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Systematic Review
Clinical Pathology

Cherubism: a systematic literature review of clinical and molecular aspects

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Abstract. The purpose of this review was to integrate the clinical, radiological, microscopic, and molecular data of published cherubism cases, in addition to therapeutic approaches, to provide more concise information about the disease. An electronic search was undertaken in September 2019. Eligibility criteria included publications having enough clinical, radiological, and histological information to confirm the diagnosis. A total of 260 publications reporting 513 cherubism cases were included. Familial history was observed in 310/458 cases (67.7%). *SH3BP2* mutations were reported in 101/108 cases (93.5%) and mainly occurred at protein residues 415, 418, 419, and 420. Retrospective clinical grading was possible in 175 cases. Advanced clinical grading was associated with tooth agenesis, but not with other clinical, radiological, and genetic features. Specific amino acid substitutions of *SH3BP2* mutations were not associated with the clinical grading of the disease. 'Wait and see' was the most common therapeutic approach. In a small number of cases, drugs were used in the treatment, with variable response. In conclusion, there is no clear correlation between the genotype and the phenotype of the disease, but additional genomic and gene expression regulation information is necessary for a better understanding of cherubism.

Key words: cherubism; genetics; *SH3BP2*; giant cell lesions of the jaws; bone lesions; bone pathology; skeletal pathology.

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Cherubism (OMIM #118400) is a rare autosomal dominant bone disorder characterized by symmetrical expansion of the jaws where giant cell lesions replace the bone. The disease was first reported in 1933[1]. The bone lesions and fibrous tissue expansions in cherubism increase before puberty and regress thereafter[2], with the lesions becoming filled in by woven bone later in life[3]. However, the disease shows variable expressivity and the clinical presentation may range from asymptomatic bilateral mandibular/maxillary swelling to deforming, life-threatening bone lesions[4–6]. Although the microscopic features of this lesion are not unique as they resemble giant cell lesions of the jaws (giant cell granulomas), eosinophilic cuff-like perivascular deposits can be seen and are suggestive of cherubism[7].

The cherubism locus was mapped to chromosome 4p16 in the late 1990s[8,9], with subsequent identification of missense mutations in the gene encoding the adapter

0901-5027/01043 + 011

protein *SH3PB2* (SH3-domain binding protein 2) within this locus in the early 2000s[10]. This genetic alteration is present in approximately 80% of the cases[10]. Although case reports and series suggest that the patient's genotype is not a clinical determinant of the clinical phenotype[2,4], the rarity of this disease can pose challenges to the analysis of any possible genotype–phenotype correlation.

Considering that more case reports of cherubism, including some with genetic evaluation of the *SH3BP2* gene, have been published in recent years, the aim of this review was to integrate the clinical, radiological, microscopic, and molecular data of published cherubism cases, in addition to the therapeutic approaches, to provide more concise information about the disease.

Materials and methods

This study followed the guidelines of the PRISMA Statement[11].

Objectives

The aim of this systematic review was to analyse the cases of cherubism published in the literature, with a focus on the possible association between clinical staging and familial history with clinical, microscopic, and molecular features.

Three focused questions were developed using the PICO format (participants, interventions, comparisons, outcomes): (1) Does the clinical staging of the disease have any relationship with other clinical, radiological, and microscopic features and the presence of *SH3BP2* variants? (2) Do familial cases have a different clinical presentation compared to sporadic cases? (3) Does the *SH3BP2* mutational spectrum have any association with the clinical presentation of the disease?

Search strategies

An electronic search without time restriction was undertaken in September 2019 in the following databases: PubMed/MEDLINE, Web of Science, ScienceDirect, J-STAGE, and LILACS. The following term was used in the search strategies: (cherubism OR cherubismus).

Google Scholar was also checked, and a manual search of all related oral pathology, maxillofacial, and specialist dental and oral journals was performed. The reference lists of the identified studies and relevant reviews on the subject were also checked for possible additional studies. Publications with patients identified by other authors as having cherubism, even those not having the term in the title of the article, were also re-evaluated.

Inclusion and exclusion criteria

Publications reporting cases of cherubism with enough clinical, radiological, and histological information to confirm the diagnosis were included. Publications not reporting details of the alterations in the jaws were excluded, as well as cases of patients with rarely associated syndromes, such as Noonan syndrome, Ramon syndrome, fragile X syndrome, Dandy–Walker syndrome, and polycystic ovary syndrome. Cases with single lesions were excluded unless they had a family history or *SH3PB2* mutations. Cases without biopsy results were excluded unless an *SH3BP2* mutation was reported. Cases with a family history were included, even if only one of the family members had the diagnosis confirmed by biopsy or molecular investigation. All cases without radiological information were excluded.

Definitions

The grading system proposed by Motamedi[12], which classifies cases by grade, class, and subclass, was used. Microscopically, the jawbone lesions of cherubism show vascular fibrous connective tissue with clusters of multinucleated giant cells. In some cases, eosinophilic cuff-like perivascular deposits are observed[7]. Cases in which more than one case was reported in the same family were considered familial.

Study selection

The titles and abstracts of all reports identified through the electronic searches were read independently by the authors. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained. Disagreements were resolved by discussion between the authors. The clinical and radiological aspects, as well as the histological description of the lesions reported in the publications were thoroughly assessed by one of the authors (R.S.G.), an expert in oral pathology, in order to confirm the diagnosis of cherubism.

Data extraction

The following data were extracted: patient's sex and age, duration of the condition before the first consultation, classification of the condition according to the clinical grading system proposed by Motamedi[12], presence of mutations in the *SH3BP2* gene, familial history of cherubism, swelling (expansion of affected bones), destruction of cortical bone, presence of clinical symptoms, locularity in radiological examinations (unilocular/multilocular), radiodensity (radiolucent/mixed), radiological limits (well-defined/ill-defined), tooth displacement, tooth root resorption, tooth agenesis, presence of eosinophilic cuffing (perivascular hyalinosis), treatment performed, and follow-up period. Authors were contacted for possible missing data.

Analysis of *SH3BP2* mutation

All cases with reported mutations in *SH3BP2* were evaluated and the mutations were recorded following the cDNA transcript ID ENST00000503393.8 sequence in the Ensembl Genome Browser database (accessed at https://www.ensembl.org/index.html), which corresponds to NCBI reference sequence **NM_001122681.2**. Notation at the protein level followed the UniProt canonical sequence (ID P78314-1, accessed at https://www.uniprot.org). For analysis, the cases were grouped by mutations, considering specific amino acid substitutions.

Analyses

Descriptive statistics were used to record the data, including the mean and standard deviation (SD) values and percentages. The Kolmogorov–Smirnov test was used to test the normality of the distribution of variables, and Levene's test was used to evaluate homoscedasticity. The Student *t*-test or Mann–Whitney test was performed to compare two independent groups, and one-way analysis of variance (ANOVA) or he Kruskal–Wallis test to compare three independent groups, depending on the normality of the data distribution and homoscedasticity. The Pearson χ^2 test or Fisher's exact test was used for categorical variables, depending on the expected count of events in a $k \times k$ contingency table. The level of statistical significance was set at $P < 0.05$. All data were statistically

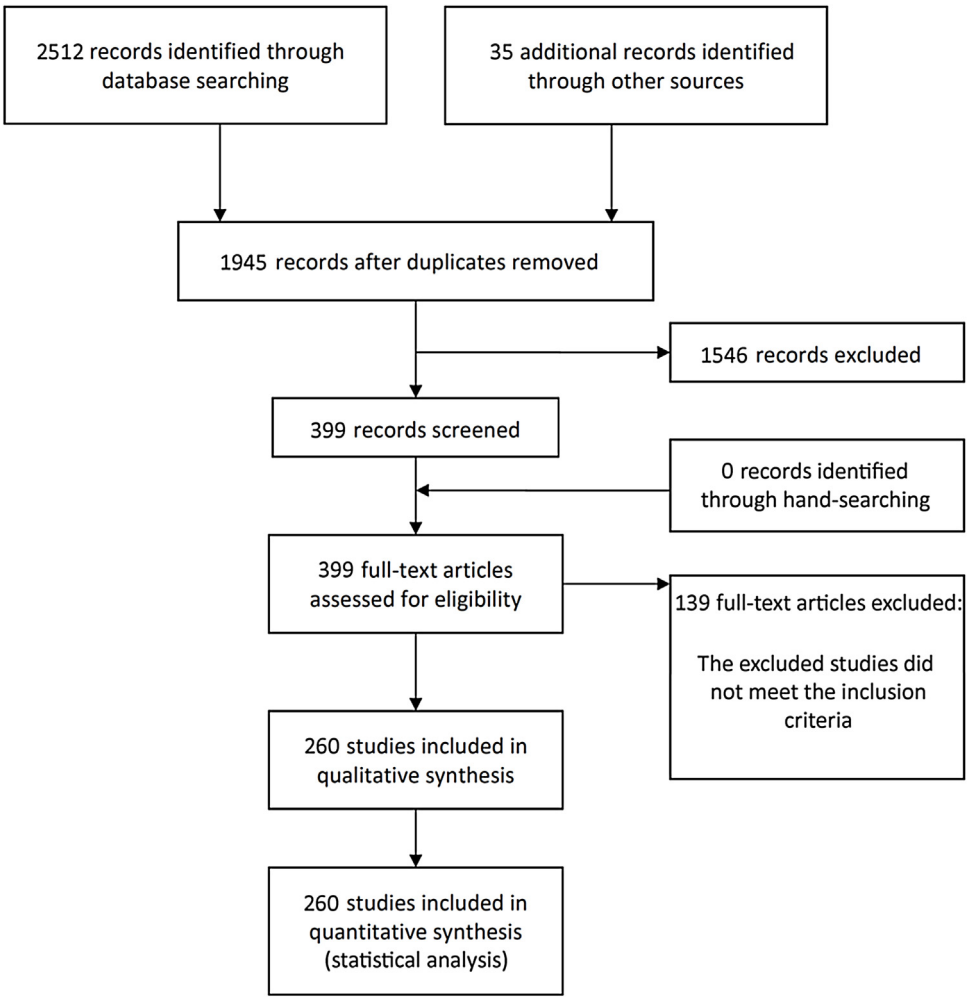

Fig. 1. Study screening process.

analysed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Literature search

The study selection process is summarized in Fig. 1. The search strategy in the databases resulted in 2512 papers, and 35 additional eligible papers were found in Google Scholar. Finally, a total of 260 publications were included (these publications are listed in the Supplementary Material Appendix).

