



Review Article

A dental approach to hereditary and congenial metabolic bone diseases

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Abstract

Bone growth requires a balance of minerals such as calcium, phosphorus, and factors of bone biomineralization. The difference between jaws' bones and the rest of the bones is the existence of teeth. Although the development of teeth has no similarities with bones, the biomineralization of both is happening at the same time. Consequently, the disturbances in the metabolism of minerals and peptides which participate in osteogenesis, have an impact on teeth, jaws, periodontal tissues, and oral mucosa. The hereditary and congenial metabolic bone diseases are being analysed and classified based on their genetic profile and oral manifestations. Regarding the categories, there are metabolic bone diseases caused by genetic mutations, like hereditary rickets, and others caused by chromosomal abnormalities, such as Down syndrome. In addition, many disorders are provoked by enzymatic dysfunction, disturbances of creation of polypeptide chain, while others have an unknown explanation. Many oral manifestations are related with problems in the dentition, oral mucosa, periodontal tissues, and jaws. Especially some syndromes present with cleft lip and palate. To conclude, there is a big variety of dental symptoms of these disorders, while the most frequent are the delayed eruption of teeth, oligodontia, a dysplastic enamel and dentine.

Keywords: Congenial, Hereditary, Metabolic bone disease, Oral manifestation, Teeth

Introduction

The human skeleton is a dynamic and complex tissue which is constructed during human development from in-utero until the age of 18 years. Bone remodeling is a lifelong process that is characterized by a balance between bone production and bone absorption. The maintenance of homeostasis of minerals such as phosphorus, calcium, hormones like vitamin D, parathyroid hormone, and other peptides, has a crucial role on the human skeletal development¹.

The teeth, located at the oral cavity, are important for chewing, talking and have a major role on facial esthetics. They consist of three types of mineralized dental tissue; enamel, dentine and cementum, and their development starts from the embryonic period until the end of adolescence, in accordance with the development of the jaws. Teeth are restrained at the socket by the periodontal ligament which surrounds the root of tooth and connect tooth with bone through collagen fibres^{1,2}.

The odontogenesis is a complicated process when the embryonic cells are differentiated to ameloblasts which produce enamel found at the dental crown, odontoblasts which compose dentin that covers most of the tooth and cementoblasts producing cementum that is restricted at the root^{2,3}. Dentin has many similarities with bone proteins, consists of a numerous proteins like collagen

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type I, III, and V, bone sialoprotein, dentin matrix protein 1, osteocalcin etc. Some proteins such as ascalbidin-D28k and alkaline phosphatase, regulate the function of calcium and phosphorus and they are composed by osteoblasts and odontoblasts². However, dentin and cementum have a decreased ability of remodeling compared to bones¹.

Ameloblasts, dentinoblasts, cementoblasts, osteoblasts and cells of periodontal ligament express the tissue non-specific alkaline phosphatase (TNsAP), which plays a role in dental and periodontal biomineralization⁴.

In addition, teeth development includes signaling pathways important for human skeleton development, such as those of WNT and kathepsin K which is related to cementum and alveolar bone development^{5,6}.

Osteogenesis and odontogenesis have differences, but their biomineralization occurs in parallel, which makes them vulnerable to mistakes caused by the developmental disorders of bone mineral metabolism³. Thus, hereditary and congenial metabolic bone diseases have many oral manifestations. These diseases are being analyzed and classified based on their genetic profile and oral features.

Genetic background of diseases

Gene mutations

Several gene mutations have been found to be related with conditions that can also present with dental manifestations. Some examples are:

Hereditary rickets

Hereditary rickets is the most well-known hereditary metabolic bone condition, presenting with soft and weakened bones due to disability to balance levels of calcium and phosphate³. This situation has an immediate impact on teeth, so rickets has numerous oral manifestations.

Rickets is categorized in 2 types; the first type includes rickets related with vitamin D, caused by mutations at the enzymes which take part in vitamin D biosynthetic pathway and its' receptor. The second type is hypophosphatemic rickets caused by an incapacity of reabsorption or transportation of phosphate at the renal tubules, which is related with genetic disease of phosphatonines and transporters of phosphate⁷.

Rickets related with vitamin D

Rickets related with vitamin D has 4 subcategories; Types 1A, 1B, 2A and 2B, which are inherited with autosomal way and presents with low levels of calcium, phosphate, abnormal levels of PTH, alkaline phosphatase and 1,25 vitamin D^{1,7,8}.

