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CURRENT THERAPY

Infantile Cortical Hyperostosis (Caffey Disease): A Review

Agnès Kamoun-Goldrat, MD, and*
Martine le Merrer, MD, PhD†

Purpose: Face swelling in infants may have several causes including infantile cortical hyperostosis (Caffey disease), an inflammatory process with swelling of soft tissues and periosteal hyperostosis of some bones. New insights show that this self-limited condition is collagen I-related.

Patients and Methods: Collagen I is the most important component of bone and dentine. We reviewed literature to lighten this new collagenopathy, the first one with self-regressive course.

Results: After describing a typical case and the clinical and radiologic features of the disease, we discuss the pathogenic pathways and management care for oral professionals.

Conclusions: Oral practitioners could be asked for differential diagnosis. Surgeons could be queried for surgical correction of the bony deformity, especially of facial and mandibular asymmetry.

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Infantile cortical hyperostosis is usually a self-limiting inflammatory disease that begins in early infancy. It is characterized by unusual irritability, soft tissue swelling, and cortical hyperostosis in multiple bones of the skeleton. Infantile cortical hyperostosis is a rare disease, and a diagnosis should be made to avoid invasive procedures.[1] Dentists or oral surgeons should be consulted first to diagnose and manage infantile cortical hyperostosis because the face bones, and particularly the mandible, are commonly affected.[2] Awareness of this rare disease may permit earlier recognition and a less intensive diagnostic workup. New insights show that this autosomal dominant disorder is collagen I mutation-related,[3,4] opening the field of collagenopathies. After a case report and description of the pathology and their incidence on the face and mandible, we discuss the pathogenic pathways and management care for oral professionals.

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Typical Case

Our patient was born October 1999 (weight, 3.31 kg; size, 49 cm; cephalic perimeter, 36 cm). Parents were non-related. The mother experienced 6 miscarriages, giving birth to a healthy boy in 1996. Another miscarriage occurred before our patient was born. At birth, an angulation of both legs was seen. X-rays showed important hyperostosis of the tibia and the distal part of both humerus. The cranial vault appears normal, but the mandible presents hyperostosis (Fig 1). Pain was present for 5 months and then disappeared. At this time, x-rays showed the femur (Fig 2), radius, and cubitus were involved (Fig 3), but hyperostosis was still resolving. The child is healthy currently, without recurrences of the flare-up.

Caffey Syndrome

FIRST DESCRIPTION

Infantile hyperostosis was described initially by Caffey and Silverman in 1945.[5] They described a group of infants with tender swelling in the soft tissues and cortical thickenings in the skeleton, with onset of these findings during the first 3 months of life.

EPIDEMIOLOGY

It has been reported that infantile hyperostosis affects 3 in every 1000 infants less than 6 months of age in the United States, with no predilection by race or gender.[6] Both familial and sporadic forms occur. The

