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Rare Genetic Disorders Affecting the Periodontal Supporting Tissues in Adolescence

Ines Kapferer-Seebacher[1], *Lena Foradori*[1], *Johannes Zschocke*[2*†] *and Reinhard Schilke*[3*†]

[1] *Department of Dental and Oral Medicine and Cranio-Maxillofacial and Oral Surgery, University Hospital for Dental Prosthetics and Restorative Dentistry, Medical University of Innsbruck, Innsbruck, Austria,* [2] *Division of Human Genetics, Medical University of Innsbruck, Innsbruck, Austria,* [3] *Department of Conservative Dentistry, Periodontology and Preventive Dentistry, Hannover Medical School, Hannover, Germany*

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***Correspondence:**
Johannes Zschocke
johannes.zschocke@i-med.ac.at
Reinhard Schilke
schilke.reinhard@mh-hannover.de

† These authors have contributed equally to this work and share senior authorship

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In adolescents periodontal destruction may be the primary manifestation of an as yet unrecognized rare systemic disease, and it may be up to the periodontist to make the correct tentative diagnosis. Many genetic diseases that present with primary periodontal manifestations in adolescence affect immune function, sometimes with only mild or absent systemic features. They include periodontal Ehlers-Danlos syndrome (lack of attached gingiva, various connective tissue abnormalities), Papillon-Lefèvre syndrome (palmoplantar hyperkeratosis), and plasminogen deficiency (fibrin deposition within mucous membranes). Other immune disorders with severe periodontitis manifesting in adolescence are usually diagnosed in early childhood due to unmistakeable systemic features. They include Cohen syndrome (developmental disorder, truncal obesity, and microcephaly), Hermansky-Pudlak Syndrome (oculocutaneous albinism, bleeding diathesis, and other systemic manifestations), glycogen storage disease type 1b, and Chediak-Higashi syndrome (pyogenic infections, albinism, and neuropathy). The structural integrity of periodontal tissue is affected in genodermatoses such as Kindler syndrome, a type of epidermolysis bullosa. In primary hyperoxaluria, inflammatory periodontal destruction is associated with renal calculi. Breakdown of periodontal tissues independent of dental plaque biofilm-induced periodontitis is found in hypophosphatasia (highly variable skeletal hypomineralization) or isolated odontohypophosphatasia, hypophosphatemic rickets and primary hyperparathyroidism. Finally, alveolar osteolysis mimicking localized periodontitis may be due to neoplastic processes, e.g., in neurofibromatosis type 1 (typical skin features including café au lait macules and neurofibromas), Langerhans cell histiocytosis (locally destructive proliferation of bone marrow-derived immature myeloid dendritic cells), and Gorham-Stout disease (diffuse cystic angiomatosis of bone).

Keywords: orphan diseases, periodontitis, adolescence, osteolysis, immune deficiency, bone metabolism

INTRODUCTION

The current "2017" classification of periodontal and peri-implant diseases and conditions distinguishes "periodontitis" from necrotizing periodontal diseases, periodontitis as a manifestation of systemic disease, and non-inflammatory periodontal manifestation of systemic disease (1, 2). Periodontitis in general is a highly prevalent condition characterized by inflammatory destruction of periodontal tissues (2). In most affected individuals it is a multifactorial disorder caused by complex interactions between various environmental and genetic factors that in combination determine the variability of disease onset, progression and severity. Different forms of the disease previously recognized in the classification of 1999 as "chronic" or "aggressive," and in the classification of 1989 as "adult," "refