

Genetic Disorders Associated with Gingival Enlargement

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1. Introduction

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 chapter we will summarize gingival enlargement that can be attributed to gene pathology.

Gingival enlargement may present in some genetic disorders secondary to certain treatments not to actual gene expression e.g. Cystinosis secondary to treatment with cyclosporine-A, or epilepsy treated with phenytoin. This category of genetic disorders will not be discussed in this chapter, but should be considered in the differential diagnosis.

Genetic disorders associated with gingival enlargement fall into four main categories according to etiology, clinical presentation and histopathological findings (Table 1). This classification is suggested as a guiding tool in differential diagnosis. The first category is *Hereditary Gingival Fibromatosis* (HGF), which represents a heterogeneous group of disorders characterized by progressive enlargement of the gingiva. HGF may appear as an isolated entity i.e. as autosomal dominant Gingival Fibromatosis or as part of a syndrome. These syndromes are rather rare but they all have gingival fibromatosis as a constant feature. The second category is *Lysosomal Storage Disorders* which are a group of disorders characterized by deposition of macromolecules anywhere in the body including the gingiva leading to gingival enlargement. Gingival enlargement in this category is not always a constant feature. It ranges from being common to being a rare feature. The third category is referred to as *Vascular Disorders* while the last category includes syndromes characterized by the presence of *characteristic dental abnormalities*.

2. Hereditary gingival fibromatosis

Gingival enlargement may present as a specific entity, hereditary gingival fibromatosis (HGF), and may appear in an isolated form. However, there are several uncommon syndromes in which gingival fibromatosis can be a feature.

Hereditary Gingival Fibromatosis	Lysosomal Storage Disorders	Vascular Disorders	Disorders Associated with Dental Abnormalities
Gingival fibromatosis (isolated)	Hurler syndrome	Sturge Weber syndrome	Wilson syndrome
Zimmerman - Laband syndrome	Maroteaux-Lamy syndrome	Klippel-Trenaunay syndrome	Goltz syndrome
Ramon syndrome	Scheie syndrome		Regional Odontodysplasia
Systemic hyalinosis	Hurler/ scheie		
Jones syndrome	Hunter syndrome		
Rutherford syndrome	Sly syndrome		
Cross Syndrome	I- Cell disease		
Gingival fibromatosis, hypertrichosis and mental retardation.	Aspartylglucosaminuria		
Neurofibromatosis type I	Alpha Mannosidosis		
Schinzl - Giedion syndrome	Niemann - Pick disease		
Costello syndrome	Anderson - Fabry disease		
	Menkes Kinky hair disease		
	Ligneous periodontitis		
	Cowden syndrome		

Table 1. Classification of genetic disorders associated with gingival enlargement.

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. Localized forms of HGF usually affect the maxillary tuberosities and the labial gingiva around the mandibular molars. However, the symmetric generalized form of HGF that affects the labial, lingual, and palatal gingiva is the most common (Baptista, 2002; Kelekis-Cholakias et al., 2002). Males and females are equally affected. (Xiao et al., 2001; Ye et al., 2005). Enlarged gingiva may be normal in color or erythematous and are firm and nodular on palpation. Although the alveolar bone is usually unaffected, gingival enlargement results in pseudo-pocketing and periodontal problems, due to difficulties in maintaining an effective level of oral hygiene. The overgrowth may also result in functional and esthetic concerns, create diastemas, impede or delay tooth eruption, and create changes in facial appearance as a result of lip protrusion. Severe overgrowth can result in crowding of the tongue, speech impediment, and difficulty with mastication, and can prevent normal closure of lips (Lynch et al., 1994; Shafer, 1983). The onset of gingival overgrowth usually coincides with the eruption of the permanent incisors, or, at times, with the eruption of the primary dentition. In very rare cases; it can be also present at birth (Anderson et al., 1969).

Since HGF has not been reported in edentulous patients, it appears that the presence of teeth is necessary for overgrowth to develop.

Histologically: HGF usually involves moderate hyperplasia of a dense, hyperkeratotic epithelium with elongated rete ridges (Araujo et al., 2003; Doufexi et al., 2005). Epithelial hyperplasia can also occur as a consequence of acanthosis, but this was found only in areas of chronic inflammation (Farrer-Brown et al., 1972; Raeste et al., 1978). HGF tissues show an increased amount of collagen fiber bundles running in all directions associated with few fibroblasts and blood vessels (Araujo et al., 2003; Doufexi et al., 2005; Martelli-Junior et al., 2000). Two populations of fibroblasts were identified in the lesions. One contains little cytoplasm around the nucleus, which is associated with dense collagen bundles. The other contains prominent cytoplasm with well developed organelles. Those fibroblasts have been considered inactive and active, respectively (Collan et al., 1982; Sakamoto et al., 2002). The connective tissue in HGF also exhibits an accumulation of elastic and oxytalan fibers (Baptista, 2002; Chavier & Couble, 1979; Doufexi et al., 2005; Hart et al., 2000; Sakamoto et al., 2002). Although a rare finding, small osseous calcifications and abundant neurovascular bundles may also be present (Gunhan et al., 1995; Kelekis-Cholakakis et al., 2002). HGF does not usually involve inflammation and local accumulation of inflammatory cells can be found only in cases where pseudo-pocketing resulted in plaque accumulation (Shafer, 1983).

Extracellular matrix production and degradation:

The hallmark of HGF is the accumulation of excess extracellular matrix (ECM). Transforming growth factor (TGF) expression is up regulated in HGF (Häkkinen & Csiszar, 2007). 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 (Steffensen et al., 2001).

2.1 Isolated hereditary gingival fibromatosis

Isolated hereditary gingival fibromatosis (OMIM #135300; Gene Map locus 2p21; other loci reported on chromosomes 5q & 11p) is mainly autosomal dominant (Fig.1), 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 (Ramakrishnan et al., 2010).