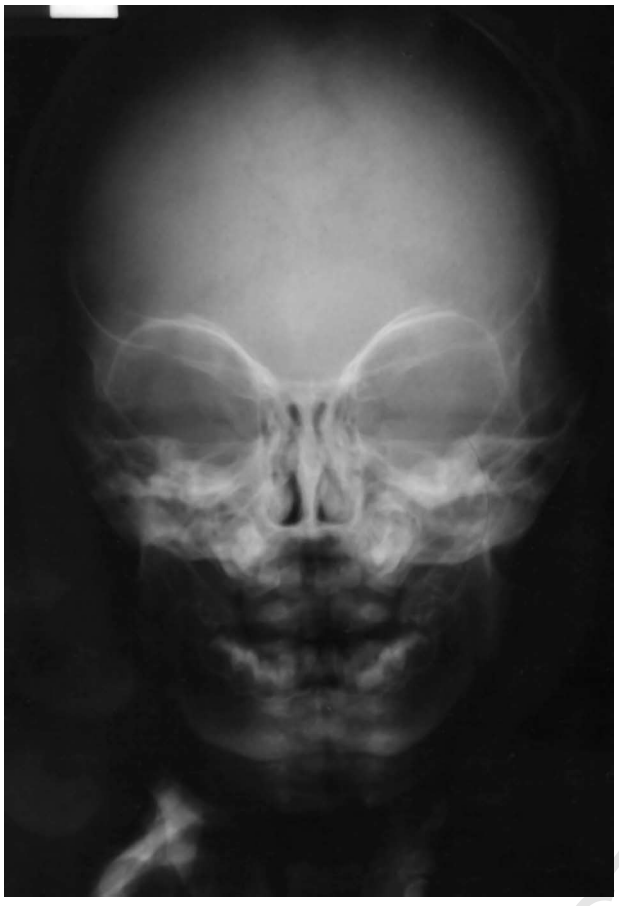

FIGURE 1. X-ray of a 5-month-old infant showing hyperostosis of the mandible.

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familial form is inherited in an autosomal dominant fashion with variable penetrance. It is present at birth in 24% of cases and tends to have an earlier onset of 6 to 8 weeks, with tibias often affected. The average age at onset for the sporadic form is 9 to 11 weeks, with the mandible concerned much more often. The incidence of the disorder is said to be decreasing.[7] Since 1968, there has been a gradual but significant decrease in the number of reports.[8]

CLINICAL FEATURES

The average age of infantile hyperostosis onset is 9 weeks, and no case has started after 5 months of age.[9] It is sometimes present at birth and has been identified in utero by x-ray or ultrasound.

An affected infant typically has the following triad of symptoms: soft-tissue swelling, bone lesions, and irritability with restlessness.[10] Some patients develop fever and anemia.[11] The swelling occurs suddenly, and is deep, often red, painful, firm, and may be tender. It concerns muscles and underlying bones with pale skin and edema,[12] but no there are associated adenopathies.[13] Lesions are often asymmetric. Affected bones include the mandible, tibia, ulna, clavicle, scapula, ribs, humerus, femur, fibula, skull, ilium, and metatarsals. When the mandible is affected, infants may refuse to eat, leading to failure to thrive. The pain may be severe enough to result in pseudoparalysis, and individual nerve involvement may result in true, localized palsies.[9] The diagnosis of Caffey disease is especially difficult during its initial stages because of the non-specific nature of the symptoms including fever, poor appetite, and non-specific laboratory abnormalities.[14] The phase of acute inflammation precedes the abnormal thickening of cortical bone.[15] Diagnosis is often made by physical examination. X-rays can confirm the presence of bone

