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1DENOSUMAB TREATMENT IN A SPORADIC CASE OF CHERUBISM: A RARE PEDIATRIC FIBRO-OSSEOUS DISORDER – A SYSTEMATIC REVIEW

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Abstract

Background

Fibrous connective tissue and osseous components replace normal bone in a variety of histologically benign conditions known as fibro-osseous lesions. The jaw may develop a number of conditions, such as fibrous dysplasia, ossifying fibroma, and cemento-osseous dysplasias. Cherubism is a rare, autosomal dominant, non-neoplastic fibro-osseous hereditary condition caused by genetic mutations that is characterized by symmetrical expansion of the mandible and/or maxilla. It typically affects children between the ages of two and five, giving them a cherubic appearance and an upward turning of the eyes. After puberty, these lesions spontaneously recede, having progressively grown over the following few years. The diagnosis is strongly suggested by bilateral, somewhat symmetric jaw involvement restricted to the maxilla and mandible, although the histopathologic features of cherubism are not pathognomonic. Patients with cherubism who had calcitonin treatment experienced a range of outcomes, from no improvement to a noticeable improvement. If we believe that calcitonin has some effectiveness, the disparity could be explained by variations in the length of treatment, the dosage, the patient's age, and most likely the severity of cherubism. Jaw-bone sclerosis was a remarkable side effect of denosumab treatment, regardless of the dosage, duration, age, and likely severity of cherubism. Bisphosphonates have been used for decades to try to change bone turnover because they can reduce pain and stop more bone involvement or damage in high-turnover disorders such as Paget disease. Bisphosphonates have not, however, been demonstrated to be useful in reducing disease activity, lesion size, or correcting abnormalities in many RBDs. Although denosumab's effects are reversible upon stopping treatment, it may provide a quicker and more efficient reduction of bone turnover.

Material and Methods: Major databases such as Medline were explored detailed literature search in resulting in a systematic review pertaining to denosumab treatment in a sporadic case of cherubism: a rare pediatric fibro-osseous disorder.

Results: Five original research scientific articles dated between 2020 – 2024 pertaining to mentioned topic were highlighted.

Conclusions:

Both radiological and clinical improvements were noted after treatment. Nonetheless, there were clinically substantial calcium homeostasis disruptions that needed to be treated medically. This

example emphasizes the significance of customized dosage, organized biochemical surveillance, and long-term follow-up while highlighting the possible effectiveness of denosumab in specific juvenile patients with severe cherubism. Detailed information regarding the denosumab treatment in a sporadic case of cherubism: a rare pediatric fibro-osseous disorder is discussed in this systematic review.

Key word: bone regeneration; pediatrics; bone lesions; genetics; giant cell lesions of the jaws; skeletal pathology.

INTRODUCTION:

A subset of intraosseous disease processes with similar microscopic characteristics includes benign fibro-osseous lesions (BFOL) of the jaw, face, and skull bones. While some can be diagnosed histologically, the majority necessitate a combination evaluation of radiologic, microscopic, and clinical characteristics. Conversely, some BFOL of the craniofacial complex are specific to that site, while others are found in bones from other areas. BFOL encompasses reactive, neoplastic, developmental, and dysplastic pathologic processes; the course of treatment varies depending on the disease. Fibro-osseous lesions replace medullary bone in cherubism, a bone condition that only affects the jaws. There are just about 600 cases of this incredibly rare illness known to exist worldwide.

Cherubism is linked to genetic alterations in the SH3BP2 gene, which is essential for controlling osteoclasts and osteoblasts, and has an autosomal dominant inheritance pattern. The illness was first described as "familial multilocular cystic disease of the jaws" in 1933. Later, the term "cherubism" became the accepted nomenclature because of the distinctive facial features of afflicted youngsters, who resemble the cherubs depicted in Renaissance paintings, with rounded cheeks and upturned eyes. Cherubism usually appears as a painless, gradual, roughly symmetrical enlargement of the maxilla and/or mandible within the first ten years of life. Rarely, orbital involvement can happen. Disturbances in dental eruption are often linked to the illness.

