Familial cherubism: clinical and radiological features. Case report and review of the literature

**Abstract**

**Background** Cherubism is a rare genetic disorder that causes prominence in the lower portion in the face. The authors present the case of an 11-year old boy showing bilateral enlargement of the mandible.

**Case report** Computer tomography evidenced the presence of characteristic cherubism changes. The genetic test confirmed heterozygote mutation c.1244G>A (p.R415Q) in second exon coding sequence of SH3BP2 gene. Radiographic examinations performed on some close relatives of the patient revealed typical changes. The patient did not require any surgical treatment and the “wait and see” protocol was applied.

**Keywords** Cherubism; Genetic disease; Radiographic analysis.

**Introduction**

Cherubism is a rare, benign, hereditary, non-neoplastic bone disease [Silva et al., 2007; Chung How Kau et al., 2012]. WHO defines it as a self-limiting, dominantly inherited disease, characterised by bilateral bone enlargement of the jaws in childhood. It often leads to the formation of the characteristic facial appearance and histologically is very similar to Central Giant Cell Lesion.

It was first described in 1933 by Jones as a “familial multilocular cystic disease of the jaws” lending to patients a full round face and an upward cast of the eyes that make them appear like angels from Renaissance paintings, so Jones suggested the name “cherubism” which is used until today [Özkan el al., 2003].

Its familial distribution may affect different generations, even though isolated non-familial cases have also been reported [Kau et al., 2012; Meng et al., 2005]. Males are affected twice as often as females with a penetrance reported to be 100% for men and between 50% to 70% for women [Kozakiewicz et al., 2001; Silva et al., 2007]. The disease is related to the mutation in the gene SH3BP2 of chromosome 4p16.3. Mutations are identified in exon 9 and they affect a sequence of 6 amino acids in positions 415-420 [Kau et al., 2012; Ongole et al., 2003].

The disease is characterised by bilateral painless enlargement of the mandible or both mandible and maxilla. It starts usually around 1-3 years of age in a previously completely healthy child [Maganzini et al., 2012; Kau et al., 2012]. It is assumed that the earlier the first symptoms of the disease appear, the more dynamic and more severe bone deformation is [Ongole et al., 2003]. Cherubism may range from undetectable clinical cases to aggressive ones that extend to the eyes, having significant orbital manifestations that may cause proptosis, looking towards heaven appearance and loss of vision [Kozakiewicz et al., 2001]. One extreme reported case progressed rapidly, resulting in death due to gastrointestinal and pulmonary infections [Silva et al., 2002].

**Case report**

An 11 years old male patient was referred by an orthodontist to a dental surgeon because of bilateral enlargement of mandible. The patient was slightly overweight, with a characteristic chubby face.

The medical history was carried out with the patient’s mother, who identified the chubby face as a characteristic of other family members, which did not arise suspicion of a disease. Because of symmetric, slow, asymptomatic progression, the beginning of the disease was difficult to define: though submandibular and cervical lymph nodes enlargement was observed at the age of 7, none of the paediatricians who followed the patient related it with cherubism.

At the age of 9, the patient visited an orthodontist because of misalignment of teeth. The panoramic x-ray was taken (Fig. 1) and it showed a disturbing image of bilateral multilocular radiolucent in mandibular angle, corpus and ramus, which revealed the lack of teeth buds 18, 17, 28, 27, 37, 38, 47, 48, displacement of lower incisor and mixed dentition.

The x-ray taken at the age of 11 years (Fig. 2) showed the evolution of the disease. Lesions were less
radiolucent, more mineralised, the bone septa were more numerous and thicker. The lack of upper, lower, second and third molars was confirmed. Impacted lower incisor (41) was noticed.

Clinical examination showed bilateral, firm, painless, non-fluctuating augmentation of mandible body. Mucosa and skin did not show pathology nor inflammation. Intraorally malocclusion and a 180° rotated lower right incisor were detected.

The patient was referred for computed tomography, blood test for the concentration of calcium, phosphorus and alkaline phosphate, as well as genetic test.

