Review paper

Observations of spontaneous cherubism based on two cases and a literature review

Własne obserwacje spontanicznego cherubizmu na przykładzie dwóch przypadków i przeglądu piśmiennictwa

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Key words: differential diagnosis, cherubism, X-ray changes.

Słowa kluczowe: diagnostyka różnicowa, cherubizm, zmiany radiologiczne.

Abstract

Cherubism is a genetically determined illness characterized by osseus lesions of the facial part of the skull. X-ray and histopathological analysis of cherubism show it to be similar to fibrosis dysplasia, a brown tumour that occurs in the parathyroids or giant cells. Our paper describes 2 cases of cherubism. In each of them, X-ray examination, histopathological analysis and genetic tests led to a diagnosis. In this study, in the first case, there was no mutation in the *SH3BP2* gene, which does not exclude the possibility that the mutation occurs in another gene. In the second case, in a patient diagnosed with cherubism after many years of observation and when clinical symptoms had worsened, genetic tests confirmed a mutation in exon 9 of the *SH3BP2* gene.

Streszczenie

Cherubizm to choroba uwarunkowana genetycznie, dotycząca kości części twarzowej czaszki. Schorzenie jest najczęściej diagnozowane u dzieci poniżej 5. roku życia. Obraz radiologiczny i histopatologiczny cherubizmu zbliżony jest do dysplazji włóknistej, guza brunatnego w nadczynności przytarczyc lub guzów olbrzymiokomórkowych. W artykule przedstawiono dwa przypadki cherubizmu. Oba przypadki rozpoznano na podstawie badania klinicznego potwierdzonego badaniami radiologicznymi, histopatologicznymi oraz testami genetycznymi. W niniejszej pracy w pierwszym przypadku nie stwierdzono mutacji genu *SH3BP2*, co nie wyklucza, że mutacja występuje w innym genie. W drugim przypadku u chorej, u której rozpoznanie cherubizm zostało ustalone po wieloletniej obserwacji i w momencie nasilenia objawów klinicznych, badania genetyczne potwierdziły mutację w egzonie 9 genu *SH3BP2*.

Introduction

Cherubism, according to the classification by Barnes *et al.*, developed in 2005 at the request of the WHO, is defined as "a benign disease inherited in an autosomal dominant manner and consisting in symmetrical, painless, bilateral enlargement of the jaw bones, which is clinically manifested by rounding facial features (chubby face) with a characteristic exposure of the limbus of the sclera, which makes the eyes look upwards. This gives the patient the appearance of cherubim depicted in Baroque paintings and works of art, hence the name of the disease 'cherubism'" [1–3]. The disease was first described in 1933 by William A. Jones, a Canadian radiologist in three of five siblings as familial multi-chamber cystic disease of the jaws, and in 1938 he described it as a disease entity and gave it the name cherubism. So far, approximately 300 cases of cherubism have been described [2–4]. Recent literature data show that cherubism is not a variant of fibrous dysplasia, as previously thought, but that its microscopic structure resembles that of giant cell granuloma [2, 5].

On the basis of an analysis of 65 patients, Anderson and McCladen determined the inheritance pattern as dominant and the mutation penetration rate is 100% for male family members and about 50–70% in female cases [6, 7]. Genetic tests revealed the presence of a mutated gene responsible for the occurrence of cherubism. The disease is caused by point mutations on the fourth chromosome (4p16.3) in the *SH3BP2* gene. The protein encoded by this gene contains the SH3 domain binding region of several proteins and acts as a cytoplasmic adapter protein. Mutations in the *SH3BP2* gene were first described by

Ueki *et al.* in 2001 [8]. Mutations in the gene encoding the SH3BP2 protein disrupt the interaction with the MSX-1 protein, which is responsible for the regulation of transcription in mesenchymal tissue during the morphogenesis of the facial part of the skull.

