

Cherubism in 8 years-old child: treatment experience

Abstract

Giant cell reparative granuloma (GCRG) is one of the most common bone tumors in adults. Child population forms 1.7% of all registered GCRG cases. Cherubism is a rare form of GCRG which is characterized by defeat of the upper and lower jaw. Treatment of cherubism is challenging since radical surgery is impossible.

Methods: A child diagnosed with cherubism was observed for three years in the Department of maxillofacial surgery of the Russian Children's Clinical Hospital. The patient received bisphosphonate therapy, however the progressive growth of the upper and lower jaws remained. Diagnosis was histologically verified. After the approval of the Ethical Committee, patient received a course of denosumab therapy.

Results: Histological examination of the tumor denosumab treatment showed a significant response which resulted in disappearance of giant cells. CT before and after the therapy showed an increase in bone density from 65HU to 385HU. The size of tumor nodes reduced, allowing to plan contour resection of the mandible. The structure and volume of the upper jaw reached the average value and did not require surgical correction.

Conclusion: Inoperable forms of GCRG and cherubism require a comprehensive approach that includes denosumab therapy with subsequent contour resection of excess bone tissue to facilitate medical and social rehabilitation of such patients.

Keywords: giant cell reparative granuloma, cherubism, denosumab, children

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Introduction

According to World Health Organization, the giant cell reparative granuloma (GCRG) is a rare disorder characterized by giant cells destroying bone tissues. Cherubism is one of the rare forms of the giant cell reparative granuloma with isolated lesion of the upper and lower jaw. Jones et al. (1933) first described the disease in connection with the "angel-like" appearance in patients.¹ This disorder appears during the first few years of life with its maximum manifestation by the age of five. The disease slowly progresses to the age of puberty, then turning into subsequent spontaneous regression. In most cases, the disease is of hereditary nature,^{2,3} although sporadic cases of the disease are described in the literature.⁴⁻⁶ The diagnosis of cherubism is based on clinical, radiological and histological data. The clinical manifestations include family form, symmetrical enlargement of the jaws in early childhood, arch-shaped palate, loss of second and third molars, and reappearance of "cycles" of the disease, lymphadenopathy, spontaneous regress or complete stop of formation growth, lack of involvement of the temporomandibular joint. Radiographic manifestations include multiple cystic-lytic symmetrical lesions of the upper and lower jaw. Conducted CTs reveal honeycomb-like changes in the cortical layer of the lower jaw. In the upper jaw, CT shows defeat tuberosity with a lesion of the maxillary sinus and the elevation of the lower orbital floor. Histology discovers fibrotic hyperplasia with multiple giant multinucleate cells. In the phase of reparation, pseudo cystic changes are possible. Differential diagnosis is ruled out between fibrotic dysplasia, osteosarcoma, juvenile ossifying fibroma, osteoma, odontogenic cysts and hyperparathyroidism. X-ray typically reveals a two-side lesion of the jaws with the presence of family cases and facilitates diagnosis without histological

verification. However, observations without hereditary character and the first appearance by the age of ten or immediately after birth are described in the literature. Yet, these reports should be regarded with skepticism.² Hereditary nature of the disease has been the subject of many studies.⁷ demonstrated that 2/3 of the families had two or three generations of patients with cherubism. In seven families, the disease manifested itself in one line of siblings. According to the authors, cherubism shows an autosomal dominant type of inheritance with 100% penetrance in men and 60-80% in women.⁷ Mangion et al.,⁸ & Tiziani et al.,⁹ established positions of the FGFR3 and MSX1 genes responsible for the development of cherubism, which are located on chromosome 4p16.3.^{8,9} Later Ueki et al.,¹⁰ found a mutation SH3-connecting protein SH3BP2, located in 4p16.3 in twelve out of the fifteen families with cherubism.¹⁰ This mutation leads to an increase in osteoclastic and osteoblastic activity in the period of teething. However, despite the revealed genetic cause of cherubism, the exact pathogenesis has not been determined. Since the regulation of bone growth is disturbed, conservative therapy can affect this process. One way to adjust this mechanism is to block the receptor activator of the signaling pathway of the NF-kappaB-ligand (RANKL). Denosumab selectively inhibits RANKL (and therefore osteoclast activity). It is used to treat postmenopausal osteoporosis. In osteoporosis cases, it simulates the effect of the RANKL inhibitor, which leads to an increase in mineralization.¹¹ RANKL is believed to be involved in the growth of tumor cells, possibly due to the development of growth factors by osteoclast-like giant cells through the paracrine loop.¹² Recent Phase II studies of denosumab in adults and skeletal-mature adolescents (aged twelve and older) with giant cell tumor of bones in children and adolescents (GCTOB) demonstrated a significant