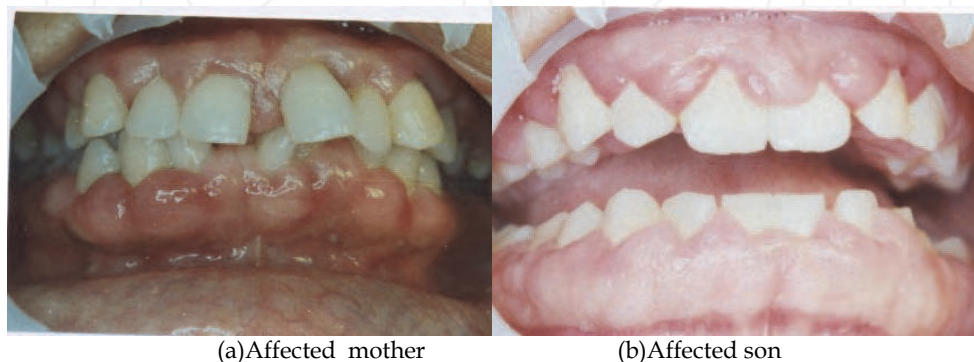


Fig. 1. Isolated autosomal dominant hereditary gingival fibromatosis.

2.2 Zimmerman – Laband syndrome

Zimmerman - Laband syndrome or Laband syndrome (OMIM #135500; Gene Map locus 3p14.3) 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 (Hoogendijk et al., 2006).

2.3 Ramon Syndrome

Ramon Syndrome (OMIM #266270) is characterized by cherubism, seizures, mental deficiency, hypertrichosis, stunted growth and juvenile rheumatoid arthritis (Suhanya et al., 2010).

2.4 Systemic Hyalinosis

Systemic Hyalinosis 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. Some tend to classify this entity into infantile systemic hyalynosis (OMIM #236490, Gene Map locus 4q21) and juvenile hyaline fibromatosis (Murray-Puretic-Drescher syndrome OMIM #228600) according to age of onset & disease severity. Individuals usually present with 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. Histopathologic features are the deposition of amorphous, eosinophilic hyaline material (fig.2) (El-Kamah & Mostafa, 2009 ; El-Kamah et al., 2010).

2.5 Jones syndrome

Jones syndrome (OMIM #135550) is autosomal dominant in inheritance. It is mainly characterized by gingival fibromatosis with progressive sensorineural deafness (Kasaboğlu et al., 2004).

2.6 Rutherford syndrome

Rutherford syndrome (OMIM #180900) is usually autosomal dominant in inheritance. Its key features are corneal opacity, mental retardation and aggressive behavior. Gingival fibromatosis in this syndrome may be associated with failure of tooth eruption (Raja et al., 2008).

2.7 Cross syndrome

Cross- McKusick- Breen syndrome or Kramer's syndrome (OMIM #257800) is characterized by hypopigmentation, mental retardation and writhing movement of hands and legs (Witkop, 1971).

2.8 Gingival fibromatosis, hypertrichosis and mental retardation

Gingival fibromatosis, hypertrichosis and mental retardation (OMIM #605400) is autosomal recessive in inheritance. It is characterized by epilepsy, finger abnormalities, hirsutism, bulbous short nose and abnormal ears (Gohlich-Ratmann et al., 2000).

2.9 Neurofibromatosis type I

Neurofibromatosis or Von Recklinghausen disease (OMIM #162200, Gene Map locus 17q11.2) is an autosomal dominant neurocutaneous disorder caused by mutation in NF1



Fig. 2. Systemic Hyalinosis.

gene. It is characterized by cafe-au-lait spots, Lisch nodules in the eye, fibromatous tumors of the skin with an increased risk of developing benign and malignant tumors. Orally, there is gingival neurofibroma. Characteristic histopathologic features: neurofibroma cells can be detected with their nuclei among the waved collagen fibers -beneath the oral mucosa. Epithelium and numerous tumor cells and capillary vessels can be seen among waved collagen fibers (El-Kamah et al., 2004).

2.10 Schinzel-Giedion syndrome

Schinzel-Giedion syndrome or Schinzel-Giedion mid-face retraction syndrome (OMIM #269150, Gene Map locus 18q21.1) is an autosomal recessive malformation syndrome characterized by severe mid-face retraction referred to as 'figure-of-eight' appearance, severe mental retardation and congenital heart defect. Neither the etiology nor detailed clinical course is known since most of the patients affected with Schinzel-Giedion syndrome die before the age of ten. However, a long-lived patient showed gingival hyperplasia that was progressive even after gingivectomy. Histopathologic examination revealed fibrous hyperplasia of the gingiva with mucoid depositions and no inflammatory changes (Kondoh et al., 2001).

2.11 Costello syndrome

Costello syndrome or Noonan like syndrome with nasal papillomata (OMIM #218040) 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. The most striking cutaneous feature is redundant skin of the neck, hands and feet. Nasal and perioral papillomas are also common between the ages of 2 and 15. Oral examination is important as Costello syndrome patients develop gingival hyperplasia usually within the first years of life and is considered as a quite distinct feature that can also aid in its differential diagnosis from Noonan syndrome and Cardiofaciocutaneous syndrome that phenotypically overlap with Costello syndrome (Digilio et al., 2008).

3. Lysosomal storage disorders

Lysosomal storage diseases are a heterogeneous group of disorders caused by lysosomal enzyme dysfunction including mucopolysaccharidosis, mucopolipidosis and others. Individually they are very rare, but this group as a whole has a prevalence of more than 1:8,000 live births (Manger, 2010). The majority of lysosomal storage disorders (LSDs) result from defective lysosomal acid hydrolysis of endogenous macromolecules and their consequent accumulation. Over 40 disorders have been described. They tend to be multisystemic and are always progressive, although the rate of progression may vary. There are several potential ways in which accumulated substrate might cause the disease. The most obvious is enlargement of the affected cell, resulting in enlargement of the respective organ such as hepatosplenomegaly, cardiomyopathy etc. (Vellodi, 2005). The buildup of undigested material, secondary to lysosomal enzyme dysfunction, results in the formation of typical histochemical and ultrastructural changes. Light microscopy often reveals engorged macrophages with a characteristic appearance, such as that of 'sea-blue histiocytes' in Niemann–Pick disease (Vanier et al., 1988).

