Clinical Paper
Congenital Craniofacial Anomalies

Clinicopathologic study of 24 cases of cherubism

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Abstract. The authors reviewed 24 cases of familial or nonfamilial cherubism. The age at onset was between 6 and 10 years. It was characterized by bilateral painless swelling of jaws and eyes-to-heaven appearance was visible when the maxillae were affected as well. Radiographs showed well-defined multilocular radiolucencies and with age, thick sclerotic borders were visible. A malocclusive and abnormal dentition, worse in the mandible can be seen. Histopathologically, numerous randomly distributed multinucleated giant cells and vascular spaces within a fibrous connective tissue stroma with or without eosinophilic collagen perivascular cuffing were apparent. Multinucleated giant cells were positive for osteoclastic specific markers, tartrate-resistant acid phosphatase and human $\alpha V \beta 3$ integrin, 23C6. Results after follow-up were available for 14 cases. Of these, no treatment was carried out in five cases, cherubism resolved (three cases) or grew slowly (two cases); curettage or surgical contouring was performed in seven cases, during the rapid growth of the lesions. This not only gave good immediate results, but also arrested active growth of remnant cherubic lesions and even stimulated bone regeneration. Segmental mandibulectomy followed by reconstruction was performed in two cases with extensive lesion and the risk of pathologic fracture of the mandible, and excellent results were obtained.

Cherubism was first described by JONES in 1933[9] as 'familial multilocular cystic disease of the jaws'. He later coined the descriptive term 'cherubism' when he likened the classical characteristics of full round cheeks and upward cast of the eyes to the angelic look of the cherubs immortalized by Renaissance art. Cherubism is characterized by bilateral expansion of the mandible and/or the maxilla that becomes noticeable within the first several years of life, becomes progressively pronounced until puberty, with gradual involution by middle age. The radiographic appearance is unique because of its diffuse, bilateral, multilocular nature. Histologically, the lesions contain numerous multinucleated giant cells scattered throughout a fibrous connective tissue stroma.

In China, the occurrence of cherubism has been reported in several cases with and without familial history[31,33–35]. The aim of this study is to investigate:

(1) The clinical and radiographic features, histopathologic appearance, biochemical markers, and the diagnosis criteria that differentiate it from other giant cell lesions in the jaws.
(2) The relationship between the natural course of the disease, its severity (application of classification systems), and possible treatment modalities.
(3) The results of surgical treatments with long-term follow-up and treatment recommendations.

Materials and methods

The patients consisted of 24 patients (17 were referred to our hospital, the remaining 7 were from other hospitals in China[31,34,35]). Of those, 19 fulfilled the following objective criteria of cherubism: (1) clinically, a painless swelling of the jaw, combined with (2) radiographic findings of multilocular (rarely unilocular) radiolucencies, often very extensive, with a few irregular bony septa, and (3) pathologic bone cavities filled in by tissue, simi-

lar to the gross and microscopic structure of a giant cell granuloma (in patients <20 years of age) or fibrous tissue (in patients >20 years of age) with or without eosinophilic collagen perivascular cuffing. In the other five patients no clinically detectable features were found and no histopathologic examination was performed, however the diagnosis of cherubism was verified by radiographic examinations and a positive family history.

Routine clinical examination was performed in all of the patients and included (1) the facial appearance, (2) the shape of the buccal and lingual bone surfaces of the jaws, normal or expansive, estimated by a comparative clinical palpation of the entire bone surface of the jaws and the remaining facial bones, (3) the dental state, and (4) the enlargement of submandibular lymph nodes.

Conventional radiographic methods including panoramic radiograph and WATER's view for lesions in the maxillary sinus, were applied. The following was observed:

(1) Loci and areas where there are lesions: Involvement of mandibular ascending rami with or without maxillary tuberosities or massive involvement of the whole maxilla and mandible with or without condyles.
(2) Shape and border of the lesions: Normal or the presence of multilocular radiolucencies; well-defined or unclear border, which is sclerotic or normal.
(3) Bony cortex: Expansion, thinness, perforation or disruption.
(4) The dental state: Normal or missing teeth, displacement, malformation, or root resorption.

All radiographs were re-evaluated by a radiologist.

The severity grades of cherubism were used with a supplement (in italics) from the SEWARD & HANKEY[23] system:

Grade I: Involvement of bilateral mandibular molar region and ascending rami, *mandible body or mentis*.
Grade II: Involvement of bilateral maxillary tuberosities as well as the lesion of Grade I, *diffused whole mandible*.
Grade III: Massive involvement of the entire maxilla and mandible except the condyles.
Grade IV: Involvement of both jaws with condyles.

