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Periodontal Disease Associated with Genetic Disorders

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Abstract

The object of this chapter was to provide an overview including relevant research progress of some genetic disorders with periodontal manifestations. A number of genetic disorders increase patient susceptibility to periodontal disease, with the latter exhibit rather rapid and aggressive presentations. Periodontal disease, perhaps could be the first detectable sign of an undiagnosed genetic disorder. It is therefore important for dental practitioners to be familiar with genetic disorders and their impact on the periodontal tissues. This chapter reviews several genetic disorders that exhibit periodontal manifestations, including hereditary gingival fibromatosis, Papillon-Lefèvre syndrome, cyclic neutropenia, Ehlers-Danlos syndrome and hypophosphatasia.

Keywords: cyclic neutropenia, Ehlers-Danlos syndrome, genetic disorders, hereditary gingival fibromatosis, hypophosphatasia, Papillon-Lefèvre syndrome, periodontal disease

1. Introduction

Periodontal disease is an inflammatory disease that affects the gingival tissues and periodontal attachment apparatus (cementum, periodontal membrane, and alveolar bone) that surround and support the teeth [1]. In its early stage or gingivitis, the gums become swollen and red due to inflammation. In the more serious form of periodontal disease or periodontitis, which is one common chronic infection in the human mouth, loss of periodontal supportive tissue, including gingiva, periodontal ligament and alveolar bone, were evident [2] with untreated periodontitis one of the major causes of tooth loss in adults. With reference to current advances in knowledge from both biological and clinical studies since 1999 or the last International Classification of Periodontal Diseases, the 2017 World Workshop Classification system for periodontal diseases was refined and revised accordingly [3–5]. In the 2017 classification system, gingival diseases include dental biofilm-induced gingivitis and non-dental biofilm-induced gingival diseases. Periodontitis classification include necrotizing periodontal diseases, periodontitis, and periodontitis as a manifestation of systemic disease [4, 5]. The treatment of periodontal disease with systemic disease at the present date remained a significant challenge. It is paramount that correct diagnosis is made so appropriate treatment can be planned and delivered. The purpose of this chapter was to review the current literature with selected case reports concerning periodontal disease associated with genetic disorders, including hereditary gingival fibromatosis, Papillon-Lefèvre

syndrome, cyclic neutropenia, Ehlers-Danlos syndrome, and hypophosphatasia. The etiology of these genetic disorders, prevalence and incidence, the clinical oral manifestations and the possible therapeutic approaches will be discussed.

2. Methodology

This chapter used a review approach aim to summarize the current literature concerning periodontal disease associated with genetic disorders, meanwhile, the chapter also provided some clinical cases including hereditary gingival fibromatosis, Papillon-Lefèvre syndrome, cyclic neutropenia, Ehlers-Danlos syndrome, and hypophosphatasia.

2.1 Literature search strategies

A review of the literature concerning periodontal disease associated with genetic disorders was conducted using PubMed, Embase, Web of Science, Google Scholar, and the Cochrane Library with no restrictions placed on country or publication date. The search involved the genetic disorders listed in the 2017 Classification System for Periodontal Diseases and Conditions [6]. The keywords used in the online searches were (the name of disorder) AND (periodontal disease OR periodontitis OR attachment loss). Additional relevant articles were also found by scanning the references of included articles as well as those citing the papers concerned.

2.2 Screening and selection criteria of studies

The identified study titles were first screened to exclude studies not relevant to periodontal disease associated with genetic disorders. For studies with apparent relevant title, the abstract would be reviewed to check and confirm potential eligibility, normally followed by careful study of the full text involved. Once eligibility is confirmed, the reference list of the included paper as well as those articles cited the latter would be reviewed for additional relevant reports. Different types of studies were included and evaluated, including case series/reports. Etiology, gene(s) involved, inheritance pattern, clinical signs and proposed therapeutic approach(es) for these periodontal diseases associated with genetic disorders were noted (**Table 1**).

In particular, five genetic disorders were given special attention: hereditary gingival fibromatosis, Papillon-Lefèvre syndrome, cyclic neutropenia, Ehlers-Danlos syndrome, and hypophosphatasia. Information regarding etiology, prevalence and incidence, clinical oral manifestations and the possible therapeutic approaches concerning these five disorders would be noted and summarized.

3. Genetic disorders that affect the periodontal tissue

According to the International Workshop in 2017, periodontal disease as a manifestation of systemic diseases is a separate disease category, systemic diseases are divided into hematological and genetic disorders [6]. Genetic disorders are caused by gene mutations or chromosome disorders that cause a change in the number or structure of chromosomes [7]. **Table 1** shows some well described genetic disorders that have a major impact on the periodontal tissue, including some disorders affecting gingival tissue (hereditary gingival fibromatosis), connective tissues (vascular Ehlers-Danlos syndrome, periodontal Ehlers-Danlos syndrome), some