Description of the studies and analyses

Table 1 presents the demographic and clinical features of all 513 cases of cherubism with enough clinical, radiological, and microscopic information to confirm the diagnosis. The disease predominantly affected males (57.2%). The patients had a mean ± SD age of 5.6 ± 3.8 years when symptoms were first perceived, and of 12.4 ± 11.0 years at first consultation for diagnosis. A familial history was reported in 310 of the 458 cases with available information (67.7%). Most of the cases were expansive (95.3%), showed a multilocular (98.4%) and radiolucent (92.6%) radiological appearance, exhibited well-defined radiological limits (95.3%), and showed tooth displacement (94.5%) and tooth agenesis (62.0%). Signs of tooth root resorption (40.1%) and destruction of cortical bone (35.3%) were also frequent radiological features reported. Histological eosinophilic cuffing was reported in 28.1% of the cases. The authors reported various surgical approaches, but in most of the cases, the 'wait and see' approach was the choice.

Different drugs for the treatment of cherubism were also used in 17 patients (Table 2); these included bisphosphonates, calcitonin, corticosteroids, denosumab, imatinib, interferon, and a tumour necrosis factor (TNF) inhibitor. Some cases showed regression of the lesions after drug treatment, while this treatment was unsuccessful in others. The first treatments with drugs were reported in the year 2000, but eight out of the 17 cases were reported in studies published from 2017 onwards.

A retrospective analysis of the clinical grading of the disease, according to Motamedi[12], was possible in 175 cases. For the grading of cherubism, it is necessary to have information about the presence of solitary or multiple lesions, location and severity of the condition, root resorption, and involvement of the condyle or coronoid processes. The main clinical, radiographic, and microscopic features according to the clinical grading of the disorder are presented in Table 3. Tooth agenesis was mainly observed in cases with advanced clinical stages. The other variables, including age, sex distribution, familial history, and presence of *SH3BP2*

Table 1. Demographic and clinical features of patients with cherubism described in the literature (cases with enough clinical, radiological, and histological information to confirm the diagnosis).

Variables[a]	
Patients (*n*)	513
Sex (*n* = 488) (%)	
Male	279 (57.2)
Female	209 (42.8)
Age when symptoms were first perceived (years), mean ± SD (range)	5.6 ± 3.8 (0–30) (*n* = 279)
Age at first consultation (years), mean ± SD (range)	12.4 ± 11.0 (1–84) (*n* = 488)
Familial history (%)	310/458 (67.7)
SH3BP2 gene mutation (%)	101/108 (93.5)
Swelling (expansion of the affected bones) (%)	382/401 (95.3)
Pain (%)	10/347 (2.9)
Radiological features	
Locularity appearance (*n* = 314)	
Multilocular (%)/unilocular + multilocular[b] (%)	309 (98.4)/5 (1.6)
Radiodensity (*n* = 312)	
Radiolucent (%)/mixed (%)	289 (92.6)/23 (7.4)
Lesion limits (*n* = 234)	
Well-defined (%)/ill-defined (%)/mixture (%)	223 (95.3)/10 (4.3)/1 (0.4)
Tooth displacement (%)	256/271 (94.5)
Tooth root resorption (%)	71/177 (40.1)
Tooth agenesis (%)	114/184 (62.0)
Destruction of cortical bone (%)	72/204 (35.3)
Eosinophilic cuffing (%)	63/224 (28.1)
Grade (according to Motamedi, 1998[12]) (*n* = 175) (%)	
I	59 (33.7)
II	43 (24.6)
III	13 (7.4)
IV	45 (25.7)
V	15 (8.6)
Treatment (as the first therapeutic approach) (*n* = 431) (%)	
'Wait and see'	226 (52.4)
Curettage	87 (20.2)
Debulking/osteoplasty	85 (19.7)
Drugs	12 (2.8)
Radiotherapy	10 (2.3)
Marginal resection	6 (1.4)
Enucleation	3 (0.7)
Resection with continuity	2 (0.5)
Time-related variables	
Follow-up time (months), mean ± SD (range)	70.7 ± 71.7 (0.5–348) (*n* = 243)
Time from the first symptoms to first consultation (months), mean ± SD (range)	82.6 ± 93.3 (0–528) (*n* = 241)
Total time from the first symptoms to last follow-up[c] (months), mean ± SD (range)	112.0 ± 96.6 (1–528) (*n* = 293)

SD, standard deviation.

[a] For the cases with available information.

[b] Lesions that presented different areas with very distinct locularity appearances: one area unilocular and the other multilocular.

[c] This 'last follow-up' could be the only consultation. This is why the mean value here is higher than the mean value for 'follow-up' above, which only counts from the first consultation to the last visit.

mutation, were not associated with the staging of the disease. The 'wait and see' approach was the leading choice for the less aggressive cases, and patients graded IV and V were more commonly treated with surgery. When the clinical, radiological, and microscopic features were compared between the patients with a history of cherubism in the family and the sporadic cases, a significant association for *SH3BP2* gene mutation in the familial cases was found (data not shown).