Biochemical analyses, such as serum calcium, serum phosphorus, alkaline phosphatase, and parathyroid hormone were performed in 17 patients referred to our hospital. For those with abnormal serum values, radiographic examination of the skeleton was performed.

Histopathologic examinations were made by incisional biopsy or during routine postoperative procedures in 19 patients; the other five refused this examination because classic clinical features were not detectable. The tissue sections were reviewed by a pathologist.

Histochemical and immunohistochemical characterization of multinucleated giant cells was performed. Using a commercially available kit (Sigma, USA), the sections were deparaffinized and stained for the expression of tartrate-resistant acid phosphatase (TRAP), an osteoclast-associated marker. Using naphthol AS-BI phosphate as a substrate, in the presence or absence of 1.0 mol/L tartrate (37 °C, 20–30 min), the product was reacted with Fast-Garnet GBC salt. The sections were then counterstained with hematoxylin stain. The frozen sections were fixed in pre-cooled acetone solution and stained immunohistochemically using an alkaline phosphatase-based method (SAP Kit, Zymed, USA) with the monoclonal antibody against human αV β3 integrin, 23C6 (Santa Cruz, USA) to determine expression of the vitronectin receptor (VNR), an osteoclast associated antigen. A new fuchsin substrate, AP-Red (Zymed, USA) was used and red staining indicated positive reactivity. The sections were then counterstained with methyl green.

Surgical correction with removal of the main part of the lesional tissue was performed in 13 of the patients; 6 received a minor surgical operation for the purpose of incisional biopsy only. No treatment was carried out in other 5.

In the follow-up study, the clinical and radiographic information was used to estimate the postoperative condition or the progress of this disease.

Results

Clinical findings

Age at onset of cherubism in the 24 patients is given in Table 1. Of those, 14 patients unveiled a positive family history of cherubism (Fig. 1). The pene-
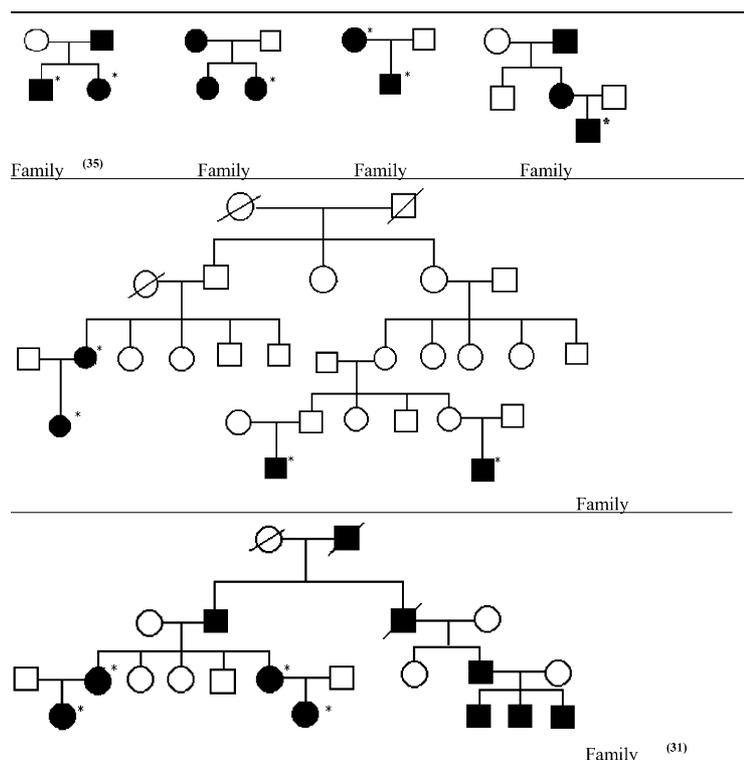
Table 1. Distribution of age at onset in patients with cherubism

Age at onset (year)	No. of cases
0–5	4
6–10	11
11–20	6
21–30	2
>30	1
Total	24

Fig. 1. Distribution of 14 patients (*) with cherubism from six positive families. Circles identify female, squares identify male and filled symbols identify affected individuals.

