PERIODONTIUM IN SYNDROMES OF HEAD AND NECK

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Abstract:

The alveolar bone, periodontal ligament (PDL) and cementum are intimately related structures in development and functions. Collectively, they form the periodontium that is of critical relevance for various periodontal diseases. The word syndrome is derived from the Greek syn (together) and dromos (running) and refers to a 'running together' or concurrence of symptoms. Even after taking into account local inflammatory conditions and drug use, occasional instances with a syndromic origin have been recorded. Present review tries to combine the relevant features of syndromes associated with periodontal and alveolar bone findings into a systemic review.

Index Terms: Syndromes, Head and neck, Periodontal and alveolar bone findings

Introduction:

In genetics, 'syndrome' refers to a pattern of multiple malformations that are thought to be pathogenetically related. (1) Cohen & Kreiborg, who stated that in medical genetics, multiple abnormalities that arise in embryonically disjointed regions are known as a syndrome. (2) Head and neck syndromes represent a complete set of anomalies that involve signs and symptoms associated with various other systems in human body along with distinct head and neck features.

Important syndromes involving the periodontal and alveolar bone are as follows (3):

1. Down's syndrome

Down syndrome (DS) is caused by trisomy 21; the person has three copies of chromosome 21, instead of the usual two copies, in all cells. This is caused by abnormal cell division during the development of the sperm cell or the egg cell. Gingivitis and periodontitis start early in life and their severity increases with age. (4) Periodontal disease is a common problem among DS individuals with an estimated prevalence between 58% and 96% for those under 35 years of age. (5) Other findings include midfacial abnormality, narrow palate, macroglossia as well as delayed teeth eruption, missing and malformation in tooth morphology. (6)

2. Papillon–Lefevre syndrome

It is a rare autosomal recessive disorder caused by cathepsin C gene mutation leading to the deficiency of cathepsin C enzymatic activity. The disease is characterized by palmoplantar hyperkeratosis, loss of deciduous and permanent teeth and increased susceptibility to infections. Consequences of this premature tooth loss will affect the patient's daily functions, such as mastication and speech. Repeated episodes of periodontitis and gingivitis lead to destruction of periodontium and subsequent premature loss of deciduous and permanent teeth. (7) Other findings include gingival ulcers, periodontal pockets, and severe, aggressive periodontitis.

3. Ehlers–Danlos syndrome

Ehlers Danlos syndrome (EDS) is a group of hereditary connective tissue disorders that manifests clinically with skin hyperelasticity, hypermobility of joints, atrophic scarring, and fragility of blood vessels. Classical EDS involves an autosomal dominant (AD) inheritance pattern, and associated mutated genes include COL5A1 and/or COL1A1, which code for type V and Type I collagen, respectively. There are the proposed criteria's for making the diagnosis of EDS. The major clinical criteria include atrophic scarring, skin hyperextensibility, and generalized joint hypermobility. Minor clinical criteria include epicanthic folds, skin fragility, soft "doughy" skin, easy bruising, hernia, complications of joint hypermobility, subcutaneous spheroids, and a family history of a first-degree relative who is affected by and meets the same clinical criteria.(8)

4. Rothmund–Thomson syndrome

Rothmund-Thomson syndrome (RTS) is characterized by a rash that progresses to poikiloderma; sparse hair, eyelashes, and/or eyebrows; small size; skeletal and dental abnormalities; juvenile cataracts; and an increased risk for cancer, especially osteosarcoma. The incidence of dental anomalies has been estimated at between 27% and 59% of cases. Intraoral findings of RTS are listed as microdontia, rudimentary, or hypoplastic teeth, multiple crown malformations, short and conical teeth, increase in prevalence of caries, malocclusion, hypodontia/oligodontia or hyperdontia, ectopic eruption, and delay in eruption.(9)

5. Book's syndrome

A rare form of ectodermal dysplasia with premolar aplasia, hyperhidrosis, premature cavities, and premature whitening of the hair. Anodontia or oligodontia can affect all teeth, but missing premolars are the most characteristic. Abnormal dental position and tooth shape anomaly may be observed.