3.1 Mucopolysaccharidosis

Mucopolysaccharidosis (MPS) are a family of lysosomal storage disorders resulting from the partial catabolism of several glycosaminoglycans (GAGs). Depending on which particular enzyme is deficient, the MPS syndromes are defined into groups MPS I through VII, with several subgroups for a total of 10 disorders. In humans, clinical features include dysmorphic features, hepatosplenomegaly, hypertelorism, macroglossia, hypoplastic and irregularly shaped teeth, hyperplastic lips and gingiva, facial dysmorphia, corneal clouding, and mental retardation. Gingival enlargement is considered as one of the main oral manifestations of Maroteaux-Lamy syndrome, and a common feature in Hurler syndrome. It is rarely reported with Scheie syndrome, Hurler/ scheie compound syndrome, Hunter's syndrome and Sly syndrome. Gingival enlargement may not be previously reported with Sanfilippo syndrome and Morquio syndrome (Sheridan et al., 1994).

3.1.1 Hurler syndrome

Hurler syndrome (Mucopolysaccharidosis IH, OMIM #607014, Gene Map locus 4p16.3) 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 (heparan sulphate and dermatan sulphate) in various tissues (Hingston

et al., 2006). Hurler syndrome is characterized by mental retardation, dwarfism, coarse facial features, flexion contractures, hepatosplenomegaly, hernias, corneal clouding (Leroy & Crocker, 1966; McKusick et al., 1965), respiratory infections and cardiac complications (McKusick & Neufeld, 1983). Gingival hyperplasia is a common feature in this disorder. Other 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 (Gardner, 1971; Keith & Weidmann, 1990; Thomas & Tandon, 2000; Worth, 1966). Histopathological reports showed Hurler cells in the gingival tissue (Gardner, 1968).

3.1.2 Maroteaux-lamy syndrome

Maroteaux-lamy syndrome or Mucopolysaccharidosis type VI (OMIM #253200, Gene Map locus 5q13) is a lysosomal storage disorder inherited as an autosomal recessive trait. It is due to deficiency of arylsulphatase B enzyme which results in accumulation of dermatan sulphate in tissues and its excretion in urine. It is characterized by growth retardation, enlargement of the skull with a long anteroposterior dimension and corneal opacities. Presence of normal intelligence as well as metachromatic inclusions in leukocytes distinguishes it from other mucopolysaccharidosis (Fig 3,a). The oral findings include short or stubby, malformed, peg-shaped, poorly formed and calcified teeth with delayed eruption. Gingival hyperplasia and hypertrophy of the maxillary alveolar ridges are often mentioned as the main oral manifestations of the Maroteaux-lamy syndrome (Fig 3,b). Also, the anterior teeth may present an open-bite relationship in association with macroglossia. (Alpoz et al., 2006; Guimaraes et al., 2010).



(a) MPS VI (usually with normal intellectual development).



(b) Gingival hyperplasia and hypertrophy of the maxillary alveolar ridges.

Fig. 3. Maroteaux-lamy syndrome.

3.1.3 Scheie and Hurler /Scheie syndrome

Scheie syndrome (Mucopolysaccharidosis IS, OMIM #607016, Gene Map locus 4p16.3) represents the mildest form of mucopolysaccharidosis. An intermediate phenotype lying in between these two variants of mucopolysaccharidosis I is the Hurler /Scheie compound

syndrome (Mucopolysaccharidosis I H/S, OMIM #607015, Gene Map locus 4p16.3) (Kelly, 1976).

3.1.4 Hunter syndrome

Hunter syndrome (Mucopolysaccharidosis II, OMIM #309900, Gene Map locus Xq28) 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 has similar but less severe manifestations than Hurler syndrome. 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 (Kelly, 1976). Hunter syndrome presents the same oral manifestations as Hurler's (Fig 4) (Gardner, 1971).



(a) MPSII, coarse facial features (prominent forehead, flat nasal bridge).



(b) Mild gingival enlargement.

Fig. 4. Hunter syndrome.

3.1.5 Sly syndrome

Sly syndrome or Mucopolysaccharidosis type VII (OMIM #253220, Gene Map locus 7q21) is a lysosomal storage disorder, transmitted as an autosomal recessive trait and caused by beta-glucuronidase deficiency. It is characterized by mental retardation, short stature and macrocephaly. The oral features include mainly thickening of the alveolar ridges and rarely gingival hyperplasia (Bittencourt et al., 2000).

3.2 Mucopolipidosis

3.2.1 I cell disease

I cell disease (Mucopolipidosis II) (OMIM #252500, Gene Map locus 12q23.3) is an autosomal recessive disorder caused by a deficiency of the enzyme N-acetylglucosamine-1-phosphotransferase which leads to the accumulation of mucopolysaccharides and mucopolipids macromolecules. Gingival enlargement is one of the most striking features of

this syndrome and the patient's lower face has a fish-like profile. It is referred to as I cell disease based on the histopathologic features because the macromolecules that accumulate inside the cell form characteristic cytoplasmic inclusions (Mahfouz et al., 2010).

3.3 Miscellaneous lysosomal storage

3.3.1 Aspartylglucosaminuria

Aspartylglucosaminuria or AGU (OMIM #208400, Gene Map locus 4q33-4q35) is an autosomal recessive lysosomal storage disorder caused by deficiency of aspartylglucosaminidase leading to the accumulation of glycoasparagines in lysosomes. The main symptom is progressive mental retardation where the patients are only able to learn new skills and abilities up to the age of 16 years. They then undergo gradual somatic and mental deterioration. 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. Edematous buccal mucosa (leukoedema) and gingival fibromatosis are common in AGU patients. The gingival overgrowths were diagnosed histologically as fibroepithelial hyperplasia (Arvio et al., 1999).

3.3.2 Alpha Mannosidosis

Alpha Mannosidosis (OMIM #248500, Gene Map locus 19q13-19q12), is a rare lysosomal storage disorder, transmitted as an autosomal recessive trait, and is due to deficient activity of alpha mannosidase, resulting in an abnormal accumulation of mannose-containing residues. It is characterized by growth and mental retardation, coarse facial features and muscular hypotonia. The oral findings include macroglossia, widely spaced teeth and firm hyperplastic nodules of the gingiva which upon histologic examination reveals infiltration with foamy histiocytes. Blood smears show cytoplasmic vacuolization of lymphocytes and monocytes (Ischigami et al., 1995).