Genetic disorders	IP	Gene	Etiology	Clinical oral signs/symptoms	Therapy	OMIM
Hereditary gingival fibroma-tosis (HGF)	AD or AR	<i>SOS1</i> <i>REST</i> <i>ZNF862</i>	Proliferative fibrous overgrowth of the gingival tissue caused by an increase in the subepithelial connective tissue elements	Proliferative fibrous overgrowth of the attached gingiva, marginal gingiva, and interdental papilla	Preventive treatment, gingivectomy, and/or gingivoplasty	135300
Down syndrome (DS)	/	/	Trisomy chromosome 21, reduced chemotaxis and impaired phagocytosis	Gingivitis; necrotizing ulcerative gingivitis; severe periodontitis; tooth mobility	Preventive treatment and periodontal therapy	190685
Leukocyte adhesion deficiency (LAD)	AR	LAD-1: <i>ITGB2</i> ; LAD-2: <i>SLC35C1</i> ; LAD-3: <i>FERMT3</i>	Defects in adhesion receptors of the white blood cells and impaired phagocytosis	Severe gingival inflammation; rapidly progressive periodontitis; recurrent aphthous ulceration	Periodontal treatment +/- adjunct antibiotics, often involve extraction of primary or permanent teeth	116920 266265 607901
Papillon-Lefèvre syndrome (PLS)	AR	<i>CTSC</i>	Mutated cathepsin-c gene, impaired neutrophil function	Aggressive periodontal breakdown; premature loss of teeth	Periodontal treatment with adjunct antibiotics; according to the age of onset, may involve extraction of deciduous teeth 6 months prior to eruption of permanent successors	245000
Haim-Munk syndrome (HMS)	AR	<i>CTSC</i>	Mutation of gene encoding for cathepsin-c, impaired neutrophil function	Severe gingival inflammation; periodontitis; early loss of teeth	Extraction of the primary teeth combined with adjunct antibiotics and periodontal therapy	245010
Chediak-Higashi syndrome (CHS)	AR	<i>LYST</i>	Impaired lysis of phagocytized bacteria, resulting in recurrent bacterial respiratory and other infections and oculocutaneous albinism.	Severe gingivitis; early-onset periodontitis; oral ulcerations	The disease posts great challenges to periodontal management: intensive prevention, meticulous mechanical therapy with antibiotics and chemical plaque control	214500
Severe congenital neutropenia (SCN),	AR or AD	<i>ELANE</i> and <i>HAX1</i>	An arrest in myeloid maturation at the promyelocyte	Gingival inflammation; severe alveolar bone loss; early loss of	Conventional periodontal treatment with antibiotics	610738

Genetic disorders	IP	Gene	Etiology	Clinical oral signs/symptoms	Therapy	OMIM
Kostmann syndrome			stage in the bone marrow	teeth; oral ulcerations		
Cyclic neutropenia (CN)	AD	ELANE	Cyclical decrease in the number of circulating neutrophils	Gingival inflammation; severe periodontitis; oral ulcers	Periodontal therapy followed by monthly debridement and extra therapy during neutropenic episodes; chlorhexidine rinsing	162800
Cohen syndrome	AR	VPS13B	Abnormal protein glycosylation and Golgi dysfunction	Periodontal disease	Prevention and conventional periodontal therapy	216550
Ehlers-Danlos syndrome (Vascular type, vEDS)	AD	COL3A1 or COL1A1	Defective collagen synthesis	Gingival recession; gingival fragility	Periodontal therapy followed by mechanical and chemical plaque control	130050
Ehlers-Danlos syndrome (Periodontal type, pEDS)	AD	C1R or C1S	Secretion or release of active C1r serine protease in the extracellular space	Severe and intractable periodontitis of early onset; lack of attached gingiva	Periodontal therapy with strict biofilm management to stop the plaque-associated periodontal hyperinflammation and probably the subsequent bone and tooth loss	130080
Glycogen storage disease 1b (GSD 1b)	AR	SLC37A4	Deficiency of glucose-6-phosphate translocase	Oral ulcers; hyperplastic gingiva; periodontal infections; prolonged bleeding	Preventive treatment, periodontal therapy and control of gingival disease	232220
Hypophosphatasia (HPP)	AD or AR	ALPL	Decreased activity of tissue nonspecific alkaline phosphatase	Absence of root cementum; premature exfoliation of deciduous teeth	Periodontal therapy with possible extraction of involved primary teeth and more conservative treatment on permanent teeth	146300

AD, autosomal dominant; ALPL, alkaline phosphatase, biomineralization associated gene; AR, autosomal recessive; C1R, complement 1 subunit r gene; C1S, complement 1 subunit s gene; COL1A1, collagen type I alpha 1 chain gene; COL3A1, collagen type III alpha 1 chain gene; CTSC, cathepsin C gene; ELANE, elastase, neutrophil expressed gene; FERMT3, fermitin family member 3 gene; HAX1, HCLS1-associated protein X-1 gene; HCLS1, hematopoietic cell-specific lyn substrate 1; IP, inheritance pattern; ITGB2, integrin subunit beta 2 gene; LYST, lysosomal trafficking regulator gene; OMIM, online Mendelian Inheritance in man; RE1, transcriptional repressor element-1, REST, RE1-silencing transcription factor gene; SLC35C1, solute carrier family 35 member C1 gene; SLC37A4, solute carrier family 37 member 4 gene; SOS, son of sevenless genes; SOS1, SOS Ras/Rac guanine nucleotide exchange factor 1 gene; VPS13B, vacuolar protein sorting 13 homolog B gene; ZNF862, Zinc finger protein 862 gene.

Table 1.
Periodontal disease associated with genetic disorders.

diseases associated with immunologic disorders (Down syndrome, leukocyte adhesion deficiency, Papillon-Lefèvre syndrome, Haim-Munk syndrome, Chediak-Higashi syndrome, Severe congenital neutropenia, cyclic neutropenia, Cohen syndrome) and metabolic disorders (glycogen storage disease 1b, hypophosphatasia) [6, 8–12].

3.1 Hereditary gingival fibromatosis

Hereditary gingival fibromatosis (HGF) is a rare, hereditary disorder characterized by a benign, non-hemorrhagic, localized or generalized fibrous enlargement of free and attached gingivae with slow progression, and was initially reported by Goddard and Gross in 1856 [13, 14]. It has been designated by such terms as gingivostomatosis, elephantiasis, idiopathic fibromatosis, hereditary gingival hyperplasia, idiopathic gingival enlargement, and congenital familial fibromatosis. The prevalence is unknown, the incidence is 1:175,000 according to phenotype and 1:350,000 according to genotype, and equal between males and females. HGF is commonly described as an isolated disorder (non-syndromic), or it can develop as a part of a syndrome (syndromic) like Cowden’s syndrome, Zimmermann-laband syndrome, Cross syndrome, Rutherford syndrome, Ramon syndrome, Jones syndrome, Costello syndrome, Ectro-amelia syndrome, and hyaline fibromatosis syndrome [15]. In this part, we mainly discuss non-syndromic HGF.