Confirmation of the diagnosis of the disease is possible thanks to molecular tests that detect the mutation in approximately 80% of patients. However, approximately 20% of patients with clinical symptoms of cherubism do not have mutations in the *SH3BP2* gene, which indicates the existence of another gene responsible for the symptoms of cherubism [8]. Individual families were also observed in which not all mutation carriers showed the features of the syndrome [9]. The severity of symptoms in patients can vary widely, so people with subtle symptoms may not be diagnosed [10].

The SH3BP2 protein also regulates the activity of the NFAT transcription factor, which is the master transcription factor in osteoclastogenesis [2, 11]. Disturbances in the functions of osteoclasts and osteoblasts result in the development of disorders characteristic of the symptoms of cherubism [12–14].

Carvalho *et al.* indicated that, in addition to genetic factors, the development of cherubism may be influenced by mesenchymal changes during the formation of the jaw bones as well as odontogenic, traumatic and hormonal factors [15].

In the diagnosis of cherubism, apart from subjective and physical examination, the radiological evaluation of the lesions and histopathological examination play an important role. The radiographic image of the bone shows symmetrical, clearly demarcated osteolytic lesions. They can cause thinning of the compacted lamellae, and even break their continuity. These cavities contain numerous bone septa in the form of bone trabeculae resembling the image of "soap bubbles". The affected teeth take the form of "floating teeth". The change in the radiological image of the bone progresses with age; the amount of spongy bone increases, giving an image of "frosted glass".

Currently, computed tomography (CT) plays the leading role in imaging diagnostics. The high sensitivity of the CT examination allows for the detection of bone changes that are not yet visible in conventional X-ray diagnostics [16, 17].

Histopathological examination is necessary to confirm a clinical diagnosis. On a microscopic image, numerous giant multinucleated cells appear surrounded by a connective tissue substrate. The fibrous stroma consists of numerous fibroblasts; it contains hemosiderin deposits and extravasated blood. A characteristic feature of the microscopic image in cherubism is the accumulation of fibroblasts in the vicinity of blood vessels in the form of eosinophilic "muffs". With the regression of changes, the connective tissue stroma is reduced and elements of newly formed neoplastic bone appear [2, 16, 18].

Treatment for cherubism is still under discussion. Therapeutic management varies depending on the severity of symptoms and includes long-term observation, pharmacotherapy and/or surgery. In pharmacotherapy, the following are used: bisphosphonates, calcitonin, corticosteroids, and monoclonal antibodies, e.g. denosumab [19, 20]. The last of these drugs, as reported in recent years, may be helpful in cases of cherubism resistant to treatment, as an alternative to surgical treatment. It can also be used after surgery to reduce the risk of recurrence [21, 22].

The treatment plan should take into account the patient's age and clinical symptoms. In the exacerbation of the disease there may be severe pain, then it is necessary to use painkillers, anti-swelling drugs and antibiotics. There have also been attempts to treat it with calcitonin and denosumab with varying degrees of success [22]. An adolescent patient should be informed that in most cases the disease goes into remission after puberty is reached, and periodic check-ups are required. Facial deformities and deformations are the most common indication for surgical treatment to improve the aesthetics of the face. Operations for modelling the facial bone structures are performed after the end of growth. According to most authors, the absence of anatomical, functional and aesthetic disorders is an indication for the application of the "watchful waiting" principle.

In the literature, cases of sporadic occurrence of non-familial cherubism have also been reported [23].

This paper presents 2 cases of sporadic occurrence of cherubism. The first case is of an adolescent female and the second is an example of a lengthy final diagnostic process. The family history of both patients was negative.

Methods

The literature review was carried out in July 2023 using the PubMed database, with the key words: cherubism and treatment, review, open-free access, recent 10 years. Two cases of spontaneously occurring cherubism are presented in this publication. Observed symptoms, diagnosis and management were compared with one of the most extensive literature reviews by Chrcanovic *et al.* [19].

