

## Review Article

# The Genetically Based Diseases of the Jaw in Childhood: A Clinical Review

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Mandibular bone lesions may be the major symptom of several pediatric diseases with different etiology and severity. Some genetic disorders may herald with mandibular involvement: this unusual site of localization often represents a misleading clinical feature. Herein we review this topic focusing on the clinical and radiologic aspects. Moreover some differential diagnosis issues with mandibular lesions caused by infectious, inflammatory or neoplastic processes are discussed.

**Keywords:** Fibrous Dysplasia; Infantile Cortical Hyperostosis; Majeed Syndrome; Cherubism; Osteomyelitis

**Abbreviations**

ICH: Infantile Cortical Hyperostosis; FD: Fibrous Dysplasia; MAS: McCune-Albright Syndrome; MS: Mazabraud Syndrome; CNO: Chronic Non-Bacterial Osteomyelitis; CDA: Congenital Dyserythropoietic Anemia; PD: Pustular Dermatitis; TRAP: Tart rate-Resistant Acid Phosphatase; DIRA: Defect Of Interleukin 1 Receptor Antagonist; CRMO: Chronic Recurrent Multifocal Osteomyelitis; SAPHO: Synovitis Acne Pustulosis Hyperostosis and Osteitis; STIR: Short Tau Inversion Recovery; JMCO: Juvenile Mandibular Chronic Osteomyelitis; ABC: Aneurismal Bone Cyst

**Introduction**

Under the term of genetic mandibular disorders are gathered different diseases which are relatively uncommon in children and clinically heterogeneous for age of onset, severity and outcome. Although some of them are known from decades, only recently the causative genes of these disorders have been identified: furthermore the underlying pathophysiological mechanisms remain still poorly understood.

It is noteworthy that different stages of bone formation and remodeling as well as differentiation of stem/progenitor cells, matrix production, mineralization or bone desorption may be negatively affected [1]: despite the primary bone damage of these genetic disorders concerns the jaw morphogenesis, their clinical symptoms are usually characterized by an inflammatory lesion (severe pain, swelling, skin redness and warmth, limitation of movement such as difficulty in opening the mouth or chewing etc) mimicking more common bone diseases (e.g. infectious osteomyelitis, inflammatory osteitis, fractures, tumors): hence it is likely that inherited jaw disorders might be underdiagnosed.

As the number and the function of many genes encoding for proteins involved in bone metabolism are still to be defined, at present the clinical and instrumental criteria still represent the more useful tools in addressing towards the correct diagnosis. Conversely, the pediatricians must always have in mind these orphan diseases in the physical examination of a patient with inflammatory involvement

of the jaw. A careful clinical evaluation of the patient is mandatory, searching for systemic (e.g. fever, widespread bone pain, weight loss) or extra-skeletal (e.g. precocious puberty, *café-au-lait* skin lesions) findings which have a pivotal role for the diagnosis. Furthermore biological assessment of calcium phosphate metabolism and imaging study (local and systemic) are useful diagnostic tools; bone biopsy still represents the gold standard for evaluating the structure and ruling out infectious or malignancies.

Molecular analysis, as a definitive diagnostic classification, may be proposed in selected cases on the basis of the above-mentioned clinical and instrumental evaluation.

Herein we synthetically review the genetically-based mandibular disorders that have their onset in pediatric age highlighting their clinical and radiological features: a large section will be focused on the differential diagnosis of these conditions and the most common misleading pitfalls.

**Mandibular Disorders****Infantile cortical hyperostosis**

Infantile Cortical Hyperostosis (ICH) is a rare cause of jaw swelling in early infancy. The disease, firstly reported by Roske [2] in 1930, was more extensively studied by De Toni in 1943. This pioneer of pediatrics and scientific founder of G Gaslini Institute where we are working are credited with having fully described the clinical aspects and recognized its genetic nature [3]. Caffey and Silverman reported other cases, reviewed their clinical and radiographic features and coined the term of infantile cortical hyperostosis [4,5].

