Cherubism in Siblings: A Case Report

(Le chérubisme chez les frères et sœurs : étude de cas)

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Sommaire

Le chérubisme est une maladie osseuse non néoplasique, qui se caractérise par une tuméfaction bilatérale des mâchoires, cliniquement apparente mais indolore, qui donne au patient l'apparence d'un chérubin. Le chérubisme peut se manifester chez un seul, ou chez plusieurs, membres d'une même famille, et souvent sur plusieurs générations. À l'examen radiographique, les lésions présentent des zones pluriloculaires bilatérales radiotransparentes. L'examen histopathologique révèle la présence de tissu conjonctif fibreux proliférant, qui contient de nombreuses cellules géantes multinuclées. Depuis que cet état a été décrit pour la première fois, en 1933, près de 200 cas ont été déclarés. Nous présentons le cas d'un frère et une sœur atteints de chérubisme et passons brièvement en revue la littérature sur ce sujet.

Mots clés MeSH : *cherubism/diagnosis; cherubism/pathology; mandibular diseases/pathology*

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Cherubism (disorder 118400 in the Mendelian Inheritance in Man database[1]), a non-neoplastic hereditary bone lesion that is histologically similar to central giant cell granuloma, affects the jaws of children bilaterally and symmetrically, usually producing the so-called cherubic look.[2,3] The disease was first described in 1933 by Jones,[4] who called it familial multilocular disease of the jaws, but after the cystic nature of the condition was invalidated, Jones and others[5] were the first to use the term "cherubism." The word "cherub" originally designated a member of the second order within the Christian celestial chorus. These were creatures with specific physical features: severe, staring eyes (including eyes on the wings and the body) and a wheel below the feet. Angels constituted another order within the celestial chorus, and angels with childish, full-cheeked faces, often gazing upward, were widely depicted in baroque art. Thus, the term "cherubism," introduced by Jones and others[5] to describe the clinical appearance of affected patients, is actually inappropriate for the disease, because the typical clinical picture resembles not a classical cherub but a baroque angel.[2]

According to the World Health Organization classification, cherubism belongs to a group of non-neoplastic bone lesions affecting only the jaws.[6] It is a rare, benign condition with autosomal dominant inheritance, and it is one of the very few genetically determined osteoclastic lesions in the human body.[7] A variety of names have been used to describe the condition, including familial or hereditary fibrous dysplasia,[8] bilateral giant cell tumour and familial multilocular disease.[9] It appears to have 100% penetrance in males and only 50% to 70% penetrance in females.[10–13] There is great variation in the clinical expression. Although the condition is known to be hereditary, in some cases there has been no detectable family history,[2,3,10] and although it usually occurs bilaterally, there have also been cases of unilateral involvement,[14] perhaps because of incomplete penetrance or new mutations.[3,11] Some investigators believe that cherubism arises from the mutation of a non-sex-linked gene responsible for the development of the jaw bones.[2]

Typically, the jaw lesions of cherubism remit spontaneously when affected children reach puberty, but the reason for this remission is unknown. The reduction in osteoclast formation caused by sex steroids and the increase in plasma concentrations of estradiol and testosterone at puberty both suggest that the genetic defect responsible for the localized increase in osteoclasts in cherubism is overridden and normalized by the increased synthesis of sex steroids.[7] In total, 175 definitive cases of cherubism have been reported.[3]

Clinical Features

Affected children are normal at birth and are without clinically or radiographically evident disease until 14 months to 3 years of age. At that time, symmetric enlargement of the

