PERIODONTAL DISEASES IN RARE SYNDROMES

ABSTRACT

Periodontal diseases can affect about 90% of the world population. Periodontitis results in connective tissue attachment and bone loss and is a major cause of tooth loss. In addition to pathogenic microorganisms in the biofilm, genetic and environmental factors contribute to the disease process. Genetic, dermatological haematological, granulomatous, immunosuppressive, and neoplastic disorders also have periodontal manifestations. As many syndromes show oral manifestations, it is important to be familiar with the oral and general manifestations and special management required for these patients to take precautions during dental treatments. This review gives an update on the rare syndromes associated with periodontal disease.

Key words: Rare Genetic syndrome, periodontal disease,

INTRODUCTION

The host response is an important in determining the extent and severity of periodontal disease. Systemic factors modify periodontitis principally through their effects on the immune and inflammatory mechanisms. Several conditions may give rise to an increased prevalence, incidence or severity of gingivitis and periodontitis. In many cases the literature is insufficient to make a definitive statement on the links between certain syndromes and periodontal disease and for several conditions only case report exist (1). As many syndromes show oral manifestations, it is important to be familiar with the oral and general manifestations and special management required for these patients to take precautions during dental treatments.

There are many syndromes that can cause periodontal disease and early loss of teeth. Only few syndromes are well known to dentists like Down syndrome, Papillon-Leveque syndrome, Leukocyte adhesion deficiency syndrome, Lazy leukocyte syndrome and Chediak-Higashi syndrome. This review gives an update on the rare syndromes associated with periodontal disease and some of them leading to loss of tooth.

Shwachman- Diamond syndrome

Although neutropenia is the most common presenting haematological feature, there is also a greatly increased risk of developing acute leukaemia later in life. Other organs which can be affected include the skeleton (metaphyseal dysostosis, epiphyseal dysplasia), teeth and oral cavity, liver, heart, kidneys, and skin. Mucositis and periodontal infections are frequently seen in individuals who are profoundly and persistently neutropenic (2). However, there is an increased incidence of tooth enamel defects (dental dysplasia) in children with SDS, including hypomaturetation, hypocalcification, and hypoplasia (3).

Hermansky-Pudlak syndrome (HPS)

Hermansky-Pudlak syndrome (HPS) is a rare group of autosomal recessive diseases whose manifestations include oculocutaneous albinism, bleeding, and lysosomal ceroid storage. Its etiology has been related to defects in 7 genes. The type of albinism associated with Hermansky-Pudlak syndrome is a tyrosinase-positive form. Secondary
to the albinism that results from Hermansky-Pudlak syndrome, visual defects, including photophobia, strabismus, and nystagmus occur. The bleeding problems of Hermansky-Pudlak syndrome result from platelet dysfunction and manifest with easy bruising, nose bleeds, and extended bleeding times. Gingival bleeding, varying degrees of gingivitis and periodontitis are described (4,5).

**Griscelli syndrome type 2**

Griscelli syndrome type 2 (also known as "Partial albinism with immunodeficiency") is a rare autosomal recessive syndrome characterized by variable pigmented dilution, hair with silvery metallic sheen, frequent pyogenic infections, neutropenia, and thrombocytopenia. Affected individuals typically have delayed development, intellectual disability, seizures, weak muscle tone (hypotonia), and eye and vision abnormalities. These individuals are prone to recurrent infections due to defective immune system. They also develop hemophagocytic lymphohistiocytosis (HLH), in which the immune system produces too many activated immune cells called T-lymphocytes and macrophages (histiocytes). Overactivity of these cells can damage organs and tissues throughout the body, causing life-threatening complications if the condition is untreated. Severe gingivitis leading on to periodontitis at young age and even total extraction has been reported (6).

**Wiskott-Aldrich syndrome (WAS)**

This is an X linked recessive disorder of lymphocytes presents with thrombocytopenia, rarely neutropenia, defective cellular and humoral function and eczema (7). IgM levels are reduced, Ig A and IgG are elevated and IgE levels can be normal, reduced or elevated. The classic form of WAS has a characteristic pattern of findings that include an increased tendency to bleed caused by a reduced number of platelets, bloody diarrhoea, recurrent bacterial, viral and fungal infections and eczema of the skin. The WAS is caused by mutations in the gene which produce a protein named the Wiskott-Aldrich syndrome Protein (WASP). Only boys are affected with this disease. There is mild to severe periodontitis with attachment and bone loss, can also cause Candidiasis, Herpes and ulcers (8).

