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Clinical and radiological characteristics of a severe form of cherubism: case report

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Cherubism is a rare, inherited condition characterized by fibro-osseous lesions of the maxilla and mandible. It has recently been localized in chromosome 4p16.3. The fullness of the lower half of the face and retraction of the lower lids gives the characteristic "eyes raised to heaven" cherubic appearance. A case report of a 11-year old boy with extensive orbital involvement of cherubism is presented. The patient has orbital manifestations including lower lid retraction, proptosis, diplopia and globe displacement. Taking into account the severity of the disease based on the modified Motamedi grading system, we decided to treat the orbit surgically and to place the patient under a post-surgery weekly follow-up to assess the spontaneous regression of the extra-ocular disease in accordance with the data reported in literature. We maintain that decompressive surgery on the orbit is desirable in severe cases of the disease to avert the risk of irreversible ocular lesions.

KEY WORDS: Cherubism - Orbit - Ophthalmologic surgical procedures.

Cherubism was described for the first time in 1933 by Jones as a "familial multilocular cystic disease of the jaws".[1-10]

It is a benign fibro-osseous dysplasia, characterized by an involvement of the mandible, the maxilla or both. The incidence of cherubism is unknown, but the age of onset is between 2 and 10 years.[2]

Cherubism is a disease transmitted with an autosomal dominant inheritance, with variable penetrance and expressiveness, presenting a penetrance of 100% in males and from 50% to 70% in females.[4] Even so, many sporadic cases are reported in literature.[11-17]

It has been associated, after the mapping of chromosome 4p16, with a mutation of the gene SH3BP2.[18-20] Starting from this discovery, a pathogenetic hypothesis has been formulated: the Gain-of-function mutation (SH3BP2) causes a disregulation of the gene *Msx-1* that is involved in the morphogenetic processes causing the fullness of the face.[2, 5, 8]

Cherubism is characterized by an asymptomatic bilateral expansion of the mandible, maxilla or both.[4] This becomes evident in early infancy and increases progressively until puberty, after which a gradual resolution of the disease is reported at different times in the patient's development.[5]

The uncontrolled growth of the superior maxilla pushes the orbital floor upwards, which leads to a dislocation of the eyeball with a consequent exposure of the lower part of the sclera (scleral show).

All this gives to the patient the upward-looking appearance typical of this disease ("eyes raised to heaven").[13] Based on such characteristics, the term "cherubism" was used for the first time in 1938, because the disease confers to the patients, who present a symmetrical swelling of the cheeks with a rounded face and an upward gaze, an appearance similar to that of the cherubs of Renaissance art (Figure 1).

The dentition is often anomalous and the patients present agenesis, ectopia and dental inclusions, radicular reabsorption and malocclusions. Radiolog-

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Figure 1.—Cherubs - Engel V (Detail from Raphael's Sistine Madonna).

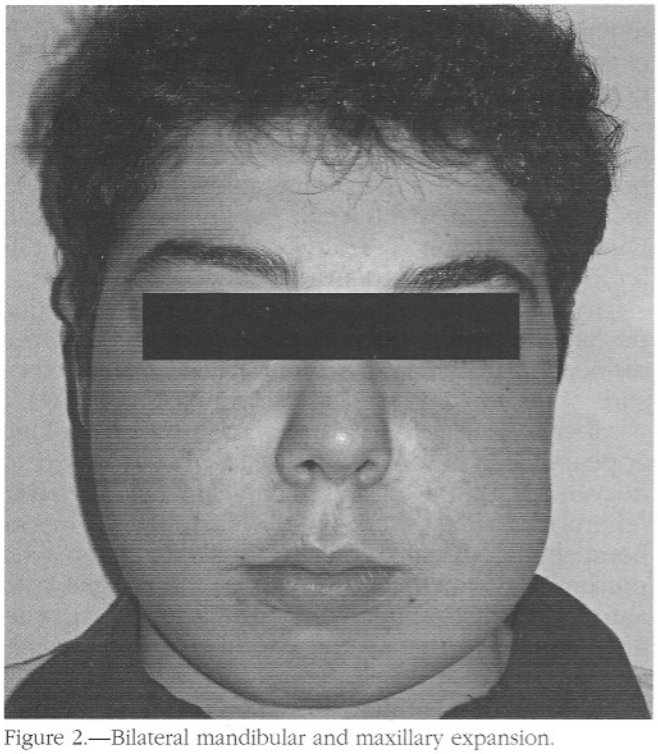

Figure 2.—Bilateral mandibular and maxillary expansion.