6. Kostmann syndrome

Severe congenital neutropenia (SCN), also known as Kostmann syndrome, is a rare heterogeneous group of diseases which is characterized by arrested neutrophil maturation in the bone marrow. (10) It is characterized by genetic mutations in HAX1 gene. It is an autosomal recessive condition that displays recurrent infections of the respiratory tract, skin, and deep tissues from the first few months of life. Presence of an absolute neutrophil count (ANC) in peripheral blood of <500/mm3 is noted in these patients. (11).Three main characteristics of this syndrome are: severe neutropenia (<0.2 × 109/L), maturation arrest of granulopoiesis at the promyelocyte stage, and death due to infections.

7. Kindler syndrome

It is a very rare, autosomal recessive disorder characterized by acral blistering in infancy, followed by photosensitivity, progressive poikiloderma, cutaneous atrophy, and various forms of mucosal involvement (12). The molecular basis of this disease is lined to loss-of-function mutations in a novel gene, kind0, encoding kindlin-1, an actin-extracellular matrix linker protein, and the gene was mapped to chromosome 20p12.3. (13) In Few patients early development of actinic keratoses, squamous cell carcinoma of the lower lip and transitional cell carcinoma of the bladder, xerostomia, hypohidrosis, corneal opacities, and thickened corneal nerves have been reported.(12)

8. Gorham–Stout syndrome

Vanishing bone disease (Gorham-Stout syndrome) is a rare entity of unknown etiology, characterized by destruction of osseous matrix and proliferation of vascular structures, resulting in destruction and absorption of bone. The syndrome can affect one or multiple bones of the patient, whose age has been reported to be from 1 month to 75 years of age. The disease is confirmed by the histopathological analysis of the lesions; the biopsy shows nonmalignant hyperproliferation of small vessels. (14)

9. Maffuci's syndrome

Maffucci syndrome is an exceedingly rare clinical entity characterized by multiple enchondromas and hemangiomas. It consists of combined occurrence of multiple enchondromas and vascular tumors. (15) The disease occurs in unilateral side of the body, and more commonly in the hand, foot and forearm. It might be associated with three types of vascular lesions: cavernous hemangiomas, phlebectasias and lymphangiectasias-lymphangiomas. (16)

10. Chediak–Higashi syndrome

Chediak Higashi syndrome (CHS) is an autosomal recessive disorder that is characterized by easy bruising, oculocutaneous albinism and recurrent pyogenic infections. The defect is caused by a mutation in the lysosomal trafficking regulator protein that leads to decreased phagocytosis and predisposition to recurrent bacterial infection. There is mutation in the LYST or the CHS1 gene. This gene is responsible for the regulation of lysosomal trafficking and the synthesis, fusion, and transport of cytoplasmic granules. It is located on the long arm of chromosome 1 [1q42-43]. (17)

11. Klinefelter syndrome (47 XXY syndrome)

Klinefelter syndrome (KS) results from 2 or more X chromosomes in a phenotypic male. The syndrome describes males with tall stature, small testes, gynecomastia, and azoospermia. The precise genetic etiology of supernumerary X chromosomes (47,XXY) was identified in 1959.(18) Extra X chromosomes lead to testicular hyalinization, fibrosis, and hypofunction, resulting in genital abnormalities, usually hypogonadism, and infertility.(19)

12. Sjogren–Larsson syndrome

Sjogren Larsson syndrome (SLS) is a rare autosomal recessive inborn error of lipid metabolism due to mutations in the ALDH3A2 that result in a deficiency of fatty aldehyde dehydrogenase (FALDH). The syndrome has a high prevalence in Sweden where it was first described, but now known to occur worldwide. The classical triad is ichthyosis, mental retardation and spastic diplegia. Preterm birth is common. "Glistening white dots" in the retina is a pathognomic clinical feature.