Observation I

A 16-year-old patient was referred by a paediatric neurologist to the Maxillofacial Surgery Clinic due to symmetrical bilateral tuberosities in the right and left angle of the mandible with accompanying pain symptoms. On the day of the visit, the patient did not report any symptoms. Physical examination revealed asymmetry in the lower section of the facial part of the skull, caused by distension of the body of the mandible and mandibular branches, more intense on the right side. No pathological changes were observed in the upper

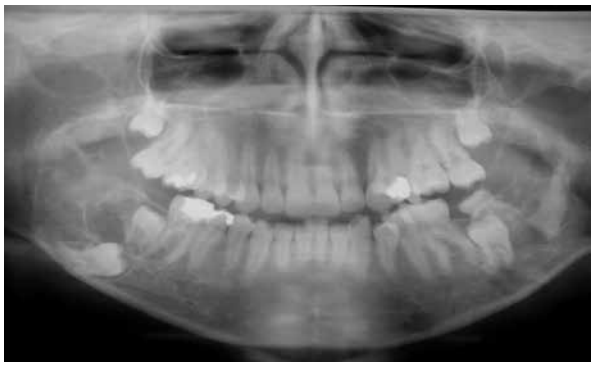

Figure 1. A 16-year-old patient, panoramic radiograph made on the day she reported for treatment

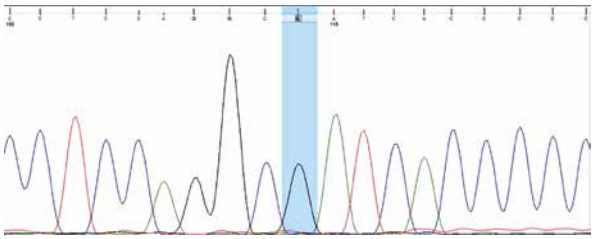

Figure 3. Fragment of the normal nucleotide sequence of exon 9 in the *SH3BP2* gene

section of the face. Intraoral hypodontia was found. A panoramic radiographic image revealed: osteolytic bone cavities in the area of the mandibular angles passing to the mandibular branches from the retained teeth 37, 38, 47, 48 (Figure 1).

CT examination of the facial part of the skull extended with a 3D reconstruction showed localized symmetrical destructive-osteolytic foci filled with soft tissue mass, with the presence of thin bone septa subject to contrast enhancement within the angles and both anterior parts of the mandibular branches. From the vestibular side, a symmetrical widening of the outline of the body of the mandible was found. There were small cavities in the thin segmental cortex (Figure 2).

The results of blood chemistry, total calcium, alkaline phosphatase, phosphorus and parathyroid hormone levels showed no abnormalities. A specimen was taken from the patient in order to establish a histopathological diagnosis. The result of the histopathological examination was inconclusive. The microscopic image indicated a reaction-reparative change of the reparative giant cell granuloma type. The differential diagnosis included bone changes in the course of hyperparathyroidism and cherubism. The reference centre was consulted on the preparations. The final result of the histopathological examination was determined as cherubism. Genetic tests were performed which consisted in the analysis of the nucleotide sequence of exon 9 in the *SH3BP2* gene. The examination did not reveal the presence of pathogenic mutations (Figure 3).