Figure 3.—Typical appearance "eyes raised to heaven".

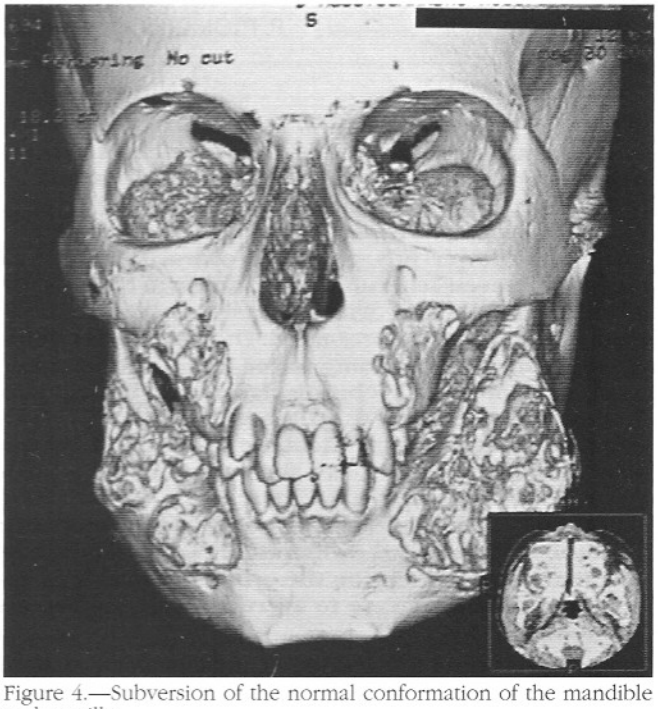

Figure 4.—Subversion of the normal conformation of the mandible and maxilla.

ically, the expansive lesions appear as radiolucent multilocular cysts, that is initially localized at the junction with the mandibular angle and then extend to the horizontal branch and the ramus. Lesions on the superior maxilla can present at the same time. These lesions are often associated with a dislocation of the teeth and dental germs.[5]

A definitive diagnosis is confirmed histologically by the identification of giant multinuclear cells, distributed randomly, associated with the presence of aeosinophilic collagen perivascular cuffin, that could be interpreted as a pathognomonic sign of the disease, immersed in a fibrous connective tissue stroma.[2, 4]

The multinuclear giant cells are positive to osteoclasts specific markers and appear to be pathologi-

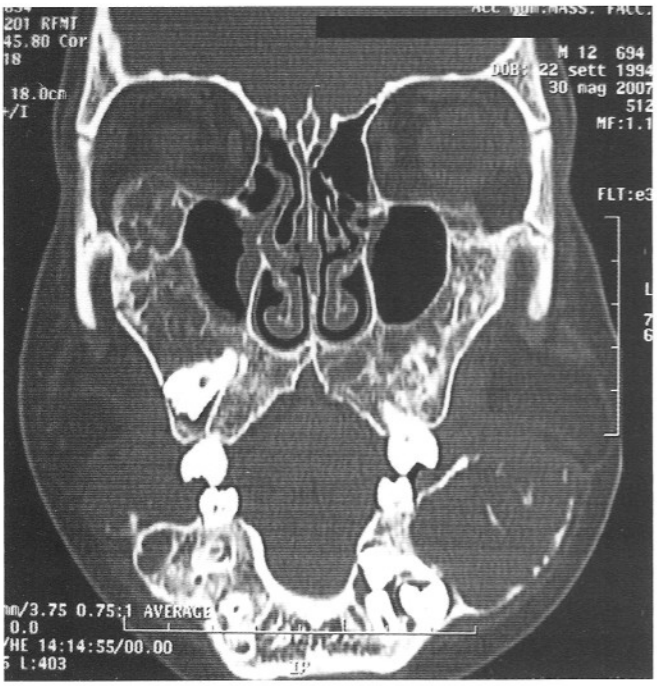

Figure 5.—Significant right orbital floor involvement.