Amelogenesis imperfecta (AI) as a distinct disease forms a group of heterogenous hereditary disorders provoked by mutations of 9 different genes. It can be linked with Vitamin D-dependent rickets type I. Clinically it presents with 4 types of enamel, hypoplastic, hypomature, hypomineralized and hypomature with taurodontism, and 14 subtypes based on Witkop's classification. The major clinical entities are the first

three. Particularly, enamel has a weakened structure and a decreased resistance being thin, soft, discolored, vulnerable to fractures and there are pulp stones⁹⁻¹¹.

Hypophosphatemic rickets (HR)

Hypophosphatemic rickets (HR) is related with FGF-23 factor, for example X-linked Hypophosphatemic Rickets (XLH), Autosomal Dominant HR (ADHR), and Autosomal Recessive Hypophosphatemic Ricket (ARHR). The ARHR type 1 can be caused by inactivating homozygous mutations in the dentin matrix acidic phosphoprotein 1 gene and ARHR type 2 is provoked by inactivating homozygous mutations in ectonucleotide pyrophosphatase/phosphodiesterase 1^{1,7,8}. XLH is caused by mutations at the gene of phosphate-regulating neutral endopeptidase PHEX, which is located at Xp22.1, resulting in increased levels of fibroblast growth factor-23. PHEX can be expressed mainly at osteoblasts, osteocytes, odontoblasts and cementoblasts. Clinical features include bone deformities, short stature, dental anomalies, muscle disability, bone pain, hyperparathyroidism, osteomalacia, osteoarthritis, and pseudofractures particularly on adults. The major dental manifestations of rickets are hypoplastic enamel, dentin mineralization defects and abscesses without any pathology of the tooth^{1,12,13}.

Hypophosphatasia (HPP)

Hypophosphatasia (HPP) is a bone disorder inherited with recessive and dominant manner. It is caused by mutation in the ALPL gene. ALPL gene encodes TNsALP, which is an enzyme of bone, teeth, liver, kidney and has the ability to hydrolyze and decrease the inorganic pyrophosphate leading to normal mineralization^{3,4}. The disorder is categorized in 6 types based on its' symptoms, severity, and the age of onset of symptoms. Some symptoms are reduced bone mineralization, premature craniosynostosis, osteomalacia, decreased bone density and musculoskeletal pain can appear during adulthood. One of the types is odontohypophosphatasia, which is independent of patients' age and involves only the oral cavity⁴. Pyrophosphate dysregulation causes problems at the cementum and results in early dental exfoliation. All types have dental manifestations, the most important being early tooth loss due to defective root acellular cementum, leading to compromised periodontal attachment^{3,4,14,15}.

Cleidocranial dysplasia (CCD)

Cleidocranial dysplasia (CCD) is caused by mutations on gene RUNX2, which has a principal role in the differentiation of osteoblasts, skeletal growth, proliferation of chondrocytes and tooth formation. It is an unusual skeletal disease inherited in an autosomal dominant way¹⁶. Patients have short stature, hypoplastic or aplastic clavicles leading to hypermobility of shoulders, a long head with prominent forehead, hypoplastic zygomatic bones, abnormal hands and otitis causing hearing loss^{17,18}. The x-rays identify lack of ossification of the skull, abnormal clavicle morphology and other bone characteristics. The principal dental

manifestations are supernumerary permanent teeth, lack of shedding of primary teeth and delayed or arrested eruption of permanent teeth¹⁷.

Osteogenesis imperfecta (OI)

Osteogenesis imperfecta (OI) is a disease of the connective tissue. It can be caused mainly by mutations in COL1A1, COL1A2 genes which are associated with collagen type 1 and II and can be found at chromosome 17 and 7, respectively, but several other genes can also be related. The disease is inherited mainly with the autosomal dominant manner, but can also be autosomal recessive. It is characterized by increased frequency of fractures and skeletal disorders, also called "brittle bone disease". Based on clinical, radiological findings and inheritance, OI is classified into 4 types. However, recent evidence of molecular studies and clinical characteristics indicate new types. Clinical manifestations include fragile bones, skeletal deformities, effects on growth and hearing ability, joint hypermobility, and easy bruising. The major dental manifestations are Dentinogenesis imperfecta (DI), hypodontia, and oligodontia^{7,19,20}.