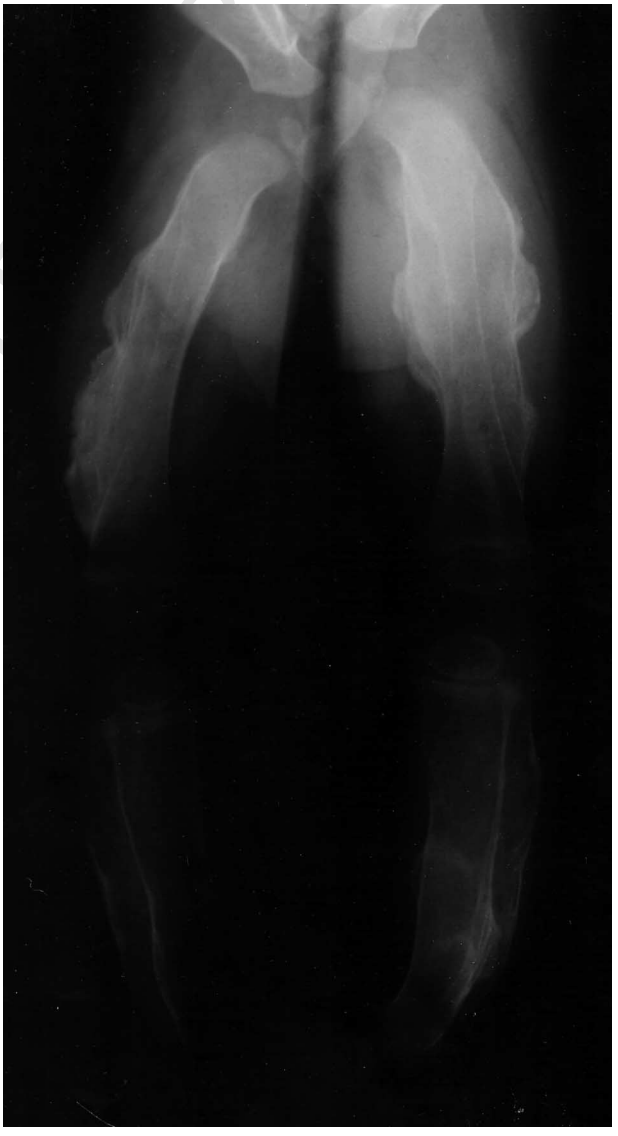

FIGURE 2. X-ray of a 5-month-old infant showing hyperostosis of both legs.

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changes and soft tissue swelling, but radiographic signs are variable during the clinical course.

RADIOLOGIC FEATURES

A hallmark of Caffey disease is periosteal new bone formation and cortical thickening that underlies the soft tissue swelling.[16-18] The diaphysis of tubular bones is involved causing spindle shape of bones, sparing bone ends, and metaphysis. Massive cortical thickening, widening of bones, bridging of bones across the introsseous membrane, and enlargement, marginal hyperostosis, and sclerosis of flat bones may occur.[17] Distribution of the lesions is characteristic. The mandible, clavicle, and ulna are the bones involved most frequently. The long bones, the ilia, lateral ribs, and skull are often affected. Scapula usually shows unilateral involvement. All bones, except phalanges, vertebral bodies, and cuboidal bones, may be implicated.[17] There are no epiphyseal changes and no growth influence.[13]

Radiographs initially show layers of periosteal new bone formation with cortical thickening. Periosteal new bone may cover the diaphysis of the bone, causing an increase in diameter of the bone. Over time, the periosteal new bone density increases becoming homogenous with the underlying cortex. The bone remodels and resumes a normal appearance eventually.

The scan of the mandible shows an increased flow, blood pool activity, and increased tracer uptake in the affected side of mandible.[2]

Radiologic characteristics on magnetic resonance imaging (MRI) include thickening of the periosteum, a low to intermediate signal intensity on T1-weighted sequences, and a high signal intensity on T2-weighted sequences in the adjacent soft tissues (including muscles) secondary to edema.[19,20] Abnormal MRI findings may sometimes precede the radiologic observation of a periosteal reaction.[21] In the same way, increased uptake of radioisotope bone scans shows areas of involvement before radiographic changes are present.[22]

PARTICULAR CASE OF THE FACE AND MANDIBLE

The mandible is the bone affected most frequently, and its involvement is virtually pathognomonic.[5] The mandible is involved in approximately 75% to 80% of cases, either alone or in association with hyperostosis of other bones.[23]

Murphree and Anez[14] reported the case of a 24-day-old infant with bilateral parotid gland swelling, thought to be secondary to child illness. Parotid swelling then resolved on a side. The mandible was described as irregular and "moth-eaten" in appearance on a computed tomography (CT) scan, with diffuse enlargement, suggesting a permeative process.

Dentists and oral surgeons could be consulted for mandibular swelling and cellulitis or osteomyelitis as infantile cortical hyperostosis should be discussed.

Surgeons can also be asked for surgical correction of the bony deformity, especially of facial and mandibular asymmetry.

BIOCHEMICAL SIGNS

No specific blood tests exist, but tests such as erythrocyte sedimentation rate (ESR) and alkaline phosphatase levels are often elevated. A complete blood count may show anemia and leukocytosis, high immunoglobulin levels, and high C-reactive protein levels,[9] confirming an inflammatory process.

