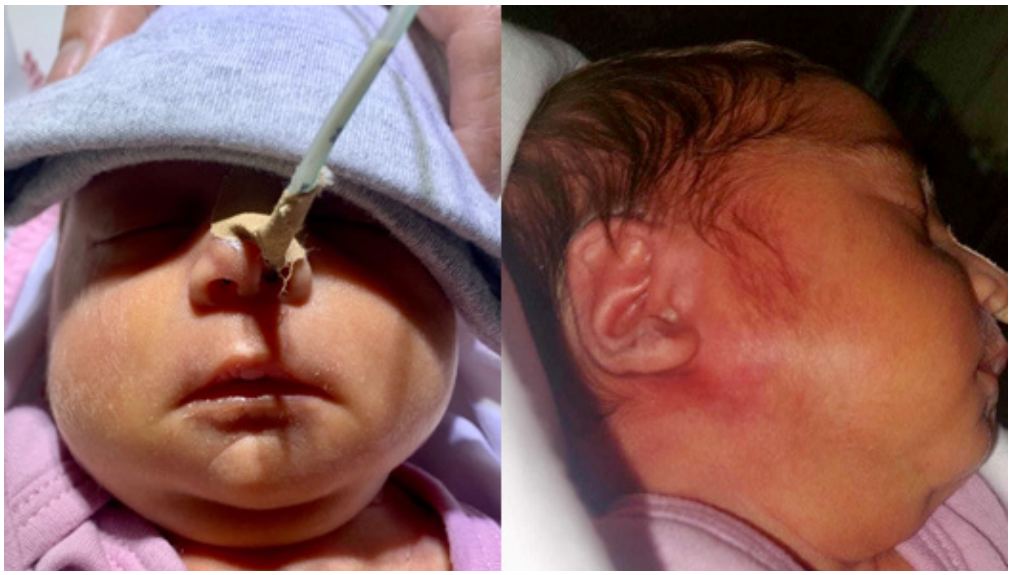
A local ultrasound scan was requested revealing an enlarged right parotid gland with globose morphology, heterogeneous texture, and increased vascularity, with no dilatation of the parotid duct and no observed collections. The findings were consistent with acute parotitis. On the fourth day of antibiotics, she repeated laboratory tests, with improvement of the platelet blood count, negative CRP, and vancomycin values within the therapeutic range. The blood culture collected at that time was negative.

She completed ten days of antibiotic therapy with vancomycin and was discharged home clinically stable on the 19th day of life with resolution of parotid swelling, presenting a normal physical exam, with adequate weight progression and exclusive breastfeeding.

At the follow-up examination, two months later, she was in good health and with no record of complications or recurrence.

Address for Correspondance:
João Sousa Marques, Rua Monte Cativo, nº 247, 4050-401, Porto, Portugal.
Email: jnsmarques93@gmail.com

Figures 1. Asymmetrical face with effacement of the mandibular angle; swelling and erythema over the right side of the parotid region.



Discussion

Neonatal acute parotitis is a rare disorder, with limited cases described in the literature and a incidence of 3.8-14/10000 among neonatal admissions in diverse revisions.[1] It has been related to be more prevalent in males, with a rate of almost 3:1.[2] It is mainly unilateral (identical association of each parotid) and classically occurs between the seventh and fourteenth days until a month of age.[3]

Though acute parotitis might affect healthy newborns, it appears to be more common in preterm infants with low birth weight, apparently associated with prolonged hospitalization with potential trauma of the oral cavity by extended enteral nutrition through naso or orogastric tube, and higher risk for dehydration, resulting in decreased salivary discharge triggering salivary stasis, promoting bacterial ascension along the salivary duct.[2,3,4,5,6] Hematogenous bacterial seeding of the parotid gland may also happen.[2,5,6] Maternal causes like breast abscess, spread of bacteria over infected breast milk, or contaminated formula have additionally been related with parotid gland infection.[2,3,4,5,6] Structural malformations, ductal blockage, sepsis, and immunodeficiency/immunosuppression leading to defective mucociliary clearance are also identified risk factors[2,3,4,5,6] In our case report, there were several risk factors: prematurity, tube feeding for various days, and possible dehydration during phototherapy.

Staphylococcus aureus is the most usual pathogen isolated (accounting for a slightly more than half of the cases). To a lesser extent are other Gram-positive cocci, Gram-negative bacilli, and rarely anaerobic agents.[1,4,5,6,7]

In our case, the presence of bacterial isolation in the blood culture and the absence of purulent drainage through Stenon's canal may support the diagnosis via the hematogenous route.

The diagnosis is established upon clinical findings, essentially the presence of parotid swelling with inflammatory signs, which may be complemented by systemic symptoms such as fever (occurring in nearly 1/3 of cases), irritability, non-compliance to eat, and clinical signs of sepsis. The discharge of purulent content through the duct is a pathognomonic sign, however it may not be noted at presentation[4,5,6,7,8], as was the case in this newborn, requiring an ultrasound confirmation of diagnosis.

Analytically, leukocytosis with neutrophilia and a rise in acute phase reactants such as CRP might be present, as in our case, although these lab assessments are non-specific and may be normal.[4,6,8]

Ultrasound findings can confirm the diagnosis, as shown in this newborn, revealing an enlarged right parotid gland with globose morphology, heterogeneous texture, and increased vascularity, with no dilatation of the parotid duct and no observed collections, being also particularly valuable for differential diagnosis, excluding predisposing factors like anatomical malformations of Stensen's duct and mechanical salivary duct obstruction.[4,8,9]

The primary empiric treatment for acute bacterial parotitis consists of intravenous broad-spectrum antibiotic therapy with coverage for the most often involved agents, specifically *Staphylococcus aureus* with a combination of an antistaphylococcal agent and a third-generation cephalosporin or an aminoglycoside followed by an adjustment after cultures' products.[6,7,9] Additionally, adequate hydration and analgesia must also be offered. Surgical intervention is only for the occasional cases lacking a response to medical treatment or those with organized abscesses.[5,6,7,8,9]

The ideal treatment extent is not quite defined, but a minimum period of 7-10 days is generally sufficient or until the resolution of symptoms.[2,4,9] Usually within the first two days of antimicrobial treatment there is an improvement, with a diminution in parotid swelling. With prompt institution of targeted antibiotic therapy complications such as facial nerve paralysis, salivary fistula and dissemination of infection to the contiguous structures, and meningitis are rare.[2,4,9] In the cases

with absence of clinical improvement in the first 48-72 h hours, imaging should be repeated to exclude abscesses or other complications.[1,2] The prognosis for this pathology is promising in most cases, deprived of recurrence, as shown in our case report.[2,4,9]

Although acute bacterial parotitis is an uncommon condition in newborns, it must be considered in case of an erythematous pre-auricular mass, with or without predisposing factors, since a timely suspicion, diagnosis, and treatment are essential to avoid complications.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Decembrino L, Ruffinazzi G, Russo F, et al. Monolateral suppurative parotitis in a neonate and review of literature. Int J Pediatr Otorhinolaryngol. 2012;76(7):930-933.
2. Costa L, Leal L.M, Vales F, et al. Acute Parotitis in a Newborn: A Case Report and Review of the Literature." The Egyptian Journal of Otolaryngology, vol. 32, no. 3, 2016, pp. 236-239.
3. Cho JY, Youn JH, Park JS, et al. The First Case of Acute Neonatal Suppurative Parotitis Caused by Escherichia coli in Korea. Neonatal Med. 2020;27(2):94-98.
4. Gupta A, Kingdon T, McKernan A. Neonatal Parotitis: A Case Report. Clinical practice and cases in emergency medicine. 2021; 6;2(5):218-21.
5. Özdemir H, Karbuz A, Ciftçi E, et al. Acute neonatal suppurative parotitis: a case report and review of the literature. Int J Infect Dis. 2011;15(7):e500-2.
6. Gameiro I, Leuzinger-Dias C, Camacho-Sampaio M, et al. A common diagnosis in an uncommon age: acute neonatal parotitis case report. Portuguese Journal of Pediatrics. 2023 754(3):194-8.
7. Pereira C, Ana Rita Prior, Abrantes M, et al. Bilateral suppurative parotitis in a newborn. Nascer e Crescer. 2017 3;26(1):53-6.
8. Dias Costa F, Ramos Andrade D, Cunha FI, et al. Group B streptococcal neonatal parotitis. BMJ Case Rep. 2015;2015 bcr2014209115.
9. Ismail EA, Seoudi TM, Al-Amir M, et al. Neonatal suppurative parotitis over the last 4 decades: Report of three new cases and review. Pediatr Int 2013; 55: 60-4.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.67

CASE REPORTS

UNDERSTANDING DRUG-INDUCED ENTEROCOLITIS

Catarina Maria Queirós Fraga, Ana Rita Barroca Macedo, Ana Carolina Coelho de Castro, Georgeta Maria Costa Alves de Oliveira.

Pediatrics Department of Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Oporto, Portugal.

ABSTRACT

Drug-induced enterocolitis syndrome (DIES) is a rare but potentially fatal non-IgE-mediated hypersensitivity reaction triggered by drugs. It often presents with gastrointestinal symptoms similar to those of food protein-induced enterocolitis syndrome (FPIES). The authors report the case of a 10-year-old girl who suffered from severe vomiting and diarrhoea after taking amoxicillin-clavulanic acid. A hospital-based oral drug challenge with amoxicillin replicated her symptoms, confirming DIES diagnosis. Supportive measures led to positive outcomes. We discuss the diagnostic criteria, management strategies and the importance of greater awareness in identifying cases of DIES. Despite its rarity, we advocate for hospital-based oral challenges when DIES is suspected, facilitating prompt diagnosis and management of potentially severe reactions.

ARTICLE HISTORY

Received : 18 April 2024

Accepted : 11 June 2024

KEYWORDS

Drug-induced enterocolitis syndrome (DIES), Non-IgE-mediated hypersensitivity, Gastrointestinal symptoms, Oral drug challenge.

Case Report

A 10-year-old female child of European origin, with no relevant past history, namely atopic disease, and a complete national vaccination program, was referred by the attending paediatrician to the Paediatric Immunology and Allergology clinic due to a suspected allergy to the combination of amoxicillin-clavulanic acid. In the episode that led to suspicion, she experienced uncontrollable vomiting and profuse diarrhoea one hour after taking 1200 mg of the drug in formulation 14:1, prescribed to treat acute otitis.

Upon reviewing the patient's medical history, the caregivers reported five other episodes of copious vomiting and diarrhoea beginning at the age of two, consistently following the administration of amoxicillin or amoxicillin-clavulanic acid. Following these occurrences, they sought urgent medical attention at private healthcare facilities, attributing the symptoms to the side effects of the medication. During three out of five of these episodes, the patient required hospitalization due to oral intolerance, completing the antibiotic regimen via intravenous administration.

About a month after the referral and seven months after the episode, she was proposed for a direct (without preceding skin tests) oral drug challenge. To avoid any potential adverse gastrointestinal reaction due to clavulanate, only amoxicillin was used instead of amoxicillin-clavulanate. Therefore, the challenge involved a full standard dose of 45 mg/kg of amoxicillin, without grading, corresponding to a total daily dose of 90 mg/kg.

At the beginning of the challenge, the patient's vital signs were normal, with a temperature of 36.7°C, blood pressure within the 50th percentile range, and heart rate of 120 beats per minute. Two and a half hours after taking the amoxicillin, she experienced lethargy, and pallor followed by nausea and three episodes of profuse vomiting. She had no skin rashes or respiratory symptoms. Her blood pressure and heart rate maintained above the 5th percentile. We administered 4 mg of intravenous ondansetron and a normal saline bolus of 10 mL/kg with progressive recovery. Three hours after the beginning of the challenge, she had colicky abdominal pain followed by two large, foul-smelling bowel movements of soft to liquid consistency, with no visible blood or mucus. No complementary study was performed. The patient was discharged after four hours of hospital surveillance, with complete clinical recovery, good oral tolerance, and no further diarrhoeal episodes. Written information was provided to advise future amoxicillin avoidance, as well as an allergy action plan in case of an accidental administration.

Discussion

In 2014, in a letter to the editor, an Italian work group described a case of food protein-induced enterocolitis syndrome-like (FPIES-like) caused by medicines in a 6-year-old child. The patient presented with vomiting, diarrhoea, pallor and lethargy after taking amoxicillin, accompanied by hypotension, tachycardia and tachypnoea, requiring intravenous fluid therapy and corticosteroids, gradually returning to baseline within two hours. At the time, researchers realised that there could be a similar entity to FPIES, what they called drug-induced enterocolitis syndrome (DIES).[1]

DIES is a non-IgE-mediated hypersensitivity reaction triggered by drugs. It is characterised by the appearance of gastrointestinal symptoms within 1 to 4 hours after the intake, sometimes along with autonomic symptoms, similar to FPIES. It's a rare syndrome that can be life-threatening.[2] However, despite its potential

Address for Correspondance:
Catarina Maria Queirós Fraga, Rua Eduardo Torres 4464-513 Senhora da Hora.
Email: catarinafragapediatra@gmail.com

severity, its awareness is scarce.[2,3] Although, to date, all the paediatric patients described have recovered completely.[4]

The incidence of DIES is unknown, probably due to its underdiagnosis. Until the first semester of 2023, less than a dozen cases in children have been described in the literature. The drugs most frequently involved were amoxicillin, amoxicillin/clavulanate and paracetamol.[2] The frequency of DIES with these agents seems to be related to the fact that they are widely prescribed in this age group. For this reason, the occurrence of this syndrome associated with drugs seems likely.[4]

Since few cases have been described, it is not possible to assess whether this entity is transitory or persistent.[4] Unlike FPIES, DIES seems to occur in people who have previously tolerated the drug.[2]

The pathophysiology of DIES is unknown, but it is postulated that the interaction of drug metabolites or the drug-protein complex with the epithelium of the gastrointestinal tract causes an increase in the permeability of this barrier, increasing the penetration of drug antigens into the lamina propria and culminating in the activation of the local inflammatory response. It is also thought that factors such as age, gender, drug dose, exposure time and intestinal microbiota can shape the gastrointestinal pathological response to drugs.[2]

Though the diagnostic criteria have not yet been perfectly established, it is accepted that DIES can be considered when there is a recurrence of repetitive and often incoherent vomiting within 1-4 hours of the drug intake, in the absence of classic IgE-mediated allergic skin and respiratory symptoms. Also, when more than three of the following are present, the diagnosis may be considered: a second episode of vomiting after ingesting the same drug; a repetitive episode of vomiting after ingesting a different drug; lethargy; marked pallor; diarrhoea within 24 hours of ingestion (usually 5-10 h); the need for a visit to the emergency department; intravenous hydration; hypotension; hypothermia; and an increase in the neutrophil count >1500/mm^3 compared to the baseline count.[2,5] Although the diagnosis is clinical, the oral drug challenge confirms or excludes the diagnosis.[4]

Oral drug challenge, also known as drug provocation tests (DPT) are widely considered to be the gold standard diagnostic test for assessing drug allergy.[6] However, there is no agreement on how to conduct DPT in children. Some experts suggest using DPTs with increasing doses for immediate reactions[7], while most studies report delayed reactions appearing hours or days after the patient has taken the full drug dose.[7,8] This indicates that a single-dose DPT can be as safe as a multi-step approach, eliminating the need for multiple or extended hospitalization.[8] Therefore, we decided to follow the single-stage DPT strategy and administered a full dose of amoxicillin to our patient. Our patient presented three episodes of profuse vomiting two and a half hours after the challenge in the absence of skin or respiratory symptoms (major criterion), lethargy, marked pallor, abdominal pain and diarrhoea, in addition to the previous episodes of vomiting after taking amoxiclavulanate, which makes this a seventh episode (four minor criteria). There are no described laboratory markers specific to DIES. However, some possible findings described to date are leukocytosis with a predominance of neutrophils and an increase in methemoglobin. These findings can support the diagnosis. Tryptase levels are usually normal. Specific IgEs, prick tests and intradermal tests are also negative.[2] In the case described, no additional tests were conducted, considering that the oral drug challenge was positive.

In line with the advocate for FPIES, for DIES and in the case described above the treatment was supportive, with intravenous administration of ondansetron and normal saline, with a good clinical response.[4] In DIES and FPIEs, corticosteroids can be used in patients with severe symptoms, although their effectiveness has not been proven.[2] On the other hand, the administration of adrenaline is not recommended, although it can be used as an adjunct to fluid therapy in the approach to hypotension.[1,2,4]

Conclusion

Despite the low frequency of DIES, the authors would like to raise awareness of the diagnosis of DIES when approaching vomiting and diarrhoea after medicine intake. They also highlight that oral drug challenges, in case of late reactions, should be performed in a hospital environment, especially in cases of moderate to severe clinical reactions, such as the case described above.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Novembre, E., Mori, F., Barni, S., et al. (2014). Drug-induced enterocolitis syndrome (DIES). Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology, 25(4), 415-416. https://doi.org/10.1111/pai.12225;
2. Di Filippo, P., Venanzi, A., Ciarelli, F., et al. (2023). Drug-Induced Enterocolitis Syndrome in Children. International journal of molecular sciences, 24(9), 7880. https://doi.org/10.3390/ijms24097880;
3. Van Thuijl, A. O. J., Landzaat, L. J., Liem, O., et al. (2019). Drug-induced enterocolitis syndrome (DIES): A clinical entity that deserves more awareness. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology, 122(5), 538-539. https://doi.org/10.1016/j.anai.2019.02.004;
4. Mori, F., Liccioli, G., Fuchs, O., et al. (2021). Drug-induced enterocolitis syndrome: Similarities and differences compared with food protein-induced enterocolitis syndrome. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology, 32(6), 1165-1172. https://doi.org/10.1111/pai.13491;
5. Worcel, J., Tarelho, M., Baron, M., Ponvert, C., et al. (2020). Drug-induced enterocolitis syndrome (DIES) in a 10-year-old girl. Archives de pediatrie: organe officiel de la Societe francaise de pediatrie, 27(1), 51-52. https://doi.org/10.1016/j.arcped.2019.11.005.