3.3.3 Niemann-Pick disease

Niemann-Pick disease (OMIM #257200, Gene Map locus 18q11-18q12 type C, 11p15), 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 include 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. Gingival biopsy upon histologic examination revealed infiltration with foamy histiocytes. Blood smear showed cytoplasmic vacuolization of lymphocytes and monocytes (Kaisare, 2007).

3.3.4 Anderson Fabry disease

Anderson Fabry disease or Angiokeratoma Corporis Diffusum (OMIM #301500, Gene Map locus Xq21-Xq22) 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, mainly the labial mucosa followed by the buccal mucosa and the gingiva. Gingival enlargement may be present secondary to dilantin therapy. Young et al. (1978) presented a case with Fabry disease where granulomatous gingivitis has been described. Histologically, angiokeratoma of the gingiva shows ceramide inclusions not only in the connective tissue, but also in the oral epithelial cells.

3.3.5 Menkes Kinky hair disease

Menkes Kinky hair disease or Menkes Steely hair syndrome (OMIM #309400, Gene Map locus Xq13) is a rare X-linked recessive neurodegenerative disorder caused by a defect of copper transport and metabolism. It is characterized by brittle, sparse and twisted hair, and generalized depigmentation of the hair. The oral findings include delayed dentition and gingival hyperplasia (McKusick, 2011).

3.3.6 Ligneous periodontitis

Ligneous periodontitis, Plasminogen deficiency or Ligneous conjunctivitis (OMIM #217090, Gene Map locus 6q22) is an autosomal recessive disorder in PLG gene. Plasminogen deficiency 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, that could be wiped away, overlay the tough part of the membrane (Fig.5,a). Other disease manifestations include; ligneous conjunctivitis (Fig.5,b), Corneal involvement that may lead to blindness in 30% of cases. Other system involvement such as laryngeal and tracheobronchial involvement resulting in voice change and obstructive pulmonary disease have been described. Characteristic histopathologic manifestations shown in (Fig.5,c) are epithelial hyperplasia and fibrin deposition underneath the epithelium and around the blood vessels. The dermis shows edema and perivascular mixed cellular infiltrate; mostly plasma cells, polymorphonuclear leukocytes, few lymphocytes, and mast cells. Amorphous hyaline-like eosinophilic material of the pseudomembranes, which resembles amyloid but negative for Congo red stain, that contains fibrin (El-Darouti et al., 2009).

3.3.7 Cowden syndrome

Cowden syndrome or Multiple Hamartomas (OMIM #158350, Gene Map locus 10q23.31) 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 (Ni et al., 2008). Recently, methylation of the KILLIN gene has also been reported in patients with similar clinical features. 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 (Tan et al., 2011).

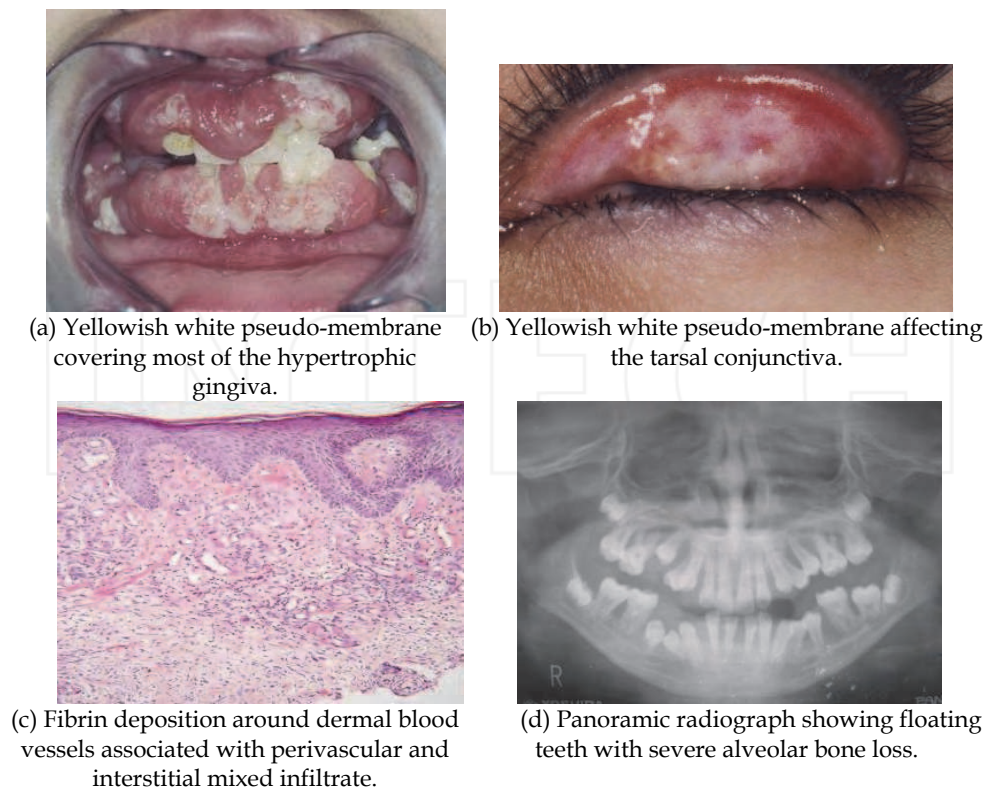


Fig. 5. Clinical and histopathological characteristics in Ligneous periodontitis and Ligneous conjunctivitis.

4. Vascular disorders

4.1 Sturge-Weber syndrome

Sturge-Weber syndrome or encephalofacial angiomatosis (OMIM #185300) 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 (Fig.6,a), unilateral vascular hyperplasia of oral mucosa and gingiva, neurological manifestations and ocular complications (Pereira de Godoy et al., 2010; Zhou et al., 2010). Sturge-Weber syndrome is characterized by an intracranial vascular anomaly and calcification, leptomenigeal angiomatosis, most often involving the occipital and posterior parietal lobes (Fig.6b).