jaws begins. Typically, the earlier the lesion appears, the more rapidly it progresses. The self-limited bone growth usually begins to slow down when the patient reaches 5 years of age, and stops by the age of 12 to 15 years.[10,11] At puberty the lesions begin to regress. Jaw remodelling continues through the third decade of life, at the end of which the clinical abnormality may be subtle.[10] The signs and symptoms depend on the severity of the condition and range from clinically or radiologically undetectable features to grotesquely deforming mandibular and maxillary overgrowth with respiratory obstruction and impairment of vision and hearing.[10] Cherubism was fatal in one case in which aspiration occurred because of the grotesque facial deformity.[15] The jaw lesions are usually painless and symmetric and have florid maxillary involvement. The lesions, which are firm to palpation and nontender, most commonly involve the molar to coronoid regions, the condyles always being spared,[10,11] and are often associated with cervical lymphadenopathy.[10,16,17] Enlargement of the cervical lymph nodes contributes to the patient's full-faced appearance and is said to be caused by reticuloendothelial hyperplasia with fibrosis.[11] The lymph nodes become enlarged before the patient reaches 6 years of age, decrease in size after the age of 8 years and are rarely enlarged after the age of 12 years.[16] Intraoral swelling of the alveolar ridges may occur. When the maxillary ridge is involved, the palate assumes a V shape.[18,19] A rim of sclera may be visible beneath the iris, giving the classic "eye to heaven" appearance.

Numerous dental abnormalities have been reported, such as agenesis of the second and third molars of the mandible, displacement of the teeth,[2,11] premature exfoliation of the primary teeth, delayed eruption of the permanent teeth,[2,10] and transpositions and rotation of the teeth.[17] In severe cases, tooth resorption occurs.[11]

Although cherubism was initially described as a familial disease affecting the jaws, cases without any apparent hereditary origin have been reported. In a few cases cherubism has been described as being connected with other diseases and conditions such as Noonan's syndrome,[13] a lesion in the humerus, gingival fibromatosis,[20] psychomotor retardation,[21] orbital involvement[19] and obstructed sleep apnea.[16]

Genetic Basis

The locus for the cherubism gene is 4p16. Linkage data suggest that the locus spans the interval between markers D4S2936 and D4S2949.[22] However, the most reasonable conclusion from the linkage data obtained in a study of 4 families by Tiziani and others[22] is that the locus for cherubism is located on the telomeric side of D4S1582. Ueki and others[23] detected point mutations causing amino acid substitutions in the SH3-binding protein SH3BP2. This adapter binding protein contains 3 modular peptide recognition domains: an N-terminal pleckstrin homology domain, a 10-amino-acid SH3 binding site and a C-terminal SH2 domain. All mutations identified so far are in exon 9, and they affect 3 amino acids within a sequence of 6 amino acids (RSPPDG) located 31 to 36 amino acids upstream of the SH2 domain and 205 to 210 amino acids downstream of the SH3-binding domain. The accumulation of cosegregating sequence variants in families with cherubism and their absence in 200 unaffected controls provide compelling evidence that the mutations in SH3BP2 cause cherubism.[23]

The onset of the abnormalities of cherubism and their organ-restricted characteristics may be related to dental development in children, when signals unique to the mandible and maxilla are transmitted throughout the extracellular matrix, triggered by the eruption of the secondary teeth. Signalling pathways involving protein SH3BP2 may well be involved in setting thresholds for the increased osteoclast and osteoblast activities that are essential for normal tooth eruption.[23]

Grading System

Arnott[14] suggested the following grading system for the lesions of cherubism: grade I is characterized by involvement of both mandibular ascending rami, grade II by involvement of both maxillary tuberosities as well as the mandibular ascending rami and grade III by massive involvement of the whole maxilla and mandible except the coronoid process and condyles. However, because many authors could not use this classification to describe their cases[2,9] Kalantar Motamedi[2] developed a different classification system, which addresses both the involvement and the aggression of the disease: grade I (divided into 5 classes) is characterized by lesions of the mandible without signs of root resorption; grade II (divided into 3 classes) by lesions of the mandible and maxilla without signs of root resorption; grade III (divided into 5 classes) by aggressive lesions of the mandible with signs of root resorption; grade IV (divided into 3 classes) by lesions involving the mandible and the maxilla and showing signs of root resorption; and grade V, which involves rare, massively growing, aggressive and extensively deforming juvenile cases involving the maxilla and the mandible and which may include the coronoid process and condyles.