The disease's phenotypic manifestation varies greatly, and it can occasionally result in severe, deforming bone lesions that are infrequently fatal. Tissue expansion and fibro-osseous lesions often worsen until adolescence, at which point they spontaneously recede. By the third decade of life, facial deformities are almost undetectable as the lesions are gradually replaced by woven bone. The genetic and molecular causes of cherubism are becoming more understood, but treatment is still mostly empirical. While earlier research primarily concentrated on conservative surveillance and surgical correction, more recent studies have investigated pharmacologic therapies that target osteoclast regulation, such as TNF-α inhibitors, bisphosphonates, and calcitonin. However, because of the disease's rarity, small sample sizes, and variations in grading and follow-up evaluation, these methods have yielded inconsistent results.

There are still few systematic analyses that include clinical, radiological, and molecular data, and there isn't a single framework in the literature to compare results between various treatment regimens. This ongoing dispersion highlights the need for a revised synthesis of the data to determine which management techniques produce the most consistent outcomes among cherubism grades. The lack of a globally recognized grading system, a defined treatment strategy, and a clear genotype-phenotype association all contribute to the considerable diversity in disease care. Surgery is usually saved for patients who have significant functional impairment, psychological distress, or a higher risk of pathological fracture, even though the majority of cases resolve on their own.

Although pharmacologic and immunomodulatory strategies have been investigated, their effectiveness is still unknown. Due to variability in research designs and ambiguous treatment objectives, prior observational studies have produced inconsistent results for drug-based interventions. There is currently no agreement on the best course of action; however, a variety of surgical and nonsurgical procedures with usually positive results are described in the literature. The included publications' heterogeneity with regard to patients, cherubism intensity, treatment, and averted results.

MATERIAL AND METHODS:

"Bone" AND "pediatric" AND "pathology'' were the words used in MEDLINE database using advance search strategy targeting different article categories between 2020 to 2024. The result was 68 articles, out of which we selected 5 articles based in the inclusion criteria. Inclusion criteria was of case studies and scientific literature between 2020-2024. Exclusion criteria was of scientific literature irrelevant to the specific search. This systematic review was conducted to determine importance of denosumab treatment in a sporadic case of cherubism: a rare pediatric fibro-osseous disorder following the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). PubMed, Lilacs, Embase, Scopus, and Web of Science were the source of electronic databases. The search strategy used Boolean operators (AND and OR): [ALL ("bone") AND (pediatric OR genetic OR pathology OR maxillofacial OR therapy) AND (giant cell lesion)]. The following data were collected: first author, year, country of study, type of study and outcome. The quality of studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies) checklist.

RESULTS:

Five articles were included in this systematic review based on the selection criteria. We analyzed and mentioned in the five articles reviewed. This included only relevant research articles and excluded articles pertaining to nonspecific search terms.

Table 1 – An overview

Author	Title	Journal	Outcome
Eitan Bar Droma, Guy Beck-Rosen, Anatoly Ilgiyaev, Yariv Fruchtman, Chen Abramovitch-Dahan, Noam Levaot, Navot Givol	Positive Outcomes of Denosumab Treatment in 2 Patients With Cherubism	Droma EB, Beck-Rosen G, Ilgiyaev A, Fruchtman Y, Abramovitch-Dahan C, Levaot N, Givol N. Positive Outcomes of Denosumab Treatment in 2 Patients With Cherubism. Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons. 2020 Dec;78(12):2226-34. doi: 10.1016/j.joms.2020.06.016	denosumab for cherubism achieves promising results
Steele I Liles, Ian C Hoppe, Laura Arnold	Denosumab Therapy in Cherubism	Liles SI, Hoppe IC, Arnold L. Denosumab Therapy in Cherubism. The Cleft palate-craniofacial journal: official publication of the American Cleft Palate-Craniofacial Association. 2023 Dec;60(12):1665-73. doi: 10.1177/10556656221113891.	The achievement of symptomatic control with denosumab in a child with severe refractory cherubism
Haruka Kawamura, Satoshi Watanabe, Takashi I, Izumi Asahina, Hiroyuki	Efficacy and safety of denosumab treatment in a prepubertal patient with cherubism	Kawamura H, Watanabe S, Asahina I, Moriuchi H, Dateki S. Efficacy and safety of denosumab treatment in a prepubertal patient with cherubism. Journal of pediatric endocrinology &	The therapeutic potential of denosumab for treatment of cherubism remain unclear