4.2 Klippel-Trenaunay syndrome

Klippel-Trenaunay syndrome or Angioosteohypertrophy syndrome (OMIM #149000, Gene Map locus 8q22.3) has a paradominant inheritance (Happle, 1993). It is characterized by a triad of features, namely, vascular nevi, venous varicosities, and hyperplasia of hard and soft tissues in the affected area (Fig.7). Despite its rarity, Klippel-Trenaunay Syndrome

should be considered in the differential diagnosis of gingival enlargement. (Anand & Roshna, 2006). Gingival capillary hemangiomas, gingival fibroma, Gingival fibromatosis, gingival hyperplasia. 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 (Fakir et al., 2009; McKusick, 2011).



(a) Congenital large port wine stain involving the right side of the face and scalp extending to the left side.



(b) CT scan showing intracranial calcification.

Fig. 6. Sturge Weber syndrome.

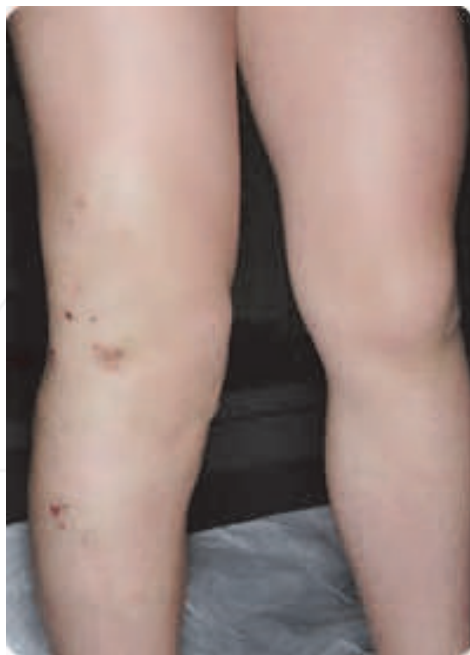


Fig. 7. Unilateral limb oedema, hemihypertrophy , nevi & prominent nodules in Klippel-Trenaunay syndrome.

5. Disorders associated with characteristic dental abnormalities

5.1 Wilson syndrome

Wilson syndrome or Hepatolenticular degeneration (OMIM #277900, Gene Map locus 13q14.3-q21.1) is an autosomal recessive disorder due to mutation in ATP7B gene caused by low ceruloplasmin. It is characterized by 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 (Huster et al., 2007). Histopathologic examination reveals granulomatous inflammation, thick irregular clumps of tortuous, red-staining abnormal elastic fibers. In a study, the lip papules may resemble elastosis perforans serpiginosa (Tovaru et al., 2010).

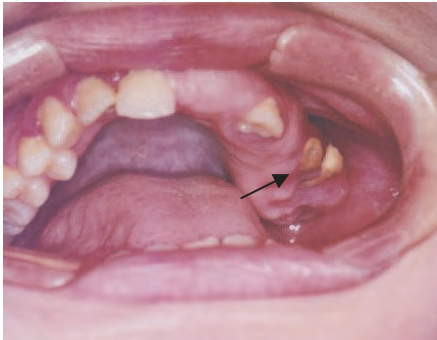
5.2 Goltz syndrome

Goltz syndrome, Focal Dermal hypoplasia or Goltz Gorlin syndrome (OMIM #305600, Gene Map locus Xp11.23.) 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.

Characteristic histopathologic features showed deposits of fat cells or adipose tissue in the dermis (Maas et al., 2009; McKusick, 2011).

5.3 Odontodysplasia

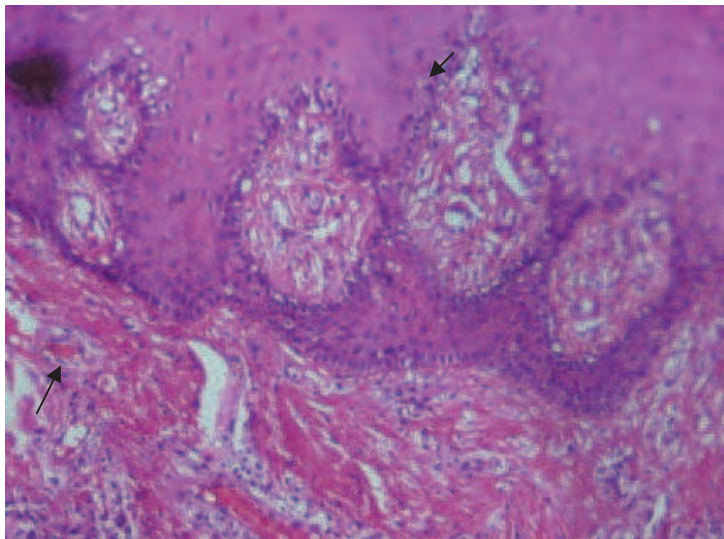
Odontodysplasia is an uncommon condition that can affect both primary and permanent dentitions. Both enamel and dentine are defected. Clinically, the teeth are mutilated in shape, pitted and yellowish to brownish in colour with excessive wear. Radiographically, enamel & dentine show lack of contrast, with decreased radiopacity rendering the tooth a ghost like appearance. The pulp chambers are wide and with open apices (Fig.8 a & b)



(a) Affected teeth are mutilated in shape, pitted and yellowish to brownish in color (arrow) with gingival enlargement in the affected side.



(b) Panoramic radiograph showing ghost like appearance of the affected teeth.



(c) Gingival biopsy showing odontogenic tissue in the epithelium and intramesenchymal calcifications.

Fig. 8. Regional maxillary odontodysplasia.

(Hamdan et al., 2004). It commonly presents as regional odontodysplasia where one or few teeth may be involved. One or more quadrants may be involved but generalized involvement is extremely rare (Shah and Gupta, 1998). Gingival enlargement is frequently reported with regional type. It may present as an isolated or associating epidermal nevus/Schimmelpenning-Feuerstein-Mims syndrome (OMIM #163200) (McKusick, 2011; Murakami et al., 1999). The exact etiology of odontodysplasia is still unknown. Genetic predisposition has been proposed but the presence of local irritating factors during tooth development has been more advocated. Gingival biopsy examination showed odontogenic tissue in the epithelium and intramesenchymal calcifications (Fig.8c).