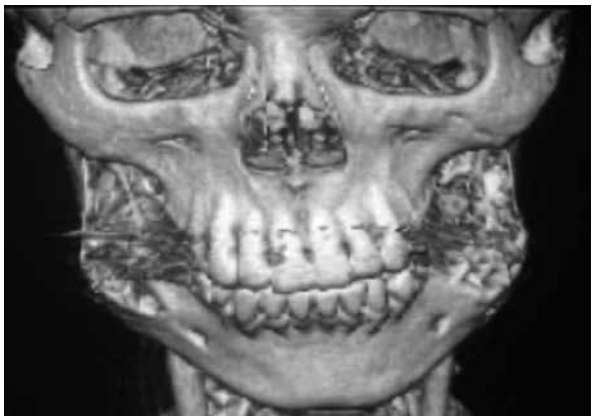

Figure 2. Computed tomography scan in 3D reconstruction

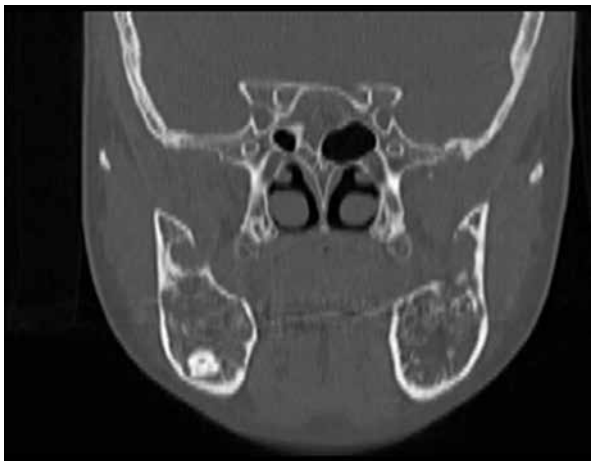

Figure 4. Computed tomography scan performed 9 years after the diagnosis

However, the test result does not exclude mutations in other exons. Due to the young age of the patient, gradual regression of symptoms and stable clinical picture, surgical treatment was not indicated. The patient was kept on observation with periodic check-up at the Outpatient Clinic. During exacerbations, she was treated symptomatically: painkillers, anti-swelling drugs and antibiotic therapy. For a long period of time, the patient did not go for a check-up because, as she stated, she did not experience any disturbing symptoms. After 8 years, clinical examination and computed tomography of the facial part of the skull showed no progression of the disease (Figure 4). Currently, the patient goes for periodic check-ups at the clinic.

Observation II

A 27-year-old woman came to the Maxillofacial Surgery Clinic due to facial pain on the right side. The pain had worsened in the period just before the visit to the clinic. In her general interview, she did

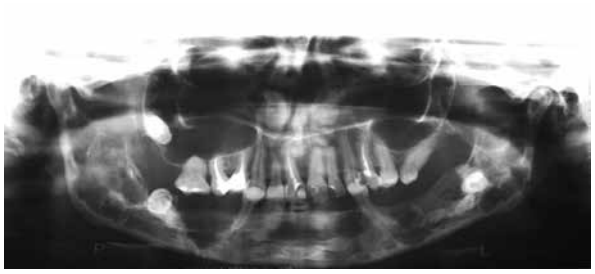

Figure 5. A 27-year-old patient, panoramic image taken on the day of the first visit to the Outpatient Clinic

not report any systemic diseases. In the clinical examination of the oral cavity, apart from numerous missing teeth in the lower dental arch, no abnormalities were found. X-ray was performed – a panoramic radiograph showed the presence of numerous destructive changes covering the entire width of the body of the mandible on the right side and the absence of teeth 18, 38, 33, 48 (Figure 5).

Based on the PAN examination, it was found that the pain symptoms reported by the patient might be related to the presence of retained teeth 18 and 48; therefore the patient was referred for surgical removal of the retained teeth (18, 48) with the simultaneous collection of tissue material from pathological foci located in the right mandibular angle. Histopathological examination revealed inflammatory granulation tissue with the presence of multinucleated giant cells, with proliferative, cell-rich fibrous tissue and inflammatory infiltrations from plasma cells. After surgical extraction of teeth 18 and 48 the pain disappeared. Based on the clinical examination together with the results of the histopathological examination, the patient was diagnosed with fibrous dysplasia of the mandible and a follow-up observation was recommended. The following years of observation did not show any disease progression. In the 5th year of follow-up, a CT check-up examination of the facial part of the skull was performed (Figures 6, 7).

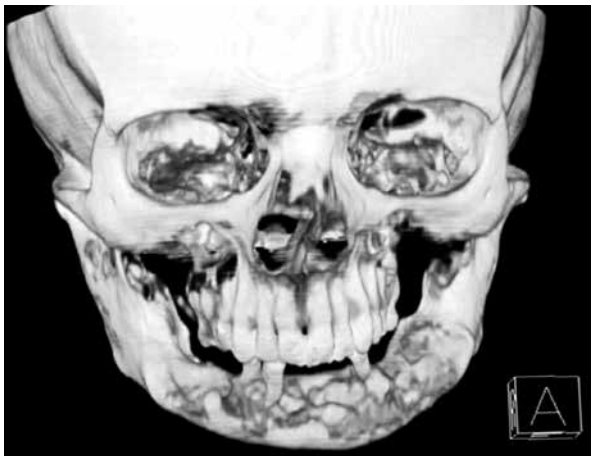

Figure 6. Computed tomography, 3D reconstruction made after 5 years of observation

