

Caffey Disease

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Creation date: September 2001

Updated: February 2005

Scientific Editor: Professor Raoul Hennekam

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Abstract

Caffey disease is a rare condition which presents most commonly in infants. It is characterized by irritability, pain, tenderness, hyperaesthesia, soft tissue swelling and redness involving one or several areas of the body. Systemic changes with fever are usually present in the early stages. The pain may be severe enough to result in pseudoparalysis and individual nerve involvement may result in true localized palsies. Other reported clinical findings include dysphagia and nasal obstruction. Inheritance is thought to be autosomal dominant in some cases. However the incidence of the disease appears to fluctuate and other environmental effects may exert an influence. An underlying viral aetiology has been implicated. The clinical course is variable and unpredictable but the acute symptoms usually resolve over the course of a few months and the outcome is good with spontaneous resolution. Relapses may sometimes occur several years later. Radiographic examination reveals periosteal new bone formation that can be quite florid and subsequently becomes compact causing pronounced cortical thickening. Management is essentially palliative, aimed at pain relief. However, some authors claim a good response to high-dose immunoglobulin. Corticosteroids have been used to hasten bone remodeling.

Key-words

Infantile Cortical Hyperostosis, fever, pain, tenderness, hyperaesthesia, soft tissue swelling, redness, periosteal new bone formation

Synonyms

Infantile Cortical Hyperostosis,
Caffey-Silverman syndrome,
de Toni-Caffey disease.

Brief description and clinical findings

In 1945, Caffey and Silverman reported a new syndrome which they called infantile cortical hyperostosis, following an earlier report by Roske, 1930.

This rare condition presents most commonly in infants, usually under the age of six months, with irritability, pain, tenderness, hyperaesthesia, soft

tissue swelling and redness involving one or several areas of the body. Systemic changes with fever are usually present in the early stages. Presentation with proptosis has been reported (Faure *et al.*, 1977). The pain may be severe enough to result in pseudoparalysis and individual nerve involvement may result in true, localised palsies. Other reported clinical findings include dysphagia (Sheppard *et al.*, 1988) and nasal obstruction.

The clinical course is variable and unpredictable but usually the acute symptoms resolve over the

course of a few months and the outcome is good with spontaneous resolution. Sometimes relapses may occur several years later (Blank, 1975; Borochowitz *et al.*, 1991; Taj-Eldin and Al-Jawal, 1971). The bony changes usually resolve completely but sometimes, when paired bones such as the tibia and fibula or radius and ulna, have been affected, a long-term complication may be that of cross-fusion. Similar fusions may occur when adjacent ribs have been involved and may result in a progressive thoracic scoliosis with respiratory compromise. Facial and mandibular asymmetry may be a long-term consequence.

Radiological findings

Radiographic examination reveals periosteal new bone formation that can be quite florid and subsequently becomes compact causing pronounced cortical thickening. The periosteal new bone is seen in bones underlying areas of soft tissue swelling. The distribution is patchy and asymmetric but is multifocal, although cases of monostotic involvement have been reported (Kaufmann *et al.*, 1977). The mandible is almost invariably involved and other commonly affected areas include the clavicles, ribs and long bones of the limbs. Typically the periosteal new bone or periosteal 'cloaking' is confined to the diaphyses of the long bones, sparing the metaphyses and epiphyses. There are a few reports of lytic areas affecting the skull vault and facial bones but this is uncommon (Boyd *et al.*, 1972; Faure *et al.*, 1977; Lachaux *et al.*, 1992). The spine, phalanges and pelvis are hardly ever involved. Increased uptake of radioisotope from a radioisotope bone scan shows areas of involvement before radiographic changes are present (Taillefer *et al.*, 1983).

Laboratory findings

Laboratory results demonstrate a high erythrocyte sedimentation rate, thrombocythaemia, high white cell count, high alkaline phosphatase levels, high immunoglobulin levels and high C-reactive protein levels (Pickering and Cuddigan 1969; Tabardel *et al.*, 1988; Temperley *et al.*, 1972).

Histopathology findings

Biopsy of affected areas shows fibrinoid degeneration in hyperostotic bone and hyperplastic collagen fibres. Acute inflammatory changes may be present and also numerous mitotic figures within mature lamellar bone.