SH3BP2 gene mutation analysis

Forty-two studies assessed *SH3BP2* mutations[4,13–53]. *SH3BP2* mutations were detected in 101/108 (93.5%) cases. Considering cases in which this information was available, 80 familial and 14 sporadic cases presented *SHP3BP2* mutations. One familial and six sporadic cases did not have the mutation confirmed. In 93.1% of the cases (94/101), *SH3BP2* mutations were identified in exon 9, within a six-amino acid interval (415R–420G) (Figs 2 and 3). The *SH3PB2* mutation c.1244G>A, leading to p.R415Q, was the most frequent mutation reported in both familial (24/80) and sporadic (4/14) cases. Table 4 shows a detailed description of the *SH3BP2* mutations reported in the literature, with the number of cases for each mutation and the clinical grading of the disease. No association was found between the clinical staging of the disease and the different *SH3BP2* mutations detected.

Discussion

The aim of this study was to integrate the available data published in the literature on cherubism. By integrating the available data on each unique condition, it is possible to refine and improve the understanding and definition of each pathological entity, providing valuable information to be used by pathologists, clinicians, and surgeons in the diagnosis and design of the treatment plan[54–58]. In this work, 513 published cases of cherubism were identified and reviewed. During the selection of the studies for the analysis, some cases with a diagnosis suggestive of cherubism were excluded because only clinical and radiological data were available. Although the clinical and radiological features of cherubism are characteristic, in this study the absence of biopsy or *SH3BP2* genetic analysis were adopted as exclusion criteria. When a familial history was positive, the cases were included if at least one of the individuals affected had the diagnosis confirmed by biopsy or genetic analysis. It is important to highlight that other bone tumours or cysts may manifest as multiple jaw lesions in young patients. In addition, as cherubism regresses with aging, it was not possible to confirm the diagnosis in some adult patients unless good documentation of the case was available in the article. Due to the retrospective nature of the study, these procedures were necessary to have a more accurate selection process.

The demographic and clinical features observed in the study group confirm what has been reported about cherubism. A slight male predominance (56%) was observed, consistent with the reported lower penetrance of the disease in females compared to males[59]. Of note, some authors have not observed such a reduced pene-

Table 2. Reported use of drugs for the treatment of cherubism lesions.

Drug	Mechanisms of action and effects	Reports in which the drug was used	Clinical results in these reports
Bisphosphonates	Bisphosphonates are a class of drugs that prevent the loss of bone density, used to treat osteoporosis and similar diseases. Bisphosphonate molecules attach to and enter osteoclasts, where they disrupt intracellular enzymatic functions needed for bone resorption.	Hart et al. (2000)	• Hart et al. (2000): Drug therapy for at least 36 months was started at the age of 23 years. Radiological examination of the jaws showed bone production.
		Kugushev et al. (2018)	• Kugushev et al. (2018): Drug therapy for unknown period of time was started at the age of 9 years. The progressive growth of the jaws persisted throughout the therapy. It was then decided to initiate drug therapy with denosumab.
Calcitonin	Calcitonin is an amino acid peptide hormone and acts to reduce blood calcium (Ca^{2+}), opposing the effects of parathyroid hormone (PTH).	Hart et al. (2000)	• Hart et al. (2000): Drug therapy was started at the age of 22 years, but it was discontinued after 12 months as the patient became nauseous after the injections and found that daily subcutaneous administration was a nuisance. Treatment was continued with bisphosphonates.
		Lannon and Earley (2001)	• Lannon and Earley (2001): Drug therapy was started at the age of 7 years, but it was discontinued after 6 months as no clinical or radiological improvement was seen.
		de Lange et al. (2007a)	• de Lange et al. (2007): Drug therapy for 15 months was started at the age of 11 years, after recurrence of the lesions and after curettage at the age of 10 years. Almost complete regression of the lesions was shown after 3 years of follow-up.
		Etoz et al. (2011)	• Etoz et al. (2011): Drug therapy for 30 months was started at the age of 14 years. ''Significant radiographic improvement was observed.''
		Fernandes et al. (2011)	• Fernandes et al. (2011): Drug therapy for 12 months was started at the age of 18 years, initiated immediately after partial curettage and filling with autogenous cancellous bone and bone marrow grafts. There was formation and replacement of the lesion by neoformed bone tissue after 4 years.
		Kömerik et al. (2014)	• Kömerik et al. (2014): Drug therapy for 6 months was started at the age of 11 years. No regression of the lesion was observed. The drug was withdrawn from the market in the country. Then partial excision of the lesion was performed.
		Mazhar et al. (2018)	• Mazhar et al. (2018): Drug therapy for 12 months was started at the age of 11 years, followed by curettage and osteoplasty at the age of 12 years. No follow-up information about the bone tissue was provided.
Corticosteroids	Although the mode of action is still not fully understood, dexamethasone has a direct effect on osteoclast formation and activity, stimulating the proliferation and differentiation of human osteoclast precursors and inhibiting the bone-resorbing activity of mature osteoclasts (Hirayama et al., 2002[a]).	Machado et al. (2017)	• Machado et al. (2017): Drug therapy for an unknown period of time at an unknown age of the patient. The therapy was unsuccessful.
Denosumab	Human monoclonal antibody. It inhibits the maturation of osteoclasts by binding to and inhibiting receptor activator of nuclear factor kappa-B ligand (RANKL).	Kugushev et al. (2018)	• Kugushev et al. (2018): Drug therapy for 6 months was started at the age of 9 years, after non-effective treatment with bisphosphonates. The bone density increased and the size of the tumour nodes reduced.