The CT examination in the area of the mandibular body and branches revealed numerous osteolytic-destructive foci of various sizes, with segmental thinning or cavities in the mandibular cortex on the lingual side, which were filled with soft tissue mass with a density of 25–45 HU. Additionally, the presence of a retained tooth in the mandibular midline was described. The results of blood chemistry, total calcium, alkaline and acid phosphatase, phosphate and parathyroid hormone levels were within the reference age norm. The CT examination result and the clinical picture

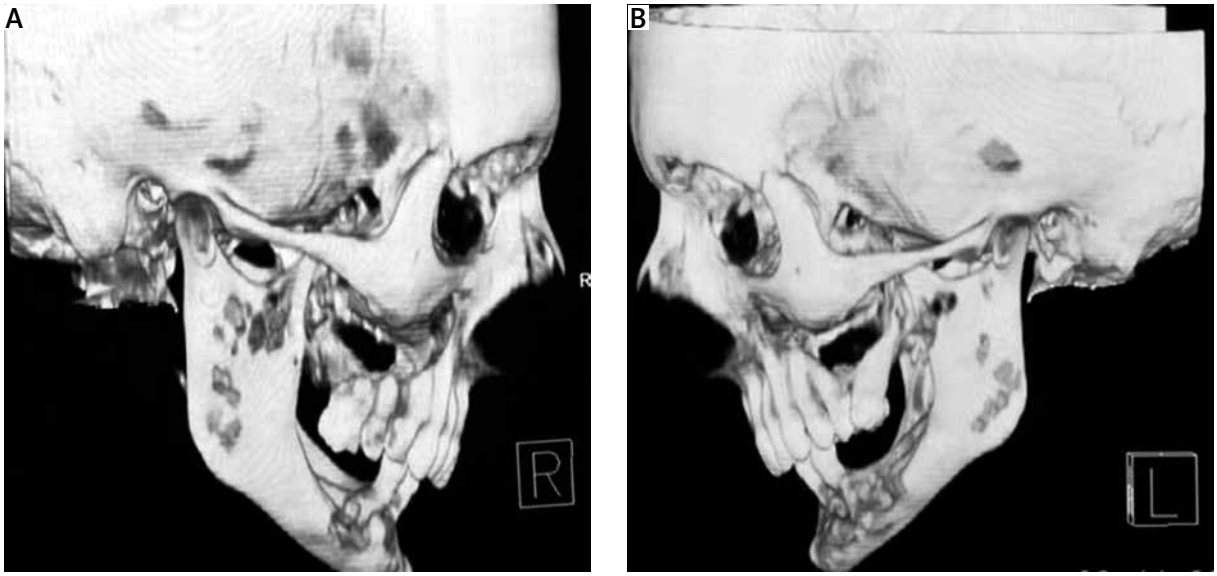

Figure 7. Computed tomography, 3D reconstruction in the 5th year of observation

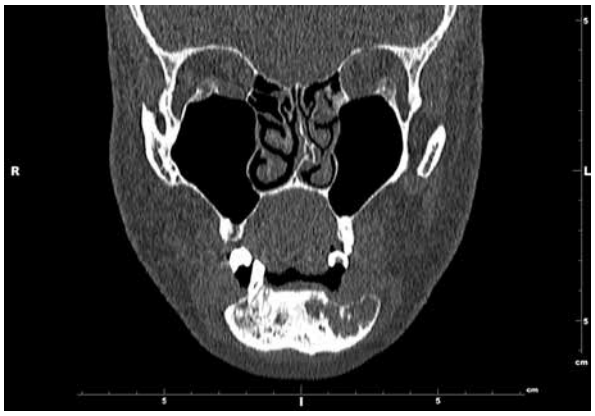

Figure 8. Computed tomography, reconstruction in the frontal plane, cross-section through the area of the mandibular symphysis in the 9th year of observation