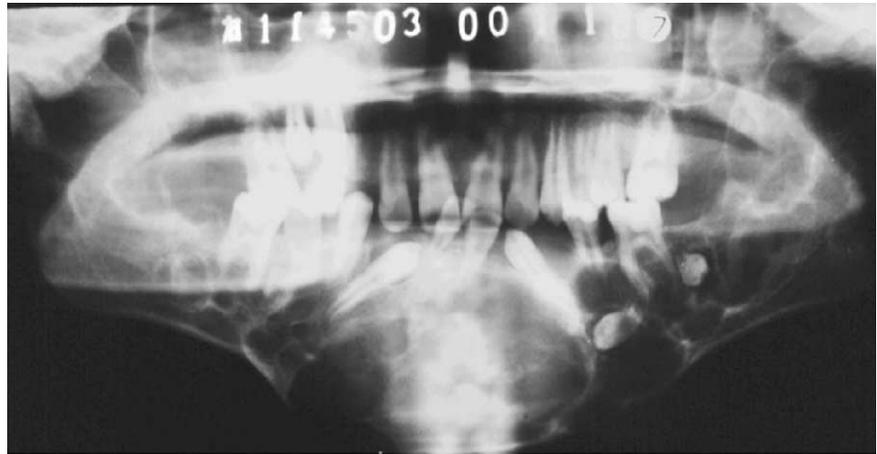Fig. 2. Facial view shows massive enlargement of the mandible.

Fig. 4. Panoramic radiographic shows bilateral lesion characterized by multilocular radiolucencies in the body and rami of the mandible.

trance is 66.7% (14/21) in males compared to 48% (12/25) in females. The symptoms and signs are painless swellings of the jaw in most patients ($n = 20$). Plump face was apparent in 19 patients (Fig. 2), and the sclera below the pupils became exposed in only three severe cases, giving the classic 'eye-to-heaven' appearance. Two patients were only mandibular protrusion.

The jaw lesions were firm and nontender on palpation with swelling of the alveolar ridges (Fig. 3). Ten patients ranging in age from 9 to 20 years had painless enlarged submandibular lymph nodes. No clinically detectable features were found in four patients.

Radiographic findings

Nineteen patients had only mandible involvement, of those, 14 were in the bilateral angles of the mandible, ascending rami and also a considerable part of the body of the mandible; five were in the entire mandible except for the condyles. Four patients were affected in the maxillae as well, of those, one was in infraorbital region and the other three were in the maxillary tuberosities. Massive lesion in both jaws involving the condyles may be seen in one patient.

Multilocular radiolucencies in the lesion areas were the typical feature with well-defined edges or sclerotic borders (Fig. 4). New bone formation in the radiolucent areas was shown in patients in their 20s. Sclerotic thickening but no expansion of bony cortex was observed in patients over 30 years of age (Fig. 5). The dental state in the lesion, such as displacement ($n = 24$), uneruption ($n = 8$), missing teeth ($n = 12$), or root resorption ($n = 6$), was observed.

Biochemical findings

Three of these patients (9-, 10-, and 12-year-old boys) showed abnormal serum phosphorus values, 1.58, 1.76, and 1.83 mmol/L, respectively (normal range 0.81–1.46 mmol/L), as well as abnormal alkaline phosphatase values, 435 and 492 U/L, respectively, for the 9- and 12-year-old boys (normal range 20–390 U/L). However, radiographic examination of the remaining skeleton showed no further involvement of other parts of the skeleton in these three boys.

Histopathological findings

In cherubism, normal bone is partly replaced by pathologic tissue. Under the microscope, it contains numerous randomly distributed multinucleated giant cells and vascular spaces within a fibrous connective tissue stroma. An increase in osteoid and newly formed bone matrix was found in the peripheral region of the fibrotic stroma in patients above the age of 20 years (Fig. 6). An eosinophilic perivascular cuffing was seen in 10 of the 20 patients who had this examination performed (Fig. 7). The multinucleated giant
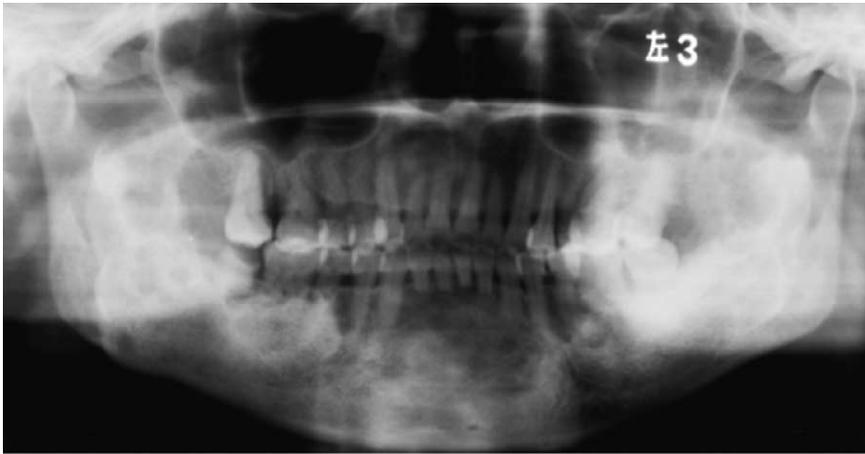

