Rare disease

Caffey disease in neonatal period: the importance of the family!

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Summary

A male newborn was apparently well until his second day of life, when increased irritability and a swelling in his right leg were noted. He was rooming-in with his mother since birth. On examination, a mass on the anterior surface of the right leg was noticed. The mass was firm, elongated, ill-defined, unmovable and painful at palpation. No overlying skin changes were seen. The newborn had a family history of neonatal bone swelling with resolution before the age of 2. Subsequent images showed hyperostosis in the diaphysis of the right tibia. After exclusion of other conditions such as trauma, osteomyelitis and congenital syphilis, the involvement of the tibial diaphysis, sparing the epiphyses and the benign course of the disease in family history, were indicative of Caffey disease. The genetic study confirmed this diagnosis. Caffey disease, although rare, should not be overlooked in the diagnostic approach to childhood bone swelling.

BACKGROUND

Caffey disease is a rare cause of bone swelling in a newborn. The manifestations of this disorder can sometimes resemble those of child's physical abuse, as well as other diseases. For this reason, a correct diagnosis of the cause of unexplained trauma, fractures or swellings in children requires that clinicians be familiar with such diseases, showing the importance of well-interpreted imaging studies in these diagnoses.^{1 2}

CASE PRESENTATION

A male newborn was apparently well until 28 h of life when his mother identified a swelling in his right leg (figure 1). He was irritable since then. Apart from the painful swollen leg, the newborn had no other systemic symptoms such as fever or poor feeding.

On examination, there was a firm tumefaction in the middle third of the anterior surface of the right leg, painful on palpation, with no changes in colour or temperature of skin over the affected limb. Apart from this, the physical examination was normal. There were no external wounds or bruises.

The mother was 33-year-old, ARh+ and gravida 3 para 2. The current pregnancy was planned and uneventful. Biochemical screening was negative. Three routine fetal ultrasounds were normal. In the third trimester (34 weeks of gestational age), serological maternal investigation was irrelevant (negative for hepatitis B virus, hepatitis C virus, toxoplasma, HIV and Venereal Disease Research Laboratory, VDRL; immune to Rubella). Cytomegalovirus serology was not studied. Group B *Streptococcus* screening test was positive.

The child was born at term (39 weeks) by normal vaginal delivery, non-traumatic with cephalic presentation. No history of prolonged rupture of membranes or maternal fever during labour. Intrapartum antibiotic prophylaxis was performed. Apgar scores were 8 and 9 at

1 and 5 min, respectively. At birth, his weight was 3490 g (25th–50th percentile), length 50 cm (50th percentile) and head circumference 35 cm (25th percentile). From birth, he was in hospital rooming-in with mother, the primary caregiver who denied any history of trauma or injury.

Figure 1 Tumefaction in the middle third of the anterior surface of the right leg.

Figure 2 Family pedigree where the mother's and two maternal uncles involvement can be seen.

He was exclusively breastfed since birth and not received any supplements including vitamin syrup.

He is the second child of non-consanguineous parents, with a previously healthy daughter. Tracing back his family history (figure 2), mother and two maternal uncles reported a 'bone disease' manifested as a swelling-bone in the neonatal period, which resolved without sequelae in the first 2 years of life (24, 12 and 5 months, respectively). In all cases, tibia was affected and one of the maternal uncles had involvement of other bones (skull, legs and arms). No family history of multiple fractures was reported.

INVESTIGATIONS

Biochemical and haematological investigations were normal (haemoglobin 17 g/dl, total white blood cell count $12\,780 \times 10^9/l$, platelet $335 \times 10^9/l$, calcium (total) 9.7 mg/dl,

phosphorous 7.4 mg/dl, urea 16 mg/dl, creatinine 0.6 mg/dl and C reactive protein 0.3 mg/dl).

x-Rays of the affected leg showed thickening of the periosteum at tibial diaphysis without epiphysial involvement and no signs of fracture (figure 3).

Maternal serology for syphilis (VDRL) was not performed after birth.

A germinal heterozygous missense mutation c.3040C>T (p.Arg1014Cys) in exon 41 of COL1A1 gene, associated with Caffey disease, was identified in the newborn, as well as in his mother and in his uncle (figure 2).

DIFFERENTIAL DIAGNOSIS

The initial diagnosis hypothesis was trauma. In a newborn with non-traumatic vaginal delivery, cephalic presentation, with normal medical examination in first day of life and who seems well until 28 h of life when

Figure 3 Anteroposterior (ap) and lateral (perfil) x-rays of right lower limb at 2 days of life, showing cortical new bone formation associated with subperiosteal thickening of tibial diaphysis.

increased irritability and a swelling in his right leg were noted, trauma (inflicted or otherwise) must be excluded. There was a single region involved and periosteal reaction of a single bone that except for the mandible, could be suggestive of trauma.³ However, the absence of external wounds or bruises and the fact that he shared the hospital room not only with his mother but also with other people (who denied any trauma) under the surveillance of hospital staff, suggested otherwise.