3.1.1 Etiology and pathogenesis

The mode of HGF inheritance is still controversial, while it is generally considered to be an autosomal dominant disease, there are a few studies demonstrating that it may also follow an autosomal recessive pattern [16]. **Figure 1** shows a Chinese pedigree with non-syndromic HGF in an autosomal dominant mode. As reported earlier, four loci (2p22.1 [MIM: 135300], 2p23.3-p22.3 [MIM: 609955], 5q13-q22 [MIM: 605544] and 11p15 [MIM: 611010]) were recognized to be related with HGF [17–20], while SOS Ras/Rac guanine nucleotide exchange factor 1 gene (SOS1) (MIM: 182530) heterozygous frameshift mutation was acknowledged causing autosomal dominant HGF in a Brazilian family [21]. From three independent families, two Turkish and one American, protein truncating mutations of RE1-silencing transcription factor or *REST* gene (MIM: 600571) were identified to cause autosomal dominant HGF [22]. In our department, we identified seventeen autosomal dominant non-syndromic HGF patients from a Chinese family (**Figure 1**). Across three generations, whole-exome sequencing then genetic co-segregation analysis were performed identifying an original Zinc finger protein 862 (*ZNF862*) gene heterozygous missense mutation to be the cause of the genetic problem [23].

Figure 1.
A Chinese pedigree with non-syndromic hereditary gingival fibromatosis (HGF).

The pathophysiologic mechanisms underpinning HGF remain elusive. Nonetheless, extracellular matrix overproduction involving major component of collagen type I was believed to be a cause of the gingival fibroblast overgrowth phenotype; on the other hand, increased production of TIMP-1 appeared to be associated with excessive collagen I accumulation in HGF fibroblasts [24, 25]. Also, Martelli-Junior and coworkers claimed that TGF- β 1, IL-6 and perhaps other specific growth factors overproduction in fibroblasts might play pivotal roles in unwarranted collagen I synthesis [26].

3.1.2 Clinical manifestations

The onset of the gingival overgrowth usually coincides with the eruption of permanent incisors, while under rare circumstances, HGF can present at birth (Figures 2–4). The overgrowth affects the attached gingiva as well as the gingival margin and the interdental papillae. The facial and lingual surfaces of the permanent teeth are generally affected, the enlarged gingiva is usually firm, smooth and occasionally nodular, with minimal or no inflammation and normal or pale in color. The upper gingiva is more severely affected and may prevent the eruption of the teeth. In severe cases, the teeth are almost completely covered. The firm yet painless enlargement of the gingiva does not commonly affect the alveolar bone but can lead

Figure 2.
HGF in Chinese elderlies.

Figure 3.
HGF in Chinese adults.

Figure 4.
HGF in Chinese children.

to the development of pseudo-pockets, which facilitate plaque accumulation due to suboptimal daily oral hygiene [13–16].

Enlarged gingival tissues due to HGF cause functional and esthetic problems. The lesion partially and at times totally cover the crowns of teeth causing pseudo-pocketing. In extreme situations, HGF could delay or even impede tooth eruption, causing diastemas, mal-position/–alignment of teeth, cross–/open-bite, excessive lip support including vermillion eversion, and/or incompetence lips. Common clinical complications secondary to gingival enlargement including but not limited to difficulties in speech, mastication, and occlusion, as well as changes in facial features. Interestingly, the condition may disappear or regress with the loss of teeth, thus suggesting that the presence of teeth might serve as one condition for the development of HGF [13–16].

3.1.3 Diagnosis

Diagnosis of HGF is usually based on clinical findings, a generalized severe gingival overgrowth without medication history, and the familial aggregation of HGF can assist in early diagnosis [27, 28]. The differential diagnosis should include gingival hyperplasia due to phenytoin, nifedipine and cyclosporine and gingival fibromatosis, which may occur as part of other genetic syndromes.

HGF related gingival fibrous enlargement typically display marked increase in submucosal connective tissue histologically. The involved connective tissue looks densely collagenized, populated scantily with fibroblasts, avascular and with signs indicating minimal inflammatory infiltrate. The overlying dense epithelial layer appears hyperkeratotic with elongated rete pegs. In situation when abnormal thickening of the stratum spinosum or prickle cell layer, i.e. acanthosis of the HGF involved epithelium, areas with chronic inflammation within the epithelium can sometimes be detected [27, 29].

3.1.4 Treatment

The maintenance of good oral hygiene and plaque control is fundamental. Treatments vary according to the degree of severity of gingival enlargement and different types of treatment modality could be employed for the excision, including conventional surgery, electrosurgery, apically positioned flap and laser ablation [14, 27, 30].

For HGF patients with mild gingival hyperplasia, supportive periodontal therapy is recommended every 3 months.

For HGF patients with modern-severe gingival hyperplasia, periodontal surgery is required (**Figures 5 and 6**), including gingivectomy, gingivoplasty, and flap surgery. Some literature indicated that laser can also be used to remove hyperplastic gingival, with higher patient comfort and less trauma. Recurrence after surgical treatment was observed within 3–10 years, and children and adolescents are more likely to recurrence than adults. Therefore, regular follow-up and good oral hygiene are very important.

For HGF patients with severe gingival hyperplasia deformation, surgical interventions that may be required include tooth extraction, osteoplasty and ostectomy.

A comprehensive medical and family history, along with clinical examination can aid early HGF diagnosis because the latter often associates with a few extra-oral features on top of familial aggregation. Gingivectomy is often the treatment of choice while long-term follow-up post-surgery is recommended for the relatively high probability of HGF recurrence.

Figure 5. Periodontal surgery (gingivectomy, gingivoplasty, and flap surgery) in a Chinese HGF patient (IV-1, **Figures 1 and 3**; pre-operation [left panels: Set of nine intra-oral photographs] and 6 months follow-up [right hand panels]).

Figure 6. Periodontal surgery (gingivectomy, gingivoplasty, and flap surgery) in a Chinese HGF patient (IV-2, **Figure 1**; pre-operation [right hand panels] and 2 years follow-up [left hand panels]).