Fig. 3. Intraoral view shows swelling of the alveolar ridges.

Fig. 5. Panoramic radiograph shows multilocular rarefactions replaced by irregular patchy sclerosis, giving a ground-glass appearance.

cells were positive for tartrate resistant acid phosphatase (Fig. 8) and expressed the vitronectin receptor.

Surgical interventions

Surgical interventions were performed in 19 patients and the results after follow-up were available for 11 patients (Table 2). Of these, 10 surgical procedures provoked no active growth of the lesional tissue. The remaining case, a 26-year-old female patient with cherubism Grade IV (i.e., an extensive cherubic lesion in both jaws involving the mandibular condyles) had experienced swelling of the jaws for 17 years. Surgical intervention (the type was unknown) had been performed eight times in other hospitals, but failed to arrest active growth of remnant cherubic lesions. When the patient was referred to our hospital, partial resection and osteoplasty was performed in the mandible, the following year in the maxillae, and osteoplasty in the mandiblar angle region the third year. All surgical treatments were successful without any complications after surgery or at later follow-ups.

Discussion

Cherubism is a rare benign bone disease with autosomal dominant inheritance. It appears to have 100% penetrance in males but only 50–70% penetrance in females[17]. However the penetrance is lower in this series (male, 66.7%; female, 48%) and 10 of the present patients are nonfamilial as has been reported in the literature[7,8]. Are these true sporadic cases of cherubism or only apparently sporadic due to some *de novo* genetic mutations, incomplete penetrance, or an inadequate family history? This question is worthy of further research.

The symptoms and signs of cherubism depend on the severity of the condition, and range from no clinically or radiologically detectable features to grotesquely deforming mandibular and maxillary overgrowth with respiratory embarrassment and impaired vision and hearing. The patients in this study had either symmetrical swellings in the mandible or mandibular protrusion only, and in three severe cases, exhibited the 'eye-to-heaven' appearance described by JONES[9] with diffuse maxillary involvement. While the swelling may be unilateral in some cases[20].

Widening of the alveolar ridges is common. With maxillary involvement, the alveolar widening may result in a narrow V-shaped palate, which sometimes causes backward displacement of the tongue. In very severe cases, the palatal vault may be obliterated, causing dysarthria, dysphagia and dyspnoea. However, this was not observed in any of the 24 patients in this study. Intraoral examination also revealed malocclusive and abnormal dentition, worse in the mandible. Abnormal dentition takes the form of premature loss of deciduous teeth and widely spaced, displaced, unerupted, or absent permanent teeth.

Painless enlargement of the submandibular lymph nodes frequently occurred in children with cherubism[11]. This was observed in 10 of our patients. It is probably a reactive hyperplasia and fibrosis which has been confirmed by microscopic examination of lymph node biopsy specimens from cherubic patients[30].