Table 2 (*Continued*)

Drug	Mechanisms of action and effects	Reports in which the drug was used	Clinical results in these reports
Imatinib	Tyrosine kinase inhibitor. Tyrosine kinases are enzymes responsible for the activation of many proteins by signal transduction cascades. The mechanism of action of imatinib in cherubism is completely speculative and requires further research (Ricalde et al., 2019).	Eiden et al. (2017)	• Eiden et al. (2017): Drug therapy for 24 months was started at the age of 5 years. After 6 months, there was a significant size regression of the bony lesions. After 2 years of therapy, only residual tissue proliferation of the maxilla and mandible was evident.
		Ricalde et al. (2019)	• Ricalde et al. (2019): 3 patients, drug therapy for 10–12 months was started at age 4, 8, and 8 years, respectively. The lesions involuted, allowing regression of symptoms, improvement and normalization of facial dysmorphology, and correction of dental malocclusion and dental eruption issues
Interferon	Interferons belong to the large class of proteins known as cytokines, molecules used for communication between cells to trigger the protective defences of the immune system that help eradicate pathogens.	Kau et al. (2012)	• Kau et al. (2012): Drug therapy for an unknown period of time was started at the age of 15.3 years. The patient already did not show any obvious facial deformity or swelling from the beginning of the therapy.
Tumour necrosis factor (TNF) inhibitors	TNF inhibitors suppress the physiological response to TNF, which is part of the inflammatory response.	Hero et al. (2013)	• Hero et al. (2013): 2 patients, drug therapy (adalimumab) for 27–31 months was started at age 4.8 and 7.3 years, respectively. In one patient, the clinical changes related to cherubism progressed steadily during the treatment and surgery was planned to reduce the cherubism-related changes. In the other patient, no clear progression of the cherubism-associated changes in the facial contour was observed during the treatment.
		Stoor et al. (2017)	• Stoor et al. (2017): Drug therapy for an unknown period of time. It did not clearly lead to regression of the lesions and did not prevent expansion in active cherubism.

The references are listed in the Supplementary Material Appendix.

[a] Hirayama T, Sabokbar A, Athanasou NA. Effect of corticosteroids on human osteoclast formation and activity. J Endocrinol 2002: 175: 155–163.

trance in females[4,9,34]. In the present study, a clinical familial history was observed in about two thirds of the cases, and in most of the familial or sporadic cases the patients presented asymptomatic swelling. Radiologically it was found that the jaw lesions were usually radiolucent, multilocular, with well-defined limits and were associated with tooth displacement, root resorption, or agenesis. Regarding the cases with sufficient information to evaluate the clinical grading, an increased proportion of cases showing tooth agenesis was observed in the group with more advanced disease. However, clinical staging was not associated with patient age, familial history, or other clinical and radiographic features. Interactions between *SH3BP2*-dependent signalling transduction pathways and mechanisms involved in dental development and jaw morphogenesis have been proposed to explain the rate of molar agenesis in patients with cherubism[15]. The fact that the clinical course of cherubism coincides with the period of development of the second and third molars corroborates this hypothesis[15].

Microscopically, eosinophilic collagen cuffing around small blood vessels is occasionally reported in cherubism. This perivascular cuffing was observed in 28.1% of the cases for which the authors had included some description of the microscopic features. Although this aspect is not always present[7,60], it can raise the suspicion of this diagnosis in challenging cases and it is considered pathognomonic of cherubism[61]. However, it was observed that this histopathological feature is not associated with the clinical grading or familial occurrence of the disease.

After the cherubism locus was mapped to chromosome 4p16[8,9], Ueki et al.[10] identified missense mutations in *SH3PB2*. In this first study showing a causative mutation for cherubism, the authors reported mutations in *SH3BP2* exon 9, which most frequently affected protein residues 418 (eight families), 415 (two families), and 420 (two families)[10]. Interestingly, on the basis of the results of the present review, residues 415, 418, and 420 are the ones in which most mutations have been described so far, followed by residue 419 (Fig. 3). No specific clinical staging profile could be established for the most frequent variants detected. Mutations outside *SH3BP2* exon 9 have been reported in a few cases, in exons 3 and 4[22,24]. The fact that most authors have only sequenced exon 9 might have contributed to the small proportion of mutations reported outside this hotspot, though.

In this review, it was revealed that *SH3BP2* mutations occurred in 93.5% of cherubism cases in which the mutation was investigated. This observation is in line with the original report by Ueki et al.

Table 3. Comparison of the demographic and clinical features between cherubism patients with different grades of the condition (according to Motamedi 1998[12]).