Blood tests showed no deviation from the norm. The CT scan confirmed the presence of cystic lesions filled with soft tissue of the corpus, angular and coronoid processes of the mandible with segmental discontinuity of the cortical bone. According to the severity of cherubism suggested by Seward and Hankey [1957], our patient had second grade bilateral lesions, confined to the lower molar regions and posteriorly up to the coronoid processes and lesions of the maxillary tuberosities [Seward and Hankey, 1957]. Similar lesions were found in the maxilla, especially in the area of the posterior and lateral wall of the sinus. The CT scan also showed bilaterally enlarged submandibular lymph nodes, tonsils and nasopharynx lymphatic tissue. The genetic test confirmed the heterozygotic mutation c.1244G>A (p.R415Q) in the second exon coding sequence of SH3BP2 gene.

The panoramic x-rays of our patient and of some members of his family were analysed: his mother (Fig. 3) (patient B), his younger brother about 8 years old (Fig. 4) (patient C), his 41-year old uncle (older brother of the patient’s mother, patient D) (Fig. 5) and his 30-year old uncle (younger brother of the patient’s mother, patient E) (Fig. 6). The radiographic features in the orthopantomographs of the two uncles were characteristic of cherubism lesions, and from the family history it resulted that patient E presented the characteristic feature of cherubism: upward cast of the eye with exposure of the sclerae below. Since this patient was not able to come to our office for examination, our knowledge was based on his sister’s statements. The clinical examination of patient D showed barely detectable bilateral bone augmentation of the mandible corpus and the family’s characteristic well pronounced cheek bones. The panoramic x-ray of patient D revealed a fully impacted lower left third molar, dislocated to the mandible ramus, and a characteristic picture of advanced lesion of the mandible bone, especially visible in region 46-43.

The clinical examination of patient B did not show pathological features. The orthopantomograph showed only a fully impacted, highly displaced lower right third molar, which could suggest the presence of cherubism, but only genetic test can confirm or deny the presence of disease.
The orthopantomograph of patient C was unremarkable.

The course of disease of patient A was not aggressive, did not cause functional nor aesthetic disorders and did not require any surgical treatment. We applied the “wait and see” protocol with checkup visits every 6 months. The patient will start orthodontic treatment.

Discussion

The replacement of a normal bone by fibrous tissue causes arch and dental abnormalities, the most common being delayed eruption of permanent teeth, premature eruption of deciduous teeth, narrow V-shaped palatal arch, root resorption, misalignment, teeth displacement and impaction, lack of buds of second and third molars [Silva et al., 2012; Maganzini et al., 2012; Hernández-Alfaró, 2011]. The swelling of the submandibular lymph-nodes may occur but no systemic abnormalities are involved [Özkan, 2003; von Wowern, 2000]. The swelling of the nodes usually appears after bone lesion. Over time the nodes undergo regression and become normal after 10-12 years of age [Ongole et al., 2003].

The lesions are predominantly observed in the mandible, maxillary occurrence is variable but always accompanied by mandibular involvement [Maganzini and Picon, 2012; von Wowern, 2000]. Bone alterations usually start in the region of the angle and ascending ramus of the mandible, continuing to the mandibular body, displacing the mandibular canal and, in some cases, extending to the middle line or coronoid process. The condylar process of the mandible is usually spared [Maganzini and Picon, 2012; Lima et al., 2010]. In 60% of cases, the disease involves the maxilla. The lesion appears bilaterally in the tuberosity region. Progression of the lesion may cause complete obliteration of the sinus and, in more severe cases, infiltration of the orbital cavities may induce exophthalmus and ocular movements limitations [Kozakiewicz et al., 2001; Beaman et al., 2004; Silva et al., 2007].

The radiographic features change during the course of the disease. At the beginning, the lesions are multiple and radiolucent, well-defined with thin bone septa. These lesions are irregular in size and usually cause a marked, profound destruction of the alveolar bone that affects tooth buds and incipient follicles. Erupted teeth seem to be floating in radiolucent spaces. Depending on the extension and the involvement of the lesions observed in the radiographic images, the Seward and Hankey [Seward and Hankey, 1957] classification grading system ranging form 1 to 3, is used to define severity of the condition.

- Grade 1: bilateral lesions, confined to the lower
molar regions and posteriorly up to the coronoid process (rarely unilateral).
- Grade 2: in addition to lesions of grade 1, lesions in the maxillary tuberosities.
- Grade 3: both jaws diffusely affected.

Later on lesions reorganise, and appear more mineralised, with thicker and more numerous bone septa. The radiologic aspect from radiolucent becomes granular [Nina von Wovern, 2000].

Diagnosis is based on medical and family history, characteristic radiographic image, evolution of lesions, changes in the concentration of calcium, phosphorus, and alkaline phosphatase in blood serum. These markers should be in the range of normal values with respect to age [Silva et al., 2007; Kau et al., 2012]. Some authors observe slightly increased alkaline phosphate level with normal calcium and phosphorus concentrations in their cases [Kozakiewicz et al., 2001; Özkan et al., 2003].

Cherubism features are similar to those of other bone diseases such as brown tumor of hyperparathyroidism, giant cell tumor and central and peripheral giant cell granuloma. Histologically, the lesion is composed of mature fibroblasts in a surprisingly pale aedematous background that contains little collagen. Multinucleated giant cells are few and occur in clusters. A distinctive feature is the presence of an acellular, eosinophilic cuff, deposit that appears to ring small vascular channels. Presence of mutation of gene SH3BP2 confirms the disease [Maganzini et al., 2012; Kau et al., 2012; Silva et al., 2007].

Treatment protocols for cherubism are not well established. Every patient should be treated individually. Cherubism is a self-limiting disease and it permits to apply the “wait and see” protocol in some cases [Silva et al., 2007; Meng et al., 2005; Özkan et al., 2003]. Between the 8th and 12th year of life formation of delicate osseous trabeculae within the translucent areas, starting from the inside of alveolar processes can be observed. The bone structure comes close to normal between the 3rd and 4th decade of life [Seward and Hankey 1957; von Wowern 2000].

Surgical treatment options include biopsies of the lesional tissue, tooth extractions in areas showing fibrous alterations, early curettage of lesions, cosmetic osteoplasty of affected jaws after regression of disease activity or in the case of functional impairment osteoplasty during active phase of growth [Kozakiewicz et al., 2001; Meng et al., 2005].

Some authors suggest that early surgical interventions do not cause active growth of lesional tissue and even early curettage or surgical contouring during the rapid growth of the lesions can stop active growth of remnant cherubic lesions and even stimulate bone regeneration [Meng et al., 2005; Roginsky et al., 2009; Dukart et al., 1974; von Wowern 2000]. Curettage with or without bone grafting aimed at preserving the teeth as long as possible might be the treatment of
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Serious choice, although it may need to be repeated on several occasions [Kozakiewicz et al., 2001; Hernández-Alfaro et al., 2011; Roginsky et al., 2009]. Other authors observe that surgical treatment during the rapid growth phase is followed by severe relapse and a more aggressive course [Roginsky et al., 2009; Seward and Hankey 1957; Riefkohl et al., 1985].

A larger removal of the lesional tissue in severely affected patients may lead to preoperative and postoperative complications and damage, which is why this course is dissuaded, unless the lesions create functional and social problems [Seward and Hankey 1957; von Wowern 2000].

Medical therapy in the form of calcitonin is theoretically appropriate. Calcitonin is recognised as an effective treatment for giant cell granuloma of the jaw. Calcitonin has been shown to cause inhibition of bone resorption by multinucleate cells in cherubic tissue in vitro, and it could be a very promising drug for the treatment of cherubism [Meng et al., 2005; Southgate et al., 1998; von Wowern 2000; Harris 1993].

Radiation therapy has been abandoned as a treatment of cherubism, because of the potential risk of osteoradionecrosis, delay on development of the facial skeleton and a potential failure of further surgical interventions, even malignant transformation of the process resulting in osteosarcoma [Kozakiewicz et al., 2001; Özkan et al., 2003; Roginsky et al., 2009; Riefkohl et al., 1985].

Conclusions

Cherubism is a very rare disease. We do not really know whether the rare occurrence of cherubism is due to the small amount of families affected by this mutation, or its often poor symptoms are not noticed by patients and doctors.

The self-limiting course of the disease causes difficulty in detection of a lesion in adult patients. In small children lesions often go unnoticed. Only patients with more severe grades of the disease tend to seek medical help.

Disclaimer

Consent for publication from legal guardian of patient was obtained.

References