Cherubism is usually an isolated disease in an otherwise mentally and physically normal child. A few case reports indicate that cherubism might be associated with other genetic disorders, such as Noonan-like syndrome or Noonan-like/multiple giant cell lesion syndrome (MIM 163955), a lesion in the humerus, gingival fibromatosis[4], and Ramon syndrome (MIM 266270)[18]. Cherubism has also been described in an individual with fragile-X mental retardation[16] but this requires further research. The disease may occasionally be associated with other
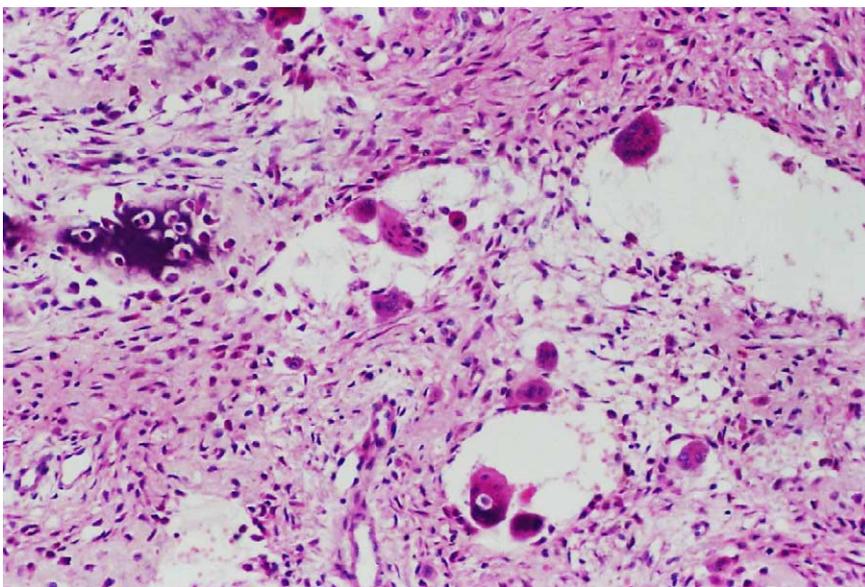

Fig. 6. Multinucleated giant cells are scattered in vascular fibrous stroma. Osteoid and newly formed bone matrix are visible (hematoxylin and eosin stain, original magnification, ×20).
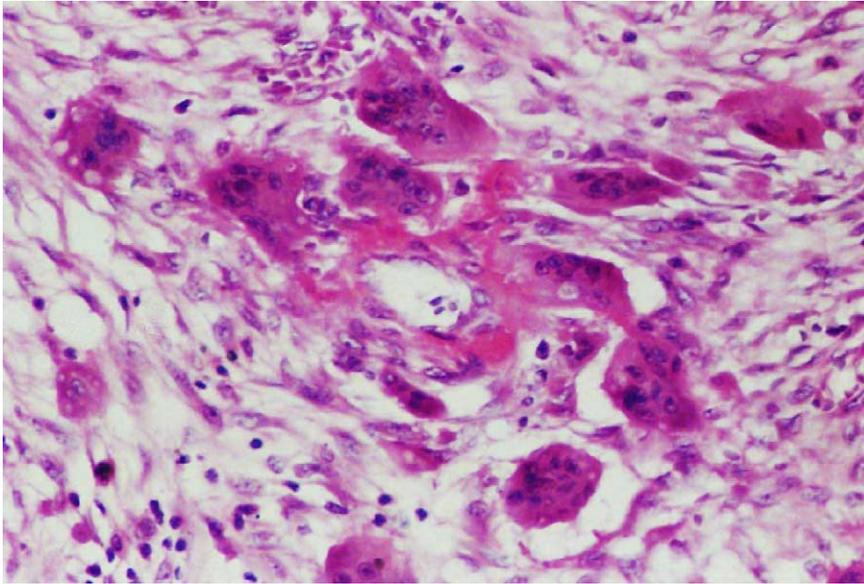
Fig. 7. Multinucleated giant cells are scattered around blood vessels and eosinophilic collagen perivascular cuffing is visible (hematoxylin and eosin stain; original magnification, ×100).

cystic foci, e.g., in the metacarpal bones, carpal bones, humerus, ribs, pelvis, femur and tibia[4,13,32], however, in this series, no case of cherubism involved other parts of the skeleton.

The biochemical markers such as serum calcium, serum phosphorus, alkaline phosphatase and parathyroid hormone are usually within the normal ranges with respect to age, and therefore they might serve to differentiate cherubism from hyperparathyroidism, because in the latter, they are all elevated. However, elevated serum phosphorus, and alkaline phosphatase levels were found in three of the present cases. However, this is expected in persons of young age. KAUGARS et al.[12] postulated that the abnormalities might be due to the patient's difficulty in consuming a normal diet.