DI can be described as a dentinal disorder with an autosomal dominant inheritance, associated with mutations at gene of dentin sialophosphoprotein (DSPP). There are 3 types, the first is pertained with OI²¹. The second type is an independent entity, that has been reported to be related with Schimke Immuno-osseous Dysplasia, analyzed below²². The third type is a rare entity. Dentin lacks mineralization, enamel is normal but sometimes it appears hypoplastic or hypomineralized. Teeth have grey to brown-yellow color, x-rays show bulbous crowns, enlarged root canals because of decreased dentinal development and pulp chamber which tends to disappear^{11,22}. DI can also appear as independent condition without bone fractures²³.

Hyperphosphatemic hyperostosis syndrome and familial tumoral calcinosis (HFTC)

Hyperphosphatemic hyperostosis syndrome and familial tumoral calcinosis (HFTC) are rare autosomal recessive diseases that have similar pathology. They are provoked by inactivating mutations of fibroblast growth factor 23 (FGF23), klotho genes, UDP-N-acetyl-alpha D galactosamine, inducing lessened amount of FGF23. The main clinical characteristics are a periarticular calcification of basic joints, calcifications of other body parts like eyes, blood vessels and hyperostosis of long bones. Patients have multiple dental problems, such as short bulbous teeth, shortened roots with dilacerations, pulp chamber and root canal obliteration, and pulp stones of pulp chambers^{7,24,25}.

Pseudohypoparathyroidism (PHP)

Pseudohypoparathyroidism (PHP) can be caused by mutations of genes GNAS, STX16 or GNASAS1, located at chromosome 20q13 that encode a-subunit of Gs protein²⁶. The disease is categorized to type 1 (1a, 1b and 1c) and type 2²⁷. In type 1a, patients have premature closure of epiphyses

leading to a reduced period of growth. Its' clinical symptoms include short stature, short bones and fingers. There is also a tendency to obesity, retarded growth, craniofacial deformities like round face, ectopic subcutaneous ossifications, mental and behavioral impact, and hormone resistance. The combination of this phenotype with hormone resistance is called Albright Hereditary Osteodystrophy. Type 1c has the same clinical characteristics, whereas pseudopseudo-hypoparathyroidism has similar clinical symptoms without PTH resistance²⁸. The main dental manifestations are a pulp calcification, irregularities of the root morphology and malocclusion^{26,27}.

Cherubism

Cherubism is an autosomal dominant bone disease which can be caused by mutations of the SH3BP2 gene. The SH3BP2 gene plays an important role on osteoblastic and osteoclastic function and can be found at chromosome 4p16.6²⁹⁻³¹. It is a benign fibro-osseous lesion located mainly at the facial bones. According to radiological evidence, there are radiolucent multifocal well defined cystic lesions which include teeth. Its' manifestations start at the age of 4 years and are limited after adolescence. Patients' face can become deformed due to a painless, symmetric, bilateral, fibro-osseous lesion, which is located at the jaws^{29,30}. The principal dental manifestations are tooth displacement, oligodontia, failed eruption, and root resorption²⁸.

Kenny-Caffey syndrome

Kenny-Caffey syndrome is provoked by mutations in the TBCE gene which encodes the tubulin specific chaperone E and is necessary for dimerization of tubulins and polymerization of microtubules. It is an osteosclerotic dysplasia of bones and is categorized as type 1 (autosomal recessive) and type 2 (autosomal dominant)³². Some clinical symptoms include short stature, abnormal facial characteristics like prominent forehead and microphthalmia. Type 1 has more prominent clinical features than type 2, and its' decreased response of the immune system makes patients vulnerable to bacterial infections^{31,33,34}. Biochemically there is hypocalcaemia due to hypoparathyroidism. Focusing on the oral findings, the most common dental anomalies are oligodontia and microdontia^{31,33}.

Pycnodysostosis

Cathepsin K is a protease which is encoded by osteoclasts leading to decreased bone absorption. Mutations of the gene related with cathepsin K located at chromosome 1q21, cause an autosomal recessive skeletal disorder called Pycnodysostosis. Clinically, there is increased bone density, short stature, osteolysis of distal phalanges, multiple pathological fractures, craniofacial abnormalities, prominent eyes and obstructive sleep apnea. It has multiple manifestations at hard tissues of teeth such as enamel hypoplasia and can cause crowded teeth^{5,35,36}.