6. Saretta F, Mori F, Cardinale F,et al. (2019) Pediatric drug hypersensitivity: which diagnostic tests? Acta Biomed. 2019 Jan 30;90(3-S):94-107. https://doi:10.23750/abm.v90i3-S.8171.
7. Khan DA, Banerji A, Blumenthal KG, et al.(2022). Drug allergy: A 2022 practice parameter update. The Journal of allergy and clinical immunology, 150(6), 1333-1393. https://doi.org/10.1016/j.jaci.2022.08.028.
8. Sáenz de Santa María, R., Bogas, G., Labella, M. et al. (2023). Approach for delabeling beta-lactam allergy in children. Frontiers in allergy, 4, 1298335. https://doi.org/10.3389/falgy.2023.1298335.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.30

CASE REPORTS

TYPE 1C CHOLEDOCHAL CYST IN A PREMATURE TWIN NEONATE: CASE REPORT AND LITERATURE REVIEW

Prashanth RR, Medha Goyal, Jyothi Sreekumari, Anitha Haribalakrishna.

Department of Neonatology, Seth G.S. Medical College and King Edward Memorial Hospital, Mumbai, India.

ABSTRACT

In this case report, we describe an uncommon presentation of choledochal cyst in a preterm infant, second of twins, born at 33+1 weeks by date, weighing 1434 g, born to an HCV positive mother. The anomaly was not identified in any antenatal ultrasound studies performed in any trimester. The clinical situation had presented us with a unique diagnostic dilemma with the first of the twins thriving well, in contrast to the second twin who developed unphysiological weight loss and neonatal cholestasis from day of life 23. Though the presentation was typically characteristic of an obstructive cause, this was overshadowed by premature status. There is a dearth of published literature regarding neonatal choledochal cyst, its presentation in preterm infants, and in twin babies.

ARTICLE HISTORY

Received : 04 May 2024

Accepted : 22 May 2024

KEYWORDS

Neonate, Choledochal Cyst, Preterm, Twin.

Introduction

The most common variant of choledochal cyst (CC) is Type 1(80-90% of all choledochal cyst.[1] They are fusiform or spherical dilatation of the extrahepatic biliary tree. All neonatal cases of choledochal cysts need early surgical intervention to prevent liver fibrosis-associated complications and to facilitate complete functional recovery. This is the first case report in literature, where we describe an uncommon presentation of Type 1c choledochal cyst in a preterm infant, second of twins, born at 33+1 weeks, weighing 1434 g, with cooccurrence of HCV infection in the mother.

Case Report

A 40 years old G2P2A1L0 delivered a male neonate at 33 weeks of gestation with a birth weight of 1434 grams. Neonate had APGAR scores of 9 at both 1 and 5 minutes, and no resuscitation was required. On revisiting history neonate was born of non consanguineous marriage via vaginal route. Mother was diagnosed to be HCV positive during routine antenatal screening at 6 months of gestation. Her HCV RNA titres were 106 and HCV antibody was reactive. Her SGOT/SGPT at the time of diagnosis was 367/140 and Total Bilirubin/Direct bilirubin-0.2/0.1. Other liver functions were normal. HIV and VDRL tests were negative. She was started on oral ribavirin but defaulted treatment. The pregnancy was conceived via in vitro fertilization with embryo transfer. Antenatal sonography was suggestive of dichorionic diamniotic (DCDA) twins with normal doppler studies. She went into spontaneous preterm labour, after adequate antenatal steroid coverage she delivered the twins via vaginal route. The index neonate second of the twin, the baby boy weighing 1434 g at birth and the other first twin baby girl weighed 1532 g at birth. The neonate remained hemodynamically stable with normal vital parameters. Anthropometric parameters at birth as per modified fenton's chart were weight 1434 g (3rd to 10th centile) length (50th-90th) and head circumference-32 cm. (50th to 90th).

The neonate was shifted to NICU was started on partial parenteral nutrition and enteral feeds with pasteurised donor human milk and the feeds were gradually hiked. He was initiated on kangaroo mother care and received other routine NICU care. Investigations including sepsis workup were normal. The feeds were gradually incremented by 30 ml/kg/day and full feeds were reached by day six of life. On day of life (DOL) 14 neonate developed late onset sepsis with pneumonia requiring non-invasive respiratory support, Inj.Piperacillin and Tazobactum (100 mg/kg/dose in 3 times a day, IV) and Inj.Amikacin (15 mg/kg/dose once a day, IV) was given for 10 days. Blood culture showed no growth.

Despite adequate feed volume and fortification of breast milk there was poor postnatal weight gain (average of 5-10 g/kg/day) and even by day 21 the neonate had not regained birth weight. Workup for sepsis including urinary tract infection, anaemia, osteopenia of prematurity and dyselectrolytemia was normal. By DOL 23 there was new onset clinical jaundice visible up to thighs and there was dark urine stain of diaper and stools were acholic. There was no fever and vital parameters were normal. Liver was 2.5 cm below right costal margin, non tender, soft in consistency. Left lobe was not palpable and there was no splenomegaly. Liver function tests done showed SGOT/SGPT-280/137, Total Bilirubin/Direct bilirubin-9.1 mg/dl/3.93mg/dl, albumin-2.5 mg/dl. INR- 1.2. Thyroid function test was normal. Repeat sepsis workup was negative. No previous

Address for Correspondance:

Prashanth RR, Assistant Professor, Department of Neonatology, Seth G.S. Medical College and King Edward Memorial Hospital, Mumbai, India.

Email: prash2635@gmail.com

liver function test was done. Neonate was diagnosed to have neonatal cholestasis and ultrasound abdomen showed fusiform dilatation noted including entire length of extrahepatic segment (1.2x0.5 cm) with distended gallbladder. In view of suspected choledochal cyst (CC), Magnetic resonance cholangiopancreatography (MRCP) was done which showed common bile duct (CBD) with fusiform dilatation in the proximal and mid portion with maximum diameter of 3.2 mm. Length of dilated segment was 1.3 cm. There was no distal obstruction with no filling defects with no intrahepatic bile duct dilatation (IHBRD). Right lobe of liver measured 5.6 cm, normal in size and signal intensity with normal contour and margins. Gall bladder was well distended. Pancreas appeared normal. Main pancreatic duct was not dilated with no evidence of anomalous pancreato-biliary duct union (APBDU). Spleen measured 4 cm, appeared normal in size, shape and signal intensity. There was no evidence of cholangitis. Based on clinical and radiological findings a diagnosis of Type 1c choledochal cyst was made. The antenatal scans were reviewed again and there was no choledochal cyst diagnosed prenatally. Since it was a twin pregnancy liver function tests and ultrasound of the abdomen of the other twin was done and was normal. The other twin had a normal NICU course with no jaundice, adequate weight gain and no complications.

Nutrition of the index twin was optimized to 160 kcal/kg/day, protein to 4 g/kg/day. He was started on preterm formula in addition to expressed breast milk via cup and spoon and direct breastfeeding. Neonate was also started on Vitamin A, Vitamin E, Vitamin D, Vitamin K and multivitamins. Oral cefixime prophylaxis was initiated along with oral ursodeoxycholic acid.

Paediatric surgery opinion was taken and early surgery has been planned upon adequate and sustained weight gain. Neonate was discharged on DOL-40 with weight of 1730 g. With adequate weight gain of 20-25 g/kg/day for 5 days. LFT before discharge showed SGOT/SGPT-280/137, Total Bilirubin/Direct bilirubin-5.3 mg/dl/2.9 mg/dl, albumin-2.5 mg/dl. Hearing screen, retinopathy of prematurity screen, ultrasound cranium and echocardiography were normal. Vaccination including hepatitis B were given as per age and neonate continues to be on multidisciplinary follow-up awaiting early surgery. Mother has been restarted on ribavirin and both the twins are currently 3 months old weighing 2800 g with normal growth and neurodvelopment, has been planned for surgery upon reaching weight of 3500 g and both twins will be evaluated for hepatitis C infection on follow-up.

Discussion

CC also known as congenital biliary dilatation are a group of rare congenital anomalies characterised by dilation of bile ducts. The incidence in Western population is reported to be 1 in 100000 – 150000 live births, although incidence as high as 1 in 1000, two third of reported cases have been reported from Japan1. The incidence of CC in our country is not known, though some studies have mentioned the anomaly to be not as uncommon as quoted in the Western studies.[2] A female preponderance as high as 4:1 or 3:1 has been reported in the West.[1]

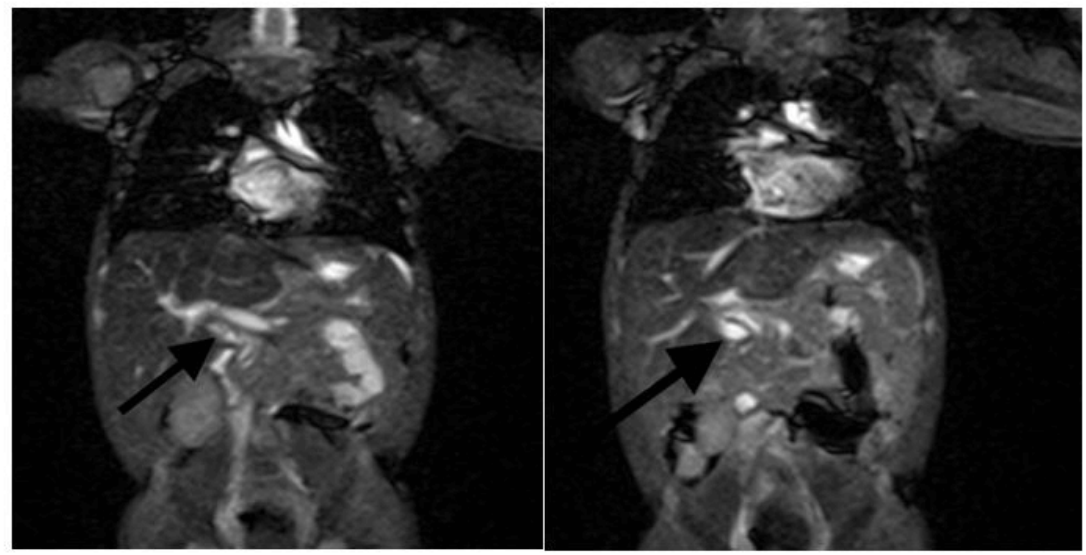
The most common variant of CC is Type 1(80-90% of all choledochal cyst).[3] They are fusiform or spherical dilatation of extrahepatic biliary tree. The most popular hypothesis regarding the pathogenesis of choledochal cyst is APBDU which is defined by a union of pancreatic and biliary ducts outside the duodenal wall and proximal to ampulla of Vater. This explains the mechanism in 90% of cases. CC that develop in the absence of APBDU may be explained by other coexisting pathophysiological causes like a weak bile duct wall, distal biliary obstruction or sphincter of oddi dysfunction. Embryologic and motility disorders have also been postulated by some authors. An important implication to be noted here is that ABPDU associated choledochal cyst patients have more evidence of pathologically confirmed inflammation including hepatitis, cholangitis and pancreatitis. Some studies have noted various congenital anomalies like duodenal atresia, colonic atresia, gastroschisis, annular pancreas, pancreatic cyst and cardiac malformations to be associated with choledochal cysts. Type 1 and Type IV cysts are found to have the highest association with malignancy.[4] Our index neonate had no evidence of APBDU on MRCP and had no other associated abnormality.

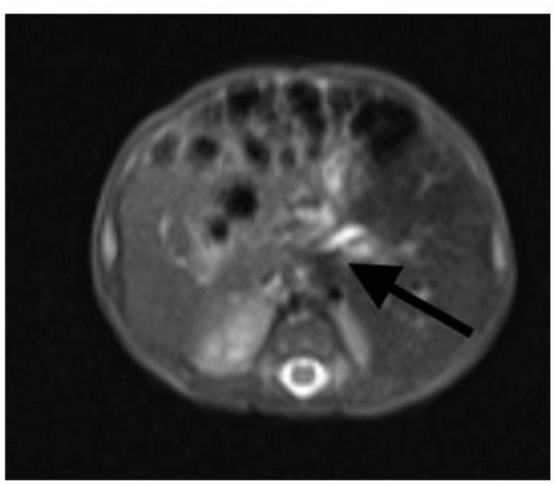
CC in neonates and infants universally presents with the typical jaundice associated with clay-coloured stools and high coloured urine similar to our patient's presentation. Very rare cases in this group have also presented with duodenal obstruction with perforation, rupture of cyst and biliary peritonitis prompting emergency biliary drainage. Hepatic fibrosis is noted as a major complication in neonates. The incidence and grade of hepatic fibrosis is found higher in antenatally diagnosed neonates with CC who present early compared to infants who present after 1 month. Cirrhosis has been documented to be as high as 67% in these patients. In such early cases the histological changes observed are similar to the findings in biliary atresia.[3]

The primary diagnostic modality for choledochal cysts is a ultrasound, supported by other imaging techniques like computed tomography (CT), Magnetic Resonance Imaging (MRI),MRCP and to a lesser extent Percutaneous Transhepatic Cholangiography(PTC) and Endoscopic Retrograde Cholangiography(ERCP) due their invasiveness and associated risks. The higher imaging modalities are usually used to demarcate the extent of involvement of duct or extra hepatic tissue once a primary diagnosis of cyst is made in ultrasonography. ERCP and MRCP modalities are commonly found to be used in complicated cases for urgent management of cholangitis or obstructing biliary stones for stabilisation before definitive surgical management. Out of all the techniques mentioned above, MRCP facilitates better delineation of the biliary cyst subtype, pancreato-biliary ductal anatomy and further surgical planning.

Cystic biliary atresia (CBA) patients which is a close differential to CC typically present earlier (<3 months of age) and their cysts appear smaller with less dilatation of the intrahepatic biliary system. An atretic gallbladder with irregular and hypoplastic biliary radicles is typical of CBA on ultrasound and cholangiography Conversely, infantile CC demonstrates a communication of the cyst with a dilated gallbladder in addition to a dilated intrahepatic biliary tree.

Figure 1. Magnetic resonance cholangiopancreatography (MRCP) axial (*top panel*) and transverse section (*bottom panel*) showing common bile duct with fusiform dilatation in the proximal and mid portion with a maximum diameter of 3.2 mm.





Cyst excision is the definitive management for CC. Historically different internal drainage procedures have been attempted, but have met with little success due to the persistence of biliary stasis. Complete surgical removal of all cystic tissue is advised as it is associated with a very high risk of malignancy.[5] Reported incidences of malignancy in unoperated cases of choledochal cysts range from 10-15%.[1] The surgical approach will be dependent on the specific type and subtype of the cyst, but generally aims to excise the cyst completely and restoration of biliary enteric drainage into duodenum or via Roux-en-Y hepaticojejunostomy.[6]

Even in developed countries where a larger chunk of these cases is antenatally diagnosed, the surgeries get postponed to 3-6 months owing to technical difficulties and associated anaesthetic risks during the neonatal period6. In antenatally diagnosed symptomatic cases of CC, many authors suggest an ideal time for definitive surgery to be anywhere between 2 weeks to 3 months, since liver damage is noted to develop early in these patients. Some neonates, irrespective of their antenatal diagnosis may be surprisingly asymptomatic: borderline elevation of bilirubin levels, gradually increasing size of the cyst and functional maturation of liver with advancement of age are some of the reasons which might explain asymptomatic status. Even in asymptomatic patients, many authors advocate early intervention, as delayed intervention is found to be associated with higher incidences of hepatic fibrosis, portal fibrosis, CBD strictures and cirrhosis.[6] To conclude, all neonatal cases of choledochal cyst need early surgical intervention irrespective of their antenatal diagnosis or their clinically asymptomatic status so as to prevent liver damage, associated complications and to facilitate complete functional recovery.

Another complicated aspect in the management of this patient was the perinatal exposure of HCV which placed the infant at a very high risk of acquiring infection. The risk of transmission is as high as one to five percent, which is increased in presence of HIV co-infection.[7,8,9] Though universal screening is not warranted in our country, current recommendations advise early testing in high-risk cases in a two-step process. Currently, there is no evidence in the literature regarding the direct causative role of perinatal hepatitis C infection in abnormal embryogenesis or immunological changes leading to the formation of choledochal cysts. The infant has to be tested for HCV RNA, between two to six months.[10,11,12] A negative test may suggest a lower likelihood of HCV infection in the infant, while a positive test indicates the presence of infection. This does not predict chronicity, as there is a very high chance of spontaneous viral clearance.[8] Irrespective of the result of the first test, all perinatally exposed infants need to be followed up at 18 months with anti- HCV antibody test. Positive tests warrant HCV RNA testing. Though treatment is deferred until 3 years in this population, these patients need regular monitoring of liver function tests for the progression of liver disease.[8]

Conclusion

Choledochal cyst type 1c is to be considered in the differential of obstructive jaundice in a preterm neonate and requires early diagnosis with MRCP for better delineation of the biliary cyst subtype, pancreatic-biliary ductal anatomy and further surgical planning. It is imperative to diagnose perinatal HCV infection in those with maternal hepatitis C infection.

