Cherubism: Clinicoradiographic Features, Treatment, and Long-Term Follow-Up of 8 Cases

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Cherubism is a rare non-neoplastic hereditary disease related to genetic mutations characterized by bilateral bone enlargement of the jaws in childhood. Documented long-term follow-up of a series of cases is presented. Four familial and 4 sporadic cases of cherubism have been treated and followed for a mean of 18 years (range, 5 to 32 years). Four of the patients were subjected to cosmetic surgical correction justified by extreme size of the jaws, whereas the other 4 underwent just biopsy or ectopic and impacted teeth removal. Fibro-osseous lesions spontaneously regressed at different levels at variable time intervals. Apparent radiographic osseous repair occurred routinely. In adult life, the patients exhibited normal facial appearance, and radiographs showed almost complete involution of the lesions. Long-term follow-up of these patients is desirable to evaluate diagnosis or regression of the lesions. Apparently, surgical intervention is unnecessary unless significant functional, esthetic, or emotional disturbances develop.

Cherubism, first described by Jones,1 is a benign, self-limiting fibro-osseous disorder characterized by bilateral expansion of the mandible, maxilla, or both. The lesions are usually symmetrical and painless. Frequently, cherubism is accompanied by dental arch and dental eruption abnormalities. Extragnathic skeletal involvement is rare. The rounded faces and occasional upward cast of the eyes with exposure of the sclera below the pupil give the patient an appearance reminiscent of the cherubs portrayed in Renaissance paintings. Affected children appear normal at birth and are mentally normal. Jaw expansion is noticed within the first years of life, becoming progressively larger until puberty. Lesion regression is expected to occur spontaneously by the end of adolescence, resolving by middle age.1

Radiographically, lesions appear as cystic multilocular radiolucencies, often beginning near the angle of the mandible and spreading to the mandibular ramus and body. Maxillary lesions may occur at the same time. Frequently, ectopic unerupted teeth are involved by lesions.1-13

The histology is limited for diagnosis, showing fibrous hyperplasia and multinucleated giant cells. These features are similar to those other bone diseases such as brown tumor of hyperparathyroidism, giant cell tumor, and central and peripheral giant cell granuloma.2-6,8-10,13

Cherubism is a familial disease1-9 in which the trait is transmitted in an autosomal dominant fashion with 100% penetrance in males and 50% to 70% penetrance in females.4 However, several isolated cases have been reported in the literature.7,9,11-13 Novel mutations in the gene encoding the binding protein SH3BP2 on chromosome 4p16.3 have been reported to cause cherubism.14-16

Studies of cherubism with long-term follow-up presenting with clinicoradiographic documentation clearly demonstrating spontaneous resolution of bone lesions are extremely rare in the literature. Here we report 8 cases of cherubism, 4 cases from the same family and 4 nonfamilial sporadic cases, followed up for a mean of 18 years. We discuss disease behavior, treatment approaches, and clinicoradiographic aspects.
Report of Cases

CASE 1

Patient 1, a boy, presented with painless facial swelling at age 6 years. Extraoral radiographs showed transparent multilocular lesions completely involving the maxilla and mandible. Maxillary sinususes were not visible. Medical and family histories were unremarkable. With a clinicoradiographic diagnosis of cherubism, the patient was scheduled for regular follow-up. By age 10, mandibular enlargement became more noticeable; this persisted until age 12, when the lesions began to decrease. At age 16, mandibular enlargement was minor, with swelling more noticeable in the maxilla; radiographs exhibited significant remission of radiolucent areas, and the maxillary sinususes were clear. At age 25, the patient exhibited slight swelling of the maxilla, and a panoramic radiograph showed multilocular lesions almost totally filled in with bone (Fig 1).

CASE 2

Patient 2, a girl, presented with bilateral painless swelling of the mandible at age 15. Her medical and family histories were unremarkable. Radiographs revealed multilocular areas involving the mandible. Biopsy findings confirmed a diagnosis of cherubism. Treatment involved regular follow-up visits. One year later, an occlusal radiograph showed outstanding osseous repair in the anterior portion of the mandible (Fig 2). Over the subsequent years, disease regression was observed. The patient was lost to follow-up at age 20.

CASE 3

Patient 3, a boy, exhibited discrete painless growth of the face at age 6 years. A panoramic radiograph showed multilocular areas in mandible and maxilla. No familial cases were reported. Biopsy findings confirmed a diagnosis of cherubism, and the patient was scheduled for regular follow-up. By age 12, the patient’s condition began to regress. At age 21, he returned for extraction of ectopic and unerupted teeth, at which time swelling was found to be constricted to the maxilla. Two years later, his remaining teeth required extraction. At this time, minor residual enlargement in the maxilla was seen, and a radiograph showed significant bone filling over the multilocular areas (Fig 3).