cally activated inside the expanding lesions.[2] These characteristics are similar to those of other osseous pathologies, such as the brown tumour of hyperparathyroidism, giant cell tumour and central and peripheral giant cell granuloma.[5]

The treatment of cherubism is controversial.

The therapies recommended include observation, calcitonin therapy, liposuction, radiotherapy and/or surgery.[2-4, 13]

Many surgeons assume an attitude of "wait and see", limiting surgical intervention to decompression of the orbits or removal of any teeth in an ectopic position. Although some surgeons suggest that surgery corrects the osseous deformities of cherubism, it is rarely recommended and can itself cause the growth of quiescent lesions.[2]

Case report

An 11-year old patient came under our observation in May 2007, after having been treated previously, at the age of 9, in another hospital. On leaving that hospital, he was diagnosed as suffering from a suspected dysplasia of the superior and inferior maxilla.

Familial anamnesis did not bring to light any data concerning the presence of cherubism in other members of his family.

TABLE I.—*Laboratory's exams.*

Exam	Value	Rif. value
Calcium	9.1	8.4-10.2 mg/dL
Inorganic phosphate	5.2	2.7-4.5 mg/dL
Alkaline phosphatase	383	53-128 U/L
Calcitonin*	5.2	Until 80 pg/mL
Osteocalcine*	156.2	60.5-89.5 ng/mL
PTH*	82.5	4.6-33,8 pg/mL

* IRMA method.

Extra-oral clinical examination revealed a bilateral expansion of the mandibular region, oral mucosa and maxilla, more evident on the left side of the face, which conferred to the face of the patient a rounded appearance (Figure 2).

The excessive growth of the right superior maxilla with significant involvement of the homolateral orbital floor resulted in the appearance of a false esophthalmus, with a consequent exposure of the sclerae beneath the eyeballs (scleral show). This gave the young patient the upward looking appearance, typical of cherubism ("eyes raised to heaven") (Figure 3).

The patient reported the presence of diplopia in the upward gaze, caused by the presence of a misalignment of the interpupillary line.

An objective intra-oral examination revealed a dental malocclusion, associated with the absence of some permanent teeth and the persistence of some deciduous teeth, some of which in an ectopic position.

Additionally, it revealed a painless swelling, at the level of the mucosa hanging over the superior and inferior alveolar ridges, caused by an expansion of the underlying osseous tissue.

Orthopantomography revealed radiological signs characteristic of cherubism: the presence of multiple radiolucent multilocular cystic lesions occupying the entire mandibular and maxillary osseous area to the exclusion of the mandibular condyles; deciduous and permanent teeth in osseous inclusion, some of which having erupted but in an ectopic position; and the presence of dental germs and radicular reabsorption.

CT radiological examination revealed a significant morphostructural alteration of the mandible and maxilla. They appeared markedly increased in volume, showing a subversion of the normal conformation due to the deposit of the non-ossified osteoid matrix and the interruption of the osseous cortex (Figure 4). The massive growth of the superior maxilla caused a reduction of the air cavities of the maxillary sinuses and a significant involvement of the right orbital floor (Figure 5).

Osseous scintigraphy (555MBq 99m CT-MDP) revealed a clear alteration caused in the fullness of the face with a disomogeneous hyperaccumulation on the mandible and the maxillae.