**XL-dyskeratosis congenital (Hoeyraal-Hreidarsson syndrome)**

This disorder is an autosomal dominant caused by mutation of TINF2gene (604319) on chromosome 14q12. Dyskeratosis congenita (DC), a telomere biology disorder, is characterized by a classic triad of dysplastic nails, lacy reticular pigmentation of the upper chest and/or neck, and oral leukoplakia. People with DC are at increased risk for progressive bone marrow failure, myelodysplastic syndrome or acute myelogenous leukemia, solid tumors (usually squamous cell carcinoma of the head/neck or anogenital cancer), and pulmonary fibrosis. Other findings can include eye abnormalities, and dental abnormalities (caries, periodontal disease, taurodontism). All the DC patients had severe disease, with variable features of aplastic anemia, developmental delay, short stature, retinopathy, microcephaly, osteoporosis, cerebellar hypoplasia, alopecia, intracranial calcification, and tooth loss (9).

**Barth syndrome**

Barth syndrome (BTHS), also known as 3-Methylglutaconic aciduria type II, is an X-linked genetic disorder. The disorder, which affects multiple body systems, is found exclusively in males. Though not always present, the cardinal characteristics of this multi-system disorder including cardiomyopathy, neutropenia (chronic, cyclic or intermittent) underdeveloped skeletal musculature and muscle weakness, growth delay, exercise intolerance, cardioliop abnormalities and 3-methylglutaconic aciduria. For many patients with cyclical neutropenia, there is a predictable pattern of oral ulcers, cervical lymphadenopathy (swollen lymph nodes in the neck) and painful gingivitis about every three weeks, coinciding with the low point in the neutropenic cycle. Gingivitis, periodontal disease, and the loss of permanent teeth are common problems across the spectrum of neutropenic syndromes (11). Most patients with an
absolute neutrophil count (ANC) persistently less than 500 have problems with gingivitis and increased periodontal disease, despite good efforts at oral hygiene (10).

**Cohen syndrome**

Most studies have shown an autosomal recessive mode of inheritance in Cohen syndrome, but autosomal dominant is also possible. Cohen syndrome is characterised by obesity, hypotonia, mental retardation, narrow hands and feet, ocular abnormalities, and characteristic faces consisting of maxillary hypoplasia, open mouth, prominent central incisors, prominent palpebral fissures. Chronic neutropenia have been observed in most of the cases and resultant destructive periodontal disease has been reported with early tooth loss (11).

**Ataxia telangiectasia, ataxia-like syndrome, Nijmegen breakage syndrome, Bloom syndrome**

Ataxia telangiectasia (A-T) (also referred to as Louis–Bar syndrome) is a rare, neurodegenerative, inherited in an autosomal recessive pattern, the disease causing severe disability. Mutations in the ATM gene cause ataxia-telangiectasia(14). The ATM gene provides instructions for making a protein that helps control cell division and is involved in DNA repair which plays an important role in the development and activity of body systems, including the nervous system and immune system. Some have an increased number of respiratory tract infections and telangiectasia of the bulbar conjunctive, ears, nose, perioral area and other skin surfaces. The immune system problems are caused by abnormalities in T cells and B cells. As a result, people with ataxia telangiectasia are more likely to get bacterial, fungal and viral infections. There have been reports of mild to severe gingivitis and periodontitis, also necrotising periodontitis has been reported (1,2)

**DiGeorge syndrome**

22q11.2 deletion syndrome which has several presentations including DiGeorge syndrome (DGS), DiGeorge anomaly, velo-cardio-facial syndrome, Shprintzen syndrome, conotruncal anomaly face syndrome, Strong syndrome, congenital thymic aplasia, and thymic hypoplasia, is a syndrome caused by the deletion of a small piece of chromosome 22 inherited from a parent as an autosomal dominant condition, commonly associated with T-lymphocyte immunodeficiency. B-lymphocyte defects also occur. Variable secondary humoral defects, including hypogammaglobulinemia and selective antibody deficiency, may be present. Various autoimmune diseases, including juvenile rheumatoid arthritis, idiopathic thrombocytopenic purpura, and autoimmune hemolytic anemia, autoimmune uveitis, and severe eczema are more prevalent. Small teeth with high arched and cleft palate and lips are found. The diminished B and T lymphocytes make them more susceptible to bacterial and fungal infections and hence variable degrees of gingival and periodontal disease.