Typically ICH occurs in the six months of postnatal age and no later than the second year of life. The babies affected disclose soft tissue swelling, bone hyperostosis with a clear subperiosteal hyperosteogenesis. Mandible is the most commonly involved bone: clavicle, radius and ulna, tibia and femur may be also affected. Since fever, severe bone pain, irritability and acute phase reactant positivity are usually found [6], ICH may be misdiagnosed with different disorders such as infectious osteomyelitis or autoinflammatory bone disease. A positive family history for a so-called neonatal osteomyelitis

is an important diagnostic aid.

The disease has generally a benign, self-limiting course and its signs and symptoms spontaneously recover within few months without clinical recurrence: a bone scar may occasionally persist [7]. It is of note that anecdotal cases of ICH with recurrence during adolescence have been recently reported [8]: upon this finding, ICH should be considered in all pediatric patients suffering from auto inflammatory bone disorders.

The radiographic hallmarks of ICH is constituted by a typical subperiosteal cortical hyperostosis leading to an increase of cortical width and density associated to a laminated, well defined subperiosteal bone apposition [9]. The bone involvement have an asymmetrical multifocal distribution: rarely it is possible to observe widespread diffusion with a predominant inflammatory component [10] or atypical features, such as the coexistence of tumoral calcinosis [11].

In 2005 Gensure et al. [12] found that ICH patients are heterozygous for missense mutation 3040C/T in axon 41 of the gene *COL1A1* altering residue 836 (R836C) in the triple-helical domain. This finding has been confirmed in other patients including a wide Italian family.

Although allelic *COL1A1* mutations have been reported in Ehlers Danlos syndrome and osteogenesis imperfecta, individuals with R836C mutation do not have clinical features suggestive for these latter diseases.

More recently a prenatal-onset ICH case has been reported [13]: however the severe and persistent bone involvement, the absence of clinical inflammation and the not well-defined etiology suggest this ICH-like phenotype may be an independent clinical entity rather than a variant of ICH [14].

### Fibrous dysplasia

Fibrous Dysplasia (FD) is a genetic not-inherited bone disorder that may affects both male and female patients. The actual prevalence of the disorder is difficult to assess considering that the disease is often misdiagnosed because of its subclinical course: anyway it has been roughly calculated that 5% to 7% of mandibular benign bone tumors are due to FD [15,16].

The disease may have a monostotic (70% of the cases) as well as a polyostotic course: usually the diagnosis is made before 30 years

of age. The polyostotic variant is more frequent in younger patients. At present there is no evidence supporting a progression from monostotic into polyostotic form [17,18]. Although lesions may develop ubiquitously, skull and namely jaw is the most common site of localization [19-21].

Since 1891, when the disease was firstly described, several cases of fibrous bone lesions have been reported often associated with cutaneous signs (hyperpigmented skin areas with irregular borders described as café-au-lait spots) and multiple endocrinopathies (hypergonadism and precocious puberty, gigantism, acromegaly, hyperprolactinemia, hyperthyroidism, hyperparathyroidism) [22,23]. This protean syndrome was termed McCune-Albright Syndrome (MAS) after the exhaustive clinical assessment made from these physicians in 1936 and 1937 [20,24]. More recently also Mazabraud Syndrome (MS), in which bone lesions are associated with intramuscular myxomas [25] has been included in the spectrum of FD.

Genetic analysis carried out in syndromic (MAS and MS) patients by Weinstein and Shenker [26,27] led to understand that the etiology of FD lies in a missense mutation related to gene *GNAS1* (20q13.2-13.3 region). This part of genome encodes the alpha subunit of the stimulatory G protein-coupled receptor (*Gsα*): a somatic dominant mutation makes *Gsα* protein able to resist to inhibitory action of GTPase, with the effect of constitutive stimulation of downstream signaling [28]. As FD is a somatic mosaic disorder, the phenotype of the disease is strictly correlate to the gestational or post-gestational age in which the mutation occurs: hence, it is likely that in MAS as much as in polyostotic form of the disease the mutation occurs earlier (also in gestational age) than in monostotic form [29]. Other studies described an over expression of *c-fos* oncogene in bone biopsy derived from FD patient: this mechanism is thought to be the first step in carcinogenesis pathway that could explain the rare cases in which this benign disease evolves in malignancy (usually osteosarcoma). Moreover the abnormal activation of *c-fos* stimulates the production and secretion of cytokines leading to bone resorption through osteoclasts activity [30].