CASE 4

In patient 4, a boy, facial alteration was first noted at age 4 years and progressively developed asymptotically. At age 12, the patient showed enlargement of the jaws, most noticeable on the right side. Panoramic radiograph showed multilocular areas involving the jaws. Family history was negative for cherubism. In the subsequent year, the patient underwent minor surgeries for removal of the upper right second premolar and biopsy, which confirmed the clinical diagnosis of cherubism. At age 14, a small corrective approach was performed in the right body of the mandible, simultaneously with extraction of the lower right second premolar. At age 20, the patient had a harmonic face, and a panoramic radiograph showed bone filling into radiolucent areas (Fig 4).

CASE 5

In patient 5, facial swelling noted at age 10 years was diagnosed as cherubism by a colleague. The patient was lost from follow-up. According to the patient, at age 18, resective surgery was performed in the right body of the mandible due to a misdiagnosis of ameloblastoma. At age 39, the
patient had a normal face, and a panoramic radiograph showed only residual mandibular radiolucencies (Fig 5).

CASE 6

Patient 6, the son of patient 5, was diagnosed with cherubism at age 6 years due to cheek enlargement and family history. A panoramic radiograph at age 9 showed multilocular transparencies completely occupying the mandible and maxilla. At age 13, painless bilateral jaw expansion was noted, and a radiograph showed remaining multilocular areas. Minor signs of osseous repair were observed in the mandibular ramus. Three minor surgeries were executed in the following 3 years for biopsy (which confirmed the diagnosis), for extraction of displaced and impacted teeth (upper right second molar and premolar; lower left canine and first and third molars; lower right canine, second premolar, and first and third molars), and in an attempt to provide orthodontically assisted eruption of unerupted upper left central incisor. At age 16, changes in cystic lesions were observed (Fig 6).

CASE 7

Patient 7, a sister of patient 5, exhibited bilateral painless facial expansion at age 8 years. At age 11, the facial growth stopped, and corrective surgery was done in the left body of the mandible. No further enlargement was observed until age 15, when residual jaw expansion began to regress. At age 40, the patient’s face was normal. A radiograph revealed typical radiopacity of bone structures in the maxilla. In the mandible, a radiograph showed residual multilocular transparencies in the coronoid processes and in the mandibular ascending rami, along with some sclerotic areas in the mandibular body (Fig 7).

CASE 8

Patient 8, a daughter of patient 7, was diagnosed with cherubism at age 5, based on painless facial enlargement and family history. A lateral extraoral radiograph showed multilocular radiolucencies in the jaws. Enlargement of the jaws persisted until age 9. Histological examination of an incisional biopsy specimen confirmed the diagnosis. At age 13, the patient demonstrated noticeable bilateral swelling of the jaws, and a radiograph showed persistent complete involvement of the jaws by the lesions, with a prominence in the right mandibular body. Four years later, involvement of the mandible and maxilla remained considerable, and...
corrective surgery was executed in the right angle and body of the mandible. Three years after the operation, diminished right mandibular swelling was seen (Fig 8).

**Discussion**

Several family studies from different countries have postulated that cherubism is a hereditary condition, transmitted in an autosomal dominant pattern. A molecular pathogenesis of cherubism has been proposed: SH3BP2 gene mutations cause dysregulation of the Msx-1 gene, which is involved in regulating mesenchymal interaction in craniofacial morphogenesis. In an affected individual, increased bone activity occurs between age 2.5 and 10 to 12 years, due to up-regulation of Msx-1. Dysfunction of Msx-1 stops at the end of molar development, leading to remineralization of lesions.

Isolated single cases of cherubism have been reported in the literature, most of them based on historic reports of the affected family members, who had not noticed any facial alteration in other relatives. It is difficult to assess whether these cases represent spontaneous mutations, because of cherubism’s variable expression and its tendency to resolve. In addition, the autosomal recessive pattern was suggested to occur in selected families. In our nonfamilial cases, beyond the historic data provided by the patients’ parents, we observed close relatives for cherubic features; however, we cannot affirm that these cases are examples of pure mutations.

In general, cherubism does not affect other parts of the skeleton or osseous metabolism; the bone markers phosphorous, serum calcium, and alkaline phos-
phatase are usually at normal levels with respect to age.2,5,10,12,13,17,18 Significant ocular disturbances, such as proptosis, superior globe displacement, and visual loss, may occur,19 although these were not observed in our cases. Patients 1, 6, and 8 showed exposure of the inferior part of the sclerae, confirming that this characteristic is occasional.4,7-9 Some studies have suggested that cherubism may be associated with other genetic diseases, such as Noonan’s syndrome20,21 and Ramon syndrome.22,23 An association with gingival fibromatosis also has been postulated.24 Aggressive manifestations of cherubism have been reported,6,12,25 including 1 extreme case that progressed rapidly, resulting in death due to gastrointestinal and pulmonary infections.26

In cherubism, the initial facial alteration becomes apparent in the first years of life.1-5,7-11,13 We cannot precisely affirm when facial swelling was first noticed in all of our patients, because they were first examined at different ages, ranging from 4 to 15 years. In the older patients, signs of cherubism likely were present well before the patients came to us.