Compliance with Ethical Standards

Funding None

Conflict of Interest None

References:

1. Singham J, Yoshida EM, Scudamore CH. Choledochal cysts: part 1 of 3: classification and pathogenesis. Can J Surg. 2009 Oct;52(5):434-40. PMID: 19865581; PMCID: PMC2769090.
2. Poddar U, Thapa B.R, Chhabra M. Choledochal cysts in infants and children. Indian Pediatrics 1998; 35:613-18.
3. Soares KC, Goldstein SD, Ghaseb MA, Kamel I, Hackam DJ, Pawlik TM. Pediatric choledochal cysts: diagnosis and current management. Pediatr Surg Int. 2017 Jun;33(6):637-650. doi: 10.1007/s00383-017-4083-6. Epub 2017 Mar 31. PMID: 28364277.
4. Soares KC, Arnaoutakis DJ, Kamel I, Rastegar N, Anders R, Maithel S, Pawlik TM. Choledochal cysts: presentation, clinical differentiation, and management. J Am Coll Surg. 2014 Dec;219(6):1167-80. doi: 10.1016/j.jamcollsurg.2014.04.023. Epub 2014 Jun 27. PMID: 25442379; PMCID: PMC4332770.
5. Jabłońska B. Biliary cysts: etiology, diagnosis and management. World J Gastroenterol. 2012 Sep 21;18(35):4801-10. doi: 10.3748/wjg.v18.i35.4801. PMID: 23002354.
6. Diao M, Li L, Cheng W. Timing of surgery for prenatally diagnosed asymptomatic choledochal cysts: a prospective randomized study. J Pediatr Surg. 2012 Mar;47(3):506-12. doi: 10.1016/j.jpedsurg.2011.09.056. PMID: 22424346.
7. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clin Infect Dis. 2014 Sep 15;59(6):765-73. doi:10.1093/cid/ciu447. Epub 2014 Jun 13. PMID: 24928290; PMCID: PMC4144266.
8. AASLD/IDSA. HCV in Children: Recommendations for HCV Testing of Perinatally Exposed Children and Siblings of HCV-Infected Children. Available at: https://www.hcvguidelines.org/unique-populations/children
9. Yeung LT, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus.Hepatology. 2001 Aug;34(2):223-9. doi: 10.1053/jhep.2001.25885. PMID: 11481604.
10. Gowda C, Smith S, Crim L, Moyer K, Sánchez PJ, Honegger JR. Nucleic Acid Testing for Diagnosis of Perinatally Acquired Hepatitis C Virus Infection in Early Infancy. Clin Infect Dis. 2021 Nov 2;73(9):e3340-e3346. doi: 10.1093/cid/ciaa949. PMID: 32640018; PMCID:PMC8563185.
11. Ghany MG, Morgan TR; AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Hepatology. 2020 Feb;71(2):686-721. doi: 10.1002/hep.31060. PMID: 31816111; PMCID: PMC9710295.
12. Leung DH, Squires JE, Jhaveri R, Kerkar N, Lin CH, Mohan P, Murray KF, Gonzalez-Peralta RP, Roberts EA, Sundaram SS. Hepatitis C in 2020: A North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper. J Pediatr Gastroenterol Nutr.2020 Sep;71(3):407-417. doi: 10.1097/MPG.0000000000002814. PMID: 32826718.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.48

CASE REPORTS

A RARE CASE OF A NEONATAL HAEMANGIOMA OF THE DISTAL PHALYNX

Issac Varghese[1], Kishore Kumar[2,3].

[1]Department of Neonatology, Royal Victoria Infirmary, Newcastle upon Tyne, England, U.K.,

[2]Senior Consultant Neonatologist & Head of Department of Neonatology, Cloud Nine Hospital, Bangalore, India,

[3]Professor (Adjunct) of Neonatology, Notre Dame University, Perth, Australia.

ABSTRACT

Background: Vascular Mass lesions are uncommon but not rare and there have been reports of haemangiomas in different body areas. However, haemangioma of the tip of a finger haven't been reported previously. The significance of this condition lies in fact that it can cause disruption of circulation, digital growth retardation and development, platelet consumption, and morbidity. In infants and young children – can be a cause of significant distress because of mouthing or other issues which can cause bleeding risk.

Case: Here we report a case which was not diagnosed antenatally, the haemangioma was seen only at birth.

Conclusion: When dealing with haemangioma, especially on digital extremities careful considerations need to be undertaken on the vascular, orthopaedic, and medicinal effects, especially on a neonatal age group.

ARTICLE HISTORY

Received : 13 August 2024

Accepted : 30 October 2024

KEYWORDS

newborn, haemangioma, distal phalanx.

ABBREVATION

IH – Infantile Haemangioma.

Introduction

Haemangiomas, also called as "strawberry marks", a benign tumour of infancy and are caused by proliferation of endothelial cells. Congenital haemangiomas are visible at birth whereas infantile haemangiomas appear later.[1] Haemangiomas are lesions originating congenitally due to faults in embryonic development. The mechanism is by the proliferation of endothelial cells.[2] Haemangiomas, present with a heightened risk of foetal anomalies along with foetal hydrops, polyhydramnios, perinatal morbidity and antenatal mortality. Here we are reporting a case of a newborn with a haemangioma of the distal phalanx of the left middle finger which was undiagnosed antenatally.

Case Report

A 2.76 Kg baby was born by elective LSCS given the previous section at 39 weeks gestation. Antenatally, the mother did not go through any triple test or any amniotic fluid sampling. The antenatal scans did not show any abnormalities. The APGAR score reading at the 1st and 5th minutes read 8 and 9 respectively. The haemangioma was noted at the delivery by the obstetrician and the neonatal doctor at delivery. The hemangioma (Figures 1-8) was dried gently and covered with wet gauze, examined for any breakage or bleeding (Figures 2, 3, 4) and the baby was handed over to the mother for skin-to-skin. It can be seen that the haemangioma was around 2 inches in diameter (Figure 3) and also spared the nail bed (Figures 4, 5, 6, 7).

Address for Correspondance:
Dr Issac Varghese, Maracheril House Pazhanganad, Kizhakkambalam PO, Ernakulam District, Kerala 683562.
Email: Issac6948@yahoo.com

The case was discussed with the senior consultant neonatologist, the paediatric surgeon, and the dermatologist. A plan was made initially to perform a full blood count at 12 hrs of age and start the baby on propranolol however the parents elected not to start propranolol as they were not comfortable with the side-effects they read online, a screening ultasonogram of abdomen was undertaken for ruling out liver haemangiomas which were reported to be within normal limits without any haemangiomas. The baby was discharged at 48 hrs of life and was planned to follow up with a paediatrician and dermatologist to see the progress of haemangioma. A biopsy was not performed as it was decided it would not yield any additional results. The baby was followed up after 6 weeks and the haemangioma had shrunk to 60% of the size.

The baby was arranged to be seen again at 6 months - coinciding with the immunization schedule.

Discussion

Infantile haemangioma (IH) is one of the most common paediatric vascular tumour at around 5-10%.[1,2] The cellular mechanism leading to this condition is not clearly defined in literature but is thought to be represented by a deviant response of pluripotent stem cells to multiple stimulus in the form of hypoxia, hypercarbia and the renal renin-angiotensin system.[3] IH presents itself during the first month of life mainly in first 2-3 weeks and follows a distinctive natural progresssion with endothelial cellular proliferation and compounding involution.[3] The signs and symptoms depends on their distribution and the depth. It is classified into superficial, mixed, and deep IH and based on growth IH with minimal or no growth.[3] There is a correlation between multifocal IH

Figure 1. Haemangioma seen from palmar aspect.

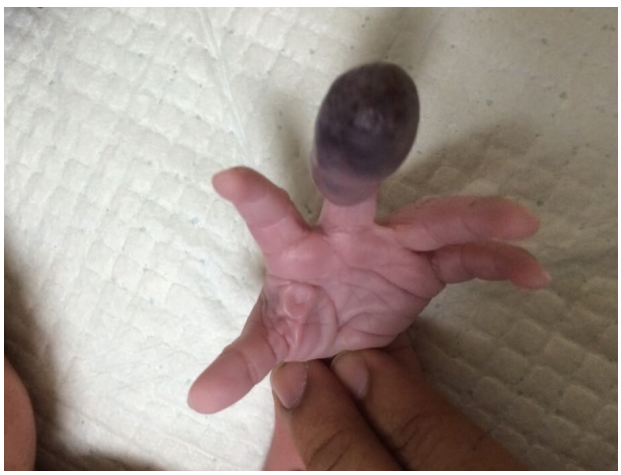


Figure 2. Haemangioma seen from palmar aspect showing full extent of size.

Figure 3. Haemangioma seen from dorsal aspect showing diamensions.

Figure 4. Haemangioma seen from dorsal aspect showing nailbed and nail.

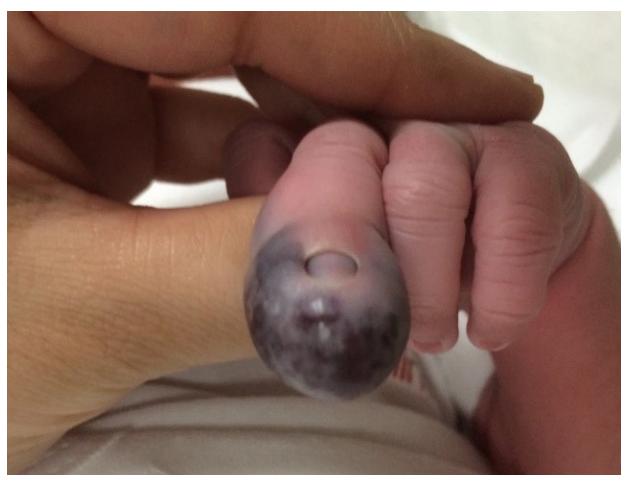


Figure 5. Haemangioma seen from dorsal aspect showing nailbed and nail in relation to finger.

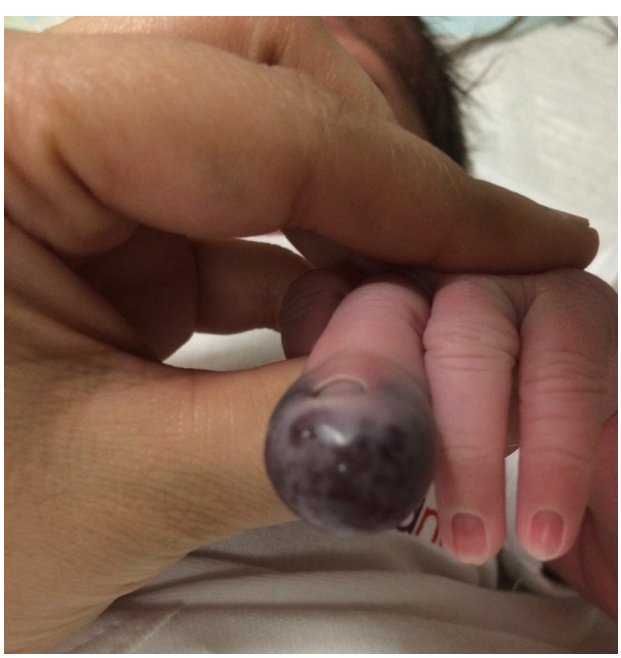


Figure 6. Haemangioma seen from grasp position showing nailbed and nail in relation to other fingers.

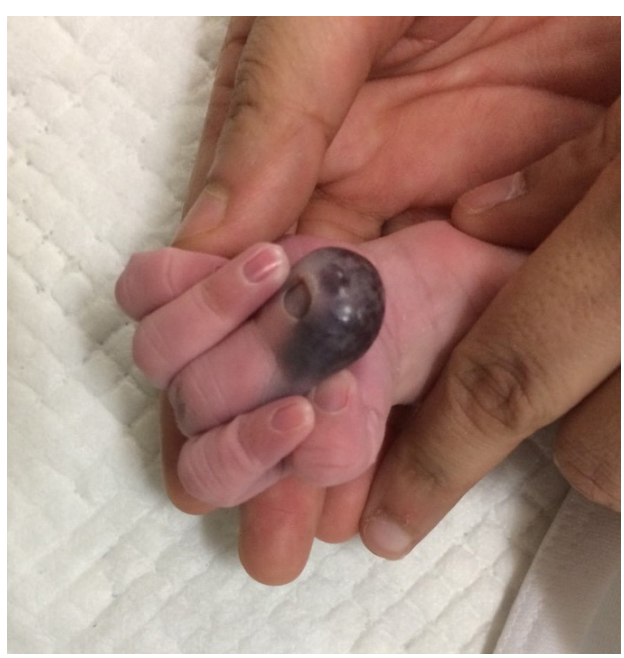
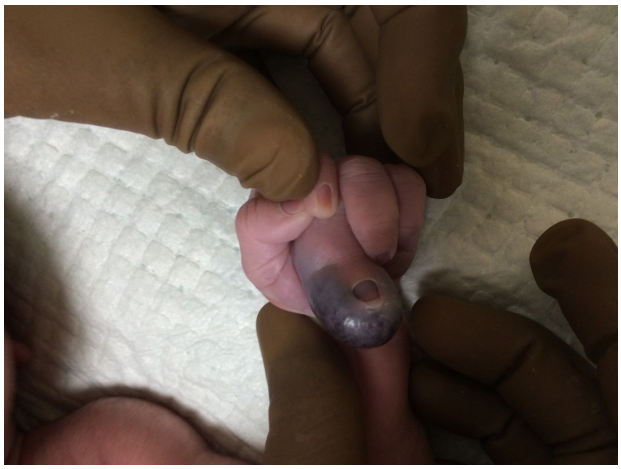


Figure 7. Haemangioma seen from dorsal aspect in comparison to an adult finger.



and hepatic hemangiomas in infant.[3] The most common practice for cut off is greater than 5 haemangiomas to ultrasound screen for hepatic hemangiomas.[4] If large haemangiomas are seen in facial proximity, it is advised to investigate for posterior fossa malformation, arterial vessel anomalies, cardiact defects such as coarctation of aorta and opthalmological anomalies as in PHACE syndrome[4] Lumbar haemangiomas should be investigated for LUMBAR Syndrome comprising of Lowerbody cutaneous IH, Urological and Genital anomalies, cutaneous ulceration, myelopathy, bone abnormalities and defects, anorectal and arterial malformations and renal anomaly.[5] The complications usually encountered with IH are ulceration, obstruction of urogenital tracts, visual obstruction, bleeding, hypothyroidism and cosmetic concerns. The differential diagnosis considered in IH are other vascular tumors and malformations, pyogenic granulomas, tufted angioma, kaposiform haemangioendothelioma, Kaposi sarcoma.[5,6] The Diagnosis is primarily clinical, one with biopsy used very rarely. Ultrasonogram can help with lesions located subcutaneously. Discussions and liaison with other specialities like dermatology and plastic surgery may me needed in certain cases

The treatment is mainly conservative.[7] The active treatment of IH involves use of propranolol and sirolimus. Active treatment is usually commenced with a review by a specialist prior to 5 weeks of age to discuss the risks involved. Propanolol can be started from an outpatient clinic and is generally started on a 1 mg/kg/ day in two divided doses and dose increases to a maintenance of 2 mg/kg/ day in 2-3 divided doses.[7,8,9,10] The treatment is to be reviewed every 2-3 months.[7] Treatment modalities such as atenolol is showing more promise in ongoing research. In lesions which are recalcitrant sirolimus may be used with liaison with other specialties.[8,9,10]

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Chamli A, Aggarwal P, Jamil RT, et al. Hemangioma. [Updated 2023 Jun 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538232/
2. Gasparella P, Singer G, Arneitz C, et al. Rapidly involuting congenital hemangioma of the liver in a newborn with incomplete Pentalogy of Cantrell: description of a new association. J Surg Case Rep 2021; 2021: rjab047. https://doi.org/10.1093/jscr/ rjab047
3. Bandera AI, Sebaratnam DF, Wargon O, et al. Infantile hemangioma. Part 1: Epidemiology, pathogenesis, clinical presentation and assessment. Journal of the American Academy of Dermatology. 2021 Dec 1;85(6):1379-92.
4. Rotter A, Samorano LP, Rivitti-Machado MC, Oliveira ZNP, Gontijo B. PHACE syndrome: clinical manifestations, diagnostic criteria, and management. An Bras Dermatol. 2018 Jun;93(3):405-411. doi: 10.1590/abd1806-4841.20187693. PMID: 29924216; PMCID: PMC6001075.
5. Iacobas I, Burrows PE, Frieden IJ, Liang MG, Mulliken JB, Mancini AJ, Kramer D, Paller AS, Silverman R, Wagner AM, Metry DW. LUMBAR: association between cutaneous infantile hemangiomas of the lower body and regional congenital anomalies. J Pediatr. 2010 Nov;157(5):795-801.e1-7. doi: 10.1016/j.jpeds.2010.05.027. Epub 2010 Jul 2. PMID: 20598318.
6. Eberson SN, Desai SB, Metry D. A Basic Introduction to Pediatric Vascular Anomalies. Semin Intervent Radiol. 2019 Jun;36(2):149-160. doi: 10.1055/s-0039-1688432. Epub 2019 May 22. PMID: 31123389; PMCID: PMC6531024.
7. Cîrstoveanu C, Bizubac AM, Mustea C, Manolache □, Istrate-Bârzan A, Sfrijan D, Marcu V, Iozsa DA, Spătaru RI. Antiproliferative therapy with sirolimus and propranolol for congenital vascular anomalies in newborns (Case reports). Exp Ther Med. 2021 Oct;22(4):1097. doi: 10.3892/etm.2021.10531. Epub 2021 Aug 2. PMID: 34504551; PMCID: PMC8383751.
8. Cavazos R, Patil MS, Gowda . Sirolimus for vascular anomalies in the first year of life: a systematic review. J Perinatol. 2024 Aug;44(8):1087-1097. doi: 10.1038/s41372-024-01868-9. Epub 2024 Jan 20. PMID: 38245657.
9. Sebaratnam DF, Bandera AI, Wong LC, et al . Infantile hemangioma. Part 2: management. Journal of the American Academy of Dermatology. 2021 Dec 1;85(6):1395-404.
10. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press http://www.medicinescomplete.com [Accessed on [16/08/2024]]

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.47

CASE REPORTS

A TROPICAL ADVENTURE IN THE IMMUNE SYSTEM

Leonor Cardoso[1], Catarina Duarte[2], Cristina Camilo[2], Leonor Boto[2], José Gonçalo Marques[3].