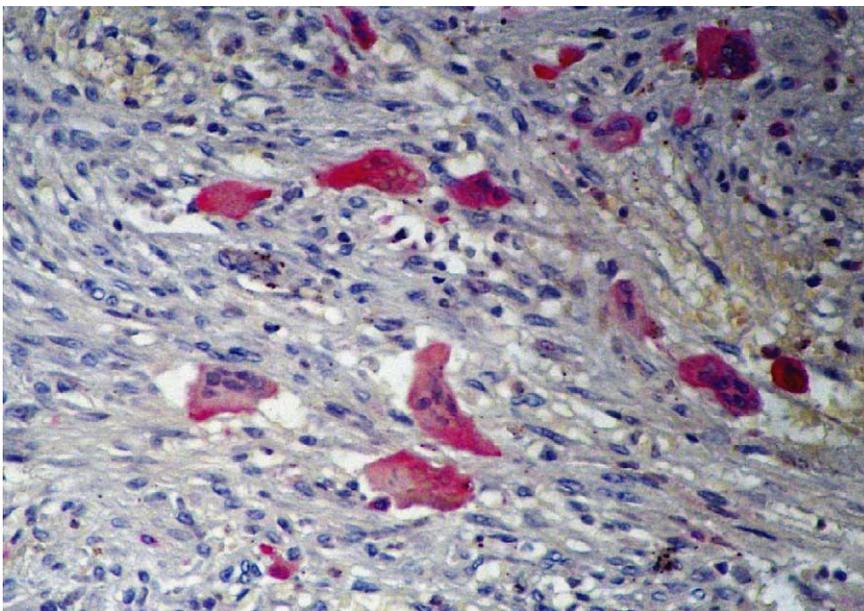Radiologically, cherubism is characterized by the quite specific finding of well-defined multilocular areas of diminished density, often very extensive, with a few irregular bony septa. In adults, the multilocular rarefactions are replaced by irregular patchy sclerosis, with progressive calcification. There is a classical (but non-specific) ground-glass appearance, as a result of the small tightly compressed trabecular pattern.

SEWARD & HANKEY[23] suggested a grading system for cherubism, based on the radiographic location of the lesions in the jaws, which has been used in later studies and has been supplemented with several subdivisions in other studies[1,15,19]. RAMON & ENGELBERG[19] classified a case of cherubism with monstrous deformity of the jaws not restricted to elevation of the orbital floor but penetrating the orbit, as severity Grade IV. The same grade was also used by AYOUB & EL-MOFTY[1] in their case of massive extension involving the mandibular condyles. In our study, involvement of the entire mandible except the condyles was also classified as Grade II, and both jaws involving the condyles as Grade IV, as mentioned in the "Materials and methods" section of this article. All the classifications above are based on the extent at the time of examination. The grade often increases on follow-up examination. MOTAMEDI[15] proposed a new grading system that addresses both the involvement and aggression of the disease but it has not been widely accepted.

The clinical and radiologic criteria suggested by CHUONG et al.[2] for classifying central giant cell granulomas into aggressive and nonaggressive types, are also valid for cherubism. It is clinically justified by the additional phase of rapid growth, the huge deformity of the mandibular body, and especially the bilateral posterolaterosuperior extension of maxillary lesions, with penetration into the retrobulbar areas of orbital cavities. Radiographically, it is justified by the perforation and disruption of wide areas of the bony cortex and marked root resorption, which has long been considered to be a more aggressive process[1,5,15,19,28] as was found in some cases presented in our current report. SILVA et al.[24] reported an extreme case of cherubism that behaved in a locally aggressive manner. An 8-year-old boy presented with severe facial swelling. The lesion progressed rapidly and 17 months later the patient died of gastrointestinal and pulmonary infections as a result of aspiration due to the gross deformity of the child.

Histological appearance of the lesions in cherubism which is similar to that of central giant cell granuloma, hyperparathyroidism and giant cell tumor in children and young adults, is not diagnostic.

Fig. 8. Multinucleated giant cells in cherubism are positive for tartrate resistant acid phosphatase (TRAP stain; original magnification, ×100).

Table 2. Types of surgical interventions and results after follow-up in 14 patients with cherubism