3.2 Papillon-Lefèvre syndrome

Papillon-Lefèvre syndrome (PLS), first reported in a French family by physicians Papillon and Lefèvre in 1924, is an autosomal recessive disorder characterized by diffuse palmoplantar erythematous, fissured hyperkeratosis, and aggressive periodontal disease that starts in the early periods of childhood. It has been designated by such terms as “keratoris palmoplantaris” and “hyperkeratosis palmoplantaris” [31, 32]. Periodontitis occurs with the early loss of deciduous teeth at the age of 2 to 4 years, followed by the loss of permanent teeth during adolescence. The prevalence is unknown, more than 300 families worldwide have been reported in the medical literature [33]. In the general population, PLS occurs in approximately one to four individuals per million, and consanguinity is reported as a significant risk factor and has been demonstrated in 20–40% of PLS patients [34]. With reference to 124 PLS cases, Haneke raise the following generalizations: (1) females and males appeared equally affected; (2) no racial predominance of the condition, apparently, could be observable; (3) however, consanguinity was associated with a third of the cases; and (4) other than periodontitis, increased susceptibility to other infections was observed in a quarter of PLS patients [32].

3.2.1 Etiology and pathogenesis

PLS is caused by changes (alterations) in CTSC gene, which encodes cathepsin C, a lysosomal protease capable of removing dipeptides from the amino-terminus portion of its respective substrates [35]. The protein is expressed at high levels in

various immune cells and certain bodily areas affected by PLS, including epithelial cells, that form the protective outer layer of the skin (epidermis), such as of the palms, soles, and knees, as well as certain cells of the gingiva. To date, more than 90 mutations in *CTSC* have been reported associate with PLS with the majority being located between Exons 5 and 7, the region encoding the heavy chain domain of cathepsin C that controls its enzymatic activity. Cathepsin C activity is proposed to play a key role in the epithelial differentiation and desquamation, while the inappropriate genetic alterations may result in nearly complete loss of cathepsin C enzymatic activity in homozygous individuals with the disease, or correspondently reduced activity of the enzyme in the family members who are heterozygous carriers [36, 37]. The present research group reported a PLS patient with a 110 kb deletion (Chr11: 88032292:88142997 [NC_000011]) and a nonsense mutation exists (Gln182Ter, CAG > TAG) in the fourth exon of the *CTSC* gene [38].

Another important related periodontitis etiologic factor is an alteration of the host defense owing to decreased function of lymphocytes, polymorphonuclear leucocytes or monocytes. However, research into such factors has not led to consistent findings and more research is necessary to decipher the underlying mechanisms that lead to the development of clinical manifestation observed in PLS [39, 40]. The subgingival plaque sampled from periodontal pockets of PLS patients resembled typical periodontitis-associated microflora, i.e. predominant gram-negative anaerobic microbes, including *Porphyromonas gingivalis* and spirochetes. Recent microbiologic report indicated that *Aggregatibacter actinomycetemcomitans* was detectable in periodontal sites in PLS patients [41].

3.2.2 Clinical manifestations

Patients with PLS present first clinical signs in the oral cavity as soon as the deciduous teeth erupt [34, 36]. Oral manifestations become apparent by the age of 2 to 3 years with rapid periodontal destruction: plaque accumulation, obvious gingival inflammation and bleeding, periodontal abscess, deep periodontal pocket formation, alveolar bone resorption, loose teeth, halitosis, following by premature exfoliation of all deciduous teeth by the age of 4 to 5 years (**Figure 7**) [38]. Radiographic investigations show generalized alveolar bone loss and migration of teeth whit no evidence of root resorption (**Figure 8**). Inflammation disappears during the edentulous period, but the disease process reappears when permanent dentition erupts, with the affected losing most of the teeth at teenage (**Figure 9**).

PLS is characterized by development of hyperkeratosis or dry scaly skin patches at early age of one to five years old. These patches usually confined to palms and

Figure 7.
Oral manifestations of a Papillon-Lefèvre syndrome (PLS) patient (3 years) with serious periodontitis (A) and her fraternal twin sister with healthy periodontal tissue (B).

Figure 8.
Panoramic radiographs of the PLS patient in Figure 7 when she was 3–5, or 8 years old.

Figure 9.
Flow chart of oral manifestations of PLS.

soles, but may spread to knees and elbows. In rare occasions, upper portions of hands and feet, eyelids, lips, cheeks, and/or other bodily surfaces may also be affected. Affected skin may appear unusually thick and red, but variation in texture and color is possible. Skin lesions may worsen upon exposure to cold which lead to pain upon movement like walking. Other symptoms that may accompany the condition are hyperhidrosis, nail dystrophy, cranial calcification, and increased susceptibility to infections. Most patients show susceptibility to mild skin infections like pyoderma or furunculosis. Severe infections like pyogenic liver abscess or pneumonia, and malignancies like melanoma have been reported in PLS patients [34, 42, 43].

3.2.3 Diagnosis

Early diagnosis and prompt treatment can potentially prevent aggressive periodontitis, tooth loss, and improve overall quality of life of patients with PLS [34, 36, 44]. PLS becomes clinically apparent at 1–5 years old; palmar-plantar hyperkeratosis or dry scaly patches of palms and soles, together with severe, aggressive, or rapidly progressing periodontitis are considered its main clinical features, with or without additional symptoms like pyogenic skin infections, nail dystrophies, and hyperhidrosis. Radiographic examination of advanced PLS cases reveal severe loss of the alveolar bone, and teeth appear to be “floating in air” (Figure 8).

Differential diagnoses should include Haim-Munk syndrome, Chediak-Higashi syndrome, juvenile periodontitis, and so on (**Table 1**). Haim-Munk syndrome (HMS) is a skin condition caused by *CTSC* mutation. It is an extremely rare disorder of keratinization of recessive inheritance that manifests with scaly, red, and thickened patches of the skin of soles of the feet and palms of the hands, pes planus, arachnodactyly, acroosteolysis, atrophic changes of nails, a radiographic deformity of fingers, recurrent abscess formations, and a severe ‘early-onset’ periodontitis [45].

Neutrophil function tests reveal anomalies of chemotaxis and phagocytosis by polymorphonuclear leukocytes. Skin biopsy shows hyperkeratosis with focal parakeratosis, moderate perivascular infiltration, hypergranulosis, and acanthosis. Biochemical analysis reveals a loss of *CTSC* activity. Molecular genetic testing can confirm a diagnosis. Molecular genetic testing can detect alterations in the *CTSC* gene known to cause PLS, but is available only as a diagnostic service at specialized laboratories [36, 44].