Radiographic Features

Radiologically, cherubism is characterized by bilateral multilocular cystic expansion of the jaws.[10] Early lesions occur in the posterior body of the mandible and the ascending rami. Maxillary lesions may occur at the same time but escape early radiographic detection because of overlap of the sinus and nasal cavities.[13] Displacement of the inferior alveolar canal has been reported.[12,17] The destruction of the alveolar cavity may displace the teeth, producing a radiographic appearance referred to as "floating tooth syndrome."[17] With adulthood, the cystic areas in the jaws become re-ossified, which results in irregular patchy sclerosis. There is a classic (but nonspecific) ground glass appearance because of the small, tightly compressed trabecular pattern.[10]

Histopathologic Features

Histologic examination of the lesions usually reveals numerous multinucleated giant cells.[10,19,24] These multinucleated

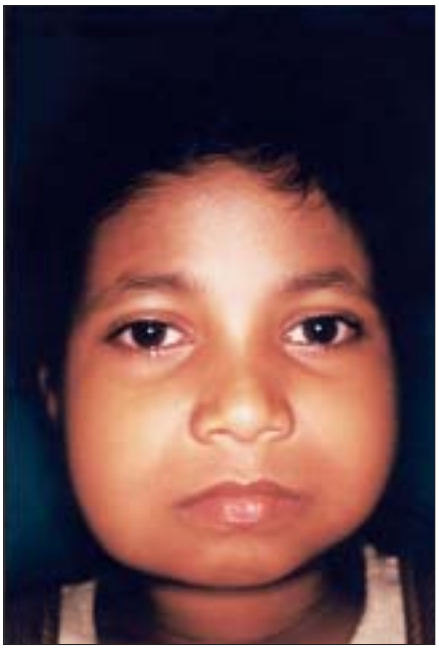

Figure 1: *Extraoral photograph of a 7-year-old girl with cherubism.*

Figure 2: *Extraoral photograph of the girl's 14-year-old brother.*

cells show strong positivity for monoclonal antibody 23c6 and tartarate-resistant acid phosphatase, which is characteristic of osteoclasts.[7,19] The collagenous stroma, which contains a large number of spindle-shaped fibroblasts, is considered unique because of its water-logged, granular nature. Numerous small vessels are present, and the capillaries exhibit large endothelial cells and perivascular capillary cuffing.[10,11] The eosinophilic cuffing appears to be specific to cherubism. However, these deposits are not present in many cases, and their absence does not exclude the diagnosis of cherubism. Older, resolving lesions of cherubism show an increase in fibrous tissue, a decrease in the number of giant cells and formation of new bone. The microscopic findings seldom permit a specific diagnosis of cherubism in the absence of clinical and radiological information.[25]

Differential Diagnosis

The differential diagnosis of cherubism consists of giant cell granuloma of the jaws, osteoclastoma, aneurysmal bone cyst, fibrous dysplasia and hyperparathyroidism.[19]

Giant cell granuloma and osteoclastoma are histologically similar to cherubism. However, giant cell granuloma is usually unilateral and usually affects patients between the ages of 20 and 40 years,[19] whereas cherubism is a symmetric lesion[7,19] affecting children. Unlike cherubism, osteoclastoma rarely occurs in the jaws. Aneurysmal bone cyst may also exhibit giant cells, but its main feature is a cavity lined with tissue other than endothelium.[19]

Both fibrous dysplasia and hyperparathyroidism contain large numbers of osteoclasts. However, histologic examination of the classic form of fibrous dysplasia reveals trabeculae of immature bone resembling Chinese characters within the proliferating stroma. These trabeculae are not rimmed by osteoblasts. Furthermore, polyostotic fibrous dysplasia first presents in the second or third decade of life. Hyperparathyroidism rarely affects the jaw in an isolated manner. Its histologic features differ from those of cherubism in that it does not contain the mononuclear stromal cell population that is characteristic of the latter. Finally, peritrabecular fibrosis is a feature of hyperparathyroidism but not cherubism. Serum concentrations of parathyroid hormone and calcium also help to distinguish these lesions.[7] Levels of serum alkaline phosphatase are generally elevated in cases of fibrous dysplasia. In cases of hyperparathyroidism, levels of serum calcium are elevated, levels of serum phosphorus are decreased and levels of serum alkaline phosphatase are generally within normal levels.