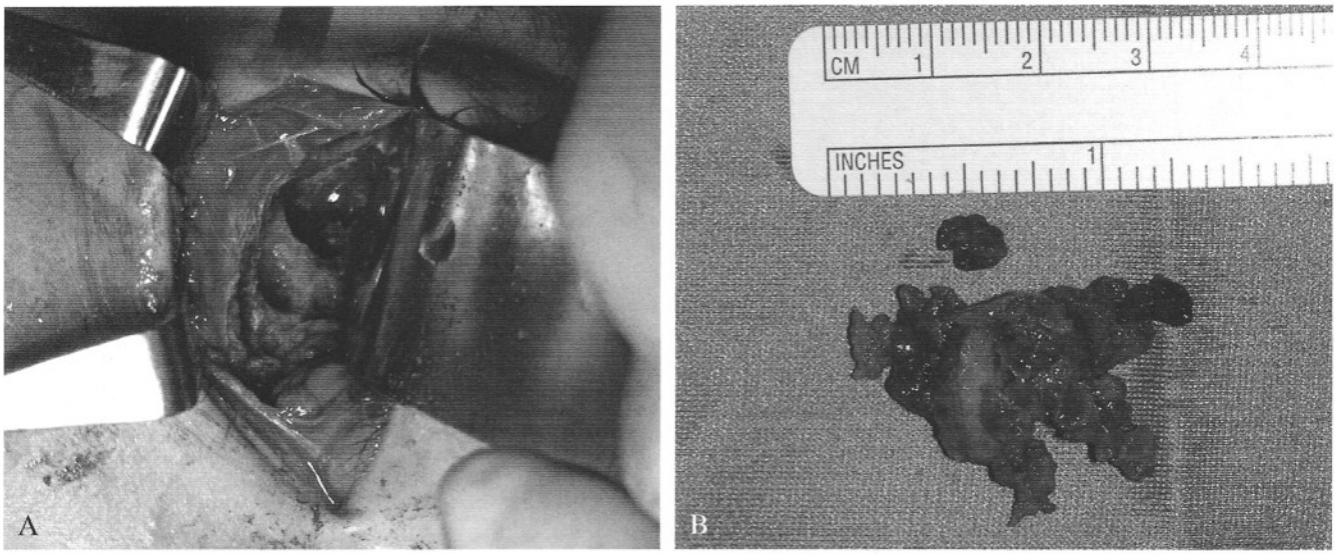

Figure 6.—A, B) Curettage of the orbital floor with a transconjunctival approach.

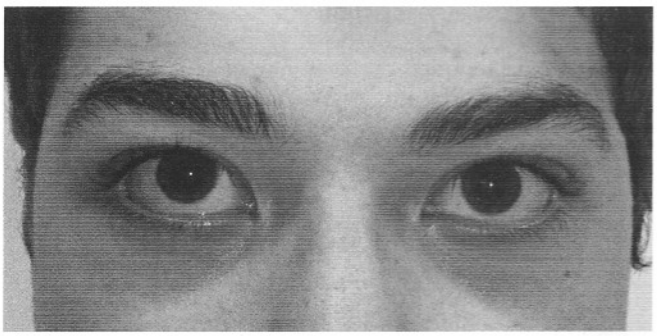

Figure 7.—Postoperative resolution of the ophthalmopathy.

Hematochemical examinations revealed an elevated level of alkaline phosphatase and inorganic phosphatase, normal calcaemia and phosphoremia and slightly elevated osteocalcin and parathormone levels (Table I).

On the base of this clinical and radiological assessment, an incisional biopsy was performed at the mandibular junction to establish a definitive diagnosis.

The histological examination of the lesion produced a positive result for cherubism.

As the patient presented esophthalmus and diplopia and there was a risk of loss of vision due to the compression on the optic nerve only the right orbital was surgically treated. A decompression of the orbit was carried out by means of a curettage of the floor with a transconjunctival approach (Figure 6). At the first post-surgical follow-up the clinical and radiological reports showed a resolution of the ophthalmopathy (Figure 7), a restoration of the orbital volume (Figure 8) and an improvement of the esthetic appearance of the face. A