Variables[a]	Grade					*P*-value
	I	II	III	IV	V	
Patients (*n*)	59	43	13	45	15	
Sex (%)						0.602[c]
Male	39 (66.1)	27 (62.8)	7 (53.8)	23 (51.1)	9 (60.0)	
Female	20 (33.9)	16 (37.2)	6 (46.2)	22 (48.9)	6 (40.0)	
Age when symptoms were first perceived (years), mean ± SD (range)	6.1 ± 3.9 (1–15) *n* = 34	4.6 ± 3.2 (0–12) *n* = 27	5.6 ± 2.8 (2 – 8.9) *n* = 7	4.2 ± 1.7 (1 -8) *n* = 29	5.3 ± 4.0 (2–18) *n* = 14	0.390[d]
Age at first consultation (years), mean ± SD (range)	9.9 ± 5.2 (2–29) *n* = 59	8.4 ± 5.1 (2–25) *n* = 43	13.6 ± 6.4 (4.5–24) *n* = 13	10.9 ± 6.5 (2–27) *n* = 45	11.3 ± 8.6 (4–33) *n* = 15	0.078[d]
Familial history (%)	29/56 (51.8)	22/43 (51.2)	7/13 (53.8)	20/40 (50.0)	9/14 (64.3)	0.920[c]
SH3BP2 gene mutation (%)	16/17 (94.1)	13/14 (92.9)	1/2 (50.0)	14/14 (100)	5/5 (100)	0.208[e]
Swelling (expansion of the affected bones) (%)	45/54 (83.3)	39/39 (100)	12/12 (100)	42/42 (100)	11/12 (91.7)	0.002[e]
Pain (%)	0/53 (0)	2/36 (5.6)	0/13 (0)	2/42 (4.8)	0/10 (0)	0.377[e]
Radiological features						
Locularity appearance						
Multilocular (%)/uni + multi[b] (%)	54 (98.2)/1 (1.8)	38 (95.0)/2 (5.0)	13 (100)/0 (0)	43 (95.6)/2 (4.4)	12 (100)/0 (0)	0.835[e]
Radiodensity						
Radiolucent (%)/mixed (%)	52 (96.3)/2 (3.7)	39 (97.5)/1 (2.5)	12 (92.3)/1 (7.7)	42 (93.3)/3 (6.7)	13 (100)/0 (0)	0.699[e]
Lesion limits						
Well-defined (%)/ill-defined (%)	50 (98.0)/1 (2.0)	38 (100)/0 (0)	13 (100)/0 (0)	39 (92.9)/3 (7.1)	9 (90.0)/1 (10.0)	0.212[e]
Tooth displacement (%)	46/53 (86.8)	36/38 (94.7)	12/13 (92.3)	39/41 (95.1)	9/10 (90.0)	0.546[e]
Tooth agenesis (%)	17/50 (34.0)	24/38 (63.2)	3/12 (25.0)	30/34 (88.2)	6/7 (85.7)	<0.001[e]
Destruction of cortical bone (%)	9/49 (18.4)	15/37 (40.5)	3/12 (25.0)	10/34 (29.4)	5/9 (55.6)	0.085[e]
Eosinophilic cuffing (%)	12/34 (35.3)	9/29 (31.0)	3/10 (30.0)	5/24 (20.8)	7/12 (58.3)	0.276[e]
Treatment (as the first therapeutic approach) (%)						
'Wait and see'	38 (70.4)	28 (68.3)	7 (58.4)	20 (46.5)	4 (26.7)	0.036[e]
Curettage	11 (20.4)	10 (24.4)	1 (8.3)	8 (18.6)	5 (33.3)	
Debulking/osteoplasty	2 (3.7)	3 (7.3)	3 (25.0)	7 (16.3)	5 (33.3)	
Drugs	3 (5.5)	0 (0)	0 (0)	6 (13.9)	0 (0)	
Enucleation	0 (0)	0 (0)	1 (8.3)	2 (4.7)	0 (0)	
Resection with continuity	0 (0)	0 (0)	0 (0)	0 (0)	1 (6.7)	

SD, standard deviation.
[a] For cases where the information on grading of the condition was available.
[b] Lesions that presented different areas with very distinct locularity appearances: one area unilocular and the other multilocular.
[c] Pearson χ^2 test.
[d] Kruskal–Wallis test.
[e] Fisher's exact test.

published in 2001; they studied 15 cherubism families and reported *SH3BP2* exon 9 mutations in 12/15 (80%) of these families[10]. According to the present analysis, the presence of *SH3BP2* mutations was not related to the clinical grading of the disease, but they were more frequently observed in the familial cases. The authors speculate that this observation results from the fact that when there was a familial history, the investigators were more prone to conduct a genetic analysis in the cases.

While *SH3BP2* mutations are the genetic basis of most cherubism cases, it is intriguing that some cases were *SH3BP2* wild-type. As suggested previously[10], cherubism in these cases might have been caused by mutations in other genes, but such genetic mutations have not yet been uncovered. The most intriguing fact surrounding the cherubism genotype–phenotype correlation is the variable penetrance, illustrated by the fact that there are asymptomatic *SH3BP2* mutation carriers who do not develop the disease. While several studies have assessed the effects of *SH3BP2* mutations in vitro[62–71] and in vivo[62,63,65–71], the functional effects of such mutations and the mechanisms of gene expression control that run the genotypic–phenotypic interaction are yet to be clarified.