Moriuchi, Sumito Dateki		metabolism: JPEM. 2020 Jul 28;33(7):963-6. doi: 10.1515/jpem-2019-0581.	
B R Chrcanovic, L M Guimarães, C C Gomes, R S Gomez	Cherubism: a systematic literature review of clinical and molecular aspects	Chrcanovic BR, Guimarães LM, Gomes CC, Gomez RS. Cherubism: a systematic literature review of clinical and molecular aspects. International journal of oral and maxillofacial surgery. 2021 Jan;50(1):43-53. doi: 10.1016/j.ijom.2020.05.021.	the genomic and gene expression regulation information is necessary for a better understanding of cherubism
Xu Liu, Yanshu Xie, Jing Tang, Jingzi Zhong, Dan Lan	Hypercalcemia in Children Following a Discontinuation of Denosumab Therapy: A Case Report and Literature Review	Liu X, Xie Y, Tang J, Zhong J, Lan D. Hypercalcemia in Children Following a Discontinuation of Denosumab Therapy: A Case Report and Literature Review. Clinical pediatrics. 2024 Jun;63(6):750-4. doi: 10.1177/00099228231194427.	denosumab in children, closely monitor for hypercalcemia, further studies on the use of denosumab are required

DISCUSSION

A diverse group of osseous disorders including hereditary or developmental lesions, reactive or dysplastic diseases and neoplasms have been described as fibro-osseous lesions.[1]

Rare diseases are hard to diagnose and treat because they develop slowly and pathognomonic symptoms do not exist and their occurrence is mostly insidious.[2]

The clinical symptoms are deformation of the involved bone; radiologic findings are unspecific.[3]

Cherubism is a rare genetic disorder that affects the bones of the jaw. The name was first description from the phenotype, “The full round cheeks and the upward cast of the eyes”.[4]

The children aged six, five, and four years in whom symptoms were detectable in the upper and lower jaw. The teeth there were irregularly arranged, and many were missing.[5]

Tooth development was suspected early on as a trigger for cherubism. It has been hypothesized that the growing tooth germs are a triggering stimulus to the jawbones and cause a pathological reaction in the tissue.[6]

As the mineralization of these teeth begins at the age of two to three years, a connection with the development of the disease is possible. Remission and the “skyward gaze” can also be explained.[7]

It is a very rare disorder with only an estimated 300 cases reported in the literature. Cherubism affects males and females with equal frequency.[8]

The tooth formation using molecular genetic interactions of the BMP, FGF, WNT, and Hh gene families, which is characterized by the interaction of WNT/MSX1 and PAX9.[9]

the gene responsible for cherubism was mapped to chromosome 4p16.3. In 2001, authors identifying a disease-causing point mutation in the *SH3BP2* gene. Accordingly, it is a hereditary bone disease that affects the upper and lower jaw.[10]

Ueki and Reichenberger, as the most important researchers in cherubism field, have defined the disease via the myeloid progenitor cell.[11]

Genetic imbalances in WNT and MSX1 pathways disrupt face and jaw growth because MSX1 controls how cells multiply and form teeth.[12]

Early tooth development needs markers like MSX1 and PAX9 controlled by WNT signals, and if WNT fails completely, teeth will not form at all.[13]