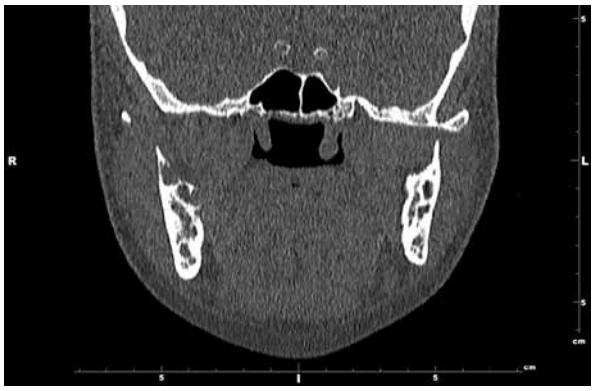

Figure 9. Computed tomography, reconstruction in the coronal plane, cross-section through the mandibular branches in the 9th year of observation

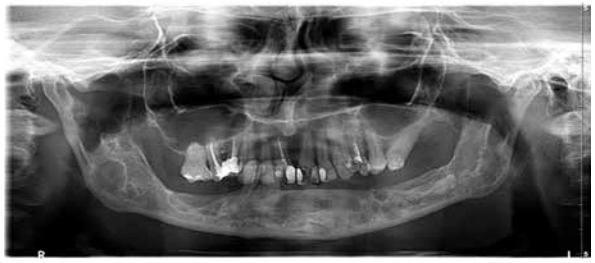

Figure 10. Panoramic X-ray taken after 9 years of observation

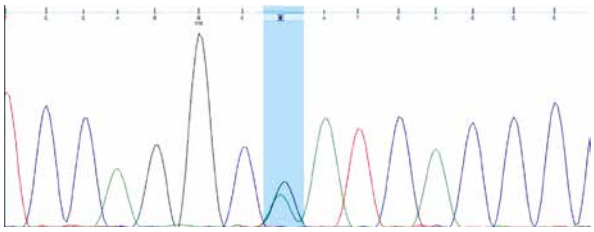

Figure 11. Nucleotide sequence – exon in *SH3BP2* gene with mutation c.1244G>A (pArg.415Gln)

confirmed the earlier diagnosis. The patient did not require surgery; the "watchful waiting" principle was applied. The patient was instructed to have periodic check-ups.

During subsequent follow-up visits, no progression of the disease was observed. In the 9th year of follow-up, the patient reported worsening loss of skin sensation on the right side of the projection of the mandibular body. Further studies were performed that showed the progression of lesions in the mandibular branches (Figures 8–10).

Bone material from the mandibular body and branches was again collected for histopathological examination, which showed numerous giant cells of the osteoclast type, without hemosiderin deposits. In the differential diagnosis, the pathologist suggested hyperparathyroidism, cherubism or an intraosseous giant cell lesion. Blood chemistry tests excluded hyperthyroidism and the presence of a giant cell lesion. Molecular tests of DNA isolated from peripheral blood lymphocytes were performed. Analysis of the nucleotide sequence of exon 9 in the *SH3BP2* gene revealed the presence of the pathogenic mutation c.1244> A (p.Arg415Gln) in a heterozygous arrangement (Figure 11). The previous diagnosis of the fibrous dysplasia as cherubism of the mandible was verified. The progression of changes in the facial skeleton did not significantly worsen the aesthetics of the facial features and did not lower the patient's quality of life. The patient remains under further clinical observation.

Results

One of the most extensive reviews of the literature on cherubism was made by Chrcanovic *et al.* [19]. The 2 cases of cherubism described in this paper fit into this review as Table 1.

Like most of the cases described in the literature review, the "wait and see" strategy was used in these 2 cases of cherubism.