clinical response to monoclonal RANKL.¹³ Effectiveness of treatment of GCTOB with denosumab is proved histologically.¹⁴ However, there was no research on the safety and efficacy of this molecule and its effects on growth and bone health in younger children. Only three case reports are described in the literature. Two cases are devoted to 10-year-old children (a girl and a boy) with giant cell reparative granuloma and one observation of a boy aged 3 years 11 months with a lesion of the upper and lower jaws. Histological examination of the tumor after denosumab treatment demonstrated a significant response, evidenced by the decrease in number or complete disappearance of giant cells and the formation of bone and fibrous tissue. After denosumab course there was no slowing of growth. The size of the tumor nodes decreased allowing surgical removal.¹⁵⁻¹⁷ The purpose of our observation is to show the effectiveness of denosumab therapy in a 9-year-old child with progressive jaw growth, as a stage of treatment and socialization of the child.

Clinical case description

A child diagnosed with cherubism was under ambulatory supervision for three years in the Department of maxillofacial surgery of the Russian Children's Clinical Hospital (RCCH). The parents of the child were consulted for the first time in RCCH when the child was five. They complained about an increase of the lower jaw. The child was treated with bisphosphonates, however, the progressive growth of the upper and lower jaw, leading to exorbitalism, persisted throughout the therapy (Figure 1). The damage to the jaws was significant, the progression of the disease was slow and surgical treatment was impossible. After receiving the approval of the Ethical Committee, we started a course denosumab. Loading doses of denosumab (120mg) were administered on the 8th and 15th day of the first month of treatment. 120mg of denosumab were administered once every 4 weeks for the rest of 5 months. The child received 500mg of calcium and 500 units of vitamin D daily. During the first three months of the therapy reduction of the upper and lower jaw and a sharpening of the corners of the lower jaw was observed (Figure 2). A decrease in the phosphorus level below the reference values occurred during the third month of treatment (Table 1). Consulting nephrologist doubled the doses of vitamin D and calcium for the rest of treatment period. Denosumab therapy was not ceased. We constantly monitored blood levels of parathyroid hormone, calcitonin, and vitamin D. The parameters of the calcium-phosphorus exchange remained within the reference values and required no correction. After the therapy was completed, we conducted a control MSCT study to assess the bone age of the child and took a biopsy of the formation. According to computed tomography, the density of the cystic-transformed upper and lower jaw increased from 35 ± 28 HU to 496 ± 127 HU (Figure 3). The size of the tumor nodes decreased, making it possible to plan the contour resection of the lower jaw. The structure and volume of the upper jaw reached average indicators for the age and did not require surgical correction.