Types of surgical intervention	Lesion area	Grade	Age (years)	Follow-up	Recurrence (Y/N)
Curettage	Bilateral mandibular ascending rami and molar regions	I	7	1 year and 2 months	N
Curettage	Bilateral mandibular ascending rami and molar regions	I	9	2 years and 3 months	N
Curettage	Bilateral mandibular ascending rami and molar regions	I	9	10 years and 9 months	N
Curettage	Bilateral mandibular ascending rami and molar regions	I	11	15 years and 4 months	N
Curettage + partial resection	Bilateral mandibular ascending rami and molar regions	I	10	5 months	N
Partial resection + bone graft	Entire mandible except the condyles	II	15	2 years and 8 months	N
Partial resection + bone graft	Bilateral mandibular body	I	12	4 years and 1 months	N
Osteoplasty	Entire mandible except the condyles	II	20	8 months	N
Partial resection + osteoplasty	Both jaws involving the condyles	IV	28	8 months	N
Incisional biopsy only	Bilateral mandibular ascending rami and molar regions	I	9	3 years and 5 months	Slowing growth
Incisional biopsy only	Bilateral mandibular angle regions	I	7	11 years	Quiescence
None	Entire mandible except the condyles	II	20	22 years	Quiescence
None	Bilateral mandibular ascending rami and molar regions	I	34	3 years and 5 months	Quiescence
None	Bilateral mandibular ascending rami and mentis	I	27[31]	4 years	Slowing growth

The histological profile is that of proliferating vascular fibrous connective tissue with abundant multinucleated giant cells that are osteoclasts since they synthesize tartrate resistant acid phosphatase, express the vitronectin receptor, and resorb bone. An increase in osteoid and newly formed bone matrix is found in the peripheral region of the fibrotic stroma in the patient over 20 years of age. Eosinophilic collagen perivascular cuffing is reported by some authors[5,21] as a specific finding of cherubism, but it could only be observed in 10 cases in our series. When this characteristic is absent, distinction from giant cell tumor and giant cell granuloma should be based on clinical and radiological appearances.

The main biologic feature of cherubism is its natural course. This study indicates that the state of normalization is reached faster in patients of Grade I than those of higher grades, in which progression continues but at a reduced rate until the third decade of life. On average, the disease manifests itself between the ages of 6 and 10 years, with initial rapid enlargement of the jaws. After puberty the lesions begin to regress. Jaw remodeling continues through the third decade of life, at the end of which, the clinical abnormality may be subtle.

The treatment of cherubism should be based on the known natural course of the disease and the clinical behavior of the individual case. In some cases it resolves without treatment as was found in our study. However, the frequency of its occurrence is unknown, since most of the recorded cases have been surgically treated before reaching puberty.

Conservative management is appropriate until functional or emotional disturbances demand surgical intervention. Curettage with or without bone grafting is the treatment of choice although it may need to be repeated on several occasions. We suggest curettage of the affected tissue, preserving the teeth as long as possible. We found that curettage or surgical contouring during the rapid growth of the lesions not only gives good immediate results, but also arrests active growth of remnant cherubic lesions and even stimulates bone regeneration as confirmed by DUKART et al.[3], although some authors[22,23] reported cases in which surgery during the rapid growth phase was followed by a severe relapse and a more aggressive course. For patients with extensive lesions and the risk of pathologic fracture of the mandible, segmental mandibulectomy followed by reconstruction with fibula free flap is suggested. Excellent results were obtained using this technique in two patients in our series.

Medical therapy in the form of calcitonin is theoretically appropriate. Calcitonin is recognized as an effective treatment for giant cell granuloma of the jaw[6], but clinical evidence in the literature to endorse its application in cherubism is lacking. Calcitonin has been shown to cause inhibition of bone resorption by multinucleate cells in cherubic tissue *in vitro*[26]. Despite its failure in some cases, further investigation of its efficacy may be warranted, perhaps with improved compliance being achieved by the use of intranasal rather than subcutaneous administration. KABAN et al.[10] reported that antiangiogenic therapy with daily low-dose interferon alpha successfully prevents the recurrence of aggressive giant cell tumors of jaws. Under physiologic conditions interferon alpha contributes to maintenance of normal bone mass by downregulating osteoclast bone resorption[27]. Interferon alpha also inhibits the production of at least one proangiogenic protein basic fibroblast growth factor (bFGF), by human tumor cells[25]. Furthermore, KABAN et al. hypothesized that interferon may stimulate osteoblasts and preosteoblasts and therefore enhance bone formation. Their report provided a new insight for further study of therapy for cherubism.

Recent genetic advances have been made in relation to cherubism with the identification of the gene to SH3BP2[29]. All the mutations identified so far[8,14,29] are located in exon 9 and result in amino acid substitutions within a 6 amino acid sequence from positions 415 to 420. This may represent a specific protein domain which, when disrupted, leads to the cherubism phenotype. This brings us one step closer to the elixir of gene therapy. However, for the moment at least, management of this condition remains in the realm of the specialist surgeon. We recommend that surgical intervention not necessarily be postponed until after puberty.

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