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Review Article

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Periodontitis and Associated Syndrome -A Review

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ABSTRACT

Periodontal disease, though primarily induced by bacteria in dental plaque, often manifests as a feature of various syndromes and genetic disorders. These syndromes may either predispose individuals to periodontal conditions or exacerbate pre-existing periodontal issues. Alterations in immune function or structural integrity of periodontal tissues are common in such syndromes, increasing vulnerability to gingival inflammation, attachment loss, and bone resorption. The multifactorial aetiology of periodontal diseases and their association with systemic and genetic syndromes, such as Gottlieb syndrome (aggressive periodontitis), highlight the polygenic and polymicrobial nature of these conditions. While non-surgical, antimicrobial, and surgical therapies remain the standard treatment approaches, their effectiveness in preserving natural teeth in patients with syndromic associations is uncertain. By reviewing syndromes linked to periodontal findings, this study aims to provide clinicians with a clearer understanding of differential diagnoses and case management. Comprehensive, long-term research on these associations is limited, making the identification and management of periodontal syndromes a continuing challenge in clinical practice. This article underscores the importance of a multidisciplinary approach to understanding and treating periodontal diseases in syndromic contexts.

Keywords: Periodontitis, Syndromes, Immunity, Inflammation

Introduction

Periodontitis, a chronic inflammatory condition of microbial origin, primarily affects the supporting structures of teeth, including the gingiva, periodontal ligament, and alveolar bone. Characterized by gingival inflammation, pocket formation, attachment loss, and eventual tooth loss, periodontitis is a significant public health concern globally. Beyond its oral manifestations, periodontitis has profound systemic implications, contributing to a growing body of evidence linking it to various syndromes and systemic diseases.

Syndromes associated with periodontitis often exhibit immune dysregulation, genetic predispositions, or structural abnormalities, making individuals more susceptible to periodontal destruction. These include metabolic syndrome, aggressive periodontitis (referred to as Gottlieb syndrome), and other genetic disorders that exacerbate the inflammatory response. Additionally, systemic conditions like diabetes, cardiovascular diseases, and neurodegenerative disorders often show bidirectional relationships with periodontal disease, complicating its clinical presentation and management [1].

Understanding the interplay between periodontitis and systemic syndromes is critical, as it not only aids in differential diagnosis but also enables comprehensive management strategies. With its multifactorial etiology, periodontitis serves as a paradigm of the complex connections between oral and systemic health, underscoring the need for an integrated approach in clinical practice and research [2].

Pathophysiology of Periodontitis in Systemic Manifestation

The pathogenesis of periodontitis extends beyond local tissue destruction, influencing systemic health through complex mechanisms. The ulcerated gingival epithelium, a hallmark of advanced periodontitis, facilitates the entry of periodontal pathogens and their toxins into systemic circulation. These pathogens trigger an immune response, leading to the release of inflammatory mediators like cytokines and prostaglandins. This