3.2.4 Treatment

A multidisciplinary approach involving the dermatologist, pediatrician, pediatric dentist, periodontist, and prosthodontist is important for the overall care of patient with PLS [34, 46]. Genetic counseling may be of benefit for affected individuals and their families. Psychosocial support is recommended for the entire family as well. Oral retinoids with aims to attenuate palmoplantar keratoderma and to diminish alveolar bone lysis remained the main line of the therapy. Oral hygiene, chemical plaque control with or without antibiotics are the recommended therapeutic protocol for reducing periodontitis progression. Eventually, primary or terminally periodontal involved teeth are extracted. Antibiotic therapy is also used in the treatment of recurrent infections. Etretinate (a synthetic retinoid) shows promising results in the treatment of PLS.

Successful periodontal management of PLS patients is the key to improve the prognosis of the dentition, preventing or delaying primary and permanent tooth loss. During the past decades, dental treatment efforts other than extraction have been attempted in PLS patients. Several articles have been published on the treatment of PLS. Ullbro et al. proposed a mode of periodontal therapy of patients with PLS [47] (**Table 2**).

Deciduous dentition	Permanent dentition
Three-monthly oral hygiene instructions and prophylaxis	Three-monthly oral hygiene instructions and prophylaxis
To extract teeth with advanced periodontal involvement	Twice daily rinsing with chlorhexidine gluconate 0.2% mouthwash
All primary teeth to be extracted at least 6 months prior to eruption of the permanent successor; with 2 weeks antibiotic regimen post extraction: amoxicillin + clavulanic acid, 20–40 mg/kg/d, q8H	Teeth with moderate periodontitis (bone loss <30% root length, probing pocket depths <5 mm): antibiotic adjunct non-surgical periodontal therapy, i.e. amoxicillin (20–50 mg/kg/d) + metronidazole (15–35 mg/kg/d), q8H × 4 weeks; followed by monthly prophylaxis
	Teeth with advanced periodontitis (bone loss >30% root length, probing pocket depth > 6 mm): consider extraction

Table 2.
Suggested mode of periodontal therapy for patients with Papillon-Lefèvre syndrome (PLS). Adopted from Ullbro et al. [47].

Most PLS patients ended up edentulous at an early age and were presented with rehabilitation problems due to severely atrophic thin alveolar ridges. Various pre-prosthetic surgical management approaches are introduced to maximize retention and stability of dentures. Along such line, dental implants are also advocated for enhancing stability and retention of prosthesis, improving comfort, masticatory efficiency and perhaps esthetics. Reports concerning installation of titanium implants in PLS patients with treated severe periodontitis to support and retain oral reconstructions indicated under good care and dedications in prevention or oral health maintenance, indicated the approach could be successful [48, 49].

3.2.5 Genetic counseling

Transmission is autosomal recessive. Genetic counseling should be offered to the parents of an affected individual informing them that 25% of their future offspring could inherit the disease-causing mutation.

3.2.6 Prognosis

Despite meticulous dental care, PLS patients eventually become edentulous at the beginning of adulthood while their life expectancy is normal [32, 42, 46].

3.3 Cyclic neutropenia

Neutropenia (absolute neutrophil count or ANC $<1.5 \times 10^9/L$), includes diagnoses ranging from normal variants like benign ethnic neutropenia to life-threatening acquired or congenital disorders like agranulocytosis. The biological consequences depend mainly on neutropenia severity and corresponding responses from the affected individual: e.g. an ANC of $1.0-1.5 \times 10^9/L$ does not normally impair host defense so far enough normally functioning neutrophils could be produced by bone marrow when needed, however the underlying cause of the low ANC need to be investigated; an ANC of $0.5-1.0 \times 10^9/L$ may increase infections risk but only if other immune defense element of the affected individual are also impaired; while an ANC of $0.2-0.5 \times 10^9/L$ normally associates with increased infections risk in most patients, an ANC $\leq 0.2 \times 10^9/L$, i.e. agranulocytosis, often implies susceptibility to opportunistic infection with high risk of severe, life threatening consequences [50].

Cyclic neutropenia (CN), first described in 1910 based on the recurrence of neutropenia, fever, and mouth ulcers in a 19-month-old boy, is a rare hematologic disease characterized by regular oscillations in blood neutrophil counts from normal levels (ANC $> 1.5 \times 10^9/L$) to severe neutropenia (ANC $< 0.2 \times 10^9/L$), usually with a cycle length of about 21 days, and lasts for 3–6 days at a time [51]. It has been designated by such terms as “cyclic hematopoiesis”, “human cyclic neutropenia”, and “periodic neutropenia”. During intervals of neutropenia, affected patients exhibit fever, mouth ulcers and are at risk for opportunistic infection. CN affects males and females in equal numbers, and the prevalence is unknown. Most cases of CN are thought to be present at birth (congenital); however, in some cases, the diagnosis may not become obvious until childhood, adolescence, or early adulthood [52, 53].

3.3.1 Etiology and pathogenesis

As mentioned above, CN may be congenital or acquired. Congenital cases include sporadic CN without apparent causes [54, 55], inherited cases transmitted

in an autosomal dominant trait related to mutations in the elastase, neutrophil expressed or gene encoding neutrophil elastase. Heterozygous mutations in *ELANE* gene have been reported in a high frequency of single base pair/amino acid mutations and identified in 80–100% of patients with CN. Neutrophil elastase is synthesized and packaged in promyelocytes at an early stage in neutrophil development. Mutations in the *ELANE* gene induce unfolded protein response-associated apoptosis at the promyelocyte stage and result in ineffective myelopoiesis, and bone marrow fail to maintain consistent production of mature neutrophils. Severe neutropenia recurs when the bone marrow supply is exhausted [56, 57].

