Case report

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Congenital cortical hyperostosis: a rare cause of inconsolable crying in a baby. Clinical case report

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ABSTRACT

Here we describe the case of a 2-month-old infant who consulted several times due to excessive crying, initially interpreted as having a gastrointestinal cause. Since the symptom persisted, a fracture was suspected due to its association with mobilization of the limbs and palpation of a mass on the anterior aspect of the right tibia. X-rays showed diaphyseal polyostotic involvement and lesions compatible with cortical involvement of long bones. Caffey-De Toni-Silverman syndrome was diagnosed and treatment with nonsteroidal anti-inflammatory drugs was initiated, resulting in symptom remission. Subsequently, the diagnosis was confirmed by the identification of the pathogenic heterozygous variant *COL1A1*. This is a rare condition with an estimated incidence of 48/100 000 individuals, and less than 150 cases have been described to date.

Keywords: *congenital cortical hyperostosis; Caffey-De Toni-Silverman;* COL1A1*; pain; colic.*

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INTRODUCTION

Infant crying in the first 2 to 4 months of life is one of the most frequent consultations in pediatrics, both in outpatient visits and emergency departments. Although this is usually a benign and self-limited problem, it is not always a trivial condition.[1]

Formerly called infantile colic, now called excessive crying, is defined as any episode of excessive crying that is difficult to control and motivates parents to make a consultation in a baby who is 2 weeks to 4 months of life.[2]

A cohort study that included a total of 483 infants and followed them prospectively until 2 years of age showed that the prevalence of excessive crying was 19% at 2 months and 12% at 4 months and concluded that most episodes resolve within the first 2 years of life.[3]

Only in some cases (between 5% and 10%), such excessive crying is related to organic diseases, such as orthopedic, hormonal, infectious, and gastrointestinal conditions.[4]

Here we describe the case of a 2-month-old patient with excessive crying of rare genetic organic cause, with an incidence of 48/100 000 individuals[5] and less than 150 cases described to date.[6]

CASE REPORT

This was a male, 2-month-old baby, the first child of a non-consanguineous couple, with no relevant perinatal history, born at term by C-section due to lack of labor progression.

At 20 days of age, he was admitted to the general pediatric ward for an episode of choking during approximately 1 minute in the context of feeding, associated with hypertonia and generalized florid complexion of spontaneous resolution. The event was interpreted as a high-risk, brief, resolved, unexplained event (BRUE) because it occurred in an infant less than 1 month old. The lab tests did not show any pathological finding. Gastroesophageal reflux disease was ruled out and he was assessed by the Department of Neurology due to a suspected seizure episode, which was ruled out because he had a normal electroencephalogram.

After this event, his parents made several outpatient consultations due to his inconsolable crying. His crying was interpreted as colic of gastrointestinal origin, and the type of feeding formula was changed. Due to the lack of response, a new healthcare provider was consulted. During the consultation, upon questioning, the parents reported that the crying worsened when picking him up or changing his diaper or clothes.

On physical examination, the patient was crying with painful facies that were relieved by rest. He remained still, with lower limb abduction, upper limb extension, and minimal head rotation during eye tracking, and he did not rotate or lift his head while in the ventral decubitus position; his hand movements were normal.

On palpation, a mass was noted on the anterior aspect of the right tibia, with no signs of inflammation in the skin. The rest of the physical exam was unremarkable. In the anthropometric assessment, his height and weight were observed to be adequate for his age.

A fracture was suspected, even though his parents denied the possibility of trauma, so X-rays were requested. These showed evidence of diaphyseal polyostotic involvement with lesions compatible with cortical involvement in the tibiae, humeri, radii, and clavicles (*Figures 1 and 2*). It was decided to hospitalize him for pain management and etiological diagnosis.

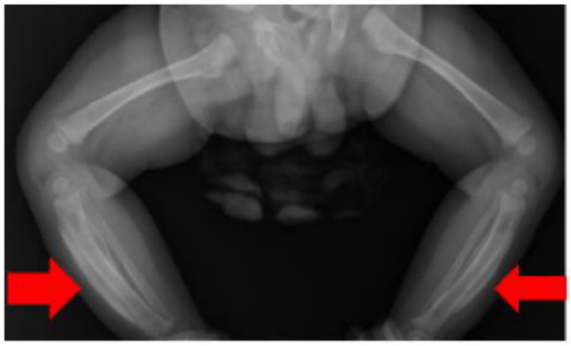
During hospitalization, he was assessed by the Departments of Orthopedics, Endocrinology, Rheumatology, and Genetics. The blood tests showed increased alkaline phosphatase levels, and this was the only positive finding. Congenital syphilis was ruled out based on the patient's venereal disease research laboratory (VDRL) and the mother's negative serology.