[1]Department of Paediatrics, ULS da Cova da Beira, Covilhã, Portugal,

[2]Paediatric Intensive Care Unit, Department of Paediatrics, Hospital de Santa Maria - ULSSM, Lisbon, Portugal,

[3]Paediatric Unit of Infectious Diseases and Immunodeficiency, Department of Paediatrics, Hospital Santa Maria - ULSSM, Lisbon, Portugal.

ABSTRACT

Infection-associated secondary hemophagocytic lymphohistiocytosis (sHLH) is a potentially life-threatening hyperinflammatory condition, rarely associated with malaria. We present a case of sHLH triggered by P. falciparum, which was also complicated by acute kidney injury (AKI) and late onset pancreatitis, following intravenous artesunate.

Male adolescent with known sickle cell disease, who presented to the paediatric intensive care unit due to P. falciparum infection with low grade parasitemia (1%), shock and multisystem failure. Empirical treatment with ceftriaxone and clindamycin was started on admission, and intravenous artesunate was administered, with rapid clearance of malaria parasites. The severity of multisystem involvement led to investigation of sHLH, which was con?rmed (ferritin 136 791 ng/mL, CD25 16 000 pg/mL). Treatment with high dose dexamethasone led to a rapid improvement. On day 5, artesunate was stopped due to acute kidney injury with severe polyuria and mild elevation of pancreatic enzymes. The patient was transferred to the ward on day 10, and discharged home on day 20.

A severe clinical course of malaria with low parasitemia should raise the suspicion of sHLH. Prompt treatment of both the infectious trigger and the hyperin?ammation allowed for a good outcome. High dose dexamethasone alone may be sufficient in this setting. Our case also illustrates potential, although rare, toxicities of intravenous (IV) artesunate therapy, underscoring the need for continuous monitoring, as well as prompt antimalarial de-escalation to minimize iatrogenic effects.

ARTICLE HISTORY

Received : 6 September 2024

Accepted : 30 October 2024

KEYWORDS

secondary hemophagocytic lymphohistiocytosis, malaria, pediatric, acute pancreatitis, acute kidney injury.

Background

Hemophagocytic lymphohistiocytosis (HLH) is considered a rare immunological disorder marked by widespread activation of the inflammatory system, affecting the bone marrow and reticuloendothelial system.[1,2,3,4,5,6,7,8,9,10]

HLH can be primary (familial) or secondary (sHLH), as a result of an infection, malignancy, or autoimmune disorder.[9,10] Infectious triggers include viruses (cytomegalovirus, Epstein-Barr virus, human herpesvirus-8, human immunodeficiency virus), bacteria (Mycobacterium tuberculosis, Salmonella typhi), and parasites (Plasmodium falciparum and less frequently Plasmodium vivax). There are few cases reporting malaria as an sHLH trigger.[5] Malaria-related HLH can be fatal, with a 90% mortality rate if left untreated,[5] highlighting the need for an early diagnosis of the primary disease and timely intervention.

Artemisinin derivatives are the first line treatment for P. falciparum and have been used worldwide for a long period of time.[7,11] We also aim to report and raise awareness for possible severe side effects of intravenous artesunate.

Address for Correspondance:
Leonor Cardoso, Av. Prof. Egas Moniz MB, 1649-028 Lisboa.
Email: leonorcardoso93@gmail.com

Case Report

A 15-year-old male with known sickle cell disease and a baseline haemoglobin (Hb) of 6.5-7.5 g/d was admitted to the paediatric intensive care unit (PICU) for suspected septic shock. He was on treatment with daily hydroxyurea and folic acid, and awaiting cholecystectomy for gallstones. The family medical history was irrelevant.

After a trip to Angola in the preceding 3 weeks, he developed fever and vomiting due to malaria with 1% *P. falciparum parasitemia*. On admission at the local hospital he received two saline boluses (10 ml/kg each) for hypotension (blood pressure 79-95/26-33 mmHg) and tachycardia, with warm extremities, palpable broad pulses, and no signs of cardiac compromise. Considering the hemodynamic instability, dopamine was started (max 12 mcg/kg/min) before PICU transfer. An echocardiogram showed good left ventricular function. Initial blood tests showed anemia (Hb 6.2 g/dL), severe hemolysis (LDH 1321, total bilirubin 16,2

Table 1. Maximum and minimum laboratory values during hospitalization in PICU.

	Day-1	Day-2	Day-3	Day-4	Day-5	Day-6	Day-7	Day-9
Leukocytes (uL)	15570	26000	24800	17300	14300	15500	12400	----------
Lymphocytes (uL)	880	900	3170	2730	1400	1740	2470	----------
Platelets (uL)	173000	97000	79000	47000	69000	75000	98000	124000
Hb (g/dL)	6,2	4,6	5,9	6,6	6,4	5,9	5,7	7,6
NTproBNP (pmol/L)	505	1715	2460	811	----------	----------	----------	----------
Troponin-T (ng/L)	8,3	16	19	--------	9	----------	----------	----------
PT (seconds)	56,7	53,6	32,2	25,2	19,6	17,1	17,4	20,2
INR	4,89	4,62	2,78	2,17	1,69	1,51	1,53	1,74
Fibrinogen (mg/dL)	176	170	214	164	163	121	----------	----------
PCT (ng/mL)	3,23	16,6	15,1	10,7	8,74	3,44	2,03	----------
CRP (mg/dL)	8,59	21,1	27,6	32,6	20,2	10,9	5,6	----------
Ferritin (ng/mL)	----------	----------	136791	----------	74297	3938	----------	----------
CD25 (pg/mL)	----------	----------	16000	----------	----------	----------	----------	----------
Creatinine (mg/dL)	0,72	1,02	1,53	1,29	1,11	0,68	0,58	0,41
Urea (mg/dL)	50	58	91	157	189	119	69	36
AST (U/L)	555	4277	4448	3899	2916	508	169	69
ALT (U/L)	246	1080	1128	1035	849	508	268	132
LDH (U/L)	1321	4475	8090	9882	6207	3938	2826	----------
GGT (U/L)	113	94	84	71	61	71	157	----------
D. Bilirubin (mg/dL)	7,91	----------	23,33	----------	25,96	16,12	----------	----------
ALP (U/L)	----------	----------	----------	350	568	516	----------	----------
Amylase (U/L)	----------	----------	----------	49	118	261	413	224
Lipase (U/L)	----------	----------	----------	---- --- ---	----------	----------	1088	----------
Triglyceride(mg/dL)	----------	----------	104	196	196	----------	----------	----------
Ammonia	56	----------	81	78	----------	----------	----------	----------

mg/dl, conjugated bilirubin 7,9 mg/dl, AST 555 U/L, ALT 246 U/L), elevated C-reactive protein (CRP) (12 mg/dl) and hyperlactacidaemia. A blood transfusion en route raised Hb to 7.2 g/dL.

On PICU admission, he was drowsy, with fever (38.5ºC) and low diastolic blood pressure. He had icteric sclera and hepatosplenomegaly. As he presented with distributive shock, with persistently low diastolic blood pressure, norepinephrine was started, up to a maximum dose of 0.4 mcg/kg/min, with concomitant down titration of dopamine. Vasoactive and inotropic drugs were suspended on Day-2, after a sustained hemodynamic response. Serial echocardiograms showed adequate ventricular function. Maximum values of NT-proBNP (2460 pg/mL) and Troponin T (19 ng/L) were seen on Day-2 of hospitalization, with maximum hyperlactacidaemia of 76 mg/dl. Two more blood transfusions were administered between Day-1 and 2, due to low hemoglobin levels (minimum 4.6 mg/dL). Coagulopathy (INR maximum 4.86, PT 56.7 sec, aPTT 47sec) and hypofibrinogenemia (176 mg/dL) were managed with fresh frozen plasma, vitamin K, and fibrinogen on Day-1. Thrombocytopenia was noted from admission (minimum 47,000/uL on Day 4), without active bleeding. Liver hepatocellular injury peaked on Day-3 (AST 4448 U/L, ALT 1128 U/L), with biliary dysfunction markers elevated from Days 1 to 5 (max GGT 120 U/L, direct bilirubin 25.96 mg/dL, ALP 568 U/L). (Table 1)

He was empirically started on clindamycin and ceftriaxone for septic shock, later switched to cefotaxime due to worsening cholestasis, for a total duration of seven days. Procalcitonin (PCT) and CRP values reached a maximum of 15.1 ng/mL and 32.6

mg/dl, on Day-3 and 4, respectively. Blood cultures became negatives. (Table 1)

Intravenous artesunate (2.4 mg/kg/dose) was started on Day-2 and was administered for five days (administered at 0h, 12h, 24h, 48h, 72h and 96h), with subsequent oral artemether-lumefantrine for three additional days.

Pancytopenia and severe multisystem involvement led to sHLH investigation, which was confirmed. High ferritin (136,791 ng/mL) and soluble CD25 (sCD25) (16,000 pg/mL) on Day-3 prompted high-dose dexamethasone initiation (10 mg/m²/day), resulting in clinical and analytical improvement, with sustained apyrexia from Day-7. Corticosteroids were tapered over two weeks due to rapid response.

Acute kidney injury (AKI) without oligoanuria was noted from Day-2 (Day-1 of artesunate), peaking on Day-3 (creatinine 1.53 mg/dL, GFR 44 mL/min/1.73m²) and normalizing after artesunate withdrawal. Hypernatremic dehydration due to marked polyuria (maximum 300-500mL/h) was seen from Day-3 (Day-2 artesunate), with peak sodium 156 mmol/L and urea 189 mg/dL on Day-5. Urinalysis showed normal urine density (Udens), adequate urinary sodium (uNa) and osmolarity (OsmU), as well as plasma osmolarity. He received IV fluids and free water, and a therapeutic trial with desmopressin was pursued, with an inconsistent response. Normal neurohypophysis on MRI and normal values of hypothalamic-pituitary axis related hormones on Day-20 made the diagnosis of central diabetes insipidus less likely.

Mild, late-onset acute pancreatitis was recognized on Day-7, with peak amylase 413 U/L and serum lipase 1088 U/L, about 24 hours after the last IV artesunate dose. Abdominal ultrasound showed no signs of relation to gallbladder lithiasis. He was managed conservatively, and pancreatitis markers were decreasing by Day-10, when transferred to the ward.

He remained neurologically stable, with no signs of nervous system infection. Electroencephalography (EEG) showed no signs of hepatic encephalopathy. He was transferred to the ward on Day-10.

The following table (Table 1) details the progression of laboratory blood tests, including critical (minimum and maximum) serum values, during his PICU stay.

Discussion

Malaria is an infectious disease caused by protozoan parasites of the genus Plasmodium, with a variety of clinical symptoms. Among the species, Plasmodium falciparum and Plasmodium vivax have been linked to sHLH so far, with P. falciparum being the predominant cause.[1] Most of sHLH cases associated with malaria worldwide have been reported in regions with high malaria prevalence, such as Sub-Saharan Africa and Southeast Asia.[1,2,3,4,5]

Although our patient came from a malaria-endemic area and had low blood parasitemia upon admission, it is crucial not to assume an asymptomatic carrier state. Immediate treatment is essential as delaying it can lead to adverse clinical outcomes.[1,2]

The exact mechanism of sHLH in the setting of malaria remains unclear, but it likely involves a combination of genetic predisposition and an excessive immune response triggered by the parasite.[1] The overlapping symptoms of malaria and HLH, such as fever, splenomegaly, anemia, thrombocytopenia, and elevated inflammatory markers, makes the diagnosis challenging. These symptoms in malaria probably result from parasite-induced cytotoxicity, microvascular issues, and organ sequestration. However, unusual findings like high ferritin, high triglycerides, and low fibrinogen levels may suggest superimposed HLH.[1,6] Persistent pancytopenia and severe multisystem failure, despite successful malaria treatment, should also prompt suspicion of sHLH.[5] Elevated sCD25 is a useful biomarker for diagnosing sHLH in children, with a sensitivity of 76.2% and specificity of 98.2%, indicating that this biomarker could be of clinical use.[9]

Intravenous artesunate is the preferred treatment for severe malaria due to its quick parasite clearance, safety, and effectiveness in reducing mortality.[11] When standard antimalarial treatments fail, leading to clinical deterioration or multiorgan failure, HLH-specific therapy, including immunosuppressants like steroids and intravenous immunoglobulin, may be necessary.[1,9] These drugs act by inhibiting the inappropriate macrophage activation [3]. Dexamethasone is favored for its ability to cross the blood-brain barrier and is typically tapered over eight weeks.[4] In our case, a high dose of 10 mg/m²/day was administered for one week and tapered over two weeks due to the patient's rapid and sustained response to treatment.

The exact pathophysiology of AKI in malaria is not well understood, but proposed mechanisms include blockage of renal microcirculation by infected erythrocytes, immune-mediated glomerular injury, and volume depletion.[12]

Our patient experienced worsening kidney function and polyuria starting on the second day after admission and the initiation of intravenous artesunate. AKI related to intravenous artesunate has also been documented.[11] The leading hypothesis is that artesunate-induced ‹pitting› of red blood cells shortens their lifespan to 7-21 days, causing severe hemolysis and free hemoglobin-mediated tubular damage. This delayed hemolysis typically occurs more than a week after treatment starts, indicated by a drop in hemoglobin and a rise in lactate dehydrogenase without recurring parasitemia.[11]

Harshil et al reported the case of a 12-year-old boy with severe malaria, who developed oliguria and edema 12 hours after starting artesunate, requiring dialysis.[12] Despite switching to oral Artemether and Lumefantrine on the sixth day, his serum creatinine peaked on the seventh day, to a maximum of 6.08 mg/dL. Dialysis continued, and by the tenth day, liver and kidney functions normalized. Additionally, a study to evaluate toxicity of artesunate in Plasmodium berghei-infected and uninfected rats, found that artesunate induced renal injury by the eighth day post-dosing, with histopathological evaluations revealing tubular necrosis in uninfected rats and in malaria-infected rats.[13] Although this mechanism could possibly contribute for AKI seen in our patient, with increased creatinine, a pre-renal component may also be implied, evidenced by a significant increase in urea levels.

Pancreatitis is an unusual cause of abdominal pain in malaria, likely due to the occlusion of pancreatic blood vessels by parasitized red blood cells.[14] This is usually associated with an acute process while the patient remains parasite-positive by microscopy. However, a case report of a 34-year-old male, who developed late-onset pancreatitis after starting intravenous artesunate suggests another possible mechanism. This pancreatitis occurred eight days post-admission, five days after the blood was parasite-negative, indicating that it might not be due to parasite sequestration. The patient was managed conservatively, and his serum amylase levels normalized with no abdominal pain after one month of follow-up.[15] Artesunate has been associated with hemolysis up to four weeks post-administration, even though the drug has long been excreted, potentially contributing to this late onset complication.[16]

The case we present is unique as it is the first documented case of late-onset acute pancreatitis probably associated with intravenous artesunate in a pediatric patient.

Conclusion

Secondary HLH associated with malaria is extremely rare, with limited literature available on this connection. The overlap between these conditions challenges the diagnosis of HLH superimposed on malaria. We emphasize that a severe case of malaria with low parasitemia should raise suspicion of sHLH. Early identification, close monitoring and treatment of both the infection and hyperinflammation can improve patient outcomes. High doses of dexamethasone for one week with a two-week tapering may be effective in this setting and diminishes the risk of corticosteroid-related side effects.

Our case also highlights two potential, though rare, toxicities of intravenous artesunate therapy – AKI and late-onset acute pancreatitis. To minimize iatrogenic effects, continuous monitoring and prompt de-escalation of antimalarial treatment should be reinforced.