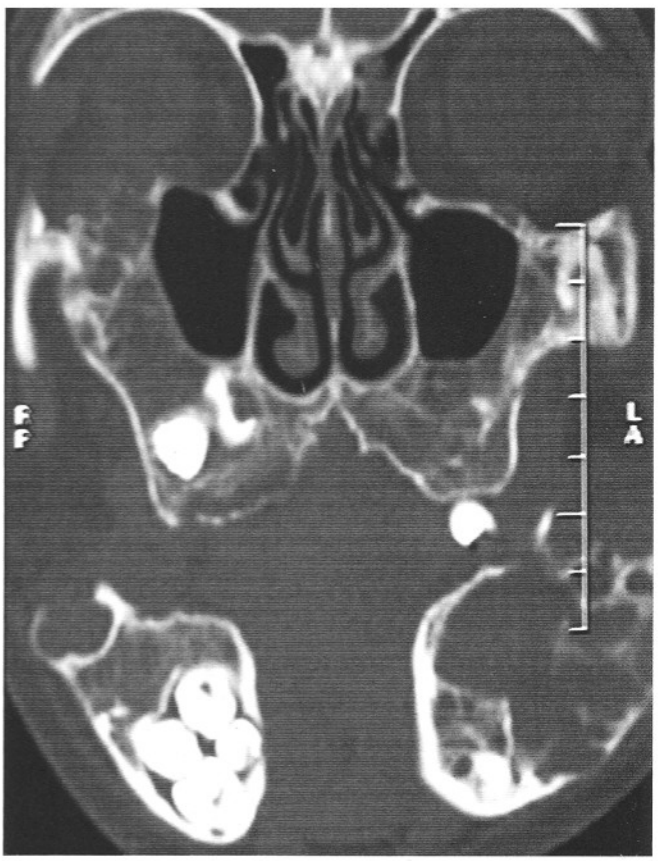

Figure 8.—Postoperative radiological outcome: restoration of the orbital volume.

TABLE II.—*Modified Motamedi system.*

Grade	Definition
I	Lesion of the mandible without signs of root resorption
II	Lesions involving the mandible and maxilla without signs of root resorption
III	Aggressive lesion of the mandible with signs of root resorption
IV	Lesions involving the mandible and maxilla with signs of root resorption
V	The rare, massively growing, aggressive, and extensively deforming juvenile lesions involving the maxilla and the mandible
VI	The rare, massively growing, aggressive, and extensively deforming juvenile lesions involving the maxilla, mandible, and orbits

weekly follow-up was planned to check the expected spontaneous resolution of the pathology.

Discussion

Cherubism is a rare non neoplastic fibro-osseous dysplasia related to genetic mutations, for which, until today, definitive epidemiological data does not exist. Approximately 280 cases of cherubism have been reported in literature.[13] Numerous grading systems have been proposed to define the severity of the disease.[14, 16] In 1998, Motamedi described five grades of the disease, defining as severe (grade V) the profile characterized by a contemporaneous involvement of the mandible and the superior maxilla.[11] CE. Raposo-Amaral *et al.* in 2007 [2] suggested the addition of a grade VI to the Motamedi classification to describe the orbital involvement, in addition to that of the mandible and the superior maxilla, which had not previously been taken into consideration (Table II). According to such a classification, our patient is to be attributed to a severe form of the disease (grade VI). He presented, in fact, a significant involvement of the orbital floor that caused the appearance of a false esophthalmus associated with diplopia and a serious risk of a loss of vision due to optic atrophy.[1, 7, 12] Based on these considerations surgical treatment involved exclusively the right orbital floor to decompress the orbit, to resolve the ophthalmopathy and to avert the risk of optic atrophy. As for the extra-ocular lesions, we limited ourselves to an attitude of "wait and see", in accordance with the data found in international literature that reports, in the majority of cases,[6, 9] a spontaneous resolution of the disease after puberty.[5, 7, 15, 17, 18]

Conclusions

The results obtained in the postsurgical follow-up suggest that an immediate decompressive surgical approach on the orbit should be taken into consideration for the resolution of ophthalmopathy and the associated risks, while waiting for the spontaneous regression of the extra-orbital lesions.

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