In order to monitor the therapy's influence on growth zones, we conducted radiography of the child's hands. The biological age of the child was estimated by the state of his bones before the treatment. Both of the X-rays were taken at age 9. They show that the bones are ahead of the of the actual (legal) age, and correspond to that of 11-12 years old, characterized by the presence of ossification site in all bones of the wrist, including pisiform bone. After denosumab treatment, growth zones were not affected. This fully corresponds to the case of denosumab treatment in two children by Karras NA.¹⁵ &

Kobayashi E et al.,¹⁶ (Figure 4). A biopsy of the formation was taken to verify the diagnosis and evaluate the effectiveness of denosumab therapy. We took material for histology intraoperatively, prior to the therapy. The bone consisted of fibrous tissue with gel-like transparent contents. The collected material consisted of two cellular components. The first component was spindle-shaped cells forming chaotically oriented bundles. The nuclei were round, oval and elongated, and in the part of the nuclei, a small nucleolus was found. Mitotic activity was not reliably determined. The second cellular component consisted of clusters of giant multi-core osteoclast-like cells. There were foci of reactive osteogenesis and hemorrhage, and deposits of hemosiderin. Such histological picture corresponds to a giant cell reparative granuloma, i.e. cherubism. Subsequent histology of bone tissue was taken after the denosumab therapy. The structure and density of the bone were comparable to a spongy bone tissue. Fragments of spongy bone tissue, mainly of lamellar structure, as well as the fragments of the mature paucicellular connective tissue with the collagenized matrix were observed. There were no giant multinucleated cells within the sample. The described changes evidence the efficiency of denosumab therapy (Figure 5). The use of denosumab is associated with a risk of osteonecrosis of the lower jaw. It is the most adverse complication of the antiresorptive drugs. Although this complication has not been observed in children, a possible negative effect of the drug on wound healing remains.^{17,18} For the entire denosumab course, any invasive treatment in the oral cavity was contra-indicated. However, there are opinions in the literature that there is no need to discontinue denosumab therapy if surgical treatment is necessary.¹⁹ In our case, we observed the healing of the incision in the mouth, in the area of biopsy, before and after the therapy. The incisions healed without complications. Since relapse cases were described within the first six months after denosumab treatment, requiring a repeated course of therapy, any surgical treatment aimed at harmonizing the proportions of the face was postponed for this period.¹⁶

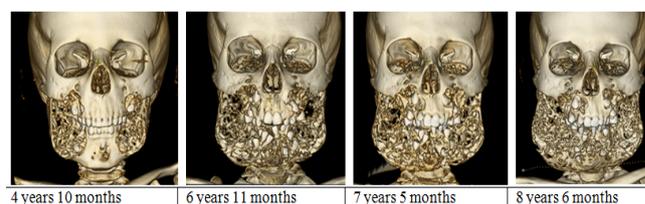


Figure 1 Dynamics of computed tomography throughout 2013–2017



Figure 2 Appearance of the child before, during and after the denosumab therapy.

Discussion

Giant cell reparative granuloma is a rarely observed disorder in children. Previously surgical treatment has been the only option for children. However, only 80% of tumors can be adequately removed, and the relapse rate varies from 10% to 75%.²⁰ Thomas et al.,²¹ completed the Phase II study of monotherapy with denosumab in patients aged 18 and older with a recurrent or inoperable form of giant

cell tumor of bones.²¹ Out of the 35 patients for whom the therapy was effective, 86% of the response was achieved after 25 weeks of treatment. A similar percentage of patients noted pain relief and improved functional status. The mechanism of action of denosumab is due to the binding to RANKL and its blockage on osteoclasts and osteoclast precursors, which prevents their differentiation and osteoclast-mediated bone reabsorption. Since giant cells in the giant cell tumor of the bones also express RANK, denosumab is considered targeted therapy.²⁰⁻²³ An attempt to compare the effectiveness of conservative treatment of giant cell reparative granuloma in the literature is limited since its occurrence is much less frequent than in the long bones of the skeleton.²⁴⁻²⁹ Despite the fact that the literature has accumulated experience of treating patients with giant cell tumor of the bone with denosumab, the effective duration of the therapy has not been determined so far.²² Many authors recommend that therapy is conducted for at least twelve months, indicating the risks of relapse with short treatment course.¹⁷ The clinical observation presented in this article is unique due to the young age of the patient. Our experience has shown that denosumab is effective in the pre-pubertal period. In addition, despite our initial concerns that therapy may lead to growth retardation, the child has maintained a normal growth rate for his age and sex. No side effects have been observed. However, the appearance of dense metaphyseal bands, a generalized increased mineral density of bone tissue and suppressed biomarkers of bone remodeling have been noted. These changes relate to a negative dynamics in bone quality and a potential increased risk of fracture, as in osteoprotective rickets.^{30,31} It should be noted that osteopetrosis could also be induced by treatment with bisphosphonates.³²⁻³⁴