The diagnosis of FD, especially in non-syndromic patients, is assessed by performing a routine X-ray. Bone pain and deformity, fatigue fracture and pathologic fracture may be heralding signs of the disease [17].

**Table 1:** Diseases and genes.

Disease	Inheritance	Gene	Mutated protein
Infantile cortical hyperostosis	AD	<i>COL1A1</i>	collagen I
Fibrous dysplasia	non mendelian	<i>GNAS1</i>	stimulatory G protein-coupled receptor ( <i>Gsα</i> )
Majeed syndrome	AR/sporadic	<i>LPIN2</i>	lipin-2
Cherubism	AD	<i>SH3BP2</i>	Src homology-3-domain binding protein 2
DIRA	AR	<i>IL1RN</i>	interleukin-1 receptor antagonist
Familial expansile osteolysis	AD	<i>TNFRSF11A</i>	RANK receptor
Early-onset Paget's disease	AD	<i>TNFRSF11A</i>	RANK receptor
Expansile skeletal hyperphosphatasia	AD	<i>TNFRSF11A</i>	RANK receptor
Idiopathic hyperphosphatasia	AR	<i>TNFRSF11B</i>	osteoprotegerin
Inclusion body myopathy, Paget's disease and frontotemporal dementia	AD	<i>VCP</i>	valosin-containing-protein

Radiographic study discloses that the normal bone is replaced by a more radiolucent tissue with ground-glass pattern; it is also possible to find liquid filled-cyst within the limits of the bone lesion. The newly formed tissue tends to replace normal bone extending from medullar canal to the bone cortex. Usually there is no periosteal reaction related to the lesion [31].

Bone lesions show a heterogeneous appearance according to the ratio between normal and dysplastic cells. Bone biopsy is recommended to recognize the main features on bone biopsy. Dysplastic cells belong to osteogenic lineage and act like osteoblasts with increased proliferation rate: these cells are able to produce extracellular matrix and woven bone [32]. The impairment in dysplastic bone matrix composition and the over activated osteoclasts surrounding the lesion cause localized osteomalacia. The trabeculae of dysplastic woven bone in the matrix are typically described as Chinese alphabet character, due to their microscopic aspect. Finally no osteoblastic rimming is usually detectable [32-34].

The natural course of the disease is unpredictable and it is strictly linked to the extension of the bone lesion which may often enlarge and impair the normal skeletal growth. Therefore frequent complications of FD are limb-length discrepancy, severe scoliosis, deformity (shepherd's crook deformity) and pathologic fractures. As stated before, malignant degeneration is rare and usually related to previous irradiation of bone lesions [17]. Obviously syndromic patients need of pediatric care for the endocrine derangement (hyperthyroidism, precocious puberty, gigantism, etc.) of the disease.

The diagnosis is based upon the clinical and radiological findings: at present it is also possible to find Gsa mutation in bone tissue [17].

Conservative approach is usually preferred in localized disease, whereas bisphosphonates represent the first line therapy for overgrowing lesions. A thorough dental hygiene is recommended before their administration, especially in patients treated with steroids, considering the higher risk of osteonecrosis of the jaw [17]. Surgical treatment may be required when deformities occur as well as for removing symptomatic lesions: curettage alone is not enough since the rate of recurrence is higher, especially in children. Allogenic bone graft is a good choice for patients with severe disease [17].

### **Majeed syndrome**

Majeed Syndrome (MJ) is an autosomal recessive inherited disease whose main features are Chronic Non-Bacterial Osteomyelitis (CNO), Congenital Dyserythropoietic Anemia (CDA) and Pustular Dermatitis (PD) [35]. Very few cases have been reported since first description of the syndrome by Majeed and colleagues in 1989 [36].

The etiology of this disease is related to mutations in *LPIN2*. It has been hypothesized that loss-of-function mutations (typical of autosomal recessive disorders) leads to impairment in the down regulation of macrophage pro-inflammatory signaling, when exposed to fatty acids [37].

The disease occurs during neonatal period or infancy with periodic fever and diffuse pustular rash with neutrophilic prevalence (Sweet syndrome). Moreover bone pain and arthritis, soft tissue swelling and dyserythropoietic anemia with specific hypochromic microcytic features are present too: maxillary bone hyperplasia has

been reported in some cases. Majeed syndrome phenotype may be misdiagnosed with neonatal sepsis. The prognosis is poor and failure to thrive associated with growth retardation, joint contracture and muscle atrophy developed [35].

