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Syndromes associated with gingival enlargement

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Abstract
A number of genetic disorders present with gingival manifestations which may be in the form of desquamative, ulcerative lesions or an enlargement of the gingiva. Gingival enlargement is a broad term that refers to gingival overgrowth without cause suggestion i.e. a strictly clinical description of the condition avoiding the flawed pathologic implications of terms used such as hypertrophic gingivitis or gingival hyperplasia. In this article we have summarized gingival enlargement that can be attributed to gene pathology.

Keywords: syndromes, gingival enlargement, gene mutation, gingivitis

Introduction
Gingival enlargement is common among patients. It can be caused by a variety of etiological factors. The most common reason is poor oral hygiene and high bacterial load that leads to gingival inflammation and enlargement. Other etiological factors include systemic drugs, systemic disease and conditions [1].

Genetic disorders associated with gingival enlargement classified into four main categories according to etiology, clinical presentation and histopathological findings. The first category is Hereditary Gingival Fibromatosis (HGF). It represents a heterogeneous group of disorders characterized by progressive enlargement of the entire gingiva. HGF may appear as an isolated entity i.e. as autosomal dominant gingival fibromatosis or as part of a syndrome. The second category is Lysosomal Storage Disorders. It is a group of disorders characterized by deposition of macromolecules anywhere in the body including the gingiva. Enlargement of gingiva is not always a constant feature in this category. The third category is referred to as Vascular Disorders while the last category includes disorders associated with characteristic dental abnormalities.

Hereditary gingival fibromatosis
Clinically HGF develops as a slowly progressive, benign, localized or generalized enlargement of keratinized gingiva that, in severe cases, may cover the crowns of the teeth. The main feature of HGF is the accumulation of excess extracelluar matrix (ECM). Transforming growth factor (TGF) expression is up regulated in HGF [2]. TGF can promote ECM accumulation by increasing ECM synthesis and can also inhibit ECM breakdown by down regulating matrix metalloproteinases (MMPs) expression and by increasing expression of tissue inhibitors of matrix metalloproteinases [3].

A) Isolated hereditary gingival fibromatosis
It is mainly autosomal dominant, though autosomal recessive inheritance has been reported. The enlargement affects both deciduous and permanent dentition. The gingiva appears firm, non-hemorrhagic and large enough to interfere with speech and, in some instances, with mouth closure [4].

B) Zimmerman – Laband syndrome
It is an autosomal dominant disorder. Apart from gingival enlargement, it is characterized by abnormal fingers, nails, nose, and ears. Other findings include splenomegaly, hepatomegaly, and hyperextensible metacarpophalangeal joints [5].

C) Ramon Syndrome
It is characterized by cherubism, seizures, mental deficiency, hypertrichosis, stunted growth and juvenile rheumatoid arthritis [6].

D) Systemic Hyalinosis / Infantile systemic hyalinosis / Juvenile hyaline fibromatosis
It is an autosomal recessive systemic disorder due to mutation in CMG2, or ANTXR2 gene. It is characterized by widespread deposition of hyaline material in all body tissues causing painful joint contractures, diffuse thickening of the skin with pearly papules and fleshy nodules and failure to thrive. Gingival enlargement is a constant feature and other oral structures may also be enlarged [7, 8].

E) Jones syndrome
It is autosomal dominant in inheritance. Its main features are gingival fibromatosis with progressive sensorineural deafness [9].

F) Rutherfurd syndrome
It is usually autosomal dominant in inheritance. It is characterized by corneal opacity, mental retardation and aggressive behavior. Gingival fibromatosis may be related with failure of tooth eruption [10].

G) Cross – McKusick - Breen syndrome/ Kramer's syndrome
It is characterized by hypopigmentation, mental retardation and writhing movement of hands and legs [11].

H) Gingival fibromatosis, hypertrichosis and mental retardation
It is autosomal recessive in inheritance. It is characterized by epilepsy, finger abnormalities, hirsutism, bulbous short nose and abnormal ears [12].

I) Neurofibromatosis type I/ Von Recklinghausen disease
It is an autosomal dominant neurocutaneous disorder caused by mutation in NF1 gene. It is characterized by neural and cutaneous manifestations, as well as skeletal, oral and jaw abnormalities including gingival enlargement [13].

J) Schinzel-Giedion syndrome (SGS)
It is a rare multiple congenital malformation syndrome defined by characteristic facial features, profound developmental delay, severe growth failure, and multiple congenital anomalies. Most individuals affected by SGS die in early childhood mainly because of progressive neurodegeneration and respiratory failure [14].

K) Costello syndrome/ Noonan like syndrome
It is a rare disease characterized by fetal and neonatal macrostomia with slow postnatal growth due to the severe feeding difficulties, distinctive coarse facial dysmorphism and mental retardation. Costello syndrome patients develop gingival hyperplasia usually within the first years of life [15].