3.3.2 Clinical manifestations

The signs and symptoms of CN usually appear at birth or shortly after, and the major clinical problem associated with neutropenia is recurrence of bacterial infections. Opportunistic infections can occur during ANC reduction, with the main clinical manifestations of fever, malaise, headache, anorexia, pharyngitis, tonsillitis, skin infections (**Figure 10**), and swollen lymph nodes, sepsis, ulcers of the oral mucous membrane (**Figure 11**), periodontal inflammation and severe periodontitis (**Figure 12**). when ANC $<500/\mu\text{L}$ for more than 7 days within the cycle, patients regularly have painful mouth ulcers, upper respiratory tract infections, skin abscesses, and suffer from malaise, whereas severe infections are very rare. Oral manifestations usually occur around early childhood, systemic symptoms, such as fever, generally diminish after adolescence, but adults with CN continue to experience oral ulcers, gingivitis, and periodontitis [52, 58].

Figure 10.
Scar formation after slow healing skin infections with a Chinese male (25 years old) with cyclic neutropenia (CN).

Figure 11.
Oral ulcers in the Chinese male (**Figure 10**) with CN.

Figure 12.
Oral manifestations of the CN patient (Figure 10) with serious periodontitis.

3.3.3 Diagnosis

CN diagnosis is often made based upon detailed history taking followed by careful clinical examination and thorough evaluation of all information collected. Then the diagnosis may be confirmed by 2–3 times/week neutrophil count monitoring over six weeks. Individuals with CN should preferably be genetically confirmed by assaying corresponding mutations in the *ELANE* gene [50, 59].

Typical CN diagnostic flow includes:

1. Medical history and physical examination: recurrent infections, oral ulcers, periodontal inflammation;
2. Complete blood cells count: circulating neutrophils vary between zero to almost normal count. ANC < 500 cells/ μ L and occurs every 21 days, lasting 3 to 6 days at a time. Monocytes, platelets, lymphocytes and reticulocytes also cycle with the same frequency. Monitoring of ANC 2 to 3 times per week for 6 weeks (Figure 13);
3. Family history aid to evaluate patients with CN;
4. Genetic testing for mutations in *ELANE*.

3.3.4 Treatment

Prompt, appropriate treatment of the infections associated with CN is important, including symptomatic and supportive treatment. Careful oral and dental care is also required. In addition, individuals with CN should avoid activities that may cause minor injuries [50, 59].

Figure 13.
Diagnostic monitoring the changes in white blood cells (WBC), neutrophils, lymphocytes, and monocytes over a course of three months concerning the CN patient (Figure 10).

Treatment with granulocyte colony-stimulating factor (G-CSF), also called Neupogen, is effective in raising blood neutrophil counts in CN patients. G-CSF treatment with G-CSF in patients with CN does not abrogate cycling, but increases the ANC, shortens the cycle periodicity from the usual 21 days to about 14 days, and prevents serious infections, reduces the symptoms and problems of infections in almost all patients [60].

Professional removal of dental plaque and calculus should be recommended monthly and during the neutropenic episodes, antibiotics may be given in order to prevent oral infection.

3.3.5 Genetic counseling

Genetic counseling is recommended for individuals with inherited forms of CN and their families, in particular the fact regarding 50% chance for CN offsprings from affected individual need to be discussed.

3.3.6 Prognosis

The development of CN is usually benign compared to autoimmune, congenital or idiopathic neutropenia. CN systemic symptoms e.g. recurrent fevers often diminish post adolescence but CN adults remained prone to oral ulcers, gingivitis, periodontitis, and various oral/facial infections [50–52].

3.4 Periodontal Ehlers-Danlos syndrome

Ehlers–Danlos syndromes (EDS) are clinically and genetically heterogeneous rare hereditary disorders categorized by varying degrees of connective tissue fragility, principally affecting skin, ligaments, blood vessels, and internal organs [61, 62]. Main clinical features comprise tissue fragility, skin extensibility, and joint hypermobility.

EDS was named by dermatologists Edvard Ehlers in 1901 and Henri-Alexandre Danlos in 1908. In 2017, the international EDS consortium published a revised EDS classification system with specific emphasis on molecular diagnosis as well as identification of causative genetic variants. The new classification recognizes 13 subtypes and periodontal manifestations are commonly observed in patients with periodontal Ehlers-Danlos syndrome (pEDS), also known as EDS type VIII, Ehlers-Danlos Syndrome, Periodontitis Type or Ehlers-Danlos Syndrome Periodontal Type [63, 64].

pEDS was considered a distinct EDS subtype [65] characterized by severe periodontitis with early disease onset with premature tooth loss, extra-orally includes pretibial hyperpigmented scarring, easy bruising and joint hypermobility. pEDS is an extremely rare EDS subtype with autosomal dominant inheritance. pEDS affects males and females in equal numbers, and the prevalence is unknown, more than 100 pEDS patients were reported [63, 64, 66].

3.4.1 Etiology and pathogenesis

pEDS was caused by heterozygous mutations in complement 1 subunit genes *C1R* and *C1S* [67], and our understanding of the pathophysiological mechanisms underlying these conditions remains very limited. Experimental evidence suggests that it is linked to secretion or release of active C1r serine protease in the extracellular space. This mechanism may cause gingival hyperinflammation in response to mild biofilm accumulation, and subsequently rapidly progressing periodontal destruction [68].

3.4.2 Clinical manifestations

A systematic review was conducted in 2017 about the clinical manifestations of pEDS, and **Table 3** shows the clinical features in 93 pEDS patients with *C1R/C1S* mutation [64, 66].

Features	Prevalence (%)
Oral	
Early severe periodontitis	99
Gingival recession	98
Lack of attached gingiva	93
Skin	
Easy bruising	95
Pretibial discoloration	80
(Mild)skin fragility	80
Prominent vasculature	50
Abnormal scarring	50
Joint	
Joint hypermobility	44
Joint pain	31
Flat feet	30
Scoliosis	22

Table 3.
Clinical features of periodontal Ehlers-Danlos syndrome (pEDS).