Due to reported impairment in inflammatory regulation several therapies have been attempted: non steroid antiinflammatory drugs (NSAIDs) and steroid as first choice, followed by monoclonal antibodies against pro-inflammatory cytokines (anakinra and etanercept) [38].

### **Cherubism**

Jones first described a "familial multilocular cystic disease of jaws" in 1933 [39] and it was called cherubism since 1938 because the classical features of disease give the children a cherubic appearance [40].

Cherubism is a very rare self-limiting fibro-osseous disease characterized by symmetrical painless swelling of mandible, maxilla or both due to multilocular radiolucent expansive lesion. These lesions appear typically at age of 2-7 years, concomitant with swelling of sub-mandibular and cervical lymph nodes only presents in the early stage of the disease. Additionally, the lesions can expand and infiltrate the orbital floor lead to a tendency of "upward gaze", exposing the sclera below the iris. Extra cranial involvement is only anecdotally reported. In some cases cherubism regresses spontaneously after puberty [41], although it can persist in adult age [42].

Several grading systems have been proposed to describe the severity of cherubism. Seward and Hankey have proposed a grading based on the location of lesions in the jaws [43]. Later, this grading system was modified by Motamedi [44] and Raposo-Amaral [45]. Firsts two grade is referred to lesion of mandible – grade 1 – or mandible and maxilla – grade 2 – without root resorption; aggressive lesions with signs of root resorption of mandible or mandible and maxilla are classified as grade 3 and 4 respectively; massively growing lesions are classified as grade 5; grade 6 describe the involvement of the orbits.

Although cherubism is a skeletal disease, it also can affects other organs. First of all, lesions can involve inferior or lateral orbit wall or the retro-bulbar spaces and cause displacement of optic nerve [46,47]. Respiratory involvement is very rare, but occasionally cherubism causes upper airways obstruction, snoring, chronic nasal infection and obstructive sleep apnea because of displacement of the tongue and other airway structure [48]. Finally, cherubism lesions can also cause disruption of primary or secondary dentition: absent teeth, rudimentary development of teeth, abnormally shaped teeth, delayed or ectopically erupting teeth have been all reported [49].

Cherubism is classically transmitted with autosomal dominant inheritance with variable penetrance and expressivity, although some seemingly recessive inheritance is described [50]. Different penetrance in male and female has been reported, but this difference can also be related to misdiagnosis in females [51].

The pathogenesis is related to mutation in the gene encoding Src Homology-3-Domain Binding Protein 2 (SH3BP2) on chromosome 4p16.3: this is an adaptor protein expressed in osteoblasts and osteoclasts. Mutations identified in cherubism were located in exone

9, within a sequence of 6 amino acid residues. [52-54] Deletion of *SH3BP2* gene can be seen in Wolf-Hirschhorn syndrome which does not share a cherubism-like phenotype. This suggests that in cherubism mutations lead to a gain-of-function, despite of a loss-of-function, of *SH3BP2* protein, increasing osteocalcogenesis and bone resorption [55]. Notably, according to animal models and some clinical findings—like to enlargement of lymph nodes—some authors classified cherubism in inflammatory disorders [51]. Diagnosis of cherubism is based on clinical findings [56]. Radiological aspects are not pathognomonic, but should raise the suspicion. Imaging shows symmetric remodeling of bones, cortical thinning and multilocular radiolucencies with a coarse trabecular pattern. *SH3BP2* gene testing is recommended to confirm the diagnosis, but if no mutation in gene is found cherubism cannot be excluded. Biopsy and histopathologic examination are not required [57]. When performed it demonstrates multinucleated osteoclast-like giant cells in fibrous stroma, spindle cells, and hemosiderin deposition [57].

Three different histological stages have been described [58]. The first stage is the osteolytic one. In this stage there are giant osteoclast-like cells TRAP positive, the tissue is well vascularised and fibroblastic cells can be found in the periphery of the lesions. Signs of hemorrhage are also present. The second stage is the reparative one, characterized by fibroblastic nodules, osteogenesis and new formation of bone matrix. In the third stage differentiating osteoblasts and mineralized matrix are found. This tissue contains more collagen fibers and fewer cells [59,60].