**Ehler–Danlos syndrome**

Ehler–Danlos syndrome is autosomal dominant, characterised by extensible skin, tissue fragility, ecchymotic petechial lesions, easy bruiseability, minimal to moderate joint hypermobility of the digits and cigarette-paper scars and in oral cavity persistent hyperplastic gingivitis (12). The periodontal disease in this syndrome can be associated to only type I, VIII, III, or IV. Only in type I is a predisposition to periodontal disease described, while type VIII presents as early onset periodontitis, premature loss of teeth, fragility of alveolar mucosa and gingival bleeding. Early periodontitis is observed in type IV EDS along with arterial and intestinal ruptures. It has been postulated that defect in type III collagen, present in 9% of gingival collagen and 16% of the total collagen of the periodontal ligament affects the integrity of the periodontal ligament (13). In addition, Fusobacterium nucleatum has been associated with the active lesion sites (14).

**Marfan syndrome**
In Marfan syndrome the mutation of a gene encoding for fibril-1 in chromosome 15 generates an alteration in the synthesis of glycoprotein forming a part of the connective tissue matrix. This generates defects in ocular lens suspensory ligament, blood vessel walls and periodontal ligament resulting in increased susceptibility to periodontal inflammation and bone resorption (15). In this disease periodontitis manifests in a chronic and severe form with horizontal and vertical bone loss in accordance to the presence of bacterial plaque. Tooth mobility is seen but is caused by periodontitis and not attributed to the primary syndrome (16).

Haim-Miam syndrome

A variation of Papillon le fevre syndrome characterised by Palmar plantar keratosis, severe early onset periodontitis and digital abnormalities including osteolysis of the distal phalanges, abnormal length of fingers and toes and hawk like hypertrophic deformity of the nails (17).

Focal Palmpoplantar and Oral mucosa Hyperkeratosis syndrome

Hyperkeratosis Palmoplantaris and attached gingiva keratosis is an unusual genetic disorder characterised by oral mucosa and dermal keratosis. This disorder has an autosomal dominant trait. Mucosa in attached gingiva, hard palate, retromolar pad mucosa, alveolar mucosa, lateral surface of tongue (sites subject to mechanical pressure and friction), skin on weight bearing and pressure areas in soles and palms, nail dystrophy and hyperhidrosis are the common manifestations. Marked white hyperkeratosis of the attached gingiva presenting like leukoplakia are a common feature but no gingival inflammation and attachment loss (17). Hyperkeratosis appears early in childhood age and increases with age.

Hypotrichosis osteolysis periodontitis (HOPP) or Striate palmoplantarkeratoderma Periodontitis

The common features are Hypotrichosis, Onychogryphosis, Acro-osteolysis, Lingua plicata, Psoriasis. The mode of inheritance is uncertain. This syndrome was first reported in a Dutch mother and daughter. The PPK followed a highly unusual reticular pattern and both the mother and daughter have a fissured tongue. This new syndrome is not related to mutations in cathepsin C gene (17). A third, unrelated, 24-year-old patient from Venezuela suffering from what appears to be HOPP syndrome confirms the existence of this syndrome as a unique entity and further delineates the phenotype (13).

Variant carvajal syndrome

This syndrome was reported in a 13-years old girl from England, Liner palmar and diffuse plantar keratoderma with episodic plantar fissures and had been under long term dental care for prepubertal periodontitis, premature root resorption of primary teeth, missing permanent teeth, wiry hair, abnormal finger nails, cardiomyopathy and potential risk for cardiac abnormalities, soft tissue and dental anomalies, and angular cheilitis (17).