Management

Management is essentially palliative, aimed at pain relief, but some authors claim a good response to high dose immunoglobulin. Corticosteroids have been used to hasten bone

remodelling and indomethacin has been used to control flare-ups (Couper *et al.*, 2001).

Differential diagnosis

In the early stages of the disease, when only one area of the body is affected, the clinical presentation may be confused with a fracture; osteomyelitis or malignant or invasive soft tissue tumour and occasionally biopsies have been undertaken. The multifocal manifestations require differentiation from multifocal osteomyelitis and congenital syphilis but the periosteal new bone in Caffey disease spares the metaphyses and epiphyses and is not associated with lytic areas of bone destruction. Leukaemia may present with systemic changes and multiple diaphyseal periosteal reactions but this is generally after the age of six months. Differentiation from Caffey disease is also required with the shearing traumatic periosteal reactions seen in non-accidental injury, from vitamin A toxicity and following long-term treatment with prostaglandin E for ductus-dependent cyanotic congenital heart disease. Periosteal 'cloaking' is a feature of some storage disorders in infancy, I-cell disease or mucopolipidosis type II and GM gangliosidosis type I, but the generalised nature of the skeletal changes and metaphyseal irregularities will differentiate these conditions. Hypertrophic osteoarthropathy (primary and secondary) both present later (Ved and Haller, 2002).

Aetiology

Inheritance is thought to be autosomal dominant in some cases (Bull and Feingold, 1974; Clemett and Williams, 1963; Fried *et al.*, 1981; Langewisch, 1975; MacLachlan *et al.*, 1984; Saul *et al.*, 1982). However the incidence of the disease appears to fluctuate and other environmental effects may exert an influence. An underlying viral aetiology has been implicated.

Unresolved issues

There are several reports of the prenatal onset of Caffey disease. Most of these cases have been severe, presenting before 35 weeks gestation and resulting in perinatal death. It is unclear if there is any relationship to the more common postnatal form of Caffey disease. A few (usually those presenting after 35 weeks gestation) follow the expected course of the postnatal form and may simply represent early presentation but many are perinatally lethal with different radiological features.

Prenatal perinatally lethal Caffey disease

Characteristically the prenatal onset, perinatally lethal cases present before 35 weeks gestation, have severe organised cortical thickening affecting ribs and long bones uniformly and the mandible is likely to be spared. The tibia is

almost invariably affected. In addition the long bones may be short and bowed or angulated. There is lung disease, prematurity and maternal polyhydramnios. Presentation after 35 weeks gestation is usually of the milder type.

Prenatal diagnosis

Prenatal diagnosis on ultrasound is usually as a result of short, angulated long bones. The diaphyses are irregular with increased echogenicity and no evidence of fractures (Dahlstrom *et al.*, 2001).

Postmortem finding

Postmortem findings show lung hypoplasia and hepatomegaly and dysmorphic features have been described (Dahlstrom *et al.*, 2001; Turnpenny *et al.*, 1993).

Genetic advice

Several sets of siblings have been described with this severe lethal form of Caffey disease and in these the inheritance may be autosomal recessive, although germ line mosaicism is also possible. Dominant inheritance also occurs within the severe prenatal form (De Jong and Muller, 1995; Drinkwater *et al.*, 1997; Schweiger *et al.*, 2003; Turnpenny *et al.*, 1993).

Differential diagnosis

Other perinatally lethal conditions with diaphyseal periosteal new bone that require differentiation from intrauterine Caffey disease include [mucopolidosis type II](#) and [GM gangliosidosis type I](#), both of which have other radiological changes with coarse trabeculae and metaphyseal irregularity. [Raine syndrome](#) has characteristic facies, microcephaly and cleft palate and is a lethal dysplasia with osteosclerosis (Raine *et al.*, 1989). The case reported by Kozlowski and Tsuruta (1989) represents a further different condition with hydrops, lung hypoplasia, renal duplication and coronal cleft vertebrae.

When bowed or angulated long bones are identified prenatally on ultrasound, differentiation is required from severe forms of [osteogenesis imperfecta](#) (Berceau *et al.*, 1991), [campomelic dysplasia](#) and [hypophosphatasia](#).

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