Lysosomal storage disorders
Lysosomal storage diseases are a heterogeneous group of disorders caused by lysosomal enzyme dysfunction including mucopolysaccharidosis, mucolipidosis and others.

A) Hurler syndrome
It is an autosomal recessive disorder caused by a mutation in the gene encoding for the enzyme alpha-L-iduronidase leading to deficiency of the enzyme and accumulation of glycosaminoglycans in various tissues [16]. Features include mental retardation, dwarfism, coarse facial features, flexion contractures, hepatosplenomegaly, hernias, corneal clouding, [17, 18] respiratory infections and cardiac complications [19]. Intraoral features include macroglossia, short mandibular rami with abnormal condyles consistent with limited opening of the mouth, spaced hypoplastic peg-shaped teeth with retarded eruption, and localized dentigerous cyst-like radiolucencies. Gingival hyperplasia is a common feature [20-23].

B) Maroteaux-lamy syndrome/ Mucopolysaccharidosis type VI
It is an autosomal recessive trait characterized by growth retardation, enlargement of the skull with a long anteroposterior dimension and corneal opacities. The oral findings contain short or stubby, malformed, peg-shaped, poorly formed and calcified teeth with delayed eruption. Other include gingival hyperplasia and hypertrophy of the maxillary alveolar ridges. Also, the anterior teeth may present an open-bite relationship in association with macroglossia [24, 25].

C) Scheie and Hurler /Sheie syndrome
It represents the mildest form of mucoplysaccharidosis. An Intermediate phenotype lying in between these two variants of mucopolysaccharidosis syndrome [26].

D) Hunter syndrome
It is an X-linked recessive disorder causing a deficiency in the enzyme, iduronate-2-sulfatase (I2S) and accumulation of dermatan sulfate and heparan sulfate in various tissues and organs. It can be distinguished clinically from Hurler syndrome by mode of inheritance and absence of corneal clouding. Conductive and sensorineural deafness are frequent. Nodular or pebble like skin rash occur, especially over the scapulae [26]. Hunter syndrome shows the same oral manifestations as Hurler's [27].

E) Sly syndrome
It is an autosomal recessive disorder caused by beta-glucoronidase deficiency. Its features are mental retardation, short stature and macrocephaly. The oral features contain mainly thickening of the alveolar ridges and rarely gingival hyperplasia [28].

Mucolipidosis
A) I cell disease/ Mucolipidosis II
It is an autosomal recessive disorder caused by a deficiency of the enzyme N-acetyleglucosamine-1-phosphotransferase and leads to the accumulation of mucopolysaccharides and mucolipids macromolecules. Gingival enlargement is one of the most important features and the patient's lower face has a fish-like profile [29].

2.3 Miscellaneous lysosomal storage
B) Aspartylglucosaminuria (AGU)
It is an autosomal recessive disorder caused by deficiency of aspartylglucosaminidase leading to the accumulation of glycoasparagines in lysosomes. The main sign is progressive mental retardation where the patients are only able to learn new skills and abilities up to the age of 16 years. The facial features coarsen with age with characteristic sagging of the facial skin. Dysmorphic orofacial features include macroglossia, malocclusions, limited mouth opening as well as thick lips. Leukoedema and gingival fibromatosis are common in AGU patients. The gingival overgrowths were diagnosed histologically as fibroepithelial hyperplasia [30].

C) Alpha Mannosidosis
It is a rare disorder, transmitted as an autosomal recessive trait. It is due to deficient activity of alpha mannosidase, resulting in an abnormal accumulation of mannose-containing residues. Its features are growth and mental retardation, coarse facial features and muscular hypotonia. The oral findings contain macroglossia, widely spaced teeth and firm hyperplastic nodules of the gingival [31].

D) Niemann-Pick disease
It is an autosomal recessive disorder caused by deficiency of a specific enzyme activity 'acid sphingomyelinase' with

subsequent accumulation of sphingolipids in cells, throughout the body. Oral findings contain thick lips, macroglossia and widely spaced teeth. Although gingival enlargement is not considered a constant feature, a case was presented with generalized grade III gingival enlargement, which recurred even after excision and thorough maintenance implying that there is a link between the disease and the gingival enlargement [32].

E) Anderson Fabry disease/ Angiokeratoma Corporis Diffusum

It is an X-linked recessively inherited disease due to deficiency of the enzyme ceramide trihexosidase that results in intracellular accumulation of the glycolipid ceramide trihexoside in vascular endothelial cells, pericytes, fibroblasts, macrophages, and other cells of the body. The disease is characterized by painful crises involving the extremities and the abdomen as well as angiokeratomas of the skin that may also involve the oral mucous membrane. Gingival enlargement may be present secondary to dilantin therapy [33].