Compliance with Ethical Standards

Funding None

Conflict of Interest None

References:

1. Almajed, M. R., Cerna-Viacava, R., Priessnitz, J., et al. (2022). A Case of Malaria-Associated Hemophagocytic Lymphohistiocytosis. Cureus, 14(8), e28386. https://doi.org/10.7759/cureus.28386
2. Fuchs, A., Orth, H. M., Germing, U., et al. (2020). Falciparum malaria-induced secondary hemophagocytic lymphohistiocytosis successfully treated with ruxolitinib. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases, 100, 382-385. https://doi.org/10.1016/j.ijid.2020.07.062
3. Phadke, V., George, R., Chaudhari, K., et al. (2014). Haemophagocytic lymphohistiocytosis: a cause of unresponsive malaria in a 5-year-old girl. Paediatrics and international child health, 2046905514Y0000000163. Advance online publication. https://doi.org/10.1179/2046905514Y.0000000163
4. McClain, L. K., Eckstein, O. (2022). Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Uptodate. Last updated: May 06, 2022.
5. Almajed, M. R., Cerna-Viacava, R., Priessnitz, J., et al. (2022). A Case of Malaria-Associated Hemophagocytic Lymphohistiocytosis. Cureus, 14(8), e28386. https://doi.org/10.7759/cureus.28386
6. Orth, H. M., Wiemer, D., Schneitler, S., et al. (2024). Hemophagocytic lymphohistiocytosis-how common and how severe is it as a complication of malaria? Retrospective case series and review of the literature. Infection, 52(2), 471-482. https://doi.org/10.1007/s15010-023-02104-w
7. Muthu, V., Dhooria, S., Sehgal, I. S., et al. (2017). Malaria-associated secondary haemophagocytic lymphohistiocytosis: Report of two cases & a review of literature. The Indian journal of medical research, 145(3), 399-404. https://doi.org/10.4103/ijmr.IJMR_740_15
8. Chaudhry, S., Arya, A., Matlani, M., et al. (2021). Pancytopenia with hemophagocytic lymphohistiocytosis in Plasmodium falciparum: A unusual presentation. Tropical parasitology, 11(1), 46-48. https://doi.org/10.4103/tp.TP_34_20
9. Zhou, X., Duan, M. L. (2021). Malaria-associated secondary hemophagocytic lymphohistiocytosis: A case report. World journal of clinical cases, 9(22), 6403-6409. https://doi.org/10.12998/wjcc.v9.i22.6403.
10. Amireh, S., Shaaban, H., Guron, G. (2018). Severe Plasmodium vivax cerebral malaria complicated by hemophagocytic lymphohistiocytosis treated with artesunate and doxycycline. Hematology/oncology and stem cell therapy, 11(1), 34-37. https://doi.org/10.1016/j.hemonc.2016.06.001
11. Leong, K. W., Singh, K. P., Leder, K., et al. (2021). Acute kidney injury secondary to severe delayed haemolysis in intravenous artesunate use for severe malaria. BMJ case reports, 14(1), e237501. https://doi.org/10.1136/bcr-2020-237501.
12. Gumasana H., Otieno W. (2021). Case report: Acute Kidney Injury, Liver impairment, Severe Anemia in a child with Malaria and Hyperparasitaemia. Global Journal of Medical and Clinical Case Reports. 001-004. 10.17352/2455-5282.000116.
13. Li, Q., Xie, L. H., Johnson, T. O., et al. (2007). Toxicity evaluation of artesunate and artelinate in Plasmodium berghei-infected and uninfected rats. Transactions of the Royal Society of Tropical Medicine and Hygiene, 101(2), 104-112. https://doi.org/10.1016/j.trstmh.2006.04.010.
14. Seshadri, P., Dev, A. V., Viggeswarpu, S., et al. (2008). Acute pancreatitis and subdural haematoma in a patient with severe falciparum malaria: case report and review of literature. Malaria journal, 7, 97. https://doi.org/10.1186/1475-2875-7-97.
15. Mahdi, A. S., Molai, M., Chandwani, J., et al. (2018). Late onset acute pancreatitis in P. falciparum malaria - An adverse reaction to intravenous artesunate?. IDCases, 12, 124-126. https://doi.org/10.1016/j.idcr.2018.04.010.
16. Roy, S., Parchani, A., Sharma, S., et al. (2020). Falciparum malaria-induced acute pancreatitis. IDCases, 21, e00911. https://doi.org/10.1016/j.idcr.2020.e00911.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.46

CASE REPORTS

MOBITZ TYPE II CARDIAC CONDUCTION DISORDER IN ADOLESCENT MALE

April Oertle[1], Justin Assioun[2,3], Stephanie Schroter[2,3].

[1]University of Illinois College of Medicine, Rockford, Illinois, USA,

2Division of Emergency Medicine, Rady Children's Hospital San Diego, San Diego, California, USA,

[3]Department of Pediatrics, University of California, San Diego School of Medicine, La Jolla, California, USA.

ABSTRACT

Atrioventricular (AV) block, characterized by delayed or interrupted transmission of electrical impulses, rarely occurs in structurally normal hearts. Mobitz type II AV block, a specific form of second-degree heart block, is rarely seen in children and is often associated with underlying cardiac pathology. We present a case of a 14-year-old male with a structurally normal heart who exhibited paroxysmal variable second degree (Mobitz type II) arrhythmia. Initial concerns of hypertrophic cardiomyopathy were raised due to high lateral lead voltages on electrocardiogram and signs of heart block on telemetry. However, further evaluation revealed no structural abnormalities. Extensive diagnostic workup, including cardiac magnetic resonance imaging and laboratory testing ruled out ischemia, myocarditis, autoimmune pathology, Lyme, and Chagas disease. The patient demonstrated stable hemodynamics but required continuous monitoring due to potential progression to complete heart block. This case highlights the need to consider various differential diagnoses in pediatric patients with cardiac conduction abnormalities, especially without structural heart disease.

ARTICLE HISTORY

Received : 01 July 2024

Accepted : 24 September 2024

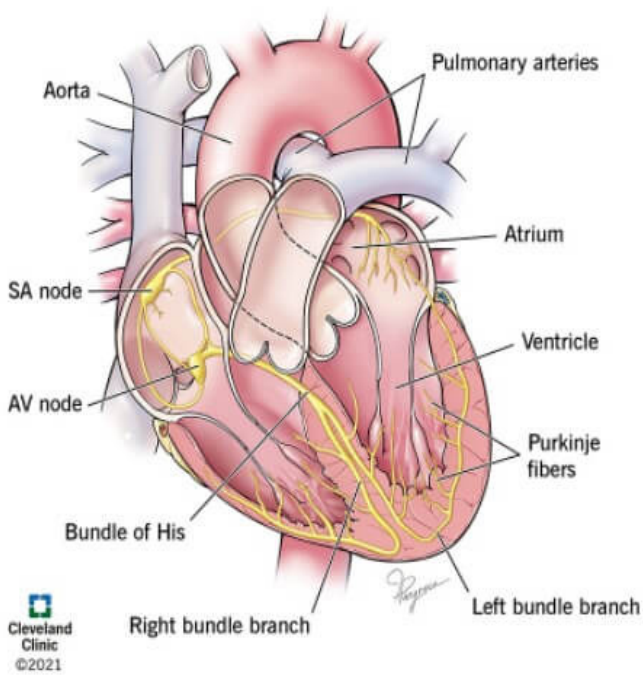
KEYWORDS

Mobitz Type II, 2nd degree AV block, AV block, cardiac conduction disorders, sinus node dysfunction.

Introduction

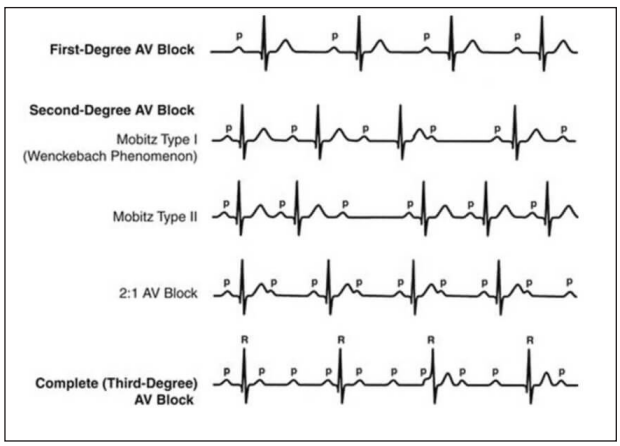
Cardiac conduction disorders manifesting in the pediatric population are uncommon, especially in children without a history of structural heart disease.[1] Primary arrhythmias are rarely documented in children, though they may occur in a structurally normal heart or with an associated congenital heart disease.[2] Atrioventricular (AV) block occurs when there is a delay or interruption in the transmission of electrical impulses from the upper chambers (atria) to the lower chambers (ventricles) of the heart.[3] This condition can result from various factors, including structural cardiac abnormalities or dysfunction within the heart's conduction system, leading to compromised heart rhythm regulation. Disturbances in cardiac conduction can manifest as either transient or permanent conditions, presenting clinically with varying degrees of delay, intermittency, or absence in the transmission of electrical impulses.[3] First-degree AV block refers to delay in the conduction from the atrium to the ventricle, characterized by a prolonged PR interval exceeding 200 milliseconds, without complete interruption.[3] Second-degree AV block involves intermittent transmission of atrial impulses to the ventricles and is further classified into Mobitz type I (Wenckebach Block or Phenomenon), Mobitz type II or two-to-one or higher AV block. Second degree AV blocks often display a pattern such as a 2:1 or 3:23. For example, in cases of 2:1 AV block, a ventricular complex (QRS, T) follows every second atrial (P) complex. In Mobitz type II AV block, the PR interval is consistent prior to the P wave that fails to conduct to the ventricles[3] (Figure 1). Mobitz type II most commonly occurs below the AV node, in the bundle of His or even in the right and left bundle branches (Figure 1). In third degree AV block no atrial impulses are conducted to the ventricles of the heart.

Figure 1. Diagram of heart with normal anatomy4, from Cleveland Clinic.



Address for Correspondance:
April Oertle, 6229 Parks Edge Dr, Loves Park, 61111, Unites States.
Email: Aoertl2@uic.edu

Figure 2. A single lead EKG showing the different types of AV block.[5] In Mobitz type II second degree AV block, the first and fifth P waves are not conducted through the AV node.[3] There is no QRS complex that follows the P wave. The PR interval is unchanged prior to the non-conducted beats. Image courtesy of: Park MK, Guntheroth WG: How to Read Pediatric ECGs, 4th ed. Philadelphia, Mosby, 2006.



Almost all Mobitz type II presentations are due to the presence of cardiac disease such as myocardial ischemia, fibrosis, myocarditis, Lyme disease, cardiomyopathy, cardiac tumors, collagen vascular disorders, or hyperthyroidism.[6] It seldomly occurs in individuals lacking pre-existing heart pathology. Reversible factors often linked with this type of blockage include myocardial infarction causing ischemia in the AV node and medications that affect conduction within the AV node, such as digoxin, beta blockers, and calcium channel blockers.[3] Mobitz type II has an increased risk of progression to complete AV block. Therefore, the treatment for Mobitz type II often requires pacemaker placement and lifelong follow up.[6] We present a rare case of a child with a structurally normal heart, without comorbidities, who was found to have variable Mobitz type II AV block on presentation.

Case Report

A 14-year-old, fully vaccinated, male with no past medical history was transferred from an adult emergency department to a Level 1 pediatric emergency department (PED) with concerns for hypertrophic cardiomyopathy due to high lateral lead voltages on initial electrocardiogram (EKG) which progressed to signs of variable Mobitz type II heart block noted on telemetry.

His chief complaint was a "funny sensation" over his left chest when going to sleep. The sensation was not painful, did not feel like palpitations, or feel like his heart was skipping a beat. He denied any shearing pain radiating to his back. He denied associated diaphoresis, shortness of breath, abdominal pain, nausea, and vomiting. The parents endorse that the child is an athlete and has never experienced any dizziness, prior syncopal episodes or other exertional symptoms. The patient did not report symptoms of diminished exercise tolerance or fatigue. He denied blunt trauma to his chest.

On further review of systems, he denied any fevers, sore throat, recent illnesses, or history of tick bites or travel to wooded areas or camping. He denied any use of illicit substances and was not taking any daily medications. He was not taking any other vitamins, herbal supplements, or teas. He had not received any recent vaccines.

Family history was negative for congenital heart disease, early cardiac disease, or unexplained sudden deaths. His paternal grandfather had a pacemaker implantation in his 60s, for an unknown reason. There was no other family history of syncope, deafness, seizures or maternal history of rheumatic or other autoimmune diseases. Of potential significance, the family is from a big city in Brazil with a recent as well as frequent visits back to Brazil. However, they reside in the United States.

On arrival to the PED, he was hemodynamically stable. His heart rate was 90 beats per minute (BPM), blood pressure was 132/65 mmHg, respiratory rate of 18 breaths/minute, and his oxygen saturation was 99% on room air. Physical exam was overall unremarkable, with normal S1 and S2, no S3 or S4 sounds. There was a I/VI soft coarse systolic murmur heard only at right upper sternal border into the neck. There was no diastolic murmur. There was no reproduceable chest pain and no clubbing of fingers or toes. Lung sounds were clear to auscultation bilaterally with no evidence of respiratory distress. No hepatomegaly palpated on exam.

Initial EKG, at the adult emergency department, showed concern for high voltages in the lateral leads (Figure 3). Prior to transfer, the patient was noted to have a variable Mobitz type II patterned arrhythmia on continuous telemetry (Figures 4, 5). On arrival to the PED, an EKG was done and is shown below in Figure 6, which show sinus rhythm with occasional premature ventricular complexes.

Figure 3. Initial presentation from adult hospital, with concerns of left ventricular hypertrophy.

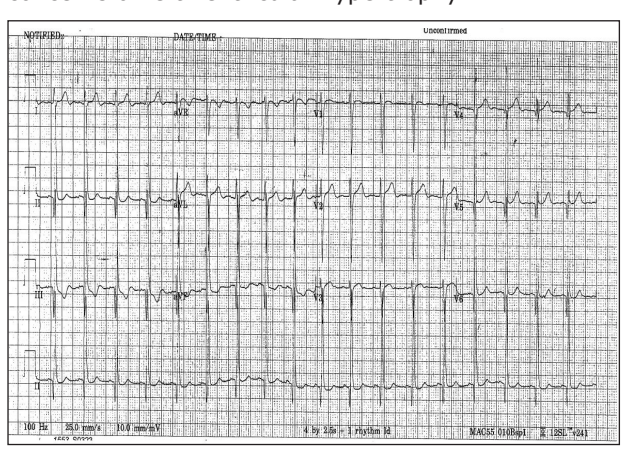


Figure 4. Rhythm strips that show variable Mobitz type II.

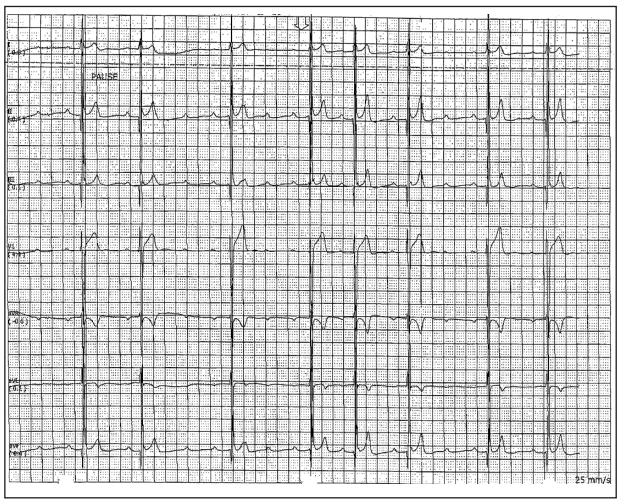


Figure 5. Rhythm strips that show variable Mobitz type II.

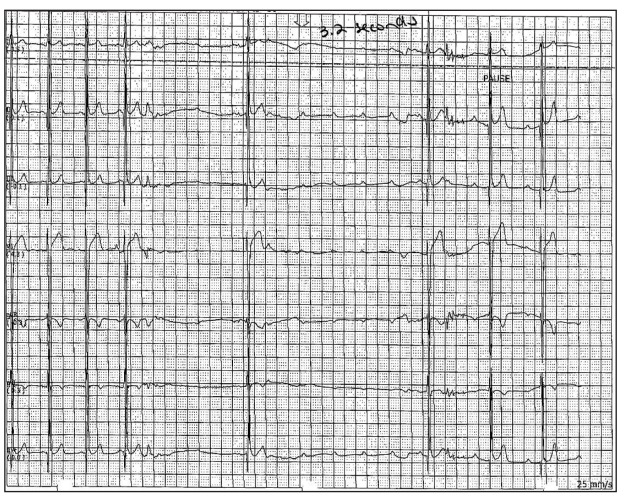
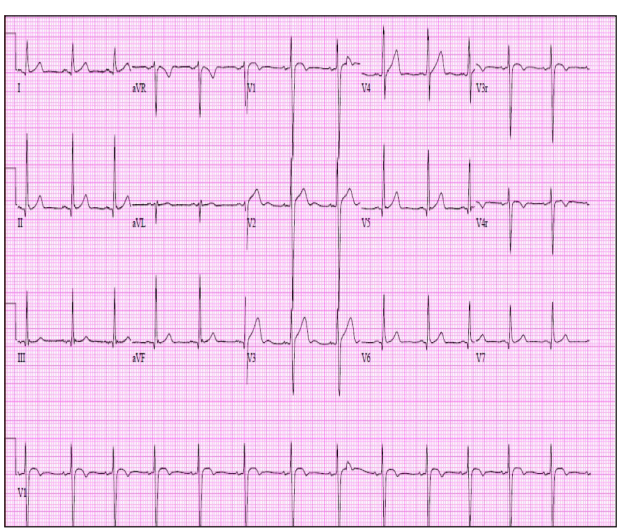


Figure 6. Normal sinus rhythm. Possible left ventricular hypertrophy. First EKG at PED.