So far, management of cherubism consists in longitudinal observation and, possibly, in surgical intervention.

### Inherited osteolytic disorders

Different inherited bone disorders (i.e. familial expansile osteolysis, expansile skeletal hyperphosphatasia, early-onset familial Paget's disease, idiopathic hyperphosphatasia or juvenile Paget's disease and the syndrome of inclusion myopathy, Paget's disease, front temporal dementia) may affect the mandible [61].

These rare disorders, characterized by an increased bone metabolism, have the phenotype of systemic bone dysplasia leading to progressive skeletal deformities, fractures and short stature: hence they are not here discussed. It is of note that the pathogenetic basis of these forms is known and a targeted therapy with monoclonal antibodies is now available for juvenile Paget's disease [62].

### Differential Diagnosis

As already mentioned, several disorders can herald with clinical and imaging features similar to those related to inherited bone disorders of the mandible. This section of review is aimed to discuss the diseases more often causing diagnostic misleading pitfalls.

#### Infectious diseases

Several bacteria are involved in childhood osteomyelitis, more frequently through hematogenous dissemination and thus with multiple localizations. In this case the fever is a leading symptom which should arise the suspicious of infectious etiology. In few patients, especially when the pathogen is barely eliminated by the immune system (such as *Brucella spp.*, *Mycobacterium tuberculosis* and *avium complex*, *Kingella spp.*) the disease may be characterized

by less severe signs and symptoms, often sharing clinical aspects with pure genetic disorders.

Tuberculosis should be always considered in the differential diagnosis because both its incidence is increasing worldwide and bones and joints represent one of the most common extra-pulmonary sites of *Mycobacterium tuberculosis* localization [63]. Primary tuberculous osteomyelitis of the mandible has been reported in children: an asymmetrical, slightly painful mandibular swelling is the heralding symptom often misdiagnosed as chronic residual dentoalveolar abscess [64]. Acute phase reactants are frequently unremarkable: also purified protein derivative test and chest screening may be negative. Imaging of the mandible usually shows a soft tissue mass associated with structural deformities and osteolytic lesion. The diagnostic gold standard remains the positive cultures on bone biopsy: however, since this procedure cannot be easy on mandible, the diagnosis may be suggestive if a tuberculous granuloma is found at the fine needle aspiration cytology [65]. This particular form of mandibular osteomyelitis should be excluded especially in endemic areas and in immune suppressed patients (primitive or drug-related).

Actinomycosis may be involved in mandibular osteomyelitis. Albeit uncommon, this form seems to have a recurrent course, poorly responsive to antimicrobial drugs: the patients with mandibular localization usually require one or multiple debridement's [66].

Congenital syphilis still remains an impacting disease that causes fetal or neonatal deaths or a multisystemic disease at birth: the affected neonates usually show low birth weight, characteristic skin rash, hepatomegaly, splenomegaly, thrombocytopenia, increasing of C-reactive protein plasma concentrations, periostitis and osteitis of the long bones: also the mandible may be involved. The biochemical abnormalities recovered within 3-6 months, whereas skeletal sequelae may persist in some patients. Congenital syphilis should always be suspected in infants with osteitis / periostitis regardless of their family history since a prompt antibiotic treatment according to standard guidelines is crucial to achieve a good long-term outcome [67-69]. Intriguingly both ICH and DIRA syndrome (an autosomal recessive disease caused by missense mutations in the *IL1RN* gene encoding the IL-1 receptor antagonist) may strongly simulate congenital syphilis, especially the latter which is characterized by neonatal onset, multifocal osteomyelitis, periostitis, skin lesions and hepatosplenomegaly [67-69].

Opportunistic osteomyelitis of jaw may occur in children with immunodeficiency or under immunosuppressive therapy [70] and in children suffering from genetic diseases characterized by bone structural abnormalities (e.g. osteopetrosis, Gaucher disease) [71,72] or peripheral neuropathy.

#### Inflammatory diseases

Chronic Recurrent Multifocal Osteomyelitis (CRMO) is a rare inflammatory bone disorder characterized by multiple foci of osteitis, often associated with musculoskeletal pain and swelling of the involved segments. Adolescents may develop a syndromic form of CRMO, called SAPHO syndrome, due to its features (Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis) [73].