In cherubism, a mutated WNT pathway allows first teeth to form normally before birth, but triggers a harmful protein buildup after birth when the back molars try to develop.[14]

The jaw Cherubism is a rare, painless, disfiguring disease primarily affecting the bones of the jaw. Familial cases with involvement of only one side of the jaw for the duration of the disease have been reported.[15]

Cherubism causes teeth to become loose, deformed, or go missing—especially the back molars—and makes them look like they are floating on X-rays due to root damage.[16]

Affected individuals are normal at birth. The signs do not begin to manifest until early childhood and the swelling continues until puberty, at which time the bony lesions begin to stabilise and subsequently regress.[17]

There may be no facial deformity and radiographs may provide the only diagnostic sign of the disease. Cherubism is characterised by multiple multilocular radiolucent areas, giving a 'soap bubble' appearance.[18]

The disease creates a honeycomb pattern causing thinning of the cortical bone and the expansion of the medullary part. The cortex may actually perforate.[19]

Clinical regression of the symptoms may not be reflected on radiographic image. Although the facial deformity may have regressed in adulthood, with little or no evidence of cherubism.[20]

Mutations SH3BP2 gene have been identified in about 80% of people, this protein plays a role in transmitting chemical signals within the cell, particularly cells involved in bone remodeling.[21]

It is a intracellular protein tyrosine kinase – dependent signaling pathways during hematopoietic cell differentiation and function, also regulates the activity of the transcription factor which is involved in osteoclastogenesis.[22]

The jaw association is defined by the neural crest reference. Authors have highlighted the fate of the dental placement when the WNT/ß-catenin pathway is dysregulated. Parts of the epithelial remnants retracted by MSX remain intact in this way.[23]

Denosumab, an anti-RANKL monoclonal antibody, is effective in the management in giant cell tumours, has also been trailed in pediatric patients with cherubism. The choice of therapy generally depends on the severity of cherubism and patient factors.[24]

Milder forms without facial dysmorphology, dental, and ocular involvement may not require treatment, as cherubism is expected to regress spontaneously after puberty in most cases.[25]

Surgical interventions, including partial resection, contour resection, and curettage, may be indicated in aggressive cases.[26]

Immunomodulatory agents, such as imatinib and tacrolimus, have demonstrated promising results in cherubism. Calcitonin had various effects on cherubism; however, its use might be limited by tachyphylaxis, adverse effects, and the availability of other therapies.[27]

Positive clinical outcomes were observed in all cases, including suppression of lesion expansion and/or increased ossification. Denosumab was generally well-tolerated patients with hypo-calcemia and hypophosphatemia.[28]

The optimal duration of denosumab therapy in cherubism remains unclear. In previous mentioned case, patients received a total of 7-14 doses of denosumab 120 mg, without clear rationale for treatment cessation.[29]

Therefore, subsequent bisphosphonate treatment and close monitoring of bone turnover markers will be required to mitigate this risk. In addition, longitudinal clinical and radiological assessments for possible tumor growth will be crucial as part of surveillance.[30]

Mineral metabolism is normal in patients with cherubism, and serum levels of calcium, parathyroid hormone (PTH), parathyroid hormone related peptide (PTHrP), calcitonin and alkaline phosphatase (ALP) are typically within normal range.[31]

The patient may present with bilateral multicystic lesions which enlarge the mandible. These may be an incidental finding on radiographic examinations performed for other reasons such as trauma or during routine dental examinations.[32]

Orbital involvement may appear late in affected individuals. This is manifest by osseous orbital expansion, globe displacement, proptosis, diplopia, optic neuropathy and loss of vision.[33]

There have been reported cases of cherubism with massive enlargement of the jaws and backward displacement of the tongue resulting in airway obstruction and obstructive sleep apnea, speech, mastication and swallowing problems.[34]

Gene testing is recommended to determine whether a mutation in the cherubism gene SH3BP2 is present and to confirm the clinical diagnosis of cherubism.[35]