BIOPSIES

Eversole et al[24,25] made the most comprehensive microscopic studies of biopsy specimens in early and late stages of the disease. Early lesions are confined to the periosteum, actually intraperiosteal. The swollen, mucoid periosteum looses its peripheral limiting fibrous layer and blends with contiguous overlying fascia, muscles, and tendons and disappears temporarily as an identifiable structure. Osteoid trabeculae appear throughout the swollen, acutely inflamed periosteum and invades juxtaperiosteal soft tissues, muscle, and connective tissue. The bone marrow also shows fibrosis.[26] In the subacute phase, the periosteum is reestablished as an entity with a peripherally limiting sheet of fibrous tissue beyond the new bone that has formed from ectopic osteoid trabeculae. In the late stage, the extra peripheral bone is removed gradually.[27]

VARIANTS

There are several reports of lytic areas affecting the cranial vault and facial bones, but this is uncommon.[28-30] The most common variant is known as prenatal Caffey disease.[31] Using ultrasound, Bercau et al[32] detected major angulations of the long bones and irregularities of the ribs. These findings suggested lethal osteogenesis imperfecta due to the assumption that the irregularly shaped bones were misinterpreted as fractures leading to the wrong diagnosis.[32,33] Further histologic examination confirmed the diagnosis of Caffey disease, and this form should be referred to as lethal prenatal cortical hyperostosis.[34] Two groups can be distinguished: *1*) severe, with onset before 35 weeks of gestation, generally associated with polyhydramnios, lung disease, nearly all long bones affected, prematurity, and high lethality[9]; and *2*) mild, with onset after 35 weeks and without complications. In both forms, the available evidence suggests both dominant and recessive inheritance.[33]

Infants with the lethal form of the disease fit a specific phenotype, with underdeveloped mandi-

ble.[25] De Jong and Muller[35] described a female fetus with narrowing of the biparietal diameter, low-set ears and hypotelorism, bilateral epicanthic folds, a dimple on the tip of the nose, a long philtrum, a carp-shaped mouth, and a high palate. There was retrognathia with a deep V-shaped tethering below the lower lip and a dimple on the chin.

De Jong and Muller[35] described perinatal death in 2 siblings. Despite the absence of parental consanguinity, the occurrence of the condition in a male and a female sibling born to healthy parents suggests autosomal recessive inheritance of the lethal prenatal onset type of cortical hyperostosis.[35,36]

DIFFERENTIAL DIAGNOSTICS

Laboratory tests, serology, and cultures show no abnormalities but help to exclude other diseases including scurvy, infection (syphilis or tuberculosis), trauma, hypervitaminosis A, pulmonary osteoarthropathy or neoplasm,[37] child abuse, hyperphosphatemia, severe chronic hypoparathyroidism,[12] prostaglandin E1 or E2 administration, Ewing sarcoma, and metastatic neuroblastoma. Periosteal "cloacking" is also a feature of some storage disorders in infancy, I-cell disease, or mucolipidosis type II and GM gangliosidosis type I.[9] The majority of these conditions can be ruled out by age group, showing mandibular involvement and observing triad of irritability, swelling, and osseous lesions.[24] Some patients present with a meaningless fever only, permitting many examinations and even treatments.[1] Osteomyelitis is the misdiagnosis most likely because of its close resemblance to infantile cortical hyperostosis.[2] Therefore, the presence of germs must be investigated. This much more common disease must be excluded, because it requires urgent treatment with antibiotherapy.[38]

TREATMENT

Based on the association of hyperostosis with administration of prostaglandin E to maintain patent ducts arteriosis, naproxen (given as a prostaglandin inhibitor) was successful in treating 1 case of recurrent infantile cortical hyperostosis.[39] Corticosteroids have been used to hasten bone remodeling, and indomethacin has been used to control flare-ups.[40] Particularly severe cases have been treated with prednisone with some success,[14] but these treatments do not act on radiologic lesions and do not prevent recurrences. Analgesics and other general supportive measures are essential.[2]

PRONOSTIC

Infantile cortical hyperostosis is a self-limited condition, meaning that it resolves on its own without treatment, usually within 6 to 9 months. There is no growth trouble observed, but complications like exophthalmos and pleuritis can be seen sometimes.[13] The disorder usually shows successive exacerbations with clearing during the second year of life, although a chronic course up to early childhood and occasionally to up to an adult age has been described with crippling deformities in the extremities and markedly delayed muscular and motor development. Late recurrence has also been reported.[35] When excessively large hyperostosis affects parallel neighboring bones such as ribs or radius, ulnar pressure may kill the contiguous periosteum with local fusion of cortical walls that act as interosseous bridges.[26] This may sometimes result in a progressive thoracic scoliosis with respiratory compromise.[9]

Infantile cortical hyperostosis can cause enough bony deformity surgical correction at a later date may be required. Facial and mandibular asymmetry may be a long-term consequence, sometimes needing surgical correction.