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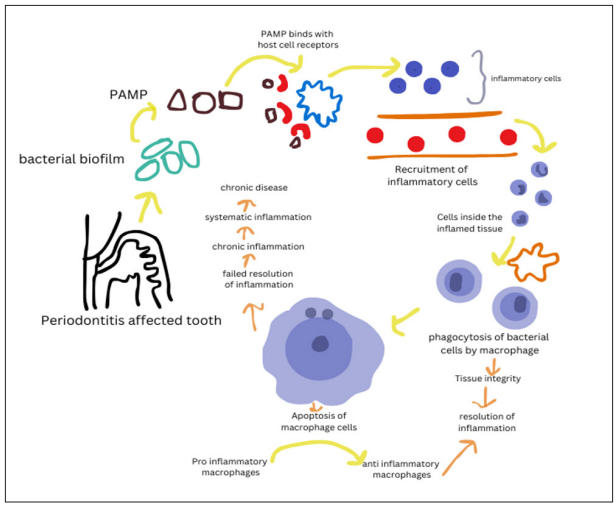
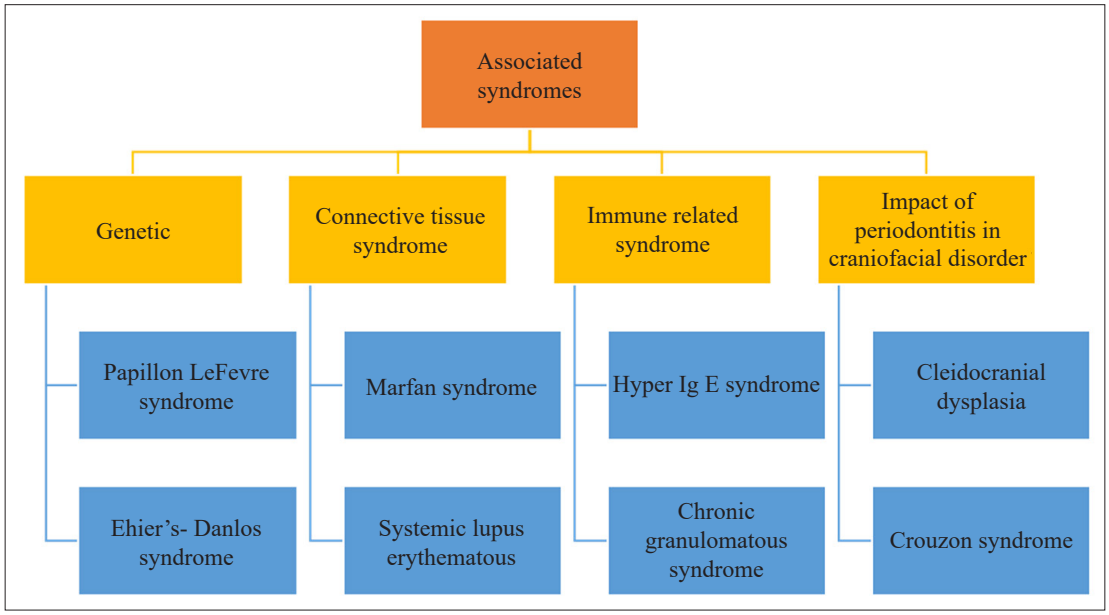
inflammatory cascade not only perpetuates local tissue damage but also contributes to systemic inflammation, potentially impacting distant organs. Additionally, the hematogenous and transtracheal spread of pathogens and inflammatory markers establishes a bidirectional link between periodontitis and systemic conditions, emphasizing the far-reaching impact of this chronic disease.

Syndromes



Inflammatory Cascade of Periodontitis-Pathogens Mediating Series of Events



Genetic Associates Syndromes

Papillon Lefevre Syndrome

PLS is a rare autosomal recessive disorder characterized by severe aggressive periodontitis affecting both deciduous and permanent dentitions, alongside palmoplantar hyperkeratosis. It was first described in 1924 by Papillon and Lefèvre. The prevalence is approximately 1 in 4 million people, with no gender or racial predilection. A significant number of cases show parental consanguinity.It is primarily caused by mutations in the Cathepsin C (CTSC) gene located on chromosome 11q14. This mutation leads to the deficiency in the enzyme cathepsin C which plays a crucial role in activating serine proteates in the immune cells, resulting in impaired immune response. The defective immune system fails to combat periodontal pathogens effectively.Additionally, hyperkeratosis of the palms and soles , a hallmark feature of PLS may be linked to defective keratinocyte function caused by CTSC mutation [3].

Clinical Features

- Dermatological Manifestations:
- Hyperkeratotic lesions on palms, soles, and knees.
- Psoriasis-like plaques on elbows and knees.
- Dystrophic nails.
- Recurrent cutaneous infections.
- Systemic Features:
- Intracranial calcification.
- Increased susceptibility to pyogenic infections, liver abscesses.
- In rare cases, mental retardation.

Oral Manifestations

- Severe gingival inflammation and pocket formation.
- Rapid loss of periodontal attachment and alveolar bone.
- Premature exfoliation of both primary and permanent teeth (primary teeth by age 5, permanent teeth within a few years of eruption).

- Gingival inflammation reduces temporarily after tooth loss but recurs with the eruption of new teeth.

Haim-Munk Syndrome

It is an extremely rare autosomal recessive disorder characterized clinically by palmoplantar hyperkeratosis, (callous patches of skin on palms and the soles) aggressive periodontitis with severe alveolar bone destruction, onychogryphosis etc [4]. It is similar to Papillon–Lefevre syndrome. Skin manifestations are more severe and periodontal disease milder. Periodontal findings include progressive periodontal disease, the periodontium in HMS may be less severely affected than in PLS but gingival inflammation and alveolar bone destruction are present and severe [5].

Ehler's- Danlos Syndrome

Periodontal Ehlers-Danlos syndrome (pEDS) is a rare subtype of Ehlers-Danlos syndrome (EDS) that is characterized by connective tissue abnormalities, including early-onset periodontitis (EOP).[5] The condition leads to severe periodontal tissue breakdown starting from the teenage years, which results in premature tooth loss. The genetic cause of pEDS has been linked to mutations in the C1R and C1S genes, which are involved in the classical complement pathway and contribute to connective tissue pathology [6].