6. Conclusion

Gingival enlargement is an important 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 coupled with other clinical features direct the physician to further investigations. Accordingly, metabolic analysis, enzymatic assay, molecular analysis to detect the candidate genes and histopathological studies may be requested. Histopathological findings are considered of diagnostic value in a limited number of cases. They may become pathonemonic when coupled with clinical examination e.g. hyaline material in hyalinosis, fat deposits in Focal Dermal hypoplasia, odontogenic cells in odontodysplasiaetc.

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8. References

- Alpöz, A.; Coker, M.; Celen, E.; Ersin, N.; Gökçen, D.; van Diggelenc, O. & Huijmansc, J. (2006). The oral manifestations of Maroteaux-Lamy syndrome (mucopolysaccharidosis VI); A case report, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 101:632-7, ISSN: 1528-395X
- Anand, PS. & Roshna, T. (2006). Rare instance of gingival enlargement in Klippel-Trenaunay syndrome: a case report, *J Contemp Dent Pract*, 7:92-8, ISSN: 1526-3711
- Anderson, J.; Cunliffe, WJ.; Roberts, DF. & Close, H. (1969). Hereditary gingival fibromatosis, *Br Med J*, 3:218-219, ISSN: 0267-0623
- Araujo, CS.; Graner, E.; Almeida, OP.; Sauk, JJ. & Coletta, RD. (2003). Histomorphometric characteristics and expression of epidermal growth factor and its receptor by epithelial cells of normal gingiva and hereditary gingival fibromatosis, *J Periodontal Res*, 38:237-241, ISSN: 1600-0765
- Baptista, IP. (2002). Hereditary gingival fibromatosis: a case report, *J Clin Periodontol*, 29:871-874, ISSN: 1600-051X

- Bittencourt, L.; Campos, V.; Moliterno, L.; Ribeiro, D. & Sampaio, R. (2000). Hereditary gingival fibromatosis: review of the literature and a case report, *Quintessence Int*, 31(6):415-8, ISSN: 1936-7163
- Chavrier, C. & Couble, ML. (1979). Ultrastructure of the connective corium in hereditary gingival hyperplasia, *J Biol Buccale*, 7:191-203, ISSN: 0301-3952
- Collan, Y.; Ranta, H.; Vartio, T.; Perheentupa, J. & Raeste, AM. (1982). Histochemical and biochemical study of hereditary fibrous hyperplasia of the gingiva, *Scand J Dent Res*, 90:20-28, ISSN: 0029-845X
- Digilio, M.; Sarkozy, A.; Capolino, R.; Chiarini Testa, M.; Esposito, G.; de Zorzi, A.; Cutrera, R.; Marino, B. & Dallapiccola, B. (2007). Costello syndrome: clinical diagnosis in the first year of life, *Eur J Pediatr*, 167:621-628, ISSN: 1432-1076
- Doufexi, A.; Mina, M. & Ioannidou, E. (2005). Gingival overgrowth in children: epidemiology, pathogenesis, and complications. A literature review, *J Periodontol*, 76:3-10, ISSN: 1943-3670
- El-Darouti, M.; Zayed, A.; El-Kamah, Gh. & Mostafa, M. (2009). Ligneous Conjunctivitis with oral mucous membrane involvement and decreased plasminogen level, *Pediatr Dermatol*, 26: 448-451, ISSN: 1525-1470
- El-Kamah, Gh.; Abd-El-salam, GH.; Hassan, NA.; El-Darouti, M. & Temtamy, SA. (2004). Neurofibromatosis 1: unusual clinical associations, *Kasr El-Eini medical Journal*, 10:45-56
- El-Kamah, Gh.; & Mostafa, M. (2009). Heterogeneity and atypical presentation in infantile systemic hyalinosis with severe labio-gingival enlargement: first Egyptian report, *Dermatol Online J*, 15:6, ISSN: 1087-2108
- El-Kamah, Gh.; Fong, K.; El-Ruby, M.; Affifi, HH.; Clements, SE.; Amr, K.; El-Darouti, M. & McGrath, JA. (2010). Spectrum of mutations in the ANTXR2 (CMG2) gene in infantile systemic hyalinosis and juvenile hyaline fibromatosis, *Br J Dermatol* . 163(1):213-215, ISSN: 1365-2133
- Fakir, E.; Roberts, T.; Stephen, L. & Beighton, P. (2009). Klippel-Trenaunay-Weber syndrome: orodental manifestations and management considerations, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 107:754-758, ISSN: 1528-395X
- Farrer-Brown, G.; Lucas, RB. & Winstock, D. (1972). Familial gingival fibromatosis: an unusual pathology, *J Oral Pathol*, 1:76-83, ISSN: 0300-9777
- Gardner, DG. (1968). Metachromatic cells in the gingiva in Hurler's syndrome, *Oral Surg Oral Med Oral Pathol*, 26:782-9, ISSN: 0030-4220
- Gardner, DG. (1971). The oral manifestations of Hurler's syndrome, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 32:46-57, ISSN: 1528-395X
- Gohlich-Ratmann, G.; Lackner, A.; Schaper, J.; Voit, T. & Gillessen-Kaesbach, G. (2000). Syndrome of gingival hypertrophy, hirsutism, mental retardation and brachymetacarpia in two sisters: specific entity or variant of a described condition?, *Am J Med Genet*, 95: 241-246, ISSN: 1096-8628
- Guimarães Mdo, C.; de Farias, SM.; Costa, AM.; de Amorim, RF. (2010). Maroteaux-Lamy syndrome: Oro-facial features after treatment by Bone Marrow Transplant, *Oral Health Prev Dent*; 8: 139-142, ISSN: 1602-1622