	Delayed tooth eruption/ Ankylosis /wrong tooth position/ Early apoptosis	Supernumerous teeth	Oligodontia	Changes on dental crown shape	Hypoplastic/ thin enamel	Hypoplastic/ thin dentin	Hypoplastic cementum	Strange root morphology	Thin root canals/pulp stones	Malocclusion
Rickets	✓				✓	✓		✓		✓
XLH	✓				✓	✓	✓	✓		
HPP	✓			✓	✓	✓	✓	✓		✓
CCD		✓	✓							
OI	✓		✓			✓		✓	✓	✓
HFTC	✓			✓	✓			✓	✓	✓
PHP	✓		✓	✓	✓			✓	✓	✓
Cherubism	✓		✓					✓		
Kenny-Caffey syndrome	✓		✓	✓	✓			✓	✓	
Pycnodysostosis	✓	✓			✓	✓		✓	✓	✓
Paget Disease	✓		✓		✓	✓		✓		
Achondroplasia	✓	✓	✓	✓						✓
SIOD			✓	✓		✓				
Down Syndrome	✓	✓	✓	✓						✓
WBS			✓	✓	✓			✓		✓
Osteopetrosis	✓		✓	✓	✓			✓	✓	
Gaucher's Disease	✓		✓	✓				✓		
Mucopolysaccharidosis	✓		✓	✓	✓			✓		✓
B-thalassemia		✓		✓	✓	✓		✓		✓
FS	✓				✓	✓				
Apert Syndrome	✓		✓							

Table 1. Dental manifestations of metabolic bone diseases. (Abbreviations: XLH=X-Linked Hypophosphatemic Rickets, HPP=Hypophosphatasia, CCD=CleidocranialDysplasia, OI=Osteogenesis Imperfecta, HFTC=HyperphosphatemicFamilialTumoralCalcinosis, PHP=Pseudohypoparathyroidism, SIOD=Schimke Immuno-osseous Dysplasia, WBS=Williams-Beuren Syndrome, FS=Fanconi Syndrome).

Paget disease

Paget disease is a multifactorial disorder caused by mutations on genes related with cytokine pathway. It has a strong genetic tendency and an autosomal recessive heredity. It is frequently seen in adults and more rarely in children. The juvenile form is called chronic idiopathic hyperphosphatasia. It is caused by deficiency of OPG, a disturbance of the homeostasis of osteoclastic and osteoblastic equilibrium, resulting in quick bone remodeling, deafness at childhood, tooth loss, fractures and skeletal deformities such as macrocephaly, short stature and other manifestations of skull and lower extremities³⁷⁻³⁹.

Achondroplasia

Achondroplasia is inherited with autosomal dominant way and is the commonest cause of dwarfism⁴⁰. A mutation on the gene which encodes the receptor 3 of fibroblast growth factor (FGFR3) can lead to hyperfunction of a protein that intervenes in the skeletal growth leading to decreased endochondral ossification, cancelling the proliferation of chondrocytes, reducing cellular hypertrophy and production of cartilage matrix⁴¹. The patients' characteristics are a short stature, short hands and legs, hydrocephalus, prominent forehead, hypoplastic mid face and a decreased length of cranial base. As a consequence, they have maxillary hypoplasia and malocclusion⁴².

Hyperparathyroidism-jaw tumor syndrome (HPT-JT)

The hyperparathyroidism-jaw tumor syndrome (HPT-JT), also called hyperparathyroidism 2 is caused by mutations at the gene of the cell division cycle number 73 in chromosome 1 (CDC73)⁴³. CDC73 encodes the protein parafibromin which is responsible for tumor restriction having an anti-proliferating action. It is a rare syndrome inherited with the autosomal dominant manner^{44,45}. Patients have tumors of the parathyroid gland including adenoma and ossifying fibromas of the upper and lower jaw. Uterine tumors and renal lesions have also been observed. The most frequent clinical symptom is primary hyperparathyroidism, while one third of cases have jaw tumors⁴³⁻⁴⁵.

Schimke Immuno-osseous Dysplasia (SIOD)

Schimke Immuno-osseous Dysplasia (SIOD) is an autosomal-recessive disease and can be caused by mutations at the SMARCAL1 gene. This gene is expressed in all developing teeth, increasing the possibility of dental anomalies caused by its' mutations. The major clinical characteristics of the disease are spondyloepiphyseal dysplasia, renal abnormalities, T-cell immuno-deficiency and facial malformations such as deltoid face, rounded nose, dental anomalies, short neck, spots on the skin with color, short limbs and bulging trunk⁴⁶⁻⁴⁸.