Clinical Features

Periodontal Manifestations

- Gingival Recession: The absence of attached gingiva and fragile gums lead to gingival recession.
- Early Onset Periodontitis (EOP): This condition leads to periodontal inflammation from childhood, progressing to early-onset periodontitis in the teens. The inflammation results in the loss of periodontal attachment and alveolar bone, leading to tooth loss at an early age [7].
- Extensive Gingivitis: A mild plaque accumulation leads to significant gingival inflammation during childhood.

Oral Manifestations

- Periodontal involvement is one of the hallmark features of pEDS. The oral manifestations include
- Premature Tooth Loss: Both deciduous and permanent teeth are affected by rapid periodontal destruction.
- Severe Periodontal Inflammation: Gingivitis in childhood quickly escalates to periodontitis in the teenage years, leading to severe alveolar bone loss and tooth exfoliation [8-10].

Connective Tissue Syndrome

Marfan Syndrome

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder caused by mutations in the fibrillin-1 gene (FBN1) on chromosome 15. Characterized by defects in connective tissue throughout the body, MFS affects multiple systems, including cardiovascular, skeletal, and ocular. Clinical manifestations of MFS are variable and include tall stature, elongated limbs, joint hypermobility, scoliosis, pectus deformities, ocular abnormalities such as ectopia lentis, and cardiovascular issues like aortic dissection. In addition to systemic manifestations, oral features are common in MFS patients, including maxillary protrusion, a high palatal arch, crowded teeth, temporomandibular joint disorders, and fragile periodontal tissues. These oral manifestations can complicate dental hygiene, potentially increasing susceptibility to periodontal diseases [11].

Systemic Lupus Erythematous

Periodontitis has significant systemic implications, with associations reported for cardiovascular diseases, diabetes, adverse pregnancy outcomes, pulmonary diseases, and various autoimmune conditions, including systemic lupus erythematosus (SLE). Emerging evidence suggests a bidirectional relationship between PD and SLE, wherein systemic inflammation in SLE exacerbates periodontal destruction, and periodontitis may modulate immune-inflammatory responses, contributing to SLE pathogenesis [12].

Clinical Findings

- Excessive autoimmune response leading to inflammation and tissue damage.
- Pathogenic autoantibodies targeting nucleic acids and protein complexes.
- Systemic involvement causing arthritis, glomerulonephritis, and other inflammatory conditions.
- Elevated susceptibility due to genetic and environmental triggers.
- Altered immune system response with nearly all cell types contributing to disease exacerbation.

Oral Manifestations in SLE

- Dysbiotic subgingival microbiota, with elevated bacterial load and pathogenic species like Prevotella oulorum, Prevotella nigrescens, Streptococcus noxia, Lachnospiraceae, and Leptotrichia.
- Higher prevalence of Candida albicans and Lactobacilli.
- Increased presence of periodontal pathogens such as Treponema denticola and Tannerella forsythia.
- Gingival inflammation and periodontal destruction, even in periodontally healthy sites.
- Association of disease activity with microbiota shifts, particularly in active SLE patients.
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Immunity Related Syndrome

Hyper Ig E Syndrome (HIES)

Hyper Ig E Syndrome (HIES), also known as Job's syndrome, is a rare primary immunodeficiency disorder characterized by high serum Ig E levels, recurrent infections, and multi-organ involvement. It is caused by mutations in genes such as STAT3, DOCK8, or TYK2. HIES presents in autosomal dominant, autosomal recessive, or sporadic forms. The condition affects males and females equally, with an estimated incidence of 1:1,000,000. The pathogenesis involves altered T-helper cell (Th) responses, skewing towards a Th2-dominant immune profile, and defective polymorphonuclear leukocyte functions [14].

Clinical Findings

Systemic Manifestations: Eczema and recurrent bacterial infections (e.g., skin abscesses, pneumonia with pneumatoceles). Coarse facial features, short stature, and hyperflexible joints. Skeletal abnormalities like scoliosis, craniosynostosis, osteopenia, and fractures [15].
Immunologic Features: Elevated Ig E levels (10,000–100,000 IU/mL). Deficiency in Th17 cells and skewed Th1/Th2 balance towards Th2. Impaired neutrophil and antibody responses [16].

Oral Manifestations

Delayed Exfoliation of Primary Teeth

- Root resorption deficiency leads to retention of primary teeth in up to 75% of cases.

Severe Periodontitis

- Rapid tissue destruction due to defective leukocyte responses and high levels of bone-resorbing cytokines (IL-1β, TNF-α, prostaglandin E2).

Tooth Anomalies

- Microdontia and supernumerary teeth.
- High-arched palate.