- Gunhan, O.; Gardner, DG.; Bostanci, H. & Gunhan, M. (1995). Familial gingival fibromatosis with unusual histologic findings, *J Periodontol*, 66:1008-1011, ISSN: 1943-3670
- Häkkinen, L. & Csiszar, A. (2007). Hereditary gingival fibromatosis: characteristics and novel putative pathogenic mechanisms, *J Dent Res*, 86:25-34, ISSN: 1544-0591
- Hamdan, MA.; Sawair, FA.; Rajab, LD.; Hamdan, AM. & Al-Omari, IK. (2004). Regional odontodysplasia: a review of the literature and report of a case, *Int J Paediatr Dent*, 14:363-7, ISSN: 1365-263X
- Happle, R. (1993). Klippel-Trenaunay syndrome: is it a paradominant trait?, *Br J Dermatol*, 128:465-466, ISSN: 1365-2133
- Hart, TC.; Pallos, D.; Bowden, DW.; Bolyard, J.; Pettenati, MJ. & Cortelli, JR. (1998). Genetic linkage of hereditary gingival fibromatosis to chromosome 2p21, *Am J Hum Genet*, 62:876-883, ISSN: 1537-6605
- Hart, TC.; Pallos, D.; Bozzo, L.; Almeida, OP.; Marazita, ML. & O'Connell, JR. (2000). Evidence of genetic heterogeneity for hereditary gingival fibromatosis, *J Dent Res*, 79:1758-1764, ISSN: 1544-0591
- Hingston, EJ.; Hunter, ML.; Hunter, B. & Drage, N. (2006) . Hurler's syndrome: dental findings in a case treated with bone marrow transplantation in infancy, *Int J Paediatr Dent*, 16:207-12, ISSN: 1365-263X
- Hoogendijk, CF.; Marx, J.; Honey, EM.; Pretorius, E. & Christianson, AL. (2006). Ultrastructural investigation of Zimmermann-Laband syndrome, *Ultrastruct Pathol*, 30:423-6, ISSN: 1521-0758
- Huster, D.; Purnat, TD.; Burkhead, JL.; Ralle, M.; Fiehn, O.; Stuckert, F.; Olson, NE.; Teupser, D. & Lutsenko, S. (2007). High copper selectively alters lipid metabolism and cell cycle machinery in the mouse model of Wilson disease, *J Biol Chem*, 282:8343-8355, ISSN: 1083-351X
- Ishigami, T.; Schmidt-Westhausen, A.; Philipsen, HP.; Baiborodin, SI.; Gelderblom, H. & Reichart, PA. (1995). Oral manifestations of alpha-mannosidosis: report of a case with ultrastructural findings, *J Oral Pathol Med*, 24:85-8, ISSN: 1600-0714
- Kaisare, S. (2007). Gingival enlargement in Niemann-Pick disease: a coincidence or link? Report of a unique case, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 104:e35-e39, ISSN: 1528-395X
- Kasaboğlu, O.; Tümer, C. & Balci, S.(2004). Hereditary gingival fibromatosis and sensorineural hearing loss in a 42-year-old man with Jones syndrome, *Genet Couns*, 15:213-8, ISSN: 1015-8146
- Keith, O.; Scully, C. & Weidmann, GM. (1990). Orofacial features of Scheie (Hurler-Scheie) syndrome (alpha-L-iduronidase deficiency), *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 70:70-4, ISSN: 1528-395X
- Kelekis-Cholakias, A.; Wiltshire, WA. & Birek, C. (2002). Treatment and long term follow-up of a patient with hereditary gingival fibromatosis: a case report, *J Can Dent Assoc*, 68:290-294, ISSN: 1488-2159
- Kelly, TE. (1976). The mucopolysaccharidoses and mucopolipidoses, *Clin Orthop Relat Res*, 114:116-33, ISSN: 1528-1132

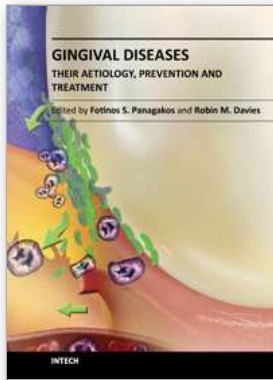
- Leroy, JG. & Crocker, AC. (1966). Clinical definition of Hurler-Hunter phenotypes, *Amer J Dis Child*, 112: 518-530, ISSN: 0002-922X
- Kondoh, T.; Kamimura, N.; Tsuru, A.; Matsumoto, T.; Matsuzaka, T. & Moriuchi, H. (2010). A case of Schinzel-Giedion syndrome complicated with progressive severe gingival hyperplasia and progressive brain atrophy, *Pediatr int*, 43:181-184, ISSN: 1442-200X
- Lynch, M.; Brightman, VJ. & Greenberg, MS. (1994). *Burket's oral medicine: diagnosis and treatment*, 9th ed., J.B. Lippincott, ISBN: 1550093266, Philadelphia
- Maas, SM.; Lombardi, MP.; van Essen, AJ.; Wakeling, EL.; Castle, B.; Temple, IK.; Kumar, VK.; Writzl, K. & Hennekam, RC. (2009). Phenotype and genotype in 17 patients with Goltz-Gorlin syndrome, *J Med Genet*, 46:716-20, ISSN: 1468-6244
- M Mahfouz, AK.; George, G.; Al-Bahlani, SS. & Al Nabhani, MZ. (2010). Difficult intubation management in a child with I-cell disease, *Saudi J Anaesth*, 4:105-7, ISSN: 0975-3125
- Manger, B. (2010). Lysosomal storage diseases, *Z Rheumatol*, 69:527-38, ISSN: 1435-1250
- Martelli-Junior, H.; Bolzani, G.; Graner, E.; Bozzo, L. & Coletta, RD. (2000). Microscopic and proliferative comparison of gingival fibroblasts from patients with normal gingiva and with hereditary gingival fibromatosis, *Pesqui Odontol Bras*, 14:123-129, ISSN: 1517-7491
- McKusick, VA. *Online Mendelian Inheritance in Man (OMIM)*, Accessed last on: 19/4/2011, Available at: <http://www.ncbi.nlm.nih.gov/omim/>
- McKusick, VA.; Kaplan, D.; Wise, D.; Hanley, WB.; Suddarth, SB.; Sevick, ME. & Maumane, AE. (1965). The genetic mucopolysaccharidoses, *Medicine (Baltimore)*, 44: 445-483, ISSN: 1536-5964
- McKusick, VA. & Neufeld, EF. (1983). The mucopolysaccharide storage diseases. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL & Brown MS (eds): *The Metabolic Basis of Inherited Disease*, pp 751-777, 5th ed., McGraw-Hill
- Murakami, A.; Skovby, F.; Andreassen, JO.; Cohen, MM Jr.; Jensen, BL. & Kreiborg, S. (1999). Oral manifestations of Schimmelpenning syndrome: case report and review of literature, *Ann Acad Med Singapore*, 28:744-8, ISSN: 0304-4602
- Ni, Y.; Zbuk, KM.; Sadler, T.; Patocs, A.; Lobo, G.; Edelman, E.; Platzer, P.; Orloff, MS.; Waite, KA. & Eng, C. (2008). Germline mutations and variants in the succinate dehydrogenase genes in Cowden and Cowden-like syndromes, *Am J Hum Genet*, 83: 261, ISSN: 1537-6605
- Pereira de Godoy, JM. & Fett-Conte, AC. (2010). Dominant inheritance and intra-familial variations in the association of Sturge-Weber and Klippel-Trenaunay-Weber syndromes, *Indian J Hum Genet*, 16:26-7, ISSN: 1998-362X
- Raeste, AM.; Collan, Y. & Kilpinen, E. (1978). Hereditary fibrous hyperplasia of the gingiva with varying penetrance and expressivity, *Scand J Dent Res*, 86:357-365, ISSN: 0029-845X
- Raja, TA.; Albadri, S. & Hood, C. (2008). Case report: Rutherford syndrome associated with Marfan syndrome, *Eur Arch Paediatr Dent*, 9:138-41, ISSN: 0029-845X