The clinical aspects and disease course observed in our patients were similar to those in previous studies.1,5,7,11,13 We cannot precisely affirm when facial swelling was first noticed in all of our patients, because they were first examined at different ages, ranging from 4 to 15 years. In the older patients, signs of cherubism likely were present well before the patients came to us.

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**Table 1. Patients’ Gender, Age at Diagnosis, Type of Intervention, and Follow-Up Period**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Classification</th>
<th>Intervention</th>
<th>Follow-Up (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Fig 1)</td>
<td>M</td>
<td>6</td>
<td>Grade 3</td>
<td>Biopsy and impacted teeth removal</td>
<td>19</td>
</tr>
<tr>
<td>2 (Fig 2)</td>
<td>F</td>
<td>15</td>
<td>Grade 1</td>
<td>Biopsy</td>
<td>5</td>
</tr>
<tr>
<td>3 (Fig 3)</td>
<td>M</td>
<td>6</td>
<td>Grade 3</td>
<td>Biopsy and impacted teeth removal</td>
<td>17</td>
</tr>
<tr>
<td>4 (Fig 4)</td>
<td>M</td>
<td>4</td>
<td>Grade 2</td>
<td>Biopsy, impacted teeth removal, and minor corrective surgery in the right body of the mandible</td>
<td>16</td>
</tr>
<tr>
<td>5 (Fig 5)</td>
<td>F</td>
<td>10</td>
<td>Grade 3</td>
<td>Biopsy, impacted teeth removal, and resective surgery in the right body of the mandible</td>
<td>29</td>
</tr>
<tr>
<td>6 (Fig 6)</td>
<td>M</td>
<td>6</td>
<td>Grade 3</td>
<td>Biopsy and impacted teeth removal</td>
<td>10</td>
</tr>
<tr>
<td>7 (Fig 7)</td>
<td>F</td>
<td>8</td>
<td>Grade 3</td>
<td>Biopsy, impacted teeth removal, and corrective surgery in the right body of the mandible</td>
<td>32</td>
</tr>
<tr>
<td>8 (Fig 8)</td>
<td>F</td>
<td>4</td>
<td>Grade 3</td>
<td>Biopsy, impacted teeth removal, and corrective surgery in the right angle of the mandible</td>
<td>16</td>
</tr>
</tbody>
</table>


life, and the face alteration disappeared. This course was observed in all patients except patient 8, who at age 20 still manifested clinicoradiographic features of cherubism. The remission of facial bone enlargement seemed to occur later in the maxilla than in the mandible. Radiographic follow-up showed that multilocular radiolucent areas gradually filled in with osseous structure, sometimes within a short period, as seen in patient 2. Sclerotic areas replaced radiolucent multilocular regions even in the 2 familial cases (patients 5 and 7) in the fifth decade of life, in contrast to the conclusion of another study7 asserting that sclerotic areas have been described only in single cases. The histological appearance was similar to that of brown tumor of hyperparathyroidism, giant cell tumor, and central and peripheral giant cell granuloma, consisting of proliferating vascular fibrous connective tissue with abundant multinucleated giant cells. In adult patients, this tissue showed an increase of bone matrix in fibrous stroma.

Seward and Hankey3 suggested a grading system for cherubism that has been since modified by other authors.6,7,9 According to the classical grading system based on the radiographic location of the lesions, 6 of our 8 patients were grade 3 (both jaws diffusely affected); 1 patient (patient 2) was grade 1, with mandibular but no maxillary involvement at the time of examination; and 1 patient (patient 4) was grade 2, with full mandibular involvement and maxillary involvement only in the tuberosities. Remission of signs of cherubism occurs most rapidly in grade 1 (lesions restricted to posterior regions of the mandible).7 We found that the lesions regressed progressively even in the patients with grade 3, both those who underwent surgery and those who did not, and in adulthood these patients had normal or close to normal facial and radiographic aspects, sometimes with minor residual marks.
Conventional surgical procedures for biopsy or impacted teeth removal were used in all cases (Table 1). In the 4 patients who exhibited significant increase in the jaws, corrective osteoplasty was performed, producing marked reduction of facial deformities with no recurrence. Consider the case of patient 5, who was lost to follow-up and underwent a hemimandibulectomy due to an incorrect diagnosis of ameloblastoma but even so exhibited remission of cherubic characteristics in adulthood. Traditionally, the general approach to treating cherubism was to follow patients, perform biopsies, remove ectopic and impacted teeth, and provide surgical correction when appropriate. Liposuction has been proposed to reduce the mass of the lesion in particular cases. When discussing treatment, we must consider the psychological problems associated with an unattractive cherubic appearance in young patients. The 4 patients who underwent surgery for osseous contouring had deformities caused by large bone expansion, mainly in the mandible.

Findings showed that the multinucleated cells in cherubism lesions were osteoclasts from a structural and biochemical standpoint, raising the possibility of treatment with calcitonin, reducing the need for surgery in cases with significant expansion. Calcitonin has been used successfully for treatment of giant cell granuloma and it has reduced bone absorption in vitro. Based on the genetic mutations related to the disease, gene therapy is expected to play a role in future treatment.

References