Cherubism: A Clinical, Radiographic, and Histopathologic Comparison of 7 Cases

Miguel Peñarrocha, DDS, PhD,* Jaime Bonet, DDS, PhD,† Juan Manuel Mínguez, DDS, PhD,‡ José Vicente Bagán, DDS, PhD,§ Francisco Vera, DDS, PhD,¶ and Ignacio Mínguez, DDS, PhD

Purpose: Cherubism is an uncommon fibro-osseous disorder of the jaws that presents with varying degrees of involvement and a tendency toward spontaneous remission. Lesions are characterized by replacement of bone with fibrovascular tissue containing abundant multinucleated giant cells. We attempted to study the relationships among the degree of cherubism, the radiographic extent of the jaw lesions, the histopathologic findings, and the clinical course of 7 patients.

Patients and Methods: In 7 patients diagnosed with cherubism, we evaluated the degree of fibrosis and perivascular cuffing, the presence of focal hemosiderin deposits, and giant multinucleated cell density (absent, few, moderate, or severe). Clinical course and progression were also assessed using a 4-point scale (improvement, no changes, modest progression, and marked progression).

Results: The patients were followed up for an average of 8.5 years. Two patients exhibited clinical and radiographic improvement, while 3 showed no changes, and 2 progressed despite surgical treatment in 1 of them.

Conclusion: The course of cherubism in 1 of our patients may represent evidence of an association between the presence of abundant multinucleated giant cells, an increased extent of the lesions, and a more aggressive behavior of the disease.

© 2006 American Association of Oral and Maxillofacial Surgeons

Cherubism is a childhood disease that exhibits an autosomal dominant hereditary pattern with variable expression. The penetrance can be up to 100% in males and up to 70% in females. Some sporadic cases have been described with no apparent familial history. Mutation of the gene encoding for fibroblast growth factor receptor III (FGF-RIII) has also been found in some cases of cherubism. The condition constitutes an uncommon, benign fibro-osseous lesion that results in progressive, painless, symmetrical expansion of the jaws with a predilection for the mandible, resulting in a cherubic facial appearance. Affected children appear normal at birth. Bilateral swelling tends to occur between 2 and 4 years of age. An increase in jaw size is noted, with maximum enlargement occurring within 2 years of onset in most cases. By age 7, the lesions become static or progress relatively slowly until puberty. During the late teens, the disease may undergo spontaneous involution, with regression of the maxillary lesions tending to occur earlier than those in the mandible. Facial appearance may return to almost normal by the fourth or fifth decade. However, some patients seek surgical recontouring of their residual deformity during their twenties.
Arnott proposed a grading system for cherubism, according to lesion location and the degree of expansion. Accordingly, grade 1 cases are limited to both ascending rami of the mandible; grade 2 cases involve the maxillary tuberosities and mandibular ascending rami (resulting in congenital absence of the third and occasionally the second molars); and grade 3 cases correspond to massive involvement of both jaws except the coronoid processes and condyles, resulting in considerable facial disfigurement. Ramon and Engelberg added grade 4 in application to cases where all of the classical features of the disorder exceeding grade 3 are present. The grade may change depending on findings at follow-up examination.

The lesions of cherubism are not distinctive histologically and are difficult to differentiate from other giant cell-containing fibro-osseous disorders. As a result, the diagnosis also depends on the clinical findings. Microscopy shows a highly vascular fibrous stroma with unevenly distributed osteoclastic-like multinucleated giant cells that tend to cluster near hemorrhagic foci and deposits of hemosiderin. Vascular channels are well formed and lined by large endothelial cells. The presence of eosinophilic, collagenous material around small capillaries is of value in the diagnosis of cherubism. Mature lesions exhibit more dense fibrous tissue, while the number of multinucleated giant cells decreases.

We studied 7 cases of cherubism in which we attempted to relate the clinical degree of the disorder, and the radiographic and histopathologic characteristics of the lesions to the course of the disease.

**Patients and Methods**

This retrospective study involved 9 patients treated over a 15-year period and diagnosed with cherubism at the Children’s Maxillofacial Surgery Department in conjunction with the Department of Oral Medicine and Surgery. We reviewed all patients diagnosed with cherubism and presenting a minimum follow-up of 1 year. Two patients were excluded from the study because of a lack of sufficient follow-up. Patients were classified according to the grading system developed by Arnott.