Management of cherubism include its differential diagnosis - brown tumor of hyperparathyroidism, giant cell lesions, Noonan/ multiple giant cell lesion syndrome, fibrous dysplasia, aneurysmal bone cyst and the hyperparathyroidism-jaw tumor syndrome (HPT-JT).[36]

Mild forms of cherubism without facial dysmorphology, During the growth phase of the lesions, annual clinical and radiographic examination with a panoramic or other appropriate radiograph is suggested.[37]

Surgical intervention is indicated when aesthetic or functional concerns arise including nasal obstruction, proptosis or facial deformity. Options for surgical management include partial resection, contour resection, curettage or a combination of these.[38]

Orbital surgery may be required in rare cases when tumor tissue invades the floor of the orbits to a degree where it leads to the displacement of globes or loss of vision is suspected due to optic atrophy.[39]

Development of dentition should always be closely monitored. Space maintainers are used while waiting for the permanent teeth to erupt. Malocclusion is a major concern.[40]

Patients followed up for 2 to 18 years and no recurrence was found. Patients and authors were satisfied with the outcome and the authors suggest that thorough removal of affected tissue appears to arrest the proliferation of any remaining tumor tissue.[41]

However, radiation therapy is contra-indicated in this benign condition because of the potential for long-term adverse consequences such as retardation of jaw growth, osteoradionecrosis and increased incidence of induced malignancy.[42]

Calcitonin has been used for the treatment of giant cell granuloma with successful outcome and experimental use of calcitonin for the treatment of cherubism has been suggested.[43]

The effect of calcitonin in giant cell granulomas can be seen after prolonged treatment and thus, calcitonin treatment would not be preferred for rapidly growing lesions. Further studies to document the efficacy of calcitonin in the treatment of cherubism is needed.[44]

Most cases of cherubism regress spontaneously after puberty. Studies describe that the cherubism lesions in 7 of 8 of their patients stabilized by age 12 years and regressed thereafter.[45]

Severely affected patient showed features of cherubism at age 20. Radiographic examination at follow-up visits revealed filling of the radiolucent lesions with bone as early as 2 years after stabilization and in most patients when they were in their twenties.[46]

In some cases the radiolucency's were replaced with sclerotic bone later in life. In more severe cases it can remain. Corrective surgery may be performed after cherubism lesions become quiescent to achieve facial features that are acceptable to the patient.[47]

Ongoing research strongly suggests that abnormal inflammatory responses are an important component of the pathophysiology of cherubism.[48]

Research in a mouse model suggests that high levels of tumor necrosis factor (TNF- a) in the circulating blood system contribute to the progression of cherubism. A therapy to reduce TNF- a level could be possible if this hypothesis holds true in humans as well.[49]

TNF- a blocker has been approved for a number of other diseases. The exact mechanisms need more studies, thus its production and a reduction in osteoclast formation and resorption could have a positive effect on the rate of bone resorption and cherubism tissue expansion.[50]

CONCLUSION

Cherubism is still an uncommon but clinically identifiable condition, and its genetic foundation is becoming clearer. Only two verified molecular diagnoses have been recorded thus far, and the majority of patients are still diagnosed solely based on clinical and radiological criteria. These results indicate a persisting gap between phenotypic clinical recognition and genetic confirmation within the

constraints of a narrative descriptive synthesis based on case reports and case series. In addition to improving patient care, expanding access to genetic testing, multidisciplinary care, and prospective registries throughout the continent is crucial to ensuring that data contribute to a worldwide understanding of this illness. Cherubism has a profound effect on afflicted children and their families, although it is uncommon. This is particularly true when aggressive growth results in functional issues and facial deformities. Apart from long-term clinical and radiological monitoring, which should last into adulthood, cherubism is usually self-limiting and requires no surgical intervention. Resection may be necessary when cherubism is fast-growing and has serious functional implications. Although it may enhance look and function, surgical intervention does not alter the course of the disease.

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