Williams syndrome

Deletions at the 7q11.23 chromosome location, that encodes elastin which plays a role at heart's function, cause Williams syndrome, also called Williams-Beuren syndrome (WBS). The syndrome can be sporadic or de novo and has autosomal dominant inheritance. It is a multisystemic disease and it is characterized by an "elfin face". Patients suffer from congenital cardiovascular problems, have behavioral problems and mental impairment and they often present with hypercalcaemia at the neonatal period, hypertension and renal abnormalities. The dominant dental manifestations are generalized diastemas, hypodontia and malocclusion⁴⁹⁻⁵¹.

Chromosomal abnormalities

Chromosomal anomalies have been associated with conditions that can also present with oral manifestations.

Trisomy 21 (Down syndrome)

Patients have an extra chromosome 21 because of an abnormal separation of chromosomes. It causes mental retardation and changes at the physical and behavioral development of patients. There is also muscular hypotonia especially of the oral cavity, for example patients have an open mouth with a big tongue. Patients' immune system has a reduced ability to respond to elements of inflammation. The major dental manifestations are hypodontia, a hypoplastic maxilla and a malocclusion⁵²⁻⁵⁴.

Trisomy 18 (Edward's Syndrome) and Trisomy 13

Patients have three chromosomes 18 and syndrome frequency increases with mother's age. This syndrome affects the cardiovascular, musculoskeletal and nervous system and provokes craniofacial clinical features. Furthermore, Trisomy 13 is a multisystemic disease which has manifestations of the central nervous system, cardiovascular system, face and fingers causing polydactyly. Historically, trisomies 13 and 18 were not compatible with life, however there is a percentage of survivors due to a variation of genotype, phenotype and medical handling. Their orofacial features are micrognathia, cleft lip and palate^{55,56}.

Disturbances at enzymatic function, formulation of polypeptide nuclear chains and disorders of unknown aitiology

Many diseases which are provoked by defective enzymatic function and formulation of polypeptide nuclear chain or have an unknown aitiology, present with oral manifestations. For instance:

Osteopetrosis

The defective function of biological molecules like osteoclasts, can induce to osteopetrosis. It is a disease which shows a diminished bone absorption leading to expanded thick bones with high fragility, risk of fracture and inflammation. X-rays indicate augmented bone density. Osteopetrosis has autosomal dominant heredity when presenting in adults, recessive in children, while it can be lethal for babies if it remains untreated. At the recessive form, patients have neurological and skeletal anomalies, anemia, thrombocytopenia, and impaired vision. However, at the dominant form, patients have manifestations only at the human skeleton. X-rays, show "bone in bone" appearance and crosswise radiolucent bands mainly at the autosomal dominant form. The major dental manifestations are a retarded eruption of teeth and abnormalities of teeth structure⁵⁷⁻⁵⁹.

Gaucher disease

Gaucher disease is a multisystemic disease and inherited by an autosomal recessive manner, causing insufficiency of the lysosomal enzyme glucocerebrosidase. The gene encoding glucocerebrosidase, can be found at chromosome 1, (1q21) and results in an increased deposition of glucocerebroside in the lysosome of many macrophages. Depending on the severity of disease, clinical characteristics vary from infantile death to absent symptoms. There are 3 clinical types categorized based on the existence or not of neurological symptoms. In types 1 and 3 patients have painful crises of bones due to the concentration of Gaucher's cells at the bone marrow provoking localized bone lesions. The main oral manifestations are pseudo cystic radiolucent lesions, thinning of cortex, median rhomboid glossitis, xerostomia anodontia and dental anomalies⁶⁰⁻⁶².

Mucopolysaccharidosis

Mucopolysaccharidosis is a hereditary disorder of lysosomal storage, caused by inborn errors of metabolism leading to enzyme deficiency. It can be classified in 7 big subcategories according to enzymatic deficiency and accumulated substrate. Each category has different features. However, there are some common symptoms like musculoskeletal deformities, joints' rigidity, severe growth retardation, rough facial characteristics, mental impairment, enlargement of organs, cardiovascular and breathing problems. The major oral manifestations include hypoplastic peg-shaped teeth, gingival hyperplasia and hypoplastic and prognathic jaws⁶³⁻⁶⁵.