Typical clinical features of pEDS are:

1. Oral features: i) early severe periodontitis (**Figure 14**) - the age of first tooth loss was between 2 and 30 years; the age of complete tooth loss was between 14 and 48 years (**Figure 15**); and 16% patients with pEDS (age < 10 years) have prepubertal periodontitis; ii) gingival recession with visible dental root, due to gingival thinning with or without destruction of the underlying periodontal bone; iii) lack of attached gingiva.
2. Skin features: i) easy bruising; ii) pretibial discoloration with nonspecific dermal consistent with trauma and hemosiderin deposition (**Figure 16**); iii) skin fragility; iv) prominent vasculature; v) abnormal scarring (**Figure 16**).
3. Joint features: i) joint hypermobility; ii) joint pain; iii) flat feet; iv) scoliosis.
4. Other features including recurrent infection, hernia, aneurysms, autoimmune disorder, organ rupture and leukoencephalopathy.

Figure 14.
Oral manifestations of periodontal Ehlers-Danlos syndrome (pEDS) patients with serious periodontitis. Left panels (set of nine intra-oral photographs) were from a Chinese male, 24 years with pEDS; right panels were from of his mother who also suffered from pEDS [69].

Figure 15.
*Orthopantomographs (OPG) of pEDS patients with severe alveolar bone loss, atrophic edentulous ridges. A1, A2, A3 were OPG images from the Chinese male (**Figure 14**, left panels) with pEDS in 2008, 2012 or 2017. B1 and B2 were OPG images of his mother with pEDS (**Figure 14**, right panels) in 2008 or 2017. C was OPG image from the affected maternal uncle who also has pEDS in 2017 [69].*

Figure 16.
Dermatological manifestations of pEDS. A and C were that of the Chinese male with pEDS (Figure 14, left panels); B was his mother (Figure 14, right panels) with pEDS [69].

3.4.3 Diagnosis

In the 2017 classification of Ehlers–Danlos syndromes, clinical criteria suggestive for pEDS were defined. Three major criteria and one of the minor criteria must be fulfilled [63].

Major criteria are (1) childhood or adolescence onset severe, intractable peri-odontitis, (2) thin/atrophic attached gingiva, (3) pretibial pigmented scars, and (4) a first-degree relative in family who also meets pEDS clinical criteria.

Minor pEDS diagnostic criteria include easy bruising, joint hypermobility (typically distal joints), skin hyperextensibility and fragility, atypical scarring, proneness to infections, hernias, marfanoid facial features, acrogeria, and prominent vasculature.

A clinical diagnosis of pEDS should be confirmed with genetic testing. pEDS was caused by dominant gain of function mutations in *C1R* or *C1S*.

3.4.4 Treatment

There is no curative treatment for pEDS. Conservative treatments were offered including oral hygiene instruction, periodontal maintenance about every 3 months or more frequently as the dentist/periodontist sees fit, systemic antibiotics, removable dental prostheses, skin sparing, injury or wound avoidance, emotional support. pEDS patients were reported to have high risk of peri-implant disease also so intense implant maintenance is mandatory [63, 64, 70].

3.4.5 Genetic counseling

Transmission is autosomal dominant. Genetic counseling should be offered to the parents of an affected individual informing them of the 50% chance that their offspring could inherit the disease.

3.4.6 Prognosis

Despite meticulous dental care, pEDS patients eventually become edentulous at an early age (mean age 20 years; range 14–48 years). Life expectancy of pEDS individual is otherwise same as their unaffected counterparts [63, 64, 66].

3.5 Hypophosphatasia

Hypophosphatasia (HPP) is a rare, systemic, genetic, metabolic disease with a deficiency in tissue nonspecific alkaline phosphatase (ALP) activity resulting in the extracellular accumulation of its substrates [71]. The clinical presentation of HPP can vary considerably between individuals and includes skeletal problems, muscle weakness, ambulatory difficulties, pain, and dental, neurologic, and renal manifestations. The first case of HPP was reported by the Canadian pediatrician John Campbell Rathbun in 1948 as a new developmental anomaly. The prevalence of HPP was estimated as 1 in 100,000 live births in the Toronto area in Canada; In Europe, the prevalence of severe cases is estimated as 1 in 300,000 [72].

3.5.1 Etiology and pathogenesis

HPP is mainly caused by alkaline phosphatase, biomineralization associated (*ALPL*) gene mutations. At least 300 *ALPL* gene mutations have been reported. The gene encoding tissue non-specific alkaline phosphatase (TNSALP) or the alkaline phosphatase expressed in bone/kidney/liver is located on chromosome 1. The HPP mutation sites are heterogenous and the disease can be inherited in an autosomal dominant or recessive manner. Inactivating mutation of *ALPL* gene leads to decrease TNSALP, which in turn causes accumulation of extracellular TNSALP substrates like phosphoethanolamine, pyridoxal-5'-phosphate and pyrophosphate hence inhibiting hydroxyapatite formation in physicochemical fashion. At the same time, extracellular pyrophosphate induces osteopontin production and the latter inhibits formation of hydroxyapatite. The aforementioned are the main mechanisms that causes early tooth loss and abnormal bone mineralization in HPP patients [73, 74].

3.5.2 Clinical manifestations

HPP is classified into six forms depending on the onset age and the clinical severity [72]. As shown in **Table 4**, HPP may exhibit perinatal presentation: a severe and possibly fatal infantile form within 6 months of life; milder childhood disease: presenting at childhood or late adolescence as early as 6–24 months; adult disease: a form of odontohypophosphatasia; or a rare benign prenatal form. Among them, odontohypophosphatasia, the least severe form without skeletal ailment, characterized by taurodontism with absence of root cementum. The latter is associated with inadequate/ineffective attachment apparatus of the tooth hence giving rise to premature exfoliation of deciduous teeth (**Figures 17 and 18**).