In a recently published case series the reported prevalence of mandibular involvement in CRMO is about 10 %, albeit the real

prevalence in pediatric CRMO/SAPHO patients is still debated [74].

At present, the etiology is poorly understood: DIRA and MS share several clinical and radiological features with CRMO/SAPHO, so a role of innate immunity and hence autoinflammation has been proposed [73,75]. Finally, some Authors hypothesized the role of bacteria (such as *Priopionibacterium acnes*) in the pathogenesis of syndromic forms of multifocal osteomyelitis (SAPHO syndrome) due to its ability to trigger activation of toll-like receptors [76].

Clinical features of CRMO/SAPHO are not pathognomonic: they mainly consist in swelling, pain and tenderness of involved bone segments. Mild fever could also be present in disseminated cases.

Imaging findings may be a useful tool in diagnosing this syndrome. Osteolytic areas immediately adjacent to the growth plate of long bones are typical radiographic signs, moreover healing associated with intense sclerosis is usual [77]. Magnetic resonance imaging characteristically shows STIR sequences hyperintensity due to bone marrow edema, usually associated with T1 hypointensity [78]. Despite the great progress brought by new generation imaging, the diagnostic gold standard remain bone biopsy aimed to exclude malignancies and infectious osteomyelitis. From biopsy-derived specimens we understood that CRMO/SAPHO lesions are initially characterized by osteolysis associated with immunologic reaction (lymphoplasmacytic infiltrate). Usually sclerosis and hyperostosis occur in later stages [79].

CRMO/SAPHO has usually a good clinical outcome, with spontaneous resolution in most cases [80]. Non steroid antiinflammatory drugs, steroids, disease modifier anti-rheumatic drugs and biological drugs can be used at different stages of the syndrome [73, 81-83]. Surgical treatment is generally inadvisable for this condition as recurrence rate is high; although jaw localization may raise esthetic concerns for the patient so bone resection and reconstruction with graft may be of help [84].

As above stated mandibular involvement in CRMO/SAPHO syndrome is largely accepted. Noteworthy in some patient mandibular involvement represents the unique site of disease: this latter form is reported by some Authors as Juvenile Mandibular Chronic Osteomyelitis (JMCO).

### Hemato-oncologic diseases

Neoplasms can present themselves as a single lesion involving the mandible or rarely as widespread metastatic bone disease: moreover, malignancies, as far as infectious osteomyelitis, require a prompt intervention to choose a correct diagnostic work-up and treatment schedule.

Histiocytosis in its localized form (Eosinophilic granuloma) is the most common disease with a good prognosis [85]. Central giant cell granuloma, a benign condition usually treated with steroid infiltration and calcitonin, may sometimes present an aggressive behavior leading to bone cystic lesion and tooth mobility [86].

Ewing's sarcoma may affect head and neck region, maxilla and mandible in children and adolescents, more rarely in children under the age of 5. The reported cases displayed an indolent course, misdiagnosed as a dental abscess. X-ray examination usually shows a bone lesion characterized by ill-defined borders often associated with

bone erosion [87]. Mature B-cell non-Hodgkin's lymphoma (African form) is another malignancy that can be sited at mandible in 5-10% of the cases [88].

Finally aneurismal bone cyst (ABC) is a very rare lesion presenting with rapid facial swelling that can be disfiguring. It may be congenital or acquired, usually related to intraosseous bleeding. Solitary bone cyst, also included in non-odontogenic lesion of the jaw, may derive from local trauma, usually extending from premolar region backward [89].

### Conclusion

The jaw may be affected by different injuries in childhood. Usually it is believed that these disorders clinically characterized by swelling, pain, pathological fractures and deformities, require only the specialized care from orthopedic or maxilla-facial surgeon. On the contrary, the involvement of the mandible in children may be the main clinical expression of systemic diseases due to specific gene mutations. Since the differential diagnosis with infectious, inflammatory, hemato-oncologic diseases can be not easy, and genetic mandibular osteopathies may be misdiagnosed.

Therefore a multi-specialized intervention involving pediatrics, radiologists, pathologists and genetic consultant is needed for correct diagnosis and appropriate treatment.

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