13. Marfan syndrome (MFS)

The defect is in the FBN1 gene on chromosome 15, which produces fibrillin, a connective tissue protein. (20) There is a broad range of clinical severity associated with MFS, ranging from isolated features of MFS to neonatal presentation of severe and rapidly progressive disease involving multiple organ systems. (21) The syndrome is associated with classic ocular, cardiovascular, and musculoskeletal abnormalities, although involvement of the lung, skin, and central nervous system may also occur. (22) FBN1 is a large gene (65 exons) located at chromosome 15q-21.1. Fibrillin-1 is a matrix glycoprotein that is the main constituent of elastic fibers. (23)

14. Sjogren's syndrome

Sjogren syndrome is chronic, systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands. There are 2 variants of Sjogren's syndrome- Primary Sjogren syndrome and secondary Sjogren syndrome. The secondary syndrome is associated with another autoimmune disease, usually rheumatoid arthritis. (24) This syndrome is characterized by destruction of exocrine glands (primary salivary and lacrimal) that produces the clinical manifestations of dry mouth, dry eyes (keratoconjuctivities sicca), and in more than 50% of cases, parotid gland enlargement. Primary Sjogren syndrome is diagnosed when the syndrome is limited to this pattern of involvement. (25) Pathogenesis of Sjogren syndrome is complex and uncertain, but thought to be similar to that of the benign lymphoepithtlial lesion. 6-10% of cases undergo transformation to lymphoma, because of infiltration of lymphocytic cell. (26)

15. Noonan's syndrome

Noonan syndrome is a developmental disorder characterised by facial dysmorphia, short stature, cardiac defects and skeletal malformations. PTPN11 which encodes the non-receptor protein tyrosine phosphatase SHP-2 (src homology region 2-domain phosphatase-2) is identified as the defective gene. The locus was mapped on chromosome 12 (12g 24.1). SHP-2 is a member of a small family of cytosolic protein tyrophosphatases (PTP). SHP-2 is the key molecule in the cellular response to growth factors, hormones, cytokines and cell adhesion molecules. It is required for activation of the mitogen activated protein (MAP) kinase cascade induced by epidermal, fibroblast and hepatocyte growth factors. (27)

16. Behcet's syndrome (Behcet's disease)

Behcet disease is an auto-inflammatory systemic vasculitis of unknown etiology. It is characterized by mucocutaneous manifestations, including recurrent oral and genital ulcerations, ocular manifestations, especially chronic relapsing uveitis, and systemic vasculitis involving arteries and veins of all sizes. It is also known as Behcet syndrome and malignant aphthosis. (28) While mucocutaneous lesions are the hallmark of Behcet disease, the most severe manifestations are uveitis, large vessel, and neurological involvement. Oral ulcers occur in 97% to 99% of patients with Behcet disease, often representing the initial clinical feature. Lesions are usually painful, recurrent, and multiple and may involve the soft palate, hard palate, buccal mucosa, tongue, gingiva, lips, and tonsils. More than 90% of oral ulcers heal without scarring.

17. Rubinstein–Tayabi syndrome

Rubinstein-Taybi syndrome (RTS) or Broad Thumb-Hallux syndrome is a genetic disorder characterized by facial dysmorphism, growth retardation, and mental deficiency. One intriguing phenomenon is the fact that RTS patients are prone to develop tumors. These show a pattern of neural and developmental origin. (29) Oral manifestations of this syndrome include limited mouth opening, a pouting lower lip, retro/micrognathia, a high arched and narrow palate, cleft uvula and palate, and rarely a cleft upper lip. Dental abnormalities occur in 67% of individuals with RTS and can include hypodontia, maintenance of deciduous teeth, talon cusps, and enamel hypoplasia. An increased rate of caries and periodontal disease has been reported in these patients. (30)

18. Guillain–Barre syndrome

Guillain–Barré syndrome (GBS) represents a group of acute immune-mediated polyradiculoneuropathies that is usually characterized by symmetrical limb weakness and areflexia. With a pathogenesis that is currently not fully understood, GBS may be defined as an aberrant immune response to infections that consequently damages the peripheral nerves. (31)

19. Melkersson–Rosenthal Syndrome

The classical form of the Melkersson Rosenthal Syndrome (MRS) consists of the clinical triad of recurring facial nerve paralysis, swelling of one or both lips and fissural tongue. (32) The most frequent finding of MRS is acute, diffuse, painless and non-pitting orofacial edema which is most frequently seen on lips. The upper lip is involved more frequently. (33) Fissures can be observed in the central area (central cheilitis), corners of the mouth (angular cheilitis) or other areas of the involved lip. (34)