Summary

Epidemiological data on cherubism confirm that it is a familial disease that occurs very rarely and is most often diagnosed in childhood. About 300 families with cherubism are described in specialist literature. In China, 24 such families have been described, and in Poland, 3 cases of familial occurrence of cherubism have been registered. The lesions are mainly located in the facial part of the skull. Changes in other locations have also been reported: ribs, pelvic bones and humerus. Some authors associate the occurrence of cherubism with other genetically determined diseases, such as Noonan syndrome, gingival fibromatosis and Ramon's syndrome [2, 4, 24]. Silva *et al.* described a case of an aggressive form of cherubism that

Table 1. The 2 cases of cherubism fit into Chrcanovic *et al*. review

Parameter	Results	Observation I	Observation II
Patients	513		
Sex (*n* = 488) (%):			
Male	279 (57.2)	0 (0/1)	0 (0/1)
Female	209 (42.8)	1 (0/1)	1 (0/1)
Age when symptoms were first perceived [years], mean ± SD (range)	5.6 ±3.8 (0–30) (*n* = 279)	16	27
Familial history (%)	310/458 (67.7)	0 (0/1)	0 (0/1)
SH3BP2 gene mutation (%)	*SH3BP2* gene mutation (%)	0 (0/1)	1 (0/1)
Swelling (expansion of the affected bones) (%)	382/401 (95.3)	0 (0/1)	1 (1/0)
Pain (%)	10/347 (2.9)	1 (0/1)	1 (0/1)
Radiological features Locularity appearance (*n* = 314):			
Multilocular (%)/unilocular + multilocular(%)	309 (98.4)/5 (1.6)	1 (0/1)	1 (0/1)
Radiodensity (*n* = 312):			
Radiolucent (%)/mixed (%)	289 (92.6)/23 (7.4)	1 (0/1)	1 (0/1)
Lesion limits (*n* = 234):			
Well-defined (%)/ill-defined (%)/mixture (%)	223 (95.3)/10 (4.3)/1 (0.4)	1 (0/1)	0 (0/1)
Tooth displacement (%)	256/271 (94.5)	0 (0/1)	0 (0/1)
Tooth root resorption (%)	71/177 (40.1)	0 (0/1)	0 (0/1)
Tooth agenesis (%)	114/184 (62.0)	1 (0/1)	1 (0/1)
Destruction of cortical bone (%)	72/204 (35.3)	1 (0/1)	1 (0/1)

dynamically led to respiratory failure and the death of a several-year-old patient [25]. In cherubism, changes in the skeletal system occur in early childhood. Structural reconstruction of bone and its replacement with fibrous tissue takes place, which leads to modelling and changing of its shape. Occlusion and occlusal disorders are observed, caused by abnormal tooth eruption, premature loss of deciduous teeth, difficult eruption of permanent teeth and resorption of tooth roots [4, 7]. Cherubism is characterized by the fastest progression in the first 2 years after the onset of the disease. The progression of changes slows down with age.

The first symptoms of tumour "withdrawal" appear at 8–12 years of age and concern the jaw. In the mandible, changes regress around the age of 15–20. Significant reduction in bone changes was observed between the 3rd and 5th decade of life [16, 24]. Laboratory tests of calcium, phosphate, alkaline phosphatase and parathyroid hormone levels often do not show any abnormalities [2, 16]. When the disease is detected by chance, it is stable and the clinical symptoms are not bothersome for the patient, the procedure of choice is the "watchful waiting" principle. Genetic tests and the detection of a gene mutation facilitate diagnosis. In this study, in the first case, there was no mutation in the *SH3BP2* gene, which does not exclude the possibility that the mutation occurs in another gene. In the second case, in a patient diagnosed with cherubism after many years of observation and when clinical symptoms had worsened, genetic tests confirmed a mutation in exon 9 of the *SH3BP2* gene.

In both of the presented cases, the only symptoms that caused the patients to seek medical attention were pain. The patients showed no obvious outward characteristics of cherubism. On the one hand, scarce disease symptoms hampered the diagnostic process, while on the other hand, they allowed for the observation of the disease over a long period of time. The final diagnosis was made in adult patients a few years after the patients entered treatment. Lack of symptoms among other family members may suggest occasional cherubism. In order to confirm the presence of non-familial cherubism, mutation of the *SH3BP2* gene should be excluded in all family members.

Conflict of interest

The authors declare no conflict of interest.

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