Oral Facial Digital Syndrome (OFDS)

Oral Facial Digital Syndrome are a heterogeneous group of developmental disorders that are characterised by X linked dominant mode of inheritance with lethality in males. The syndrome is characterised by malformation of the face, oral cavity and digits. Clinical features include facial dysmorphism, facial asymmetry, micrognathia, broad nasal bridge, hemifacial microsomia, down turned eyes, bradydactyly, clinodactyly of fingers with small foot, polycystic kidney disease and CNS malformation. Oral features include maxillary prognathism with incompetent lips with gingival enlargement with periodontitis leading to early loss of teeth (18).

Singleton-Merten Syndrome

Patients affected are autosomal dominant who exhibit skeletal deformities, especially of the hands and feet, multiple ligamental ruptures, joint subluxation, acro-osteolysis, osteoporosis, idiopathic glaucoma, primary infertility, short stature...
and idiopathic calcification of the aortic arch and valve. They have early loss of primary and permanent teeth. Radiographs of one patient showed dentinal dysplasia (19).

**Hujdu-Cheney Syndrome**

Loosening and early loss of teeth in childhood and early adulthood is common in this condition which has autosomal dominant inheritance. The other clinical manifestations include joint laxity, multiple osteolytic lesions and short stature (19).

**Coffin-Lowry Syndrome**

The important features of X linked Coffin-Lowry syndrome are mental retardation, characteristic facial features and skeletal anomalies. Female heterozygotes present variable clinical features and less severe. Linkage analysis has placed the possible position of the locus for the condition at Xp22-22p22 Early oral clinical signs are developmental delay, typical face, thick hands with tapering digits, a transverse hypothenar crease, general hypotonia, extensible joints and persistent anterior fontanel and fullness of forearms due to increased subcutaneous fat. Hypodontia have been reported in several cases not due to lack of formation or eruption but due to premature exfoliation (19).

**Ramon Syndrome**

This disorder has been reported in 6 individuals with cherubism, gingival fibromatosis, seizures, mental deficiency, hypertrichosis, short stature and juvenile rheumatoid arthritis. Mode of inheritance may be autosomal recessive and has also been reported in patients with neurofibromatosis, Noonan syndrome and Noonan like syndrome with polyarticular pigmented villonodular synovitis (20).

**Kindler Syndrome**

Gingival fragility with tendency to bleed severely and early and rapidly progressive periodontitis (aggressive periodontitis) were common features in Kindler Syndrome (21). Other features vary between cases and include: photosensitivity; acral hyperkeratosis; nail dystrophy; webbing and contractures of the fingers and toes; alopecia; acinic changes; mucosal involvement, including urethral, vaginal, anal, esophageal, and oral commissural stenosis (narrowing or constricting); eversion of the eyelids; pigmentation of the lips; and malformation of the nails. Common dermatologic findings include congenital skin blistering that resolves slowly with age; mild photosensitivity that improves with age; and early, generalized, progressive poikilodermia with extensive atrophy.

**Hurler's Syndrome**

Hurler syndrome, also known as mucopolysaccharidosis type I (MPS type I) Hurler's disease, also gargoylism, is a genetic disorder which is autosomal recessive that results in the build up of glycosaminoglycans due to deficiency of alpha-Liduronidase, an enzyme responsible for the degradation of mucopolysaccharides in lysosomes. Without this enzyme, a build up of heparan sulfate and dermatan sulfate occurs in the body and excretion in the urine. Hurler syndrome is often classified as a lysosomal storage disease, and is clinically related to Hunter Syndrome. Gingival overgrowth covering partial or full crown of upper anterior teeth is a common finding which may be due to mouth breathing and plaque and also due to deposition of heparan and dermatan sulfate. Other manifestations include macrocheilia, macroglossia, open mouth with protruding tongue, numerous impacted teeth and larger interdental space, and teeth dislocation (21). Growth retardation, craniofacial malformation, characteristic facies, scoliosis, stiff joints and chondrodystrophy are common. Corneal clouding that can lead to blindness, learning disability, cardiac failure, hypertension, and lung infection may also occur.

**Hunter Syndrome**<sup>*</sup> (MPS II) (Mucopolysaccharidosis II)

Oral feature include widely spaced teeth, tongue is enlarged, neck is short, and general features are coarse facies, thick lips and nose, thick, hirsute skin, joint-stiffness/claw hand deformity, hepato-
spleenomegaly (21). This disorder is a mild form of Hurler syndrome.