Increased Risk of Infection

- Periodontal infections may progress rapidly, leading to systemic complications like head and neck infections if untreated.

Chronic Granulomatous Syndrome

Chronic Granulomatous Disease (CGD) is a rare congenital immune deficiency syndrome affecting 1 in 250,000 individuals. It results from mutations in genes encoding components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, critical for the respiratory burst in neutrophils and macrophages [17]. This defect impairs the body's ability to kill bacteria and fungi, leading to recurrent severe infections and hyperinflammatory responses. The most common form is X-linked CGD (XCGD) due to mutations in the CYBB gene, while rarer autosomal recessive forms arise from mutations in CYBA, NCF1, or NCF2 [18].

Oral Manifestations

Although not life-threatening, oral complications are prevalent in CGD and can significantly affect quality of life. These include:

1. Mucosal ulcers: Multiple aphthous-like ulcers have been reported, with histology showing inflammatory infiltrates, occasional eosinophils, and mononuclear histiocytes.
2. Gingivitis and periodontitis: Severe gingivitis and generalized pre-pubertal periodontitis are common, likely exacerbated by neutrophil dysfunction and a hyperactive inflammatory response.
3. Granulomatous lesions: Granulomas involving the lips, palate, or gingiva may arise, characterized by chronic inflammation and epithelioid cells.
4. Other findings: Geographic tongue, enamel hypoplasia, rampant caries, and plaque-induced gingivitis are frequently observed [19-21].

Impact of Periodontitis in Craniofacial Disorder

Cleidocranial Dysplasia

Cleidocranial dysplasia (CCD) is a rare genetic disorder primarily associated with mutations in the RUNX2 gene, also known as Core Binding Factor Alpha 1 (CBFA1), located on chromosome 6p21. This gene is pivotal in osteoblast differentiation and bone formation. Both dominant and recessive patterns of inheritance have been described, with spontaneous mutations accounting for 20–40% of cases. The global incidence of CCD is approximately 1 in a million [22].

Oral Manifestation

Dental Findings:

- Retention of deciduous teeth.
- Delayed eruption of permanent teeth.
- Presence of multiple impacted supernumerary teeth, predominantly in the mandibular premolar and maxillary anterior regions.
- Narrow, highly arched palate.
- Cementum and Alveolar Bone Anomalies:
- A notable lack of cellular cementum in erupted and unerupted teeth.
- Short roots with spike-like apices due to inadequate alveolar bone resorption.
- Ankylosis of deciduous teeth, attributed to halted tooth resorption and dense new bone formation [23].

Periodontal Implications:

- Impaired RUNX2 gene function leads to haploinsufficiency, disrupting osteoclast recruitment essential for normal alveolar bone resorption.
- Deficient bone remodeling may contribute to periodontal defects, impacting overall oral health [24].

Periodontitis and CCD

CCD patients are prone to periodontal issues due to anatomical and genetic factors. Delayed eruption and the presence of supernumerary teeth create challenges in maintaining proper oral hygiene, predisposing patients to plaque accumulation and subsequent periodontitis. Periodontal inflammation is further exacerbated by impaired osteoclast activity, leading to compromised bone support around teeth [25].

Crouzon Syndrome

Crouzon syndrome is an autosomal dominant genetic disorder caused by mutations in the FGFR2 gene, and less commonly in FGFR3. Mutations in FGFR1, MSX2, TWIST1, EFNB1, NELL1, GLI3, and TCF12 genes have also been implicated. These mutations lead to premature fusion (synostosis) of craniofacial sutures, affecting growth and craniofacial structure. The syndrome affects approximately 1 in 60,000 live births, making it one of the most common craniosynostosis syndromes.

Craniofacial and Intraoral Characteristics

The premature synostosis in Crouzon syndrome results in distinct craniofacial and intraoral features:

Craniofacial Features

- Deformities like brachycephaly, scaphocephaly, or oxycephaly.
- Midfacial hypoplasia with retro positioning of the zygomaticomaxillary complex.

- Concave facial profile and exophthalmos due to shallow orbits.
- Deviated nasal septum leading to a beaked nose.

Intraoral Features
- Narrow, high-arched palate.
- Decreased upper dental arch dimensions.
- Severe crowding of teeth, anterior and posterior crossbite.
- Deciduous teeth often grossly decayed due to poor oral hygiene and lack of awareness.
- Erupted first permanent molars typically healthy and in occlusion.
- Succedaneous teeth generally healthy but occasionally exhibit macrodontia.

Periodontal Implications
Crouzon syndrome predisposes individuals to periodontal issues due to both structural and behavioral factors:

1. Anatomical Barriers to Hygiene
The narrow and crowded dental arches create difficulty in maintaining oral hygiene, increasing plaque accumulation.