Treatment

As Laskin[26] stated, "the treatment of cherubism should be based on the known natural course of the disease and the clinical behaviour of the individual case." Therefore, surgery to correct the jaw deformities of cherubism is rarely indicated. If necessary, surgery is usually undertaken after puberty, when the self-limitations of the lesions have been reached, unless esthetic considerations or severe functional problems justify earlier treatment.[3,18,19] Although exacerbation has sometimes been reported after surgery, it is believed that surgery ultimately accelerates the involution process.[10] Liposuction[27] has been used to change the contour of the jaws in a patient with cherubism. The procedure involved removal of the fibro-osseous tissue, which has the consistency of firm Jell-o and which is difficult to remove with bone ronguers and curettes. A blunt suction lipectomy cannula was used to curette the abnormal tissue, which was then aspirated by the high-suction apparatus.

Radiation has been used successfully, but it is discouraged because of possible retardation of jaw growth[10,11] as well as the risks of osteoradionecrosis and induction of malignancy.[10]

The treatment of choice is curettage, but equally good results have been obtained with simple contouring to produce a more cosmetically acceptable appearance.[11,19]

Medical therapy in the form of calcitonin is theoretically appropriate.[10] The findings of Southgate and others[7] raise the possibility that treatment with calcitonin may curtail the disease and obviate the need for surgery.

Case Report

Two siblings, a 7-year-old girl and her 14-year-old brother, with slowly growing bilateral swelling of the jaws