Osteomyelitis was also regarded as a possible diagnosis, due to the swollen and tender extremity. Nevertheless, a bone infection was thought to be unlikely because the newborn showed good physical condition with normal vital signs and no fever. In addition, bone changes are not usually present in early acute osteomyelitis and children with osteomyelitis usually have increased acute-phase reactants' levels (C reactive protein) and possibly increased or left-shifted white blood cell count, which did not occur in this case.

Despite a negative VDRL in the third trimester of pregnancy, this test was performed more than 4 weeks before delivery, not excluding a recent infection. As abnormal long-bone radiographs with diaphyseal periostitis are a common manifestation of early congenital syphilis (60–80%) and may even be the only manifestation in infants born to mothers with untreated syphilis, we had to consider congenital syphilis as a possible diagnosis too. However, in congenital syphilis the skeletal changes usually involve not only diaphysis but also metaphysis of the long bones and the lesions are usually symmetric. In this case, maternal serology for syphilis (VDRL) to exclude or confirm this diagnosis was not performed after birth.

There are other causes of periosteum thickening, including scurvy and hypervitaminosis A, but these were not considered in differential diagnosis as they usually do not affect such small infants.⁴

After the exclusion of the conditions aforementioned, the characteristic triad of irritability, swelling and bone lesions with periosteal reaction involving the tibia diaphysis sparing the epiphyses, the age at presentation and benign family history, pointed to the Caffey disease. Subsequently, the genetic study confirmed this diagnosis.

TREATMENT

Symptomatic treatment with acetaminophen was given, with good clinical response. The newborn was discharged on the third day of life, keeping surveillance on an out-patient basis and with recommendation for analgesic therapy during periods of increased irritability.

OUTCOME AND FOLLOW-UP

With 1 month of age, the swelling in the middle third of the right leg persisted, without other inflammatory signs, rarely requiring medication. Radiography of the right leg showed worsening of hyperostosis with thickening of the cortex in the diaphysis of the right tibia (figure 4).

DISCUSSION

Caffey disease or infantile cortical hyperostosis is a proliferative bone disease, resulting in new bone formation at the periosteum, sometimes exuberant, becoming compact and with a pronounced cortical thickening.²

Figure 4 Anteroposterior (ap) and lateral (lat) x-rays of right lower limb at 1 month of life, showing worsening of periosteal reaction of tibial diaphysis.

Skeletal growth is a strictly controlled phenomenon. While bone growth in length is performed by adding endochondral bone formation in metaphyseal spongy bone, the growth in diameter is achieved by subperiosteal new bone apposition. The periosteum is a fibrous connective tissue capsule that covers the external surface of the bone, except articular surfaces that are covered by hyaline cartilage. Periosteum has an outer layer which resembles other dense connective tissues and an inner layer, more cellular that contains the osteoprogenitor cells. The size of the marrow cavity is controlled by a combination of bone apposition versus resorption at the endocortical surface. In Caffey disease, there is an exacerbated subperiosteal intramembranous bone formation (hyperostosis), triggered by local inflammation (periostitis). This excess of bone tissue could be resorbed either at the endocortical surface with an expansion of the marrow cavity and a more persistent deformity, or at the exocortical surface, with no effect on the size of the marrow cavity.⁵

Two forms of cortical hyperostosis or Caffey disease have been described: prenatal and infantile. The prenatal form is characterised by extensive hyperostotic bone involvement, angulations and shortening of long bones, polyhydramnios and fetal hydrops, being a rare disorder with a high death rate due to prematurity and lung hypoplasia. The diagnosis of this form is based on ultrasound findings (as early as 14 weeks of gestation, average 27 weeks) of short and angulated bones with irregular diaphyses. Conversely, in the reported case, the pregnancy was uneventful, with normal ultrasounds and a term delivery of a healthy newborn. Consequently, the prenatal form of the Caffey disease should be excluded.⁶ The prenatal form of Caffey disease appears to be an autosomal recessive disorder.^{7 8}