G) Menkes Kinky hair disease/ Menkes Steely hair syndrome

It is a rare X-linked recessive neurodegenerative disorder caused by a defect of copper transport and metabolism. Its features are brittle, sparse and twisted hair, and generalized depigmentation of the hair. The oral findings contain delayed dentition and gingival hyperplasia [34].

H) Ligneous periodontitis/ Plasminogen deficiency/ ligneous conjunctivitis

It is an autosomal recessive disorder in PLG gene. It is characterized by gingival swelling involving both the maxillary and mandibular arches, pinkish waxy painless masses that have no tendency to bleed with palpation and hyperplastic gingival papillae concealing most of the teeth. Areas of the gingiva covered with tough yellowish white membrane, thin pseudomembrane [35].

I) Cowden syndrome/ Multiple Hamartomas

It is an autosomal dominant inherited disorder. In 80% of cases it is due to mutation in the PTEN tumor suppressor gene. Others may have mutations in certain subunits of succinate dehydrogenase, mitochondrial enzyme [36]. Oral manifestations include cobblestone-like papules of the gingiva and buccal mucosa. However, the disease is characterized by learning disabilities, autism, and/or mental retardation, macrocephaly and multiple hamartomatous lesions, especially of the skin, mucous membranes, breast and thyroid. Verrucous skin lesions of the face and limbs, and multiple facial trichilemmomas are common findings. Hamartomatous polyps of the gastrointestinal tract, mucocutaneous lesions, and increased risk of developing neoplasms have been reported [37].

Vascular disorders

A) Sturge Weber syndrome/ Encephalofacial Angiomatosis

It is almost always a sporadic disease. However, there have been reports of cases with autosomal recessive and dominant inheritance. It has four main features; unilateral cutaneous nevi along trigeminal nerve sensory distribution, unilateral vascular hyperplasia of oral mucosa and gingiva, neurological manifestations and ocular complications [38, 39].

B) Klippel - Trenaunay syndrome / Angioosteo hypertrophy syndrome

It has a paradominant inheritance [40]. It is characterized by a triad of features, namely, vascular nevi, venous varicosities, and hyperplasia of hard and soft tissues in the affected area. Other oral manifestations include high arched palate, unilateral hypertrophy, or increase in size of periodontal tissues, tongue capillary hemangiomas, unilateral macroglossia, increase in size of fungi-form papillae, unilateral increase in lips size, teeth malformation, diastema formation, premature eruption of teeth on affected side, delayed exfoliation of primary teeth, early mineralization of roots on affected side, accelerated growth of teeth, anterior open bite, cross bite and floor of mouth capillary hemangiomas [41, 34].

Disorders associated with characteristic dental abnormalities

A) Wilson syndrome/ Hepatolenticular degeneration

It is an autosomal recessive disorder due to mutation in ATP7B gene caused by low ceruloplasmin. Its features include multiple small red papules of the lips, gingival enlargement, early onset periodontitis, and repeated oral candidiasis. Enamel hypoplasia is the characteristic dental feature. The basal ganglia and liver undergo changes that express themselves in neurological manifestations and signs of cirrhosis [42].

B) Goltz syndrome/ Focal Dermal hypoplasia / Goltz Gorlin syndrome

It is an X-linked dominant mode of inheritance in 90% of the cases caused by PORCN gene mutation. It is characterized by atrophy and linear pigmentation of the skin, herniation of fat through the dermal defects, multiple papillomas of the mucous membranes or skin. Digital anomalies e.g. syndactyly, polydactyly, camptodactyly, and absence deformities. Partial anodontia is the characteristic dental feature. Other oral manifestations include lip papillomas, gingival enlargement and hypoplastic teeth. Histopathologic features showed deposits of fat cells or adipose tissue in the dermis [43, 34].

C) Odontodysplasia / Isolated or associating epidermal nevus/ Schimmelpenning-Feuerstein-Mims syndrome

It is an uncommon condition that can affect both primary and permanent dentitions. Both enamel and dentine are defected. Clinically, the teeth are mutilated in shape, pitted and yellowish to brownish in colour with excessive wear. Enamel & dentine show lack of contrast, with decreased radiopacity rendering the tooth a ghost like appearance radiographically. The pulp chambers are wide and with open apices [44]. Gingival enlargement is commonly reported with regional type [34, 45]. Genetic predisposition has been proposed but the presence of local irritating factors during tooth development has been more advocated.

Conclusion

Gingival enlargement is main feature in many genetic disorders. It can be one of the main diagnostic features in some of these disorders e.g. ligneous periodontitis. In others gingival enlargement united with other clinical features direct the physician to further investigations. Accordingly, metabolic analysis, enzymatic essay, molecular analysis to detect the candidate genes and histopathological studies may be requested. Histopatological findings are considered of diagnostic value in a limited number of cases. They may become pathonemonic when joined with clinical examination.

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