- Ramakrishnan, T. & Kaur, M. (2010). Multispeciality approach in the management of patient with hereditary gingival fibromatosis: 1-year follow up: a case report, *Int J Dent*, 2010:575979, ISSN: 1687-8736
- Sakamoto, R.; Nitta, T.; Kamikawa, Y.; Kono, S.; Kamikawa, Y. & Sugihara, K. (2002). Histochemical, immunohistochemical, and ultrastructural studies of gingival fibromatosis: a case report, *Med Electron Microsc*, 35:248-254, ISSN: 0918-4287
- Shafer, WG. (1983). *A textbook of oral pathology*. 4th ed., W.B. Saunders, Philadelphia
- Shah, N. & Gupta, YK. (1998). Generalized odontodysplasia- a case report, *J Indian Soc Pedod Prev Dent*, 16:40-3, ISSN: 1998-3905
- Sheridan, O.; Wortman, J.; Harvey, C.; Hayden, J. & Haskins, M. (1994). Craniofacial abnormalities in animal models of mucopolysaccharidoses I, VI, and VII, *J Craniofac Genet Dev Biol*, 14(1):7-15, ISSN: 0270-4145
- Steffensen, B.; Häkkinen, L. & Larjava, H. (2001). Proteolytic events of woundhealing coordinated interactions among matrix metalloproteinases (MMPs), integrins, and extracellular matrix molecules, *Crit Rev Oral Biol Med*, 12:373-398, ISSN: 1544-1113
- Suhanya, J.; Aggarwal, C.; Mohideen, K.; Jayachandran, S. & Ponniah, I. (2010). Cherubism combined with epilepsy, mental retardation and gingival fibromatosis (Ramon syndrome): a case report, *Head Neck Pathol*, 4:126-31, ISSN: 1936-0568
- Tan, MH.; Mester, J.; Peterson, C.; Yang, Y.; Chen, JL.; Rybicki, LA.; Milas, K.; Pederson, H.; Remzi, B.; Orloff, MS. & Eng, C. (2011). A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 subjects, *Am J Hum Genet*, 88: 42-56, ISSN: 1537-6605
- Thomas, S. & Tandon S. (2000). Hurler syndrome: a case report, *J Clin Pediatr Dent*, 24:335-8, ISSN: 1557-5268
- Tovaru, S.; Parlatescu, I.; Dumitriu, AS.; Bucur, A. & Kaplan, I. (2010). Oral complications associated with D-penicillamine treatment for Wilson disease: A clinicopathologic report, *J Periodontol*, 81: 1231-1236, ISSN: 1943-3670
- Vanier, M.; Wenger, D.; Comly, M.; Rousson, R.; Brady, R. & Pentchev, PG. (1988). Niemann-Pick disease group C: clinical variability and diagnosis based on defective cholesterol esterification. A collaborative study on 70 patients, *Clin Genet*, 33:331-348, ISSN: 1399-0004
- Vellodi, A. (2005). Lysosomal storage disorders, *Br J Haematol*, 128:413-31, ISSN: 1365-2141.
- Witkop, CJ Jr. (1971). Heterogeneity in gingival fibromatosis, *Birth Defects Orig Artic Ser*, 7:210-21, ISSN: 0547-6844
- Worth, HM. (1966). Hurler's syndrome. A study of radiologic appearances in the jaws, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 22:21-35, ISSN: 1528-395X
- Xiao, S.; Bu, L.; Zhu, L.; Zheng, G.; Yang, M. & Qian, M. (2001). A new locus for hereditary gingival fibromatosis (GINGF2) maps to 5q13-q22, *Genomics*, 74:180-185, ISSN: 1089-8646
- Ye, X.; Shi, L.; Cheng, Y.; Peng, Q.; Huang, S. & Liu, J. (2005). A novel locus for autosomal dominant hereditary gingival fibromatosis, GINGF3, maps to chromosome 2p22.3-p23.3, *Clin Genet*, 68:239-244, ISSN: 1399-0004

- Young, W.; Sauk, JJ.; Pihlstrom, B. & Fish, A. (1978). Histopathology and electron and immunofluorescence microscopy of gingivitis granulomatosa associated with glossitis and chellitis in a case of Anderson-Fabry disease, *Oral Surg Oral Med Oral Pathol*, 46:540-54, ISSN: 1528-395X
- Zhou, J.; Li, NY.; Zhou, XJ.; Wang, JD.; Ma, HH. & Zhang, RS. (2010). Sturge-Weber syndrome: a case report and review of literatures, *Chin Med J*, 123:117-21, ISSN: 0366-6999

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Gingival diseases are a family of distinct pathological entities that involve the gingival tissues. These signs and symptoms of these diseases are so prevalent in populations around the world that they are often considered to be "normal" features. The diseases are now classified into two main groups namely: Plaque-Induced and Non-Plaque Induced Gingival Diseases. This book provides dentists, dental hygienists, dental therapists and students with a comprehensive review of gingival diseases, their aetiology and treatment.

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