B-thalassemia

B-thalassemia is the most severe form of congenital anemia manifested at the first months of infancy. It provokes growth retardation, anemia and skeletal anomalies during development. Hemosiderosis is frequent and skin color is pale and grey. The orofacial symptoms are a consequence of bone changes related to hypertrophy and enlargement of bone marrow because of ineffective erythropoiesis. As a result, patients have frontal bossing, an upper lip retraction, a protrusion of premaxilla bone, making them have chipmunk face. The most frequent oral features are enlarged maxilla, dental malocclusion and atrophic glossitis⁶⁶⁻⁶⁸.

Fanconi syndrome (FS)

Fanconi syndrome's (FS) aetiology remains unclear as many factors play a role, such as genetic agents, inner metabolic mistakes, or systematic diseases. Patients appear with renal proximal tubule dysfunction leading to insufficient absorption of amino acids, phosphate, glucose, bicarbonate and electrolytes. The main clinical characteristics are polyuria, growth retardation, rickets, osteomalacia, metabolic acidosis, bone deformities and renal disorders. The principal dental manifestations are delayed eruption of teeth and alterations of the enamel and dentin structure⁶⁹⁻⁷⁰.

Oral manifestations of hereditary and congenital metabolic bone diseases

The oral manifestations of hereditary and congenital metabolic bone diseases were divided into three groups, the first group included dental symptoms, the second symptoms of oral mucosa and periodontal tissues and the last one involved the upper and lower jaw. All these features are analyzed above and presented with details at the following three tables.

Dental manifestation of metabolic bone diseases

Dental manifestations and the conditions they appear at are presented in Table 1.

Major dental symptoms

Tooth loss is the basic characteristic. Sometimes, it is referred as an oligodontia due to agenesis or non-erupted teeth^{2,25,59}. Another characteristic which appears frequently is root anomalies, such as short roots, thin root canal, enlarged pulp chamber in fat or strange shape^{17,58}. In addition, most disorders have consequences in hard tissues, for instance thin or hypoplastic enamel, dentin with similar properties, whereas only 2 diseases have an impact at cementum^{1,3,5,14,27,34,53,63,65,66}. Delayed eruption of teeth, due to either ankylosis or automatically, is another frequent symptom^{4,12,13,26,34,36,57,68,69}. Malocclusion appears in many conditions when patients have crowded teeth, frontal open bite, posterior crossbite, and dental Class II or III malocclusion^{24,35,39,41}. Changes of dental crown shape, for instance peg shaped, bulbous shaped or taurodontism can be observed^{23,31,32,37-39,54,55,64,68}.

Secondary dental features

Calcium enriched root canal or pulp stones, an early apoptosis of deciduous or permanent teeth were also found^{17,28,30}. Supernumerous teeth and dental caries appear sometimes^{1,26,27,31,32,39,53-55,57,64,67}. However, wrong position of erupted teeth, root absorption and discolored teeth present rarely^{5,34,35,63,65,66}.

Manifestations at oral mucosa and periodontal tissues

Manifestations of the oral mucosa and periodontal tissues are presented in Table 2.

The majority of metabolic bone diseases affects periodontal tissues. Specifically, gingivitis, periodontitis and hyperplastic gums are observed in the majority of metabolic bone disease^{4,5,34,35,40,49,63,65}. Furthermore features such as a loose periodontal ligament, extremely thin or lost alveolar bone without a periodontal disease are found at others^{37,38,60}.

Tongue manifestations include macroglossia in down syndrome, atrophic glossitis in b-thalassemia, geographic tongue in other syndromes and median rhomboid glossitis in Gaucher's and Paget's disease^{5,34,35,40,41,64}. In addition, other conditions observed include candidiasis due to immunodeficiency, gingival pigmentation, angular cheilitis and discoloration of oral mucosa^{48,66}.

The characteristic of hypophosphataemic rickets is abscesses without any pathology of the tooth, while a xerostomia appearing in Gaucher's disease and B-thalassemia can be combined with a susceptibility on caries^{1,12,13,65,67,70}.

Manifestations on upper and lower jaw

Manifestations of the upper and lower jaw are presented in Table 3.