The high-arched palate and crowded dentition make cleaning challenging, further elevating the risk of gingivitis and periodontitis.

2. Behavioral and Awareness Issues
Parents' lack of awareness and the child's potential mental or physical challenges can lead to neglect of oral hygiene practices.

3. Functional Impairments
Altered dental arch dimensions and occlusal issues may exacerbate masticatory dysfunction, leading to plaque retention.

4. Periodontitis Progression in Crouzon Syndrome
- The altered craniofacial structure and intraoral environment may accelerate the onset and progression of periodontitis.
- The presence of decayed deciduous teeth can act as reservoirs for pathogenic bacteria, potentially spreading infection to permanent teeth and periodontal tissues [26].

Other syndromes
a. Kindler Syndrome
Kindler syndrome has been proposed as a medically predisposing condition for destructive periodontal disease.

Clinical findings
- Genodermal disorders
- Blistering of skin following mild trauma,
- Poikiloderma
- Thin wrinkled skin devoid of surface markings

Periodontal findings include
- Tooth mobility
- Spontaneous gingival bleeding
- Earlier accelerated
- Attachment loss
- Desquamative lesions of gingiva.

b. Struge Weber Syndrome
The general findings include brain calcifications, ocular disorders, hemiplegia, epilepsy and port wine stains confined to skin area supplied by the trigeminal nerve.

The gingiva shows
- Mild Vascular Hyperplasia
- Massive hemangiomatous proliferation limited to one side.
- Gingival lesions may resemble pyogenic granuloma [27].

c. Sjogren Syndrome
There is a higher risk for periodontal breakdown of teeth in patients with Sjogrens syndrome

Clinical findings
- Keratoconjuctivtis Sicca
- Xerostomia and Rheumatoid Arthritits

d. Chediak Higashi Syndrome
The findings include involvement of cell organelles of cells
- Platelets
- Melanocytes
- Phagocytes

Such individuals suffer from aggressive periodontitis with rapid periodontal breakdown [28].

Challenges in Diagnosis and Management
The coexistence of systemic disorders and syndromes with periodontal diseases significantly complicates diagnosis and management. Many syndromes, such as Papillon-Lefèvre syndrome, Ehlers-Danlos syndrome, and Down syndrome, present with overlapping oral manifestations like severe gingival inflammation, early-onset periodontitis, or connective tissue defects, making it challenging for clinicians to identify the primary etiology of oral symptoms. For instance, the periodontal damage in Papillon-Lefèvre syndrome may mimic aggressive periodontitis but requires a different therapeutic approach. Similarly, in Down syndrome, the underlying immune dysregulation and anatomical variations may confound standard periodontal assessments.

Management becomes further challenging due to the following factors:
- **Delayed Diagnosis:** Systemic manifestations often overshadow oral health issues, delaying the identification of periodontal diseases.
- **Limited Treatment Options:** Many systemic conditions restrict the use of certain medications or surgical interventions due to contraindications or patient tolerance.
- **Host-Response Impairment:** Syndromes with inherent immune or connective tissue deficiencies reduce the effectiveness of standard periodontal therapies, increasing the risk of recurrent infections.
- **Compliance Issues:** Patients with syndromes, especially paediatric and those with cognitive impairments (e.g., Down syndrome), require tailored behavioural and clinical strategies, which demand more time and expertise.
- **Multidisciplinary Coordination:** Successful management often requires collaboration between dentists, paediatricians, geneticists, and other specialists, which may not always be practical in routine clinical settings.

To overcome these challenges, clinicians must employ precise diagnostic tools, including genetic testing and advanced imaging techniques. Personalized care plans focusing on the patient's systemic condition, coupled with the use of minimally invasive and host-modulating therapies, are crucial for optimal outcomes. Additionally, early intervention and education of caregivers can significantly enhance management success in such complex cases [29].

Conclusion

Periodontitis-associated syndromes present significant challenges for clinicians due to the complex interplay between systemic disorders and oral manifestations. Syndromes such as Down syndrome, Papillon-Lefèvre syndrome, and Chediak-Higashi syndrome, among others, highlight how systemic conditions can exacerbate periodontal tissue destruction, alter immune responses, or complicate routine oral care. The variability in clinical presentations, compounded by diagnostic overlaps and management difficulties, underscores the importance of multidisciplinary approaches to treatment. Effective management demands a tailored strategy that addresses both the systemic disorder and periodontal pathology, emphasizing early diagnosis, coordinated care, and patient-specific interventions to optimize oral and systemic health outcomes.

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