Given the EKG findings, cardiology was consulted on arrival and the following labs were obtained: complete blood count with differential (CBCd), complete metabolic panel (CMP), erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), troponin I, brain natriuretic peptide (BNP), which had no significant abnormalities. Specifically, the troponin I level, a crucial biomarker associated with cardiac damage, was measured at less than 0.01 ng/mL (normal <0.05 ng/mL), further confirming the absence of myocardial ischemia at that time. Additionally, the EKG results did not exhibit any discernible signs of acute or prior ischemic myocardial injury. BNP was 11 pg/mL (normal <100 pg/mL). Urine drug screen was negative. Laboratory tests that resulted after emergency department evaluation included negative: Sjogren's antibodies (SS-A/SS-B), echovirus antibody panel, and Lyme antibody screen.

Chest X-Ray was normal with no signs of cardiomegaly or pulmonary congestion. The patient was admitted to the cardiology service for further evaluation. On admission, echocardiogram (ECHO) and cardiac MRI demonstrated a normal left ventricular size, normal left ventricular systolic function, and a left ventricular ejection fraction of 59%. Right ventricular size and right ventricular systolic function were also normal with an ejection fraction of 54%. There was no evidence of segmental or diffuse myocardial fibrosis on post-contrast late gadolinium enhancement imaging.

Exercise Stress test demonstrated a VO2 peak of 60.5 ml/kg/min (111% of predicted value for age). Patient maintained sinus rhythm with intact AV conduction throughout test with a peak heart rate of 197 bpm. Patient also exhibited normal pulmonary function test pre- and post-exercise.

The patient completed three-day event patch monitoring which demonstrated sinus rhythm most of the time with rare premature atrial contractions, rare premature ventricular contractions, rare Mobitz I (Wenckebach) block, and brief 2:1 AV Block overnight. An implantable loop recorder was placed (ILR) and has detected six sinus pauses >3 seconds, but no further Mobitz II AV block, or other abnormal tachyarrhythmias, bradyarrhythmias, or atrial fibrillation. Follow-up includes monthly ILR checks, with electrophysiology clinic every six months. One year post-presentation, the patient, an otherwise healthy athlete, remains asymptomatic.

Discussion

Cardiac conduction disorders are uncommon in neonates and children.[7] Congenital heart block occurs in approximately 1 per 15,000 to 20,000 live births.[8] It is termed congenital when detected in utero, at birth, or within the initial month of life. Childhood AV block manifests sometime between one month of age and up to 18 years of life. This condition may arise independently in a structurally normal heart.[7,8] Symptomatic patients require cardiac pacing, while asymptomatic individuals may benefit from prophylactic pacing to mitigate the risk of sudden death.[7] Advanced second or third-degree AV block is one of the most common indications for permanent pacemaker implantation in children.[9]

For a pediatric patient presenting with heart block, a comprehensive set of laboratory tests is essential to

elucidate the underlying etiology, guide management, and determine prognosis. Initial evaluation should include a CBC and CMP to assess for systemic involvement and metabolic disturbances that could contribute to or result from the heart block. Electrolyte imbalances, particularly abnormalities in potassium, calcium, and magnesium, can significantly affect cardiac conduction and must be identified and corrected.[10] Additionally, assessment of renal and hepatic function through the CMP can reveal potential secondary cases of heart block such as uremia or hepatic dysfunction.[11]

To investigate infectious and inflammatory causes, testing for markers of inflammation (e.g. CRP, ESR) and specific infections is important. Serological tests for Lyme disease should be considered, especially in endemic areas, given its association with heart block. Furthermore, autoantibody testing, including anti-Ro/SSA and anti-La/SSB antibodies, is warranted to evaluate for underlying autoimmune conditions.[7] Thyroid function tests (TSH, free T4) should be performed to exclude thyroid dysfunction, as both hyperthyroidism and hypothyroidism can impact cardiac conduction and cause heart block.[12] Thyroid function tests were normal in our case.

Additionally, genetic testing may be indicated, particularly in cases of congenital heart block or when there is a family history suggestive of inherited arrhythmias.[2] Our patient did not have a family history suggesting a cardiac disorder. Lastly, in cases of suspected cardiomyopathy, cardiac biomarkers such as BNP or N-terminal pro-BNP (NT-proBNP) can provide information on the degree of cardiac involvement and heart failure.[13] Collectively, these laboratory investigations provide a comprehensive approach to diagnosing the etiology of heart block in pediatric patients, allowing for targeted therapeutic interventions and better-informed prognostic assessments.

Mobitz type II AV block, a specific form of second-degree heart block, is relatively rare in the pediatric population. Whereas Mobitz type I block can be a normal finding during sleep.[14] Mobitz type II is generally accepted to be pathologic and has the potential to progress to complete heart block.[6] We were unable to find any studies on the prevalence or incidence of Mobitz type II AV blocks in the pediatric population and more specifically in pediatric patients with a structurally normal heart.

Patients diagnosed with Mobitz type II second degree AV block commonly exhibit a range of symptoms. The absence of one or more P waves conducting to the ventricles can precipitate fatigue, dizziness, presyncope, or syncope, commonly known as Stokes-Adams attacks.[2] This phenomenon arises from the inherently slower intrinsic cardiac pacemakers in the ventricles compared to those in the atria. Furthermore, apart from the irregular pulse and potential bradycardia, physical exam findings are often nonspecific.[3] Notably, individuals with infrequently nonconducted P waves and a normal sinus heart rate may experience minimal or no symptoms.[3] However, if the baseline heart rate is already displaying sinus bradycardia, this can lead to a significant decrease in cardiac output.[3] The decrease in cardiac output can result in cardinal signs of inadequate blood flow or heart failure. Interestingly, in our case the patient only complained of a new onset ill-defined "funny sensation" while falling asleep.

Exercise stress testing is valuable for identifying the location and severity of AV blockages.[6] Typically, supra-His blockages improve during exercise due to heightened sympathetic activity.[6] If second or third-degree AV blockages occur during exercise, it suggests a disruption in the His-Purkinje system's conduction.[6] Elevations in heart rate, such as induced by physical exertion, administration of atropine, or atrial pacing have the potential to exacerbate Mobitz type II second-degree AV block.[3] In this condition, the increased heart rate can accentuate the blockage of electrical impulses between the atrial and ventricles, intensifying the disruption in cardiac conduction and potentially leading to more pronounced symptoms.[3]

Familial AV conduction block is associated with a genetic predisposition. This condition has been found to be linked with various mutations in the SCN5A gene.[2] These genetic alterations contribute to disruptions in AV conduction, highlighting the complex interplay between inherited traits and cardiac function. No cardiac genetic testing has been done on our patient to date. Autoimmune-mediated congenital AV block is linked with a substantial neonatal mortality rate, with 5% to 30% of cases progressing to dilated cardiomyopathy, highlighting the critical need for early detection and prevention.[7] Sporadically, pediatric patients may present with AV block of unknown etiology, devoid of maternal antibodies, structural cardiac anomalies, or discernible causes. The scientific literature concerning the origin and clinical progression of these cases of apparent idiopathic heart block is notably limited. However, a pioneering study conducted by Barteau et al., investigating the heritability of pediatric idiopathic heart block, revealed compelling evidence of a significant genetic predisposition underlying congenital and childhood nonimmune isolated AV block.[15] This underscores the importance for physicians at all levels to consider familial screening, as it may yield substantial insights into heritability, even in instances where the condition initially manifests as sporadic and appears idiopathic.[3]

The majority of Mobitz type II presentations can be attributed to the existence of cardiac diseases, including but not limited to myocardial ischemia, fibrosis, myocarditis from Lyme disease, various forms of cardiomyopathy, cardiac tumors, collagen vascular disorders, and hyperthyroidism.[15] HCM is a rare but significant cardiac condition in children, characterized by asymmetric hypertrophy of the left ventricle.[16] While HCM primarily affects the structure of the myocardium, its consequences often extend to the electrical conduction system of the heart. This can potentially lead to heart block, bradycardia, or sudden cardiac death.[16] For our patient, the ECHO and cardiac MRI results revealed a normal cardiac profile, characterized by the absence of any indications of left ventricular hypertrophy or HCM. This diagnostic assessment provided reassurance regarding the structural integrity and function of the child's heart, indicating that there are no apparent abnormalities in the size or thickness of the left ventricle. There was no evidence of cardiac

tumors or myocardial fibrosis, eliminating concerns related to neoplastic growths that could impact the heart's structure and function.

AV conduction disorders have been observed in conjunction with acquired cardiac pathologies, exemplified by conditions such as Lyme disease, Kawasaki disease (KD), and Chagas disease.[3]

Lyme disease, caused by the *Borrelai burgdorferi* bacterium, can lead to Lyme carditis which manifests days to months after initial exposure to the bacterial spirochete.[17] The patient's Lyme antibody titers were negative. With a lack of detectable Lyme antibodies and the absence of historical risk factors, the possibility of Lyme disease as an underlying cause for the cardiac conduction abnormality was effectively eliminated.

Similarly, KD, the most recognized vasculitis of childhood is characterized by systemic inflammation of small and medium sized vessels which may incite inflammation in the coronary arteries; it is a leading cause of acquired pediatric heart disease.[18] Kawasaki disease (KD) typically presents with high fever, mucocutaneous inflammation, and cervical lymphadenopathy, primarily affects the coronary arteries and other cardiovascular structures. KD was eliminated from the differential due to the lack of high fevers in the patient's history, negative findings on physical exam (no characteristic signs: extremity changes, rash, erythema of lips and oral mucosa, conjunctival irritation, lymphadenopathy) and he did not meet KD criteria on laboratory evaluation (normal white blood cell count, CRP< ESR).[19]

Additionally, a neglected tropical disease, Chagas disease, caused by the protozoan *Trypanosoma cruzi*, is notorious for its chronic cardiomyopathic effects, which can impair the conduction of electrical signals within the heart.[20] Cardiac symptoms of chronic Chagas disease can include arrhythmias, heart failure, and sudden death. Our patient had a recent trip to Brazil and frequently visits family in Brazil where Chagas disease is endemic.[21] Therefore, Chagas disease was added to the differential. The patient did not have a history of fevers, headaches, fatigue, nausea, or vomiting. The patient's physical exam was negative for hepatosplenomegaly, skin rashes, or swollen lymph nodes. Additionally, there were no signs or symptoms of myocarditis, megaesophagus, or megacolon. Furthermore, the patient only travelled to major cities in Brazil. Therefore, Chagas disease was lower on the differentials as etiology to the patient's arrythmia and has not been tested to date.

Unstable patients with Mobitz type II second-degree AV block require urgent treatment, typically involving beta-adrenergic agonists like isoproterenol, dopamine, dobutamine, or epinephrine, along with temporary cardiac pacing. Hemodynamically unstable signs include hypotension, altered mental status, shock, and ongoing chest pain.[3] Stable patients do not require immediate therapy but should be continuously monitored with transcutaneous pacing pads in place due to the instability of Mobitz type II block, which often progresses to complete AV block.[3] Complications can include sudden cardiac death. Our patient had an ILR placed and has been hemodynamically stable. Monthly ILR evaluations have revealed 6 sinus pauses following the loop recorder implantation, with no other arrhythmias noted.

In most cases, individuals with non-reversible AV node disease require the implantation of a permanent pacemaker.[3] However, the patient did not receive a pacemaker as they did not meet Class I indications for emergent pacemaker intervention, primarily due to the infrequent nature of their sinus node dysfunction (SND).[9] SND refers to physiologically inappropriate atrial rates, either due to abrupt pauses or sustained bradycardia.[9] Class 1 SND is when there is a correlation between the symptoms with age-inappropriate bradycardia.[9] Current guidelines emphasize that sinus pauses alone are no longer absolute indications for pacemaker placement.[9] In this case, a pacemaker would only be considered reasonable (Class IIa) if no reversible or secondary etiologies were identified and the patient experienced symptoms during exercise, or possibly (Class IIb) if they had minimal unexplained symptoms.[9]

A comprehensive second-pass workup, including normal cardiac magnetic resonance imaging and an exercise stress test that demonstrated a maximal heart rate of 197 beats per minute without cardiac symptoms, further supported the decision against immediate pacemaker intervention. Given these findings, the pediatric electrophysiology team discussed an ILR to monitor for recurrence of AV block and other potential symptoms, which the family opted for instead of a leadless pacemaker. Six-month follow-ups with the pediatric electrophysiology clinic continue to report stable findings and no new abnormalities.

Conclusion

The presented case of a 14-year-old male with a structurally normal heart who was diagnosed with a high-grade variable (1:1 or 5:1) Mobitz type II arrhythmia highlights the complexity and diversity of conduction disorders in the pediatric population. Mobitz type II heart block is an uncommon condition, especially in children. The case emphasizes the importance of considering a broad differential diagnosis. While many etiologies and differentials have been ruled out in this patient, the etiology to his arrythmia remains unknown.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Brucato, A., A. Jonzon, Friedman, D., Allan, L. D., Vignati, G., Gasparini, M., Stein, J. I., Montella, S., M. Michaelsson, & J. Buyon. (2003). Proposal for a new definition of congenital complete atrioventricular block. Lupus, 12(6), 427-435. https://doi.org/10.1191/0961203303lu408oa.
2. Mangi, M. A., Jones, W. M., Mansour, M. K., & Napier, L. (2023). Second-Degree Atrioventricular Block. PubMed; StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK482359/
3. Baruteau, A.-E., Pass, R. H., Thambo, J.-B., Behaghel, A., Le Pennec, S., Perdreau, E., Combes, N., Liberman, L., & McLeod, C. J. (2016). Congenital and childhood atrioventricular blocks: pathophysiology and contemporary management. European Journal of Pediatrics, 175(9), 1235-1248. https://doi.org/10.1007/s00431-016-2748-0.

4. Cleveland Clinic. (2021). Heart Conduction: What Is It & How It Works. Cleveland Clinic. https://my.clevelandclinic.org/health/body/21648-heart-conduction-system.
5. Park, M. K., & Guntheroth, W. G. (2006). How to read pediatric ECGs. Mosby/Elsevier.
6. Saleh, F., Greene, E. A., & Mathison, D. (2014). Evaluation and management of atrioventricular block in children. Current Opinion in Pediatrics, 26(3), 279-285. https://doi.org/10.1097/mop.0000000000000100.
7. Brucato, A., et al. "Proposal for a New Definition of Congenital Complete Atrioventricular Block." Lupus, vol. 12, no. 6, June 2003, pp. 427-35. DOI.org (Crossref), https://doi.org/10.1191/0961203303lu408oa.
8. Bordachar, P., Zachary, W., Ploux, S., Labrousse, L., Haissaguerre, M., & Thambo, J.-B. (2013). Pathophysiology, clinical course, and management of congenital complete atrioventricular block. Heart Rhythm, 10(5), 760-766. https://doi.org/10.1016/j.hrthm.2012.12.030.
9. Shah, M. J., Silka, M. J., Silva, J. R., Balaji, S., Beach, C., Benjamin, M., Berul, C. I., Cannon, B. C., Cecchin, F., Cohen, M. J., Dalal, A., Dechert, B. E., Foster, A., Gebauer, R., Gonzalez, C., Kannankeril, P. J., Karpawich, P. P., Kim, J., Mani Ram Krishna, & Kubuš, P. (2021). 2021 PACES Expert Consensus Statement on the Indications and Management of Cardiovascular Implantable Electronic Devices in Pediatric Patients. JACC: Clinical Electrophysiology, 7(11), 1437-1472. https://doi.org/10.1016/j.jacep.2021.07.009.
10. Fisch, C. (1973). Relation of Electrolyte Disturbances to Cardiac Arrhythmias. Circulation, 47(2), 408-419. https://doi.org/10.1161/01.cir.47.2.408.
11. Mohler, H. K. (1929). Heart Block and Uremia. Journal of the American Medical Association, 92(9), 706. https://doi.org/10.1001/jama.1929.02700350014007.
12. Ata, F. (2024). Atrioventricular block in patients with hyperthyroidism: a narrative review. Journal of International Medical Research, 52(1). https://doi.org/10.1177/03000605231223040.
13. Tsai, S.-H., Lin, Y.-Y., Chu, S.-J., Hsu, C.-W., & Cheng, S.-M. (2010). Interpretation and Use of Natriuretic Peptides in Non-Congestive Heart Failure Settings. Yonsei Medical Journal, 51(2), 151. https://doi.org/10.3349/ymj.2010.51.2.151.
14. Adlakha, A., & Shepard, J. W. (1998). Cardiac arrhythmias during normal sleep and in obstructive sleep apnea syndrome. Sleep Medicine Reviews, 2(1), 45-60. https://doi.org/10.1016/s1087-0792(98)90053-3.
15. Alban-Elouen Baruteau, Albin Behaghel, Swanny Fouchard, Philippe Mabo, Schott, J.-J., Dina, C., Chatel, S., Villain, E., Jean-Benoit Thambo, François Marçon, Véronique Gournay, Rouault, F., Alain Chantepie, Guillaumont, S., François Godart, Martins, R. P., Béatrice Delasalle, Bonnet, C., Alain Fraisse, & Schleich, J.-M. (2012). Parental Electrocardiographic Screening Identifies a High Degree of Inheritance for Congenital and Childhood Nonimmune Isolated Atrioventricular Block. Circulation, 126(12), 1469-1477. https://doi.org/10.1161/circulationaha.111.069161.
16. Seggewiss, H., & Rigopoulos, A. (2003). Management of Hypertrophic Cardiomyopathy in Children. Pediatric Drugs, 5(10), 663-672. https://doi.org/10.2165/00148581-200305100-00002.
17. Bolourchi, M., Silver, E. S., & Liberman, L. (2018). Advanced Heart Block in Children with Lyme Disease. Pediatric Cardiology, 40(3), 513-517. https://doi.org/10.1007/s00246-018-2003-8.
18. Cohen, E., & Sundel, R. (2016). Kawasaki Disease at 50 Years. JAMA Pediatrics, 170(11), 1093. https://doi.org/10.1001/jamapediatrics.2016.1446.
19. Newburger, J. W., Takahashi, M., & Burns, J. C. (2016). Kawasaki Disease. Journal of the American College of Cardiology, 67(14), 1738-1749. https://doi.org/10.1016/j.jacc.2015.12.073.
20. Sabaini, B., Deorlan Pereira Dias, Márcia Moraes Cangussú, Porto, V., Daniel Dias Sampaio, & Luciano, F. (2023). Seroepidemiology of Chagas disease in at-risk individuals in Caraíbas, a city with high endemicity in Bahia State, Brazil. Frontiers in Public Health, 11. https://doi.org/10.3389/fpubh.2023.1196403.
21. Forsyth, C. J., Manne-Goehler, J., Bern, C., Whitman, J., Hochberg, N. S., Edwards, M., Marcus, R., Beatty, N. L., Castro, Y., Coyle, C., Stigler-Granados, P., Hamer, D., Maguire, J. H., Gilman, R., & Meymandi, S. (2021). Recommendations for Screening and Diagnosis of Chagas Disease in the United States. The Journal of Infectious Diseases, 225(9). https://doi.org/10.1093/infdis/jiab513.

Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.6

ORIGINAL ARTICLE

CHARACTERIZATION OF SLEEP PATTERNS AND DISTURBANCES IN SCHOOL-AGED CHILDREN: A CROSS-SECTIONAL STUDY IN AN ISLAND POPULATION

Catarina Andrade[1], Beatriz Câmara[1], Sónia Freitas[2], Cristina Freitas[1], Paulo Sousa[1].

[1]Pediatrics, Hospital Central do Funchal, SESARAM, EPERAM, Funchal, Portugal,

[2]Dr. Maria Isabel Mendonça Research Center, SESARAM, EPERAM, Funchal, Portugal.

ABSTRACT

Introduction: Sleep is crucial for physiological balance. Despite being neurobiologically determined, it is influenced by behavior. Sleep disturbances affect 20-30% of children and adolescents, with biopsychosocial consequences and risk of persistence into adulthood. This study aims to explore sleep patterns among children, assess the prevalence and impacts of sleep disturbances, and determine associated risk factors to support the establishment of a sleep consultation service.

Methods: Epidemiological, observational, cross-sectional study of sleep habits in children aged 6-10 years in an island region. The Portuguese version of the Children Sleep Habits Questionnaire and questions for epidemiological characterization were administered to caregivers from February to June 2022. Statistical analysis was conducted using SPSS version 25.0.

Results: The study garnered 507 responses, with no sex predominance and a median age of 8 years. Around 36.3% exhibited signs of sleep disturbances, unrelated to age or sex. Discrepancies were noted between caregivers' perceptions and actual disturbances. Variations in sleep schedules between weekdays and weekends were observed, along with a link between sleep issues and health problems like allergies, school performance, sports activities, and caffeine intake, but not with screen time, even though 26% exceeded two hours of daily screen use. The mean BMI in the sleep disturbance group was higher, but not statistically significant. A positive correlation was evident between the total sleep duration of children and their caregivers.

Conclusions: The observed high prevalence of sleep disturbances aligns with existing literature and highlights the necessity for healthcare interventions and enhanced education on sleep hygiene.

ARTICLE HISTORY

Received 10 September 2024

Accepted 03 October 2024

KEYWORDS

Sleep Habits; Sleep Quality; Sleep Deprivation; Primary Schools; Caregivers.

ABBREVIATIONS:

CSHQ-PT - Children Sleep Habits Questionnaire; IgE - Immunoglobulin E; NREM - Non-Rapid Eye Movement; OSAS - Obstructive Sleep Apnea Syndrome; REM - Rapid Eye Movement; SD - Standard Deviation; SPP - Portuguese Society of Pediatrics.

Introduction

Sleep is defined as a restorative physiological state, characterized by the suppression of cortical functions, reduced perception and response to stimuli, and a decrease in muscle tone, heart rate, and respiratory rate. Sleep is crucial for maintaining physiological balance among various systems, contributing to energy conservation, thermoregulation, cardiovascular functions, immune responses, and endocrine-metabolic activities, such as growth hormone production and appetite regulation. It also plays a significant role in cognitive functions, including memory consolidation and mood regulation.[1]

Humans spend about one-third of their life sleeping. The alternation between wakefulness and sleep constitutes a fundamental rhythm, dependent on homeostatic and circadian processes, and is particularly significant during childhood. Throughout development, there is a progressive maturation in the organization of sleep, characterized by a reduction in total daily sleep time and a convergence towards adult patterns, with alternating periods of REM (Rapid Eye Movement) and NREM (Non-Rapid Eye Movement) sleep in increasingly prolonged cycles, and a decrease in the REM/NREM ratio.[2,3] In this context, consensuses have been established for normative sleep patterns in pediatric ages. The Portuguese Society of Pediatrics (SPP) offers specific recommendations for sleep duration and nap times according to age, similar to the American Academy of Pediatrics, which has previously emphasized the importance of establishing sleep duration guidelines as a health-promoting measure.[4,5]

Sleep may be deemed inadequate due to alterations in duration or quality. Although it is a neurobiologically determined process, it is significantly influenced by behavioral components. Consequently, among many factors, sleep habits are modulated by the interaction with and examples set by caregivers, beliefs, established routines and rules, and the sleeping environment.[6] Thus, it is essential to establish sleep hygiene measures from the first year of life, reinforcing

Address for Correspondance: : Catarina Andrade, Avenida Luís de Camões, n.º 57; 9004-514 Funchal.
Email: kcatajandrade@gmail.com

them throughout development, especially during stages of increased independence, such as school age. Comorbidities that impact sleep quality, such as developmental, neurological and/or respiratory disorders, and obesity, are also recognized.[7]

Sleep disturbances, affecting 20-30% of children and adolescents, are categorically classified according to the International Classification of Sleep Disorders into: sleep-related breathing disorders, sleep-related movement disorders, parasomnias, insomnia, central disorders of hypersomnolence, circadian rhythm disorders, and other sleep disturbances.[8,9] Sleep deprivation can lead to daytime consequences which may also serve as warning signs for diagnosing these nosological entities, including excessive sleepiness, irritability, behavioral/mood changes, compromised academic performance, increased risk of accidents, hypertension, and obesity. Concurrently, these issues contribute to increased susceptibility to family dysfunction by also affecting the duration and quality of the parents' sleep.[7] The lack of identification and management of sleep problems can contribute to their persistence into adulthood, making timely diagnosis and intervention crucial.

The current study aims to characterize sleep habits in order to assess the prevalence of sleep disturbances in the general school-aged population, identify associated risk factors and consequences, and evaluate the relevance of establishing a Sleep Consultation Service within a Pediatric Department of a Tertiary Hospital.

Methods & Materials

Study Design

An epidemiological, observational, and cross-sectional study was conducted to characterize the sleep habits of school-aged children in the Madeira Islands, utilizing a questionnaire administered to caregivers.

Target Population and Sample

The study targeted all children aged 6 to 10 years residing in the Madeira Islands. Based on a total of 10457 children in this age group living in the region in 2020, according to estimates from the Regional Directorate of Statistics of Madeira, a sample size of at least 313 participants was calculated for a 95% confidence level and a 5% margin of error, using the OpenEpi statistical tool.

The sample was formed based on the willingness of caregivers to complete the questionnaire. In this context, inclusion criteria were set as follows: children aged between 6 and 10 years, completion of the entire questionnaire, and affirmative compliance with informed consent.

Data Collection

Data were collected through the administration of a questionnaire to caregivers at all public and private primary education institutions between February and June 2022. The questionnaire was distributed digitally via Google Forms, in collaboration with the Regional Secretary of Health and Civil Protection, the Regional Secretary of Education, Science and Technology, and the educational institutions in the Madeira Islands, to ensure data protection.

Legal guardians of the participants provided informed consent for the collection, analysis, and publication of the data. The study was approved by the Ethics Committee of SESARAM, EPERAM (S.22001836/2022).

Instruments

The questionnaire included a first part (Supplemental material), which is the Portuguese version of the Children Sleep Habits Questionnaire (CSHQ-PT). It aims to assess caregivers' perception of the existence of sleep problems, characterize sleep habits, and identify potential sleep disturbances through questions related to the main signs and symptoms. It consists of 45 questions divided into the following domains: "bedtime", "behavior during sleep", "waking in the morning", and "daytime sleepiness". Responses are based on the previous week's reference period and are categorized as "rarely" (once a week or never), "sometimes" (two to four times a week), and "usually" (five to seven times a week). Responses are scored from one to three points, respectively (except for items marked in the questionnaire which are scored inversely), with a higher total score suggesting more sleep problems. The original questionnaire's authors defined the Sleep Disturbance Index by summing 33 of the 45 items, which were conceptually organized into eight subscales related to sleep problems, namely: "bedtime resistance", "sleep onset", "sleep duration", "sleep anxiety", "night awakenings", "parasomnias", "sleep breathing disorders", and "daytime sleepiness".[7,10] The Children Sleep Habits Questionnaire has been validated for the Portuguese population aged 2 to 10 years, with a cut-off point of 48 points established for screening sleep disturbance, with a sensitivity of 83% and specificity of 69%.[7,11]

The second part of the questionnaire (Supplemental material) served as a complement for epidemiological characterization, including analyses of somatometry, pathological history, academic performance, physical exercise, screen exposure, dietary patterns, and social context, including the sleep habits of caregivers.

Data Analysis

For binary variables, clinical characteristics were presented as frequencies. Data for continuous variables were reported as mean ± standard deviation (SD); for non-normal distributions, median (minimum-maximum) was shown. The Chi-square test was applied to categorical variables and the Student's t-test or Mann-Whitney test was used for numerical variables, as appropriate. Spearman's correlation was utilized to analyze relationships between variables. Statistical analysis was conducted using SPSS version 25.0 (IBM, Armonk, NY, USA). All p-values were two-tailed and considered statistically significant at $p<0.05$.

Results

A total of 536 responses to the questionnaire were obtained, with 29 participants excluded: 18 due to lack of consent, 9 for not meeting the age-related inclusion criteria, and 2 due to duplicate entries. This resulted in a final sample of 507 children, which is representative of the target population. The questionnaires were predominantly completed by mothers (466; 91.9%), with the remaining 41 filled out by fathers (36; 7.1%) and other household members (5; 1.0%).

Table 1. Sociodemographic characterization of the children and their responsible caregivers in the sample.

Variable	n	%	Variable	n	%
Child's gender			**Age of female/male caregivers**		
Female	253	49,9	<20 years	1/0	0,2/0,0
			20-30 years	40/14	7,9/2,8
			30-40 years	228/176	45,0/34,7
Male	254	50,1	40-50 years	231/280	45,6/55,2
			>50 years	7/37	1,4/7,3
Child's age			**Educational qualifications of female/male caregivers**		
6 years	110	21,7	4th grade	10/33	2,0/6,5
7 years	126	24,9	6th grade	31/81	6,1/16,0
8 years	93	18,3	9th grade	82/128	16,2/25,2
9 years	118	3,3	12th grade	180/138	35,5/27,2
10 years	60	11,8	Bachelor's degree	172/96	33,9/18,9
			Master's degree	30/27	5,9/5,3
			Doctorate	2/4	0,4/0,8

Regarding the sample characterization, 253 (49.9%) participants were female and 254 (50.1%) were male, with a median age of 8.0 years (Table 1). The average sleep duration was slightly higher in females (9.41 hours vs. 9.32 hours), though not statistically significant (p=0.277). A negative correlation was established between total sleep duration and child's age, but this was not statistically significant (p=0.438).

In the total score of the CSHQ-PT, a median of 45.0 points (range 33-76; maximum possible 99 points) was observed, with no relationship to sex (p=0.827) or age (p=0.115) (Figure 1). A strong and positive correlation was found between the subscale scores (Table 2) and the total questionnaire score, except for subscale 2, labeled "sleep onset," where the only item is scored inversely ("Usually" = 1; "Sometimes" = 2; "Rarely" = 3). Among the participants, 184 (36.3%) scored above 48 points, indicative of a screening compatible with sleep disturbance. In contrast, only 77 (15.2%) of the caregivers affirmatively answered the initial question regarding whether they considered the child to have any sleep or falling asleep problems. Consequently, a significant difference (p<0.0001) was established between the caregivers' perception and the presence of disturbance as objectively measured by the questionnaire.

Among the risk factors related to daily sleep routines, it is noteworthy that bedtime responses on weekdays ranged from 19:30 to 23:30 and on weekends from 21:00 to 23:50. Meanwhile, the range of wake-up times on weekdays was between 06:00 and 10:00 and on weekends between 06:30 and 12:00. A significant variation was demonstrated between weekday and weekend sleep schedules (p<0.0001). It is important to note regarding the regularity and consistency of sleep habits, in the item "Goes to bed at the same time every day," only 7 (1.4%) participants indicated "Usually," and in the item "Sleeps the same number of hours every day," only 20 (3.9%) participants recorded "Usually." The average total sleep duration was significantly higher in the group of children without sleep disturbances (p<0.0001). Regarding autonomy at bedtime, it is important to mention the item "Falls asleep alone in their own bed," where 307 (60.6%) participants indicated "Rarely".

The results demonstrated that children who engage in sports activities exhibit less sleep disturbance compared to those who do not (p=0.037), regardless of the duration of the exercise (p=0.296) and the time interval between exercise and bedtime (p=0.156). No significant differences were found between the time interval from the last meal to bedtime and the presence of sleep disturbances (p=0.061). However, significant differences were observed between the consumption of caffeinated beverages and the presence of sleep disturbances (p=0.017). Regarding screen exposure, no statistically significant results were established between the total daily usage duration (p=0.220), use in the bedroom (p=0.210), and the time interval between use and bedtime (p=0.204) and the presence of disturbances, although it is noteworthy that 26.2% (133) of the sample used screens for more than two hours per day.

Regarding risk factors associated with personal medical history, 42.0% (213) reported health issues, particularly allergic conditions - "rhinitis" 122 (24.1%), "asthma" 53 (10.5%), and "atopic skin" 82 (16.2%). Additionally, 25% (127) of the sample reported having multiple medical conditions. Among neurodevelopmental disorders, 31 (6.1%) indicated "speech difficulties," 45 (8.9%) "learning difficulties," 43 (8.5%) "hyperactivity or attention problems," and 9 (1.8%) "autism". It was demonstrated that children with pathological antecedents have a significantly increased risk for the

Figure 1. Distribution of total CSHQ-PT scores by age.

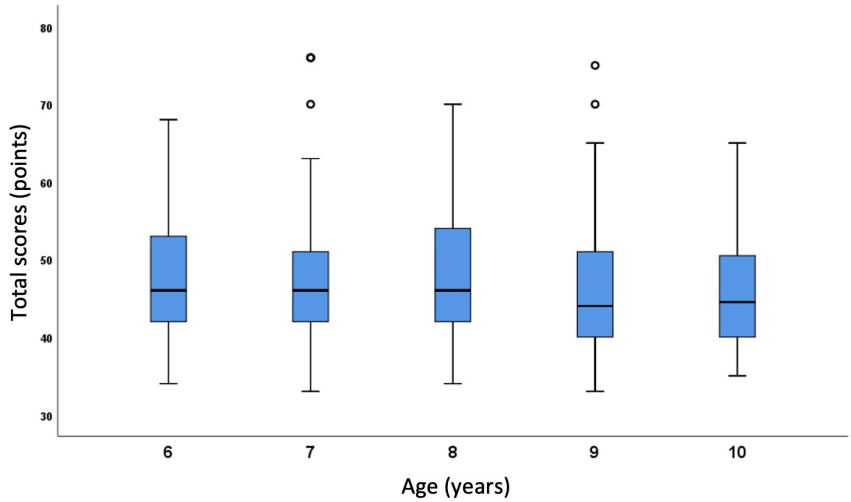


Table 2. Scores by subscales of the CSHQ-PT.