PATHOGENY

Many hypotheses for its pathogenesis have been suggested including infection, genetic, immunologic, viral[41] allergic reactions in collagen tissues,[11] and vascular origins.[21]

Autosomal dominant inheritance of Caffey disease has been suggested[42] and confirmed by many reports.[43,44] Review of the pedigrees show evidence of incomplete penetrance.[45,46] Parental gonadal mosaicism is another possibility.[35]

Gensure et al[3] recently undertook genetic linkage studies of 3 unrelated families, 2 prenatal cases, and 1 sporadic case. They located a genetic defect on chromosome 17q21, and described a novel missense mutation (R836C) affecting the gene encoding the α1(I) chain of type 1 collagen present in bone, skin, ligaments, and teeth.

Alterations of the major component of bone, skin, and dentine matrix has never been involved in self-limited conditions until now. For example, mutations in A1 or A2 chains of collagen I are involved in a brittle bone disease like osteogenesis imperfecta (growth failure, fractures, bone deformities with wide severity) or in Ehlers-Danlos (skin and joint hyperextensibility). These pathologies are never self-limited conditions, therefore, this new mutation described by Gensure et al[3] is the first one implicated in spontaneous regressive course. Authors give some hypothesis about this new phenotype: mutation R836C occurs in the triple helical domain of A1(I) chain, substituting X in Gly-X-Y repeating amino acid triplets. The analysis of collagen fibrils shows increased disulfide crosslinking, which can explain Caffey phenotype. Caffey mutation occurs in a binding site for matrix proteins like IL-2, perhaps leading to perturbated interactions. R836C substitution should lead to reduce thermal

stability of the collagen triple helix. The absence of hyperostotic lesions in adults may be explained by the differences in periosteal bone formation in adults and infants.[47]

It would be of great interest to explore the dental conditions of Caffey patients (data not available) to discover the macroscopic or microscopic consequences of such alteration on dentine formation. Although dentinogenesis imperfecta is correlated to mutation in Dentin SialoPhosphoProtein gene, dentinogenesis imperfecta in osteogenesis imperfecta patients also may occur. Perhaps Caffey patients have new forms, transient one or minors not excluded, of dentine alterations, helping us to understand pathogenic pathways of this unusual collagenopathy. Involvement of oral professionals is needed for proper differential diagnoses, particularly with cellulitis and osteomyelitis, which need emergency treatment. Because of the non-specificity of clinical signs, the pathology has to be well-known to avoid invasive procedures for patients. Mandible changes are correlated with other symptoms, and swelling of the face requires further x-ray exploration of the long bones.

Swelling of the mandible in infants should be investigated for several pathologies, including cellulitis, osteomyelitis, and Caffey disease. The mandible is most often concerned, leading to dentist or oral surgeon consultations. When swelling of the mandible, oral practitioners have then to search radiologic signs on long bones of this self-limited condition. Long-term deformities of the bones involved are possible, but rare. Surgeons may be asked for surgical correction of the bony deformity, particularly in regard to facial and mandibular asymmetry.

Recently, Gensure et al[3] showed that infantile cortical hyperostosis is related to collagen I mutation, with no explanation for temporal and spatial defects. Because collagen I is one of the most important components of dentine, teeth alterations of Caffey patients need to be explored to better understand the pathogenic pathways and collagenopathies of this disease.

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AQ1— Please verify suitability of suggested short title or provide one.

AQ2— Please verify degree information as set by CE.

AQ3— Please verify affiliation information and provide position/department information for both authors.

AQ4— Is "self-limited" correct here?

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