Sometimes, the upper or lower jaw appear hypoplastic resulting in prognathism of each non-hypoplastic jaw. A hypoplastic upper jaw is a common phenomenon, while a

	Manifestations at tongue	Candidiasis	Gingival pigmentation	Yellowish oral mucosa	Angular cheilitis	Periodontal diseases	Abscess	Thin or lost alveolar bone	loose periodontal ligament	Xyrostomia
Rickets						✓	✓	✓		
XLH							✓	✓		
HPP						✓				
PHP						✓				
Cherubism						✓				
Pycnodysostosis	✓					✓				
Paget disease									✓	
Achondroplasia	✓					✓				
Down Syndrome	✓				✓	✓				
WBS						✓				
Osteopetrosis						✓			✓	
Gaucher's Disease	✓	✓	✓			✓		✓		✓
Mucopolysaccharidosis	✓					✓				
B-thalassemia	✓			✓	✓	✓				✓

Table 2. Manifestations at the oral mucosa and periodontal tissues. (Abbreviations: XLH=X-Linked Hypophosphatemic Rickets, HPP=Hypophosphatasia, PHP=Pseudohypoparathyroidism, WBS=Williams-Beuren Syndrome).

	Prognathism of jaws	Hypoplastic jaws	Hypoplastic or flattened condyle	Altered at morphology of mandibular	Cysts, pseudocysts	Osteonecrosis, osteomyelitis, osteosarcoma
CCD	✓	✓				
OI		✓				
PHP		✓				
Kenny-Caffey syndrome		✓				
Pycnodysostosis		✓				
Paget's disease	✓					✓
Achondroplasia		✓				
Down syndrome	✓					
Trisomy 13,18		✓				
WBS	✓	✓				
Osteopetrosis						✓
Gaucher's disease			✓	✓	✓	✓
Mucopolysaccharidosis	✓	✓	✓	✓	✓	
Treacher- Collins syndrome		✓				
Apert syndrome	✓					

Table 3. Manifestations at jaws. (Abbreviations: CCD=Cleidocranial Dysplasia, OI=Osteogenesis Imperfecta, PHP=Pseudohypoparathyroidism, WBS=Williams-Beuren Syndrome).

hypoplastic mandibula presents rarely^{5,26,27,31,32,34,40,53-55}. A prognathism of mandibular appears at a same frequency with prognathic maxilla^{16,37,39,41,47,65,67,71-75}.

Gaucher's disease and Mucopolysaccharidosis show special manifestations, for example a hypoplastic, flatted, short condyle and mandibular altered morphology. These diseases have radiolucent lesions such as cysts and pseudocysts^{59-61,64}.

Some rare manifestations are osteomyelitis or osteonecrosis after invasive procedures at osteopetrosis and Gaucher's disease^{56,58,60}. In addition, osteosarcoma presents at Paget's disease and ossifying fibromas appear in HPT-JT^{37,38,43}.

Clefts

Clefts are manifested at syndromes such as Treacher-Collins, Stickler and Apert. They can also be found in Trisomy 13 and 18.

Treacher-Collins syndrome is inherited with autosomal dominant way and related with mutations at gene TCOF1, POLR1D, or POLR1B. However, when it concerns genes POLR1C or POLR1D, it presents recessive heredity. Some clinical features include hearing loss, zygomatic aplasia or hypoplasia, and micrognathia⁷¹.

Stickler syndrome is a connective tissue disorder leading to ophthalmic problems such as myopia, cataracts, up to total vision loss. Clinically, there is hypoplastic mid third of face, mild spondyloepiphyseal dysplasia, premature arthritis, joint hypermobility, scoliosis and osteochondritis. It is inherited in an autosomal recessive way due to mutations of genes COL9A1, COL9A2, or COL9A3, while after mutations of genes COL2A1, COL11A1, or COL11A2 syndrome has an autosomal dominant heredity^{72,73}.

Apert syndrome is inherited with autosomal dominant way, and is sometimes provoked by a new mutation of the FGFR2 associated with increased parents' age during conception. Some clinical manifestations include craniosynostosis, midface hypoplasia, prognathism leading to malocclusion, syndactyly of hands and feet, and many special characteristics of soft tissues and bones^{74,75}.

Conclusion

It can be concluded that there are many dental manifestations of hereditary and congenial metabolic bone diseases, such as a delayed eruption of teeth, oligodontia, a dysplastic enamel, dentine, and other features. Also, many oral manifestations can be observed at the oral mucosa, periodontal tissues, jaws, and some syndromes present with clefts lips and palate. Dentists should be well-informed about these manifestations in order to recognize them through clinical examination and x-rays, giving a special dental care. In addition, a cooperation between doctors and dentists is necessary, on the grounds that, dentists can refer patients for genetic consultation and treatment from experts.

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