Subscales (Min-Max)	**Median Score**
"Bedtime resistance" (6-18)	8
"Sleep onset" (1-3)	2
"Sleep duration" (3-9)	3
"Sleep anxiety" (4-12)	6
"Night awakenings" (3-9)	3
"Parasomnias" (7-19)	8
"Sleep breathing disorders" (3-9)	3
"Daytime sleepiness" (8-23)	13

presence of sleep disturbances (p<0.0001), unrelated to regular medication intake (p=0.287), despite 82 (16.2%) participants being reported to take usual medications, mostly non-sedative antihistamines. The average Body Mass Index was higher in the group with sleep disturbances, but not statistically significant (p=0.468). Among participants, 7 (1.4%) exhibited possible nocturnal enuresis, marking "Sometimes" or "Usually" for the item "Wets the bed at night".

For the "Sleep-Related Breathing Disorders" subscale, an average score of 3.6 points was observed. Among the responses, 36 (7.1%) participants indicated "Sometimes" or "Usually" for "Snores loudly," 15 (3.0%) for "Appears to stop breathing during sleep," and 22 (4.3%) for "Snores or has difficulty breathing".

Regarding social context risk factors, total sleep duration showed a negative correlation with the age of both female and male caregivers (Table 1), although not statistically significant (p=0.263 and p=0.591, respectively). It also demonstrated a positive correlation with the educational qualifications of both female and male caregivers (Table 1), again without statistical significance (p=0.567 and p=0.170, respectively). A significant positive correlation was evident between the total sleep duration of the child and that of the female caregiver (r=0.133, p=0.003) and the male caregiver (r=0.148, p=0.001). No significant differences were found regarding sleep disturbances in children between single-parent and nuclear family households (p=0.885).

To assess the consequences of sleep disruption, the impact on academic performance was evaluated. No significant differences were found regarding sleep disturbances across the four years of primary education (p=0.402). In the subjects of Portuguese Language and

Table 3. Academic performance in the previous period of the children studied.

Disciplina	Grade							
	Very Good		Good		Satisfactory		Unsatisfactory	
	n	%	n	%	n	%	n	%
Portuguese Language	226	44,6	189	37,3	86	17	6	1,2
Mathematics	228	45	199	39,3	71	14	9	1,8
Environmental Studies	301	59,4	151	29,8	49	9,7	6	1,2

Mathematics, statistically significant differences were observed between the final grades (Table 3) and the presence of sleep disturbances (p=0.005 and p=0.009, respectively). No such correlation was established for the subject of Environmental Studies (p=0.285).

Discussion

Sleep in pediatric ages has garnered increasing attention from the scientific community, due to the recognition of its importance for overall health, as well as the consequences that disturbances entail.

Until this study, the characterization of sleep habits among children in the Madeira Islands had not been documented. For this reason, the study targeted the school-aged community to avoid biases inherent in more circumscribed subgroups, using a previously validated questionnaire. Although it is a subjective instrument, it allows for the collection of a larger number of responses in a population-based screening, with the questionnaire being completed by responsible adults in the participants' natural environment, without associated costs.[7]

The average sleep duration of the sample under study falls within the 9 to 11 hours recommended by the Portuguese Society of Pediatrics (SPP) for the age group of 6 to 10 years, without significant differences between genders and with a tendency for shorter duration as age increases, which is expected in the progression towards the adult sleep pattern.[2] Mendes et al. (2004), in a study characterizing the sleep habits of school-aged children residing in Lisbon, recorded an average nighttime sleep duration also within the appropriate range (9.8 hours), similar to that described for other regions of the country.[12] The study by Silva (2014), which also used the CSHQ-PT, targeted children aged 2 to 10 years residing in Lisbon, Setúbal, and Alentejo, documented an average nighttime sleep duration that decreased from 10.1 hours at age 6 to 9.7 hours at age 10, also showing no differences between genders.[7] Indeed, there is no evidence in the literature supporting the effect of gender on sleep patterns in school-aged children, hence the recommendations are similar for both genders.[13]

In the current study, 36.3% of participants scored above the threshold consistent with sleep disturbances, a value higher than the prevalence of sleep disturbances reported in the literature, but consistent with Silva's 2014 study, which revealed a positive screening in 39% of children.[7,8] Interestingly, our study found a significant discrepancy between the number of participants with scores suggestive of sleep disturbance and the perception of the caregivers, a phenomenon also noted in Silva›s 2004 study, where the prevalence of sleep problems from the parents› perspective was only 10.4%, roughly a quarter of the percentage of participants with disturbances according to the questionnaire.[7] The lack of recognition of the prevalence of sleep problems by caregivers may suggest a relative tolerance for behavioral issues associated with sleep, as well as unawareness of children's actual sleep needs, underscoring the urgency for investment in health literacy that emphasizes the importance of sleep.

Similar to findings by Silva (2014), our study also observed a later bedtime and wake-up time on weekends, with significant variation compared to weekdays, as well as a lack of consistency in sleep routines.[7] In school-age children, greater autonomy in the sleep onset process is expected, a finding not demonstrated in the present study. This contrasts with the studies by Silva (2014) and Clemente (1997), where the percentages of children who usually fell asleep alone in their beds were significantly higher, at 72% and 73.8% respectively.[7,14] The findings of our study support what is reported in the literature regarding the presence of a cultural influence, where countries in Southern Europe are characterized by later and more irregular sleep schedules and greater parental involvement at bedtime.[15] These results enable us to identify various risk factors inherent to poor sleep hygiene and crucial to the percentage of sleep disturbances reported, despite the average total sleep duration being adequate.

Physical activity was associated with less sleep disturbance, which is supported by literature suggesting that exercise impacts sleep efficiency, continuity, and architecture, and is proposed as a non-pharmacological measure for managing sleep disturbances.[16] Although our study did not demonstrate a significant relationship between screen exposure and the presence of sleep disturbances, literature has shown that screen time is associated with delays in bedtime and consequently impacts the total duration of sleep.[17] Additionally, multifactorial approaches show that high levels of physical activity (≥60 minutes of moderate to vigorous activity per day), low levels of sedentary behavior (≤2 hours of screen exposure per day), and adequate sleep duration (9 to 11 hours per night) are synergistic in their beneficial impact on mental health indicators in children and adolescents.[18]

Caffeine intake was associated with the presence of sleep disturbances, noteworthy is that caffeine can be found in children's diets through elements other than coffee itself, notably in energy drinks increasingly consumed among the young population. Although data

in the literature are limited, the impact of caffeine appears to be related not just to the dose but also to the time interval between ingestion and bedtime, with shorter intervals leading to increased sleep latency, similar to what is described in adults.[19]

Regarding pathological antecedents, there was a predominance of pathologies related to atopy. Indeed, in a retrospective study by Zhang (2016) on children undergoing treatment for snoring, a significantly higher proportion of abnormal total serum Immunoglobulin E (IgE) levels was demonstrated in children with severe Obstructive Sleep Apnea Syndrome (OSAS) compared to those with mild to moderate OSAS. The authors concluded that allergic sensitization could contribute to the exacerbation of an underlying OSAS.[20] Particularly in the case of rhinitis, symptoms that interfere with sleep are common, and it is documented that therapies reducing nasal congestion can impact sleep quality. Therefore, identifying and treating rhinitis are important steps to prevent the deterioration of sleep quality in children with underlying sleep-related breathing disorders.[21]

Regarding the subscale titled "Sleep-Related Breathing Disorders", the current study achieved an average score that is comparable to the average obtained in Silva's 2014 study.[7] According to parental perception, breathing pauses were noted in 3.0% of participants, a figure that aligns with the prevalence of 1.2%–5.7% described in the literature for OSAS. This finding should be appropriately assessed with objective and standardized sleep studies.[22]

According to the literature, sleep disturbances are particularly common in children with neurodevelopmental disorders. This association may be caused by neurobiological mechanisms underlying the pathophysiology and/or by symptoms inherent to the neurodevelopmental disorder itself.[7] The estimated incidence of sleep disturbances ranges from 32-71.5% in children with autism spectrum disorders, 25-50% in children with attention deficit hyperactivity disorder, and 24-86% in children with unspecified intellectual deficits. Besides being common, sleep disturbances in these groups tend to be chronic. Early recognition and management of these disturbances have an impact on functional abilities, treatment response, and quality of life for these patients and their families.[23] However, it is necessary to consider that certain behavioral changes, such as irritability and restlessness, which do not fully meet the criteria for a neurodevelopmental disorder, can be signs of sleep deprivation, without the obvious presence of excessive daytime sleepiness.[24]

In our sample, a higher average Body Mass Index was documented in children with sleep disturbances, which corroborates data from the literature supporting a cross-sectional and longitudinal association between sleep duration and obesity.[25] This is a multifactorial association, influenced by variables such as diet. Moreira et al. (2010), in a study on dietary patterns among 1976 Portuguese children aged 5 to 10 years, found that longer sleep duration was positively associated with a healthier diet.[26] Data extrapolated from adults reiterate hormonal mechanisms to explain the association between sleep duration and obesity, with lower levels of leptin observed in individuals experiencing sleep deprivation, consequently enhancing signals for caloric intake.[27]

Regarding nocturnal enuresis, its association with sleep-related breathing disorders is well documented in the literature. However, it is important to note that enuresis is significantly influenced by poor sleep hygiene.[28]

Concerning risk factors related to the social context, a positive correlation was observed between the literacy level of responsible adults and the sleep duration of the child, similar to findings by Crispim et al. (2011). Less educated families constitute risk groups for sleep deprivation.[29] A significant positive correlation was established between the total sleep duration of the child and the total sleep duration of the caregivers. This underscores that children›s habits are shaped by the family›s habits and that children›s sleep disturbances have repercussions on the sleep of the rest of the family. Sleep deprivation in parents leads to daytime fatigue and mood changes, impacting parental performance.[30]

The literature emphasizes that sleep disturbances impair attention levels, learning capacity, memory, stimulus processing, and executive functions. Therefore, the impact on academic performance is an accurate measure to evaluate the consequences of sleep compromise in school-aged children, a finding that was evident in our study.[31]

The use of a validated questionnaire in a representative sample of school-aged children in the Madeira Islands will enable comparison with subsequent studies, as well as long-term monitoring of sleep habits.

However, it should be noted as a limitation that, like our study, most research characterizing sleep in pediatric ages is observational in nature, which allows for the identification of possible associations between variables but does not enable the establishment of cause-and-effect relationships. Additionally, the results were obtained through subjective and retrospective evaluation using a questionnaire, and are dependent on the perception of the caregivers.

Conclusion

In conclusion, the high prevalence of sleep disturbances identified corroborates literature data and justifies assessment by healthcare professionals. There is an urgent need for greater investment in education and motivation of populations regarding sleep hygiene, strategically beginning with education and health professionals.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

References:

1. Oliveira G, Saraiva J, eds. Lições de Pediatria. Vol I. Coimbra: Imprensa da Universidade de Coimbra; 2017.
2. Sociedade Portuguesa de Pediatria (SPP) - Secção de Pediatria Social (SPS). Recomendações SPS-SPP: Prática da Sesta da criança nas creches e infantários, públicos ou privados. Criança e Família. https://criancaefamilia.spp.pt/media/fwkj5qte/versao-educadores-e-pais_recomendacoes-sps-spp-sesta-na-crianca.pdf. June 1, 2017. Accessed July 10, 2024

3. Galland B, Taylor B, Elder D, et al. Normal sleep patterns in infants and children: a systematic review of observational studies. Sleep Med Rev. 2012; 16(3): 213-22. doi: 10.1016/j.smrv.2011.06.001.
4. Sociedade Portuguesa de Pediatria (SPP) e Associação Portuguesa do Sono (APS). Higiene do sono da criança e adolescente. Apsono. https://apsono.com/images/higienesono.pdf. Accessed July 10, 2024.
5. Paruthi S, Brooks LJ, D'Ambrosio C, et al. Recommended amount of sleep for pediatric populations: a consensus statement of the American Academy of Sleep Medicine. J Clin Sleep Med. 2016; 12(6):785-786. doi: 10.5664/jcsm.5866.
6. Mindell JA, Owens J. The Clinical Guide to Pediatric Sleep: Diagnosis and Management of Sleep Problems. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2010
7. Silva FMG. Hábitos e problemas do sono das crianças dos 2 aos 10 anos. In: Repositório da Universidade Nova de Lisboa [database online]. Faculdade de Ciências Médicas da Universidade Nova de Lisboa. https://run.unl.pt/handle/10362/14234. 2014. Accessed January 4, 2022.
8. Bruni O, Novelli L. Sleep disorders in children. BMJ Clin Evid. 2010; 2010:2304.
9. Darien Il, International classification of sleep disorders. 3rd ed. American Academy of Sleep Medicine; 2014.
10. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep. 2000;23(8):1043-51.
11. Parreira AF, Martins A, Ribeiro F, et al. Clinical Validation of The Portuguese Version of the Children's Sleep Habits Questionnaire (CSHQ-PT) in Children with Sleep Disorder and ADHD. Acta Med Port. 2019;32(3):195-201. doi: 10.20344/amp.10906.
12. Mendes LR, Fernandes A, Garcia FT. Hábitos e perturbações do sono em crianças em idade escolar. Acta Pediatr Port. 2004; 35(4):341-347.
13. Iglowstein I, Jenni OG, Molinari L, et al. Sleep duration from infancy to adolescence: reference values and generational trends. Pediatrics. 2003; 111(2):302-7.
14. Clemente V. Sono e Vigília em Crianças de Idade Escolar: Hábitos, comportamentos e problemas. Faculdade de Psicologia e Ciências da Educação, Universidade de Coimbra. 1997. Accessed July 15, 2024.
15. Jenni OG, O'Connor BB. Children's Sleep: An Interplay Between Culture and Biology. Pediatrics. 2005; 115(1 Suppl):204-16. doi: 10.1542/peds.2004-0815B.
16. Dworak M, Wiater A, Alfer D, et al. Increased slow wave sleep and reduced stage 2 sleep in children depending on exercise intensity. Sleep Med. 2008; 9(3):266-72. doi: 10.1016/j.sleep.2007.04.017.
17. Hale L, Guan S. Screen Time and Sleep among School-Aged Children and Adolescents: A Systematic Literature Review. Sleep Med Rev. 2015; 21:50-8. doi: 10.1016/j.smrv.2014.07.007.
18. Sampasa-Kanyinga H, Colman I, Goldfield GS, et al. Combinations of physical activity, sedentary time, and sleep duration and their associations with depressive symptoms and other mental health problems in children and adolescents: a systematic review. Int J Behav Nutr Phys Act. 2020;17(1):72. doi: 10.1186/s12966-020-00976-x.
19. Wikoff D, Welsh BT, Henderson R, et al. Systematic review of the potential adverse effects of caffeine consumption in healthy adults, pregnant women, adolescents, and children. Food and Chemical Toxicology. 2017; 109:585-648. doi: 10.1016/j.fct.2017.04.002.
20. Zhang J, Zhao J, Chen M, et al. Airway resistance and allergic sensitization in children with obstructive sleep apnea hypopnea syndrome. Pediatr Pulmonol. 2016; 51:426-30. doi: 10.1002/ppul.23264.
21. D'Elia C, Gozal Dm, Bruni O, et al. Allergic rhinitis and sleep disorders in children coexistence and reciprocal interactions. Pediatr (Rio J). 2022;98(5):444-454. doi: 10.1016/j.jped.2021.11.010.
22. Ishman SL, Maturo S, Schwartz S, et al. Expert Consensus Statement: Management of Pediatric Persistent Obstructive Sleep Apnea After Adenotonsillectomy. Otolaryngol Head Neck Surg. 2023; 168(2): 115-130. doi:10.1002/ohn.159.
23. Lihabi AA. A literature review of sleep problems and neurodevelopment disorders. Front Psychiatry. 2023; 14:1122344. doi: 10.3389/fpsyt.2023.1122344.
24. Carter KA, Hathaway NE, Lettieri C. Common sleep disorders in children. Am Fam Physician. 2014;89(5):368-77.
25. Matricciani L, Paquet C, Galland B, et al. Children's sleep and health: a meta-review. Sleep Med Rev. 2019; 46:136-150. doi: 10.1016/j.smrv.2019.04.011.
26. Moreira P, Santos S, Padrão P, et al. Food Patterns According to Sociodemographics, Physical Activity, Sleeping and Obesity in Portuguese Children. Int J Environ Res Public Health. 2010; 7(3): 1121-1138. doi: 10.3390/ijerph7031121.
27. Leproult R, Cauter EV. Role of Sleep and Sleep Loss in Hormonal Release and Metabolism. Endocr Dev. 2010; 17:11-21. doi:10.1159/000262524.
28. Choudhary B, Patil R, Bhatt GC, et al. Association of Sleep Disordered Breathing with Mono-Symptomatic Nocturnal Enuresis: A Study among School Children of Central India. PLoS One. 2016; 11(5):e0155808. doi: 10.1371/journal.pone.0155808.
29. Crispim JN, Boto LR, Melo IS, et al. Acta Pediatr Port 2011:42(3):93-8. doi: 10.25754/pjp.2011.4226
30. Owens J. Classification and Epidemiology of Childhood Sleep Disorders. Prim Care. 2008; 35(3):533-46, vii. doi: 10.1016/j.pop.2008.06.003.
31. McCoy JG, Strecker RE. The cognitive cost of sleep lost. Neurobiol Learn Mem. 2011; 96(4): 564-582. doi:10.1016/j.nlm.2011.07.004.