As cherubism is usually a self-limiting disease with signs of involution of the tumour-like lesions to be expected after puberty, the usual management of affected individuals consists of longitudinal observation[28]. In line with that, the 'wait and see' approach was the treatment choice reported for most of the cases reviewed, especially for the less aggressive cases. Early surgical intervention is contraindicated because it appears to predispose to recurrences[72]. Some cases of regrowth after minor surgical procedures have been reported[45,73–75]. However, it is still not well established whether surgery could really have induced tumour progression or whether surgery in these cases was performed in patients becoming symptomatic in a phase of rapid growth that continued after surgery[45]. Surgical treatment appears to be unnecessary when the condition is of low grade in the absence of

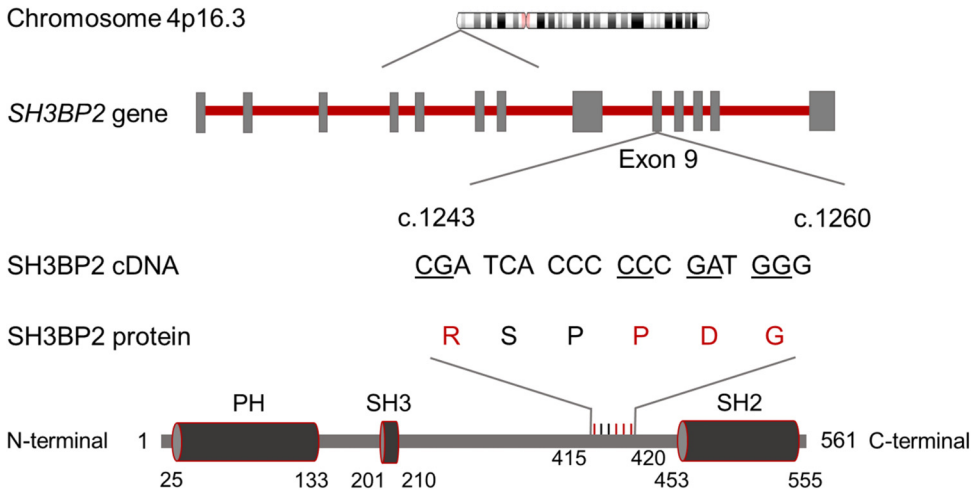

Fig. 2. Schematic diagram of the *SH3BP2* gene and protein, and the localization of exon 9 mutations reported in cherubism. All of the exon 9 mutations reported occurred between cDNA positions c.1243 and c.1259, which code for amino acids 415, 418, 419, and 420, known mutation hotspots. These amino acids are between the SH3-binding and the SH2 domains of the SH3BP2 adapter protein. Mutations outside these hotspots have been reported in a few cases and are not illustrated here (see Table 4).

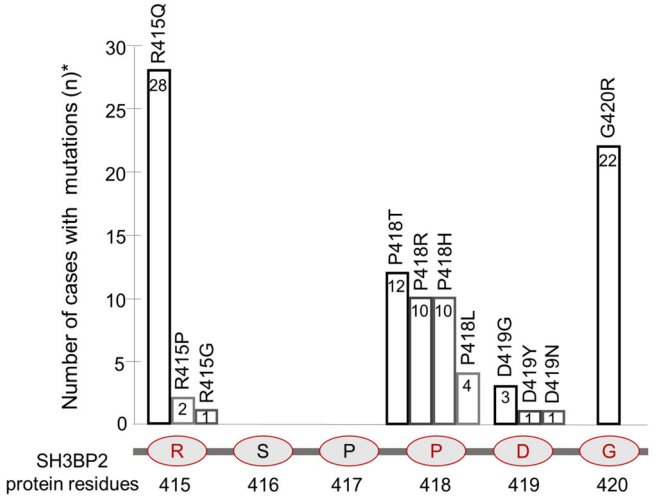

Fig. 3. Distribution of the *SH3BP2* exon 9 mutations according to SH3BP2 protein residues. Exon 9 mutations occurred in 94 cases of cherubism, and the bars show the number of cases with specific mutations at each hotspot amino acid (415, 418, 419, and 420) of the SH3BP2 protein. Most cases presented residue 418 mutations, followed by residue 415, 420, and 419 mutations, respectively. The cDNA notation of the mutations that led to each amino acid substitution are shown in Table 4. The mutations reported by Ueki et al.[10] are not included in this figure, as the authors did not specify the exact number of families affected by each specific amino acid substitution at a given position, nor did they detail the number of individuals with mutations in each family. Ueki et al. reported P418L/R/H in eight families, G420E/R in two families, and R415P/Q in two families. The mutations reported by Li et al. (Li et al. 2009, Supplementary Material Appendix) are not included in the figure, as the article is written in Chinese and it is not clear from the abstract whether the G420E, R415Q, and R415P mutations detected occurred in only one sample each or if they were recurrent in more cases.

secondary disturbances. Enucleation or curettage may be indicated in more aggressive cases, to reduce the maxillofacial deformity after puberty and to ensure a successful outcome without the risk of progression requiring additional resection[76]. A surgical intervention consisting preferably of surgical recontouring is indicated mainly when aesthetic or functional concerns arise, including nasal obstruction, proptosis, presence of major deformities that may cause psychological problems for the patient, impaired speech, and chewing or swallowing difficulties[28,77]. Thus, although there is a general rule of 'wait and see' until after puberty, surgery or some drug therapy may be necessary at an early age in some cases. After the 'wait and see' approach, the present review identified curettage and debulking/osteoplasty as the main procedures used to deal with the condition.