Based on the clinical and radiological findings, Caffey-De Toni-Silverman syndrome was diagnosed presumptively. The patient received nonsteroidal anti-inflammatory drugs for pain management and occupational therapy for motor rehabilitation. Given his good course, he was discharged from the hospital. Subsequently, the sequencing of the *COL1A1* gene was positive for a pathogenic heterozygous variant in exon 41 c.3040C>T(p.Arg1014Cys), which confirmed the diagnostic hypothesis.

He continued with the same treatment for 5 months, with progressive dose reductions. The mass in the right tibia remained palpable, but painless, with no implications in the neurological development. The patient continued with a favorable course and a height and weight progression according to his age.

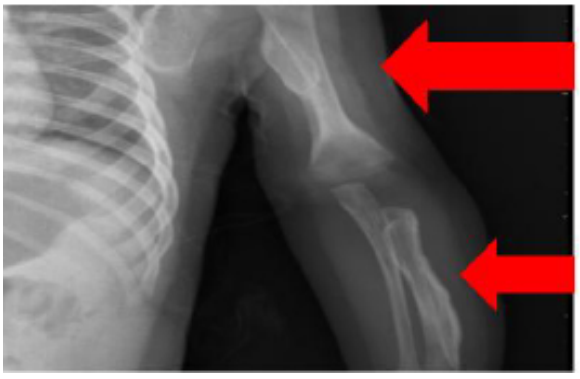
Subsequently, the mother was tested, and the same pathogenic variant was detected. At present, she has no symptoms and it is unknown whether she had any symptoms during her early childhood.

Figure 1. X-ray of lower limbs



Cortical hyperostosis in both tibiae.

Figure 2. X-ray of upper left limb



Cortical hyperostosis in left humerus and radius.

DISCUSSION

Caffey-De Toni-Silverman syndrome, also called infantile cortical hyperostosis, is a rare condition associated with excessive infant crying. It is estimated to have an incidence of 48/100 000 individuals;[5] to date, less than 150 cases have been described since its discovery.[6] However, given that it resolves spontaneously in early childhood, it is probably underdiagnosed.[7]

It is caused by a mutation resulting from the substitution of arginine to cysteine within the helical domain of the α1 chain of type I collagen on chromosome 17q2, which is the fibril former and is found in most connective tissues; it is abundant in bones, corneas, dermis, and tendons.[7] A massive subperiosteal neoformation occurs affecting the diaphysis of long bones, as well as the ribs, shoulder blades, lower jaw, and clavicles.[8]

Although the underlying pathophysiology of cortical hyperostosis is unknown, it has been suggested that it may be triggered by endogenous prostaglandin production. A study examined patients with this syndrome and revealed elevated prostaglandin E1 levels.[9] In addition, several studies in newborn infants with ductal-dependent cyanotic heart disease who received prophylaxis to prevent duct closure with prostaglandins E1 and E2 indicated that most patients developed cortical hyperostosis.[10–12] It is worth noting that many of these reports emphasize that cortical hyperostosis tends to return after discontinuation of prostaglandin therapy.

The clinical characteristics of infantile cortical hyperostosis are irritability, fever, soft tissue edema, and thickening of the underlying cortical bone. The radiological findings include hyperostosis in the diaphyses of the bones with preservation of the epiphyses. Lab tests show evidence of increased C-reactive protein, erythrocyte sedimentation rate, alkaline phosphatase, and immunoglobulins, suggesting an inflammatory disease.[7]

The diagnosis is confirmed by genetic

studies that evidence the mutation, which has an autosomal dominant inheritance pattern with incomplete penetrance.[8]

Several causes may be considered in an infant with excessive crying; only 5% to 10% have an organic cause. Given the high prevalence of child abuse, in the presence of an infant with inconsolable crying that worsens with mobilization, it is mandatory to rule out fractures or bone lesions as the origin of the pain during the physical examination. If these signs are observed, imaging studies should be requested to assess both current and previous fractures. Case reports have found that inconsolable crying in infants may provoke abuse by their caregivers.[13,14]

Other differential diagnoses to consider include hypervitaminosis A, which is characterized by bone pain and inflammation and the finding of multiple fractures; osteomyelitis, which presents with fever and alteration of inflammatory markers together with radiological alterations not compatible with those found in this patient;[8] congenital syphilis, which was very unlikely due to negative maternal serology; and bone tumors that are frequently unique.

The condition described here is generally self-limited, with spontaneous resolution within 6 months to 1 year of life, although remission and relapse may sometimes occur, either at the same or a different site up to 2 years of life.[15] It does not predispose to any long-term bone abnormality, so it only requires symptomatic treatment, such as nonsteroidal anti-inflammatory drugs.

The importance of this case lies in considering the infrequent causes of a common reason for consultation, such as inconsolable infant crying. When a bone mass is found in a patient with a low probability of physical abuse, benign, self-limited —although rare— pathologies, such as Caffey-De Toni-Silverman syndrome, should be taken into consideration to prevent unnecessary invasive diagnostic procedures. An early diagnosis makes it possible to start an adequate treatment and improve the quality of life of the patient and their family. ■

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