3.5.3 Diagnosis

HPP diagnosis is based on clinical manifestations, laboratory assays, and genetic testing. Clinical manifestations and low alkaline phosphatase activity can confirm a diagnosis of HPP [72, 75]:

1. Prominent clinical symptoms of HPP include the following: i) Dental: premature or nontraumatic tooth loss with the root intact; ii) Skeletal: severe hypomineralization, skeletal deformities, craniosynostosis, rachitic chest, rickets, bowing, short stature, osteomalacia, bone pain, frequent fractures; iii) Muscular: muscle weakness, hypotonia, muscular/joint pain, waddling gait, difficulty walking. Other Symptoms may include: i) Respiratory: respiratory insufficiency, respiratory failure; ii) Neurologic: vitamin B₆-responsive

Clinical Form	Inher- itance	Age of onset	Clinical features	Dental defects	Prognosis
Perinatal lethal	AR	In utero and at birth	Most severe form; Nearly always fatal soon after birth	N/A	Lethal
Benign prenatal	AD	In utero	Mild postnatal course with spontaneous improvement in bony symptoms	N/A	Benign
Infantile	AR	< 6 months	Respiratory failure within weeks to months of birth	Premature loss of deciduous teeth	Mostly lethal
Child-hood	AR (fre- quent) or AD (rare)	≥ 6 months- 18 years	Wide range of severities: Short stature Bone pain/fractures	Premature loss of deciduous teeth	Benign
Adult	AR or AD	≥ 18 years	Stress fractures: metatarsal, tibia Chronic bone pain	H/O premature deciduous tooth loss	Benign
Odonto- hypo-phospha- tasia	AR or AD	Before 4–5 years	Loss of alveolar bone	Early Exfoliation of primary teeth. Hypoplastic Cementum, dentin. Enlarged pulp chambers. Dental caries	Benign

AD, autosomal dominant; AR, autosomal recessive.

Table 4.
Clinical forms of hypophosphatasia (HPP).

Figure 17.
Oral manifestations of a boy at 2- (upper panels)/7-years old (lower panels) with hypophosphatasia (HPP), odontohypophosphatasia form.

Figure 18.
Exfoliated deciduous teeth showing intact root with distinct lack of cementum. Clinical views of the exfoliated mandibular right lateral incisor (tooth 82): the intact root with hypoplasia of the cementum and external apical root resorption (A, B), Cone beam CT image of the tooth 82 (C) with enlargement of the pulp chamber and root canal.

seizures, increased intracranial pressure; iii) Renal: hypercalciuria, nephrocalcinosis, renal damage; iv) Growth: failure to thrive, delayed or missed motor milestone, short stature.

2. Laboratory assays: Low ALP is the biochemical hallmark of hypophosphatasia. When clinical manifestations of HPP are present, checking for low ALP activity can confirm a diagnosis. In patients with a family history of HPP, testing for low ALP at the first presentation of clinical symptoms may be appropriate. **Figure 19** shows the results of age- and gender-adjusted alkaline phosphatase activity.

3. Genetic testing: *TNAP* gene mutations screening is crucial to HPP diagnosis confirmation especially when biochemical and clinical data appear ambiguous. The genetic test is also a useful prerequisite for genetic counseling for families affected by severe HPP who are in need for molecular prenatal diagnosis.

HPP is often misdiagnosed because its signs and symptoms can overlap with those of other disorders, including nutritional rickets, X-linked hypophosphatemic rickets, and osteogenesis imperfecta. ALP can differentiate HPP from nutritional rickets and other metabolic disorders (**Table 5**).

3.5.4 Treatment

HPP treatment varies depending on its stage and classification and focus on supportive therapy to minimize disease-related systemic manifestations [72, 75, 77], including: i) Vitamin B6 for seizures in affected patients; ii) Surgery to relieve intracranial pressure or repair fractures, experts recommend managing pseudo-fractures secondary to hypophosphatasia by internal fixation with a load-bearing

Figure 19.
Age and gender adjusted alkaline phosphatase (ALP) reference ranges.

Biochemical Indicators	Disorder			
	HPP	Nutritional rickets	x-linked hypophosphatemic rickets	Osteogenesis imperfecta
ALP	↓	↑	↑	normal
PLP	↑ or normal	—	↓	—
Calcium	↑ or normal	↓	normal	normal
Phosphate	↓ or normal	↓	↓	normal
Parathyroid hormone	↓ or normal	↓	↓ or normal	normal
Vitamin D	normal	↓	↓ or normal	normal

Table 5.
Alkaline phosphatase (ALP) level differentiating hypophosphatasia (HPP) from other metabolic disorders [76].

device without removal; iii) Pain management, such as NSAIDs. High-dose vitamin D, calcium supplements, and bisphosphonates should not be given when HPP is suspected, as they have been shown to exacerbate symptoms of HPP; iv) Dental care to preserve primary dentition. It is often needed to extract primary teeth with high mobility, but on the permanent dentition it is suggested to follow a more conservative therapy and try to keep all teeth as long as possible.

A causal enzyme therapy replacement with asfotase-alfa was approved by FDA in 2015. Asfotase-alfa improves respiratory insufficiency, bone mineralization, and long-term survival, and has a very good safety profile [75, 78].

3.5.5 Genetic counseling

Severe forms of HPP (perinatal and infantile) are inherited via an autosomal recessive fashion, while milder HPP appears to transmit in autosomal recessive or autosomal dominant manner. The risk of severe HPP recurrence therefore, is considered at around 25% while moderate HPP transmission could be 25% (recessive transmission), 50% (dominant transmission) or varying (usually <50%) due to the variable expressivity of dominant HPP forms [71, 72].

3.5.6 Prognosis

The perinatal HPP is often lethal within days if not weeks after birth with approximately 50% of the affected infants succumbing to respiratory complications. Report on prolonged case survival was lacking for infantile or childhood HPP. Patients affected by adult HPP or odontohypophosphatasia, on the other hand, were expected to enjoy a normal lifespan [71, 72, 75].

4. Conclusion

Periodontal disease and especially periodontitis are often the major clinical characteristic of these genetic disorders. In light of the fact periodontal disease may be the first detectable sign of an undiagnosed genetic disorder and/or indicator for the latter's activity progression, oral health professions shall acquire essential knowledge and be cognizant regarding the rare occasions that these diseases could be encountered. In this chapter, we discussed some genetic disorders associated to periodontal disease, we hope this work can help dental practitioners to be familiar with these genetic disorders and their negative impacts on the periodontal tissues hence poor oral/periodontal health of the affected.

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Conflict of interest

The authors declare no conflict of interest.

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