A quantitative assessment of the histopathologic parameters was carried out (all histologic studies were made by F.V., based on a 4-point scale: absent, few, moderate, or marked): giant multinucleated cell density, interstitial hemorrhage, inflammatory activity, and the density of fibrosis. Three subtypes were considered: I, predominance of multinuclear cells; II, predominance of inflammatory activity; and III, predominance of fibrosis (Table 1), characterized as follows:

<table>
<thead>
<tr>
<th>Subtype I</th>
<th>Subtype II</th>
<th>Subtype III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giant cells</td>
<td>++/++</td>
<td>+/++</td>
</tr>
<tr>
<td>Interstitial hemorrhage</td>
<td>+/++</td>
<td>++/+</td>
</tr>
<tr>
<td>Inflammatory component</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Subtype I: Great abundance of large giant cells totally occupying the lesion surface. High cell density: 160 to 180 giant cells per ×200 field, intermingling with small areas of interstitial microhemorrhage. Subtype II: Lesser presence of giant cells, which represent only part of the lesion. Abundant active inflammatory component, with extensive vascularization, associated to giant cells of variable size. Low cell density: 10 to 15 giant cells per ×200 field, intermingling with inflammatory and interstitial microhemorrhagic areas. Subtype III: Abundant fibrosis with a reduced presence of giant cells. The inflammatory component is scarce, although there may also be interstitial microhemorrhagic areas. Low cell density: 5 to 8 giant cells per ×200 field, associated to an extensive and often dense or highly cellular fibrotic component.

Patient evolution was also assessed by a 4-point scale: 1) improvement (lesion reduction during the process); 2) no change (no significant lesion changes); 3) progression (slow and moderate lesion growth); and 4) marked progression (rapid and constant lesion growth, and/or alterations appearing in other systems).

**Results**

The 7 patients (4 girls, 3 boys) were between 2 and 7 years of age at the onset of clinical evidence of disease, and presented a mean age of 8.2 years at the time of the diagnosis (Table 2). Five of the cases described were nonfamilial, and cases 4 and 5 were siblings; none of the remaining family members of these 2 patients were affected. In all cases, clinical examination revealed enlargement of the mandibular angle. Maximum growth was recorded between 4 and 5 and 7 and 8 years of age. Five patients (cases 2, 3, 4, 5, and 7) presented bilateral midfacial swelling caused by involvement of the upper jaw. In case 3, in which the involvement was greater, there was thickening of the maxillary alveolar processes, with partial obliteration of the palatal vault (Fig 1). In the permanent dentition, dental crowd-
FIGURE 1. Case 3. A, Facial appearance of the patient showing symmetrical swelling of the mandibular angles. B, Intraoral image showing thickening of the alveolar processes, with partial obliteration of the palatal vault. C, Panoramic radiograph showing bilateral, sharply defined, multilocular maxillary and mandibular radiotransparencies.

*Two siblings (case nos. 4 and 5).

ing and/or malpositioning was observed in all patients except 1 (case 6).

Radiographically, all patients exhibited symmetrical multilocular transparencies in the mandibular rami and angles. Two patients (cases 2 and 7) also showed involvement of the coronoid processes, and case 7 moreover presented involvement of the mandibular symphysis. The condyles were unaffected in all cases. The upper jaw was affected bilaterally in 5 patients (cases 2, 3, 4, 5, and 7), and in case 7 there was additional partial bilateral infiltration of the maxillary sinuses. In all cases the x-rays revealed retained permanent teeth that were displaced from their usual position, and absent third molars (with occasional absence of second molars as well). Maxillofacial computed tomography in 4 patients (cases 2, 4, 5, and 7) revealed these bone alterations in greater detail (Fig 2). Case 2 showed mastoid bone involvement presumably resulting from occupation of these structures by dysplastic soft tissues.

In all patients, the histopathology showed substitution of bone by proliferating fibrous tissue exhibiting mature fibroblasts embedded within an intercellular matrix, with a number of unevenly distributed multinucleated giant cells. Eosinophilic vascular cuffing was seen in all cases, as well as focal hemosiderin deposits. Assessment of the histopathologic parameters is reported in Table 1 (Fig 3).

Of the 6 patients in whom surgical intervention was limited to the obtention of a biopsy, cases 1 and 3 were found to improve clinically and radiologically, with a follow-up duration of 9 and 8 years, respectively. Cases 2, 5, and 6 remained practically without change (up to ages 14, 10, and 12 years, respectively), while case 4 showed progression between 5 to 7 years of age, with a clear increase in bilateral midfacial swelling.

In case 7, at the age of 6 years, there was a significant deformity of the mandibular rami, and bone remodeling was carried out. Posteriorly, the lesions suffered marked progression. This girl progressively lost all of her permanent teeth, with exfoliation of the resorbed roots. Serum calcium and phosphorous levels were normal. Starting at the age of 12, several wine-red soft tissue masses developed in the mandible (Fig 2G); these lesions were ulcerated as a result of chewing trauma with the upper jaw, and were excised on a number of occasions to facilitate chewing. Biopsies of these lesions always showed similar features, with abundant multinucleated giant cells. Nonetheless, the control of disease progression proved elusive, and the lesions continued to grow.

Discussion

Radiographically, cherubism is characterized by bilateral, multilocular, radiolucent areas within the jawbones. The lesions usually appear around the mandibular angle and spread to the ascending rami and body of the lower jaw. The maxillary processes may also be involved, and lesions can spread to other facial bones. The extent of the lesions varies from minor to massive involvement of both jaws. In our study, plain x-rays and computed tomography images demonstrated lesions confined to the jaws in 6 cases, and with additional facial bone involvement in case 2 (mastoid bone). According to the grading system developed by Arnott, our cases would be classified as grade 1 (2 cases), grade 2 (3 cases), grade 3 (1 case), and grade 4 (1 case).