In our case, the classical mild infantile form seems more likely. It was first described in 1930 by Roske (Europe), but was further characterised by Caffey and Silverman in 1945.^{6 9 10} The classical presentation of this

disease has an onset within the first 6 months of life and includes a triad of irritability, swelling and bone lesions with underlying cortical bone thickening.^{2 6 9 10} The swelling appears suddenly, is deep and firm, and may be tender, as occurred in our case. Fever may also occur. It has been described in many bones, most often involving the mandible (95% of cases), as well as ribs, shoulder blades and long bones (affect only the diaphyses, sparing the epiphyses and metaphyses). It is often multifocal and asymmetric,² although cases of monostotic involvement have also been reported.¹⁰

Although the aetiology of Caffey disease is not completely understood, familial and sporadic forms appear to exist. Some of these sporadic cases have been attributed to administration of prostaglandins E1 and E2 for treatment of ductal-dependent cardiac lesions, with radiographs changes occurring in 62% of all infants receiving prostaglandins infusion for more than 60 days. Review of familial form, with autosomal-dominant pattern of inheritance, showed evidence of variable penetrance, as there were obligate carriers who lacked episodes of cortical hyperostosis. However, the signs and symptoms can be subtle and even missed in some of these unaffected carriers.⁸

Affected members of some families with Caffey disease, including both infantile and prenatal form, were found to be heterozygous for a missense mutation (c.3040C>T) in exon 41 of the gene encoding the $\alpha 1$ chain of type I collagen (COL1A1, 17q21), altering residue 836 (R836C) in the triple-helical domain of this chain.^{2 6-9} This mutation was identified in our newborn, as well as in his mother and in his uncle.

The COL1A1 gene is responsible for other collagen diseases such as osteogenesis imperfecta and Ehlers-Danlos syndrome, and for this reason, studies place the Caffey disease in the family of type I collagen-related diseases.^{2 11}

Caffey disease is rare, being reported to affect 3 per 1000 children under 6 months, with no sex or racial predilection.^{2 6} It has a low prevalence, probably due to underdiagnosis.⁴

Diagnosis may be delayed as this disorder mimics a wide range of diseases, including osteomyelitis, chronic hypervitaminosis A, bone tumour, scurvy and prolonged PGE1 infusion.⁷ The effects of Caffey disease can also resemble those of child physical abuse. However, a misdiagnosis of child abuse can also pose a significant burden to the child, the parents and the suspected aggressor, being of crucial importance that clinics be aware of other conditions that may mimic a non-accidental injury, such as infantile hyperostosis.^{7 12}

While no laboratory tests are specific for diagnosis of infantile cortical hyperostosis,⁷ radiography is the most valuable diagnostic study in infantile cortical hyperostosis, showing layers of periosteal new bone formation, with cortical thickening. Soft-tissue swelling is evident as well. Other diagnostic imaging studies have not proved to be helpful.²

Awareness of the existence of this rare condition and its typical clinicoradiological profile will avoid the patient being subjected to unnecessary investigation and treatment.⁷

No specific treatment exists for Caffey disease. Management is mainly palliative, aimed at pain relief. Some authors described a good response to immunoglobulin, corticosteroids and non-steroidal anti-inflammatory, but

generally these agents do not have any effect on the bone lesions. For this reason, there is no consensus on its use.

Caffey disease is a self-limited disease, sometimes with periods of exacerbation/remission and usually resolves without sequelae by 2 years.^{2 3} However, when paired bones such as tibia and fibula, or radius and ulna, are affected, cross-fusion may be a long-term complication.¹⁰ Although some authors refer that the bone changes persist into adolescence and adulthood, others as Gensure *et al* report that studied patients with COL1A1 mutations had no skeletal deformity after childhood. In the study of four generations of a family affected with Caffey disease (Cerruti-Mainardi *et al*¹³), COL1A1 mutation was identified in nine members of this family, reaching all target height and showing no bone changes sequelae in adulthood.

Learning points

- Caffey disease or infantile cortical hyperostosis is an inflammatory proliferative bone disease, which has an onset within the first 6 months of life and usually resolves without sequelae by 2 years.
- It is characterised by a triad of systemic symptoms (irritability and/or fever), soft-tissue swelling and underlying cortical bone thickening; most often involving the mandible (95% of cases), as well as ribs, shoulder blades and long bones (affect only the diaphyses, sparing the epiphyses and metaphyses).
- In most cases, a good clinical history, basic laboratory evaluation and plain radiographs demonstrating periosteal involvement are sufficient to confirm this diagnosis.
- Caffey disease, although rare, should not be forgotten in the diagnostic approach to early childhood bone swellings.
- A high index of suspicion is necessary to establish this diagnosis, avoiding protracted investigations and unnecessary treatment for this otherwise self-limiting illness.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Prior AR, Moldovan O, Azevedo A, Moniz C. Caffey disease in neonatal period: the importance of the family!. *BMJ Case Reports* 2012;10.1136/bcr-2012-006996, Published XXX

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