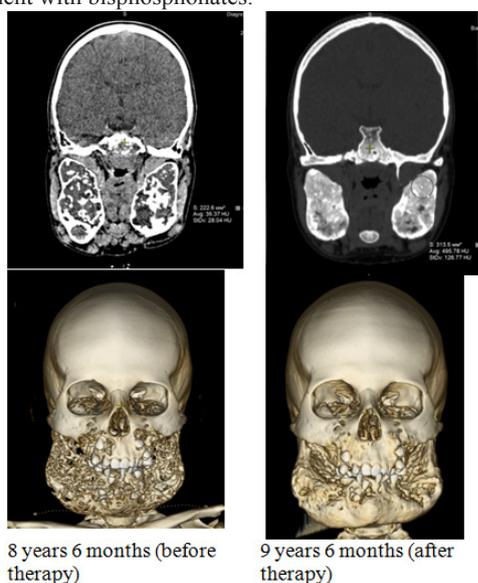


Figure 3 Dynamics of bone density before and after denosumab treatment.

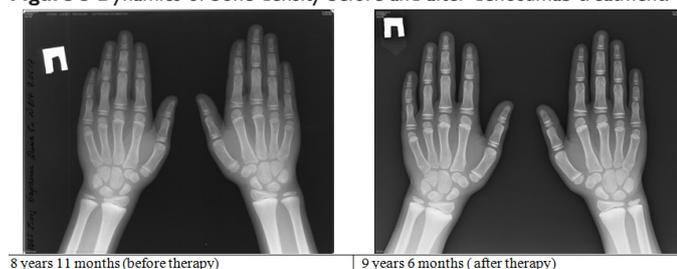


Figure 4 Dynamics of bone age according to radiography of hands.

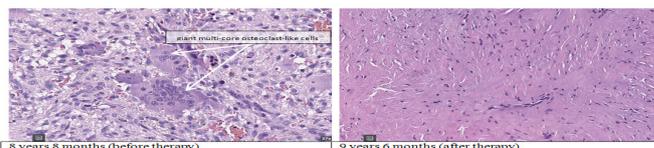


Figure 5 Histological pictures before and after the denosumab treatment

Table 1 Calcium and phosphorus levels during denosumab treatment

	Months of therapy					
	1	2	3	4	5	6
Alkaline phosphatase u/l	212	125	149	133	82	127
Phosphorus, mmol/l	1,15	1,06	1,04	1,23	1,3	1,28
Calcium total mmol/l	1,98	2,07	2,16	2,2	2,185	2,17

Conclusion

Inoperable forms of giant cell reparative granuloma and cherubism, a pronounced transformation of the upper and lower jaw require a complex treatment approach is required. It should include a course of denosumab therapy followed by contour resection of excess bone tissue in order to facilitate medical and social rehabilitation of such patients. Our experience and two cases described in the literature (10 years old girl and boy) by Karras NA¹⁵ & Kobayashi E et al.,¹⁶ have not shown a negative effect of the therapy on the growth zones. Start of denosumab therapy at the first signs of cherubism, typically at the age of 5-6 years, can prevent vast deformation of the jaws.

Acknowledgment

None.

Conflict of interest

The author declares no conflict of interest

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