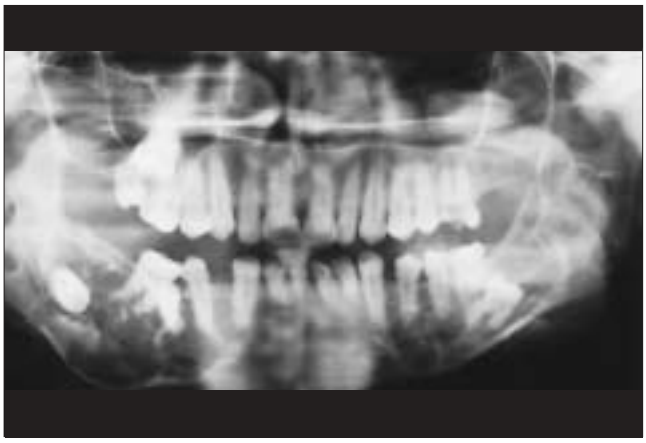

Figure 3: *Orthopantomogram of the girl.*

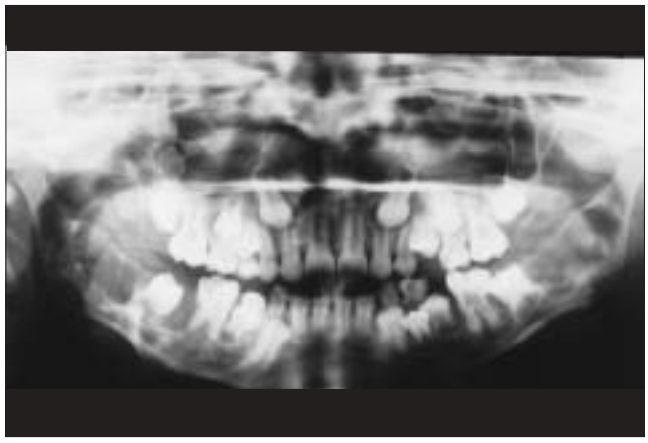

Figure 4: *Orthopantomogram of the boy.*

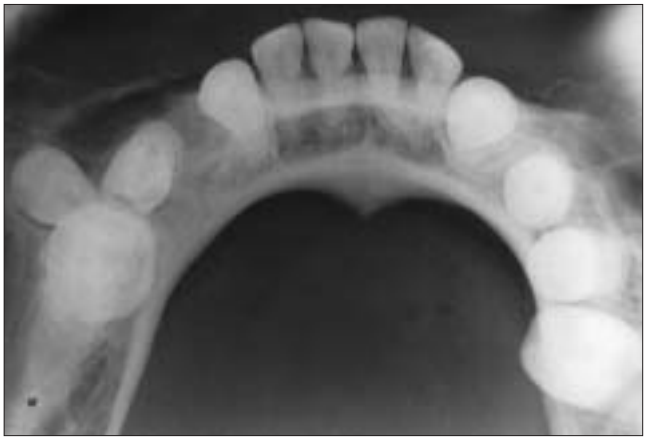

Figure 5: *Mandibular occlusal view of the girl.*

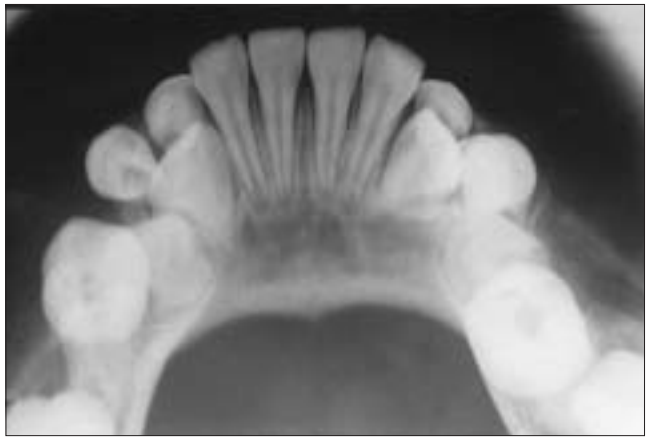

Figure 6: *Mandibular occlusal view of the boy.*

were brought to our hospital by their parents. Both children were otherwise healthy and had no relevant medical history. The parents reported that the swelling of their daughter's jaws had been noticeable for the past 3 years. The girl's mandible was swollen bilaterally and was hard and nontender on palpation (Fig. 1). The lymph nodes were not palpable. Intraoral examination revealed no abnormalities in the dentition. The boy had a similar swelling, which was described as having regressed significantly with time (Fig. 2). This swelling was also firm and nontender on palpation. The brother had mild spacing between his lower canine and premolar, as well as an unerupted premolar and second molar on the right side. No other members of the family were known to have such facial deformities.

Orthopantomograms (OPGs) of the siblings revealed bilateral radiolucencies extending over the body and ramus of the mandible; however, the condyles were unaffected (Figs. 3 and 4). The girl's OPG showed a locule in the maxillary tuberosity region on the right side (Fig. 3). The boy's OPG revealed abnormalities in the dentition, including transposition of the right upper second premolar distal to the first molar. The right upper second molar, the right lower second molar, the second premolar and the left lower second molar were impacted (Fig. 4). Mandibular occlusal radiographs revealed expansion of the cortical plates in both cases (Figs. 5 and 6).

The results of laboratory tests, which included determination of serum calcium, phosphorus and alkaline phosphatase, were normal. These tests help to differentiate cherubism from fibrous dysplasia and hyperparathyroidism. Histopathologic evaluation of the lesions showed proliferating fibrous connective tissue containing numerous multinucleated giant cells. Cherubism was diagnosed in both cases. The boy's lesion was classified as grade I, class 5 and the girl's as grade II, class 1, according to the grading system proposed by Kalantar Motamedi.[2] However, in the girl only the right maxillary tuberosity seemed to be involved. Because the disease is generally self-limiting and subsides with age, because the lesions were not causing any functional problems and because the parents were not concerned about appearance, no treatment was given and the parents were advised to bring their children for periodic checkups to monitor the condition.

Conclusions

The descriptions in our report conform with most other reported cases of cherubism. The triad of clinical, histologic

and radiologic findings helps in the diagnosis of cherubism. However, laboratory investigations of serum calcium, phosphorus and alkaline phosphatase are necessary to differentiate this condition from other similar lesions.

Given previous reports of orbital and airway involvement, a multispecialty approach is suggested in the management of cherubism. The consequences of benign neglect have not been adequately documented, but because most such lesions resolve with age, patients can simply undergo routine checkups to monitor for aggressive transformation or systemic involvement, unless the lesions cause any functional disturbance. In that case, surgical curettage seems to be the ideal treatment modality. Now that the gene for cherubism has been identified, it is likely that an effective therapy will be designed. ◆

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