Crest syndrome or Limited scleroderma

The visible signs of limited scleroderma are tight, thick skin on fingers, hands and face. Changes in the functioning of oesophageal muscles can cause difficulty swallowing and chronic heartburn resulting in constipation, diarrhoea, bloating after meals, unintended weight loss and malnutrition. Severe Raynaud's phenomenon can obstruct blood flow to the extremities and may cause ulcers of the fingers and toes, leading to gangrene of fingers or toes, which may require amputation. Excess collagen collects in the tissue between the lungs air sacs, making the lung tissue stiffer. Increased blood pressure in the arteries between the heart and lungs makes the heart work harder and eventually weakens it. Severe tightening of facial skin can make it difficult to open the mouth wide enough to brush teeth. Acid reflux can destroy tooth enamel, and changes in gingival structures may cause severe bone loss and early loss of teeth (22). Many people with limited scleroderma experience very dry eyes and mouth.

Weary-Kindler and Kindler syndromes

These are two different syndromes, but sharing similar features. Kindler syndrome is an autosomal recessive disorder characterized by epidermolysis bullosa, congenital poikiloderma, PPK, photosensitivity, skin atrophy, and mucosal lesions (22). whereas Weary-Kindler syndrome is a dominantly inherited disorder with features similar to those reported in the Kindler syndrome except for skin atrophy, photosensitivity, and mucosal lesions. Dental abnormalities (22). include early onset periodontitis of primary and part of permanent dentitions, severe periodontal bone loss and periodontitis, swollen, fragile bleeding gums and early exfoliation of deciduous as well as permanent dentition. Spontaneous bleeding from gums suggests it to be due to microblistering and breakdown of periodontal tissues due to minor trauma of normal occlusal function.

Klinefelter's syndrome

Klinefelter syndrome is the set of symptom resulting from additional X genetic material in males. Also known as 47,XXY or XXY, Klinefelter syndrome is a genetic disorder in which there is at least one extra X chromosome to a standard human male karyotype. Klinefelter syndrome is a chromosomal condition that affects male physical and cognitive development. Affected individuals typically have small testes; shortage of testosterone can lead to delayed or incomplete puberty, gynecomastia, reduced facial and body hair, and infertility. Some affected individuals also have genital differences including undescended testes (cryptorchidism), the opening of the urethra on the underside of the penis (hypospadias), or an unusually small penis (micropenis). Studies show that this disorder has its effect on the formation of enamel deposition and dental growth leading to taurodontism. The occurrence of periodontal disease may be due to the morphological features and tooth size and also because of psychological problems and low IQ levels (22). The persons have incidence of periodontal disease and loss of tooth.

Prader-Willi syndrome

Prader-Willi syndrome is a complex genetic disease caused by lack of expression of paternally inherited genes on chromosome 15q11-q13. Clinical and radiographic findings of a previously diagnosed PWS confirmed the diagnosis of periodontitis. The most striking oral findings were anterior open bite, and crowding and attrition of the lower first molars (24). The interactions of multiple genes affected in PWS may increase the susceptibility to periodontal breakdown via effects on the host immune response; a recent report has shown that an over activation of the innate immune system and increased chronic low-grade inflammation has been observed in patients with PWS (25).

Wilson Syndrome

Wilson syndrome or Hepatolenticular degeneration (OMIM #277900 on 13q 14.3-q21.1) is an autosomal recessive disorder due to mutation in
ATP7B gene caused by low ceruloplasmin. It is characterised by multiple small red papules of the lips, gingival enlargement, early onset periodontitis, and repeated oral candidiasis. Enamel hypoplasia is the characteristic dental feature (21).

**CONCLUSION**

Dentists have to recognize these syndromes before treating these patients as they may need special care and precautions. The effective way of prevention of oral disease is an effective oral hygiene program with periodic assessment and regular professional hygiene together with a constant patient motivation for oral hygiene. Patients suffer from frequent periodontal infections in spite of efficient and effective oral hygiene. Invasive dental treatment should be avoided during the acute episodes when the immune system is depressed. Twice a day mouth washes are advised to reduce plaque accumulation.

**REFERENCES**