The above syndromes along with their relevant features are as follows: (Table: 1)

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Syndromes	Genetics	Relevant periodontal findings features	Other relevant extra oral findings
Down's syndrome	Trisomy 21	-Early-onset periodontitis -Premature loss of mandibular anterior teeth	-Congenital cardiac anomalies -Mongoloid slanting of eyes -Flat face -Prone to acute necrotizing lesions
Papillon–Lefevre syndrome	Autosomal recessive disorder caused by cathepsin C gene mutation	-Severe alveolar bone loss -Exfoliation of both deciduous and permanent teeth	-Hyperkeratosis of palms and soles, knees, dorsum of fingers and toes
Ehlers–Danlos syndrome	Group of inherited collagen and extracellular matrix protein disorders	-Gingival bleeding marked -Periodontal disease -Generalized membranous gingival enlargement	-Defect in collagen synthesis -Hypermobility of joints -Marked elasticity of skin -Gorlin sign -Rubber man contortionist
Rothmund–Thomson syndrome (poikiloderma congenita)	Autosomal recessive caused by mutation of the RecQ4 gene	-Associated with early-onset periodontitis	-Skin changes -Prone to skin malignancies
Book's syndrome (premature aplasia, hyperhidrosis, canities prematura syndrome)	Autosomal dominant with high penetrance	Missing bicuspids	-Hyperhidrosis -Premature greying of hair
Kostmann syndrome		-Ulcerative gingival lesions -Periodontal disease	-Congenital neutropenia -Low absolute neutrophil count -Prone to bacterial infections
Kindler syndrome		-Tooth mobility -Spontaneous gingival bleeding -Earlier accelerated attachment loss -Desquamative lesions of gingiva	-Several genodermal disorders -Blistering of skin following mild trauma -Poikiloderma -Thin wrinkled skin devoid of surface markings
Gorham–Stout syndrome (Gorham disease, Vanishing bone disease)		-Loosening of teeth	-Progressive replacement of bone by fibrous tissue -Massive loss of bone -Occasional mandibular fracture
Maffuci's syndrome		-Recurrent gingival hyperplasia -Deep pockets -Alveolar bone loss -Mobility of many teeth	-Multiple hemangiomas with endochondromas
Chediak–Higashi syndrome		-Susceptibility to rapidly destructive periodontitis	-Affects organelles and involves melanocytes, platelets and phagocytes
Klinefelter syndrome (47 XXY syndrome)		-Increased gingival inflammation	-Males have an extra X chromosome -Small testicles -Reduced fertility

Sjogren–Larsson syndrome		-Gingivitis -Periodontitis -Mental retardation -Epilepsy	-Non-bullous congenital ichthyosiform erythroderma -Spastic diplegia or quadriplegia -Mental retardation
Marfan syndrome		-Severe periodontitis	-Tall stature -Aortic／mitral valve prolapse -Ectopia lentis
Sjogren's syndrome (sicca syndrome)		-Periodontal status disputed	-Keratoconjunctivitis sicca -Xerostomia -Rheumatoid arthritis
Noonan's syndrome		-Advanced periodontal disease in the absence of local factors	-Congenital heart malformations -Characteristic facial features -Learning problems -Impaired clotting
Behcet's syndrome (Behcet's disease)		-Chronic periodontitis	-Chronic, relapsing systemic vasculitis
Rubinstein–Tayabi syndrome		-Severe periodontitis -Attachment loss -Bleeding on probing	-Mental, motor, growth retardation -Small stature -Respiratory infections -Broad thumbs and toes
Guillain–Barre syndrome		-Periodontium may harbor cytomegalovirus and promote viral replication	-Rapidly ascending neural paralysis -Hyporeflexia -Areflexia
Melkersson–Rosenthal Syndrome (Rossolimo's syndrome, Rossolimo–Melkersson–Rosenthal Syndrome)		-Chronic generalized periodontitis	-Type of orofacial granulomatosis with involvement of lips and involvement of tongue

Table 1: Summary of the syndromes associated with Periodontium