It was not possible to draw clear conclusions on the use of drugs as a therapeutic approach for cherubism. Besides the low number of cases described in the literature, these drugs were used in isolated cases, with different protocols, for different periods, and probably with the patients at different stages of disease progression.

The limitations of this study include the retrospective nature of the included studies. As such, it was not possible to retrieve information on all variables from all cases, which would have improved the quality of the statistical analyses[78,79]. Another issue is the limited number of cases with information on *SH3BP2* mutations. Additionally, many of the cases were followed up for a short period time.

In conclusion, there is no clear correlation between the genotype and the phenotype of the disease, but additional genomic and gene expression regulation information is necessary for a better understanding of cherubism. The limited number of cases with *SH3BP2* mutation assessment precludes a proper evaluation of the possible association with the clinical presentation of the disease.

Table 4. Description of the *SH3BP2* mutations reported in the literature, with the number of cases for each mutation[a].

Exon	SH3BP2 Mutation (cDNA)	Replacement in *SH3BP2* protein	Number of cases	Clinical grading (*n*)	References
3	c.147delC	p.R49RfsX26	1	V (*n* = 1)	Carvalho et al. 2008
4	c.320 C>T	p.T107M	1	[b] (*n* = 1)	Carvalho et al. 2009
9	c.1243 C>G	p.R415G	1	IV (*n* = 1)	Eiden et al. 2017
9	c.1244 G>A	p.R415Q	28	I (*n* = 5) II (*n* = 9) III (*n* = 1) IV (*n* = 3) V (*n* = 2) [b] (*n* = 8)	Kadlub et al. 2016, Gupta et al. 2019, Jiao et al. 2015, Machado et al. 2017, Pérez-Sayáns et al. 2013, Sakaki et al. 2015, Sekerci et al. 2014, Sidorowicz et al. 2018, Tuna et al. 2012, Preda et al. 2010
9	c.1244 G>C	p.R415P	2	I (*n* = 1) II (*n* = 1)	Argyris et al. 2018
9	c.1252 C>A	p.P418T	12	I (*n* = 3) IV (*n* = 2) [b] (*n* = 7)	de Lange et al. 2007b, Frazier et al. 2018, Machado et al. 2017, Piona et al. 2015, Tuna et al. 2012, Prescott et al. 2013
9	c.1253 C>G	p.P418R	10	II (*n* = 1) IV (*n* = 2) V (*n* = 1) [b] (*n* = 6)	Kadlub et al. 2016, Imai et al. 2003, Kadlub et al. 2015, Lee et al. 2008, Satoh-Kuriwada et al. 2007, Shoji et al. 2019, Mikoajczak et al. 2015, Kim et al. 2007
9	c.1253 C>T	p.P418L	4	II (*n* = 1) IV (*n* = 1) [b] (*n* = 2)	Friedrich et al. 2016, Hero et al. 2013, Prescott et al. 2013
9	c.1253 C>A	p.P418H	9	I (*n* = 2) IV (*n* = 3) V (*n* = 1) [b] (*n* = 3)	Hero et al. 2013, Hyckel et al. 2005, Machado et al. 2017
9	c.1253_1254 delCCinsAT	p.P418H	1	II (*n* = 1)	Sangu et al. 2013
9	c.1255 G>T	p.D419Y	1	I (*n* = 1)	Dinckan et al. 2012
9	c.1255 G>A	p.D419N	1	I (*n* = 1)	Lietman et al. 2006
9	c.1256 A>G	p.D419G	3	I (*n* = 1) [b] (*n* = 2)	Li and Yu 2006
9	c.1258 G>A	p.G420R	21	I (*n* = 1) II (*n* = 1) [b] (*n* = 19)	Prescott et al. 2013, Singh et al. 2014, Gupta et al. 2019, Lo et al. 2003
9	c.1258 G>C	p.G420R	1	IV (*n* = 1)	Suárez-Obando and Viasus 2009

The references are listed in the Supplementary Material Appendix.

[a] Forty-two studies assessed mutation, but there are only 40 studies in this table for the following reason: although Brix et al. (2006) and Dincă et al. (2014) looked for the mutation, the patients investigated by them did not present it. There was no specific information about the mutation in five cases (Papadaki et al., 2012; Wagel et al., 2012; Khirani et al., 2013; Elshafey 2014; Hauret-Clos et al., 2016), not included in the table.

[b] Insufficient clinical and radiographic information for clinical staging.

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Ethical approval

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Patient consent

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijom.2020.05.021.

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