In general, cherubism does not have a poor prognosis. It has been noted that the condition does not progress beyond puberty. As the patient grows to adulthood, the jawbone lesions tend to resolve, and a progressively more normal jaw configuration is noted. Maxillary lesions are the first to regress, while mandibular lesions are often still active at age 20. Our patients were followed up for an average of 8.7 years after the onset of clinical manifestations. Two cases improved spontaneously, 3 remained stable, and cases 4 and 7 worsened. In case 4, worsening was noted from 4 to 8 years (a critical age when the lesions complete their evolution), while in case 7 progression was attributed to the particularly aggressive nature of the disease despite surgical treatment.

Because cherubism is considered to be a self-limiting condition that improves over time, treatment depends on the individual patient’s functional and esthetic needs. Most investigators prefer to wait until the end of puberty before performing surgery. Early surgical intervention is contraindicated because it appears to predispose to recurrences. Surgery is only indicated in cases characterized by impaired speech, chewing or swallowing difficulties, or with the presence of major deformities that may cause psychological problems for the patient. Clinical management and surgical treatment decisions are dependent upon individual evaluation in accordance with the degree of disease involvement. Surgical treatment appears to be unnecessary for grade 1 and 2 cases in the absence of secondary disturbances. Excision of tissue through enucleation or curettage appears to be necessary in more aggressive cases (grade 3), to reduce maxillofacial deformity after puberty and to ensure a successful outcome without the risk of progression requiring additional resection.

The course of the disease was as expected in 6 of our 7 patients, with worsening between 4 and 7 years of age, followed by clinical and radiographic evidence.
FIGURE 2. Case 7. A, Facial appearance. Note the marked bilateral facial swellings. B, Panoramic radiograph showing bilateral, sharply defined, multilocular radiotransparencies in both jaws (age 7). C, Patient at 11 years of age. Note the extensive loss of teeth and root resorption in the remaining teeth. D, The same patient, at 12 years of age, showing lesion progression. E, At age 14, the patient lost all remaining teeth; bilateral radiotransparencies persist. F, Coronal computed axial tomography view of the jaws, showing symmetrical bilateral involvement of the mandibular rami. Note the maxillary expansion and lytic changes. G, Ulcerated soft tissue mass of the mandibular alveolar process (patient at age 14).

of improvement. The course was different in case 7, however, with worsening from 4 years of age until control was achieved at age 14. This was the only case requiring surgical management because the patient already had significant deformities including intraoral exophytic lesions.

Long-term studies have shown the convenience and effectiveness of surgery in cherubism. Conservative approaches to management are advisable.\textsuperscript{14} Among our patients, surgery was only performed in case 7, to correct bothersome lesions and facial deformity. Curettage with remodeling of the cortical layer was carried out in the same procedure because most investigators regard this as the best approach.\textsuperscript{15,16} Following surgery in a 5-year-old boy, Zachariades et al\textsuperscript{12} used homogeneous bone grafts to replace the diseased tissue to avoid pathologic fracture of the mandible. Since then, these authors observed gradual involvement of other sites in the jaws, with the displacement of teeth and tooth germs. Koury et al\textsuperscript{17} described a case in which the usual course of the lesions changed dramatically during treatment, with unilateral growth associated with vascular proliferation after surgical recontouring. The most active areas show a vascular, loose stroma and more numerous giant cells, whereas slower-progressing lesions show increased collagen, fibrosis, and a decreased number of giant cells. These authors suggested that it is very possible that surgery caused such vascular transformation.

In some cases of cherubism, giant cells may be so abundant that the histologic image alone can pose genuine differential diagnostic difficulties versus central giant cell granuloma or brown tumor of hyperparathyroidism. Giant cell granuloma can be excluded on clinical grounds, because it is not a bilateral condition, is not inherited, does not regress in adulthood, and has a predilection for the anterior mandible. In turn, bone changes in hyperparathyroidism rarely cause unilateral jaw lesions, but do produce abnormal serum calcium and phosphorus levels.\textsuperscript{18-20} In cherubism, eosinophilic collagen cuffing can be ob-
served around small blood vessels. Such perivascular hyalinosis is considered pathognomonic of cherubism. This finding was evident in the tissue samples of all of our patients, although with varying frequency and intensity.

The tissue alterations were characteristic and were identified in all cases. Multinucleated giant cells formed small disperse agglomerations or were distributed around capillaries, and were particularly abundant in case 7, which showed the worst clinical course. In this case there were abundant multinucleated giant cells noted in the first biopsy. Recontouring surgery was performed several times. It would appear that in this case the condition was intrinsically aggressive, and did not correspond to aggressive transformation induced by surgery, as in the case reported by Koury et al.

In one of our patients, there appeared to be an association between the presence of abundant multinucleated giant cells, extensive lesion size, and more aggressive disease behavior. Whether the abundance and density of giant multinucleated cells is related to increased aggressiveness of the condition remains to be clarified by future studies.

References