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Cherubism: An Update on Etiopathogenesis, Diagnosis & Treatment

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ABSTRACT: A skeletal dysplasia characterized by symmetrical bilateral fibro-osseous lesions affecting exclusively the mandible and maxilla, is termed as Cherubism. Interestingly, this genetic disorder manifests in children between the age of 2-6 years, grows till puberty and stabilizes by end of 2nd decade, when they are generally not detectable. This fibro-osseous lesion although is self-limiting and needs a wait and watch approach in treatment, can be aggressive at times causing concern and needing intervention. This article aims to explore the updates on the causes, symptoms, diagnosis, and treatment options associated with this benign but yet a lesion of concern.

KEYWORDS: Fibro-osseous; Children; Bilateral jaw; Multilocular cystic; Hereditary; Eye upturned to heaven

I. INTRODUCTION

Cherubism is a rare disease of autosomal dominant inheritance characterized by painless, frequently symmetrical, enlargement of the jaws as a result of the replacement of bone with fibrous tissue [1]. The disease is also called familial fibrous dysplasia of the jaws. The condition derives its name from the distinctive cherubic, or angelic facial features of full round cheeks and the upward cast of the eye in affected individuals due to the abnormal growth of bone [2,3]. Although cherubism is a non-life-threatening condition, it can significantly impact a person's appearance and quality of life.

II. ETIOPATHOGENESIS

A molecular pathogenesis of cherubism, with the detection of a mutation in the gene encoding SH3 - binding protein 2 (SH3BP2) on chromosome 4p16.3 [4,5]. and possible degradation of the Msx-1 gene which is involved in the regulation of mesenchymal interaction during craniofacial morphogenesis is put forth [6]. It is believed that the different clinical manifestations of cherubism are due to the changes secondary to mutations or incomplete penetrance [5]. This mutation is usually sporadic, occurring during early embryonic development and is not inherited from parents. However, there have been cases where cherubism is inherited as an autosomal dominant disorder [1]. Although rare, there are reports of the cases in which no criteria of heredity could be established, or in which an autosomal recessive pattern of inheritance was suggested. In addition to genetic factors, other possible causes of cherubism such as mesenchymal alterations during jaw development, an odontogenic origin or even hormonal and traumatic factors have been suggested [4].

Cherubism is a location-stable phenomenon found only in the jaws with multiple occurrences [7]. The specific genetic mutation responsible for cherubism causes an overproduction of cells called osteoclasts, which are responsible for breaking down and remodeling bone tissue. This excessive bone resorption leads to the development of fibrous tissue and abnormal bone growth in the affected areas, primarily the jaws and cheeks [6,8].

III. CLINICAL CHARACTERISTICS AND SYMPTOMS

Cherubism is usually diagnosed in children aged 2 to 7 years, with the observation of exacerbation of its manifestations within the first 2 years after diagnosis [9] and of stabilization or even regression after puberty [1,10]. Boys are more affected than girls at the proportion of 2:1 [4].

Clinically, cherubism is characterized by bilateral enlargement, in most cases, of the mandible and/or maxilla, causing a rounded face and swollen cheeks accompanied by upward-looking eyes. The swelling is bony hard with an intact overlying mucosa. Other features include dental malocclusion and absence of pain. The concomitant presence of cervical and/or submandibular lymphadenopathy and an increase susceptibility to infections have been reported. The excess

fibrous tissue and bone creates spaces for bacteria to accumulate, leading to recurrent infections in the affected areas [11,12,13].

Based on the clinical behavior and radiographic findings cherubism has been classified as quiescent, non-aggressive and aggressive. Quiescent cherubic lesions are usually seen in older patients and do not demonstrate progressive growth. Non-aggressive lesions are most frequently present in teenagers. The aggressive form of cherubism presents as large, rapidly growing lesions causing tooth displacement, root resorption, thinning and perforation of cortical bone and occurs in young children [2,3].

Dental alteration

Dental alterations associated with cherubism include early exfoliation of deciduous teeth, impaction and/or displacement of teeth [1,12], which radiographically seem to float in radiolucent areas, conferring the so-called "floating tooth appearance" [10]. In addition, ectopic tooth eruption, agenesis of permanent teeth, mainly of the second and third molars [14], due to involution of their germs [15], and root resorption of existing teeth are observed [16]. These alterations result in malocclusion as well as in problems of phonation and swallowing, the latter being exacerbated by flattening or inversion of the palatal cleft [1,5,6,11].

Biochemical parameters

With regard to biochemical parameters, serum calcium and phosphorus concentrations and TSH, FSH, LH, T4 and T3 hormone levels are usually within normal limits, but elevated alkaline phosphatase levels have been noticed [17].

Radiographic findings

Radiographically, cherubism is characterized by expansive radiolucent, generally multilocular lesions clearly delimited by cortical bone and distributed bilaterally in the posterior quadrants of the mandible and/or maxilla [4]. Bone alterations generally starts in the region of the angle and ascending ramus of the mandible, continue to the mandibular body, displacing the mandibular canal, and in some cases extending to the coronoid process [18,19]. Involvement of the condyle is rare [6]. In the maxilla, the injury process starts in the maxillary tuberosity region. When process is starting in mandible, maxillary lesions manifest at a later time [15]. In more severe cases, infiltration of the orbital cavities may cause exacerbated exophthalmia and limiting ocular movements [6].

The lesions of cherubism can be classified based on the extent of involvement in radiographs [1,12,16].

Grade I: Bilateral involvement of the ascending ramus of mandible

Grade II: Bilateral involvement of the ascending ramus of mandible and Maxillary tuberosity

Grade III: Complete involvement of the maxilla and mandible compromising the coronoid processes and condyles

The impacted teeth will be displaced resorption of the root has also been reported. The mandibular canal is often displaced. The facial sinuses frequently appear to be obliterated, resuming their pneumatic function after regression of disease activity [15].

Investigations & Diagnosis

The radiographic techniques used for the diagnosis of suspected cases of cherubism include posteroanterior radiography of the jaws, tele radiography [12], and orthopantomography [4,11]. Computed tomography is a useful tool for the assessment of the damage caused by the process either during the analysis of disease progression or during surgical planning [11]. Advancements in virtual three-dimensional reconstruction of anatomic structures based on computed tomography or cone beam computed tomography data can provide for more predictable individual treatment planning. Magnetic resonance imaging is useful for identifying orbital involvement [20].

The histopathological findings in cherubism includes multinucleated giant cells scattered throughout collagenous and vascularized fibrous connective tissue. The connective tissue might be highly cellular with less collagen fibers or highly cellular with dense fibers, depending on the progression of the lesion. This connective tissue is richly vascularized which is associated with giant cells. Presence of bony spicules and hemosiderin deposits are also a possibility. It is believed that these giant cells have osteoclastic activity. Southgate et al. [17], found that the multinucleated cells in cherubic lesions had phenotypic characteristics of osteoclasts, resorbing bone in vitro. The specific histological finding of cherubism is the presence of eosinophilic perivascular cuffing which, however, is not always present and histology is of limited diagnostic significance [21].



Laboratory tests contribute to the characterization of disease since hematological parameters such as calcium and phosphorus are normal and only alkaline phosphatase levels might be elevated [1,19,21] which is attributed to the phase of development in most individuals affected by the disease.

Cytogenetic and molecular studies used in diagnosis of cherubism such as fluorescence in situ hybridization and quantitative analysis of Msx-1 expression in different tissues have been useful [14].

Treatment

Currently, there is no cure for cherubism. However, treatment focuses on managing the symptoms, improving facial appearance, and addressing functional concerns.

Treatment options include waiting for stabilization and spontaneous remission of the disease, tooth extraction in areas showing fibrous alterations, cosmetic osteoplasty of the affected jaws after regression of disease activity or, in the case of functional impairment, curettage of the lesions and treatment with calcitonin [22].

The policy of waiting for disease regression, followed by the evaluation of physiological bone remodeling, is the most recommended. However, it is still uncertain whether this approach is the most effective one since only a few cases of long-term follow-up have been reported. Amongst the few cases of these follow up cases reported, curettage or jaw osteoplasty surgery was indicated early. Curettage has been suggested to be a good approach since this intervention stimulates bone replacement [21].

In extreme cases in which important functions are impaired, surgical intervention should be performed as early as possible. Radiation therapy has been abandoned as a treatment of cherubism because of the potential risk of osteoradionecrosis or even malignant transformation of the process resulting in osteosarcoma [23]. Prosthetic treatment to replace the missing teeth would be fixed partial dentures and overdenture. Implant placement into porous bone might result in lack of osseointegration and lead to complication and hence should be avoided [13].

There are many experimental therapies that are being explored in the treatment of cherubism, based on their use in other fibro-osseous lesions. One such approach is Anti-TNF therapies. If found effective, it can be hoped that the interval from laboratory discovery to clinical use would be short [20]. Denosumab, a monoclonal antibody against the RANKL, has shown to have a very potent inhibitory effect on osteoclasts, opening new therapeutic doors in the treatment of osteolytic disorders and other osseous lesions [24]. However, pediatric data on the use of Denosumab is limited. A significant implication in the use of Denosumab is the high risk of hypocalcemia following initiation of therapy and rebound hypercalcemia upon discontinuation of treatment [22].

Since calcitonin was first used for central giant cell granuloma, daily subcutaneous administration of human calcitonin has become the most common method of therapy in fibro-osseous lesions. The use of calcitonin therapy for cherubism has been rarely documented. In an in vitro study, the positive effects of calcitonin on bone resorption within cherubic lesions was found to be positive. The failure of calcitonin therapy was related to poor compliance by the patient to which an intranasal mode of delivery has been suggested. The dose, type, and administration method of calcitonin has been documented in many reports [25]. More recently the use of salmon calcitonin has become more popular than using human calcitonin because of its increased potency and availability [26]. But several nonspecific side effects such as nausea, skin rash at injection site and anaphylaxis have been reported with the use of salmon calcitonin [27]. A meta-analysis conducted to assess the risk of malignancies in calcitonin-salmon treated patients although revealed an increased incidence in the risk of overall malignancies using intranasal calcitonin, the correlation was considered weak and the conclusions questioned by other sources [28].

IV. CONCLUSION

Cherubism, that occurs in children, although not a potentially fatal disease, can have visible consequences and can cause some morbidity to the affected. Early diagnosis, regular monitoring, and appropriate interventions, including dental and surgical treatments, can help manage the symptoms and improve the quality of life for individuals with cherubism currently. Ongoing research into the genetics and pathophysiology of cherubism may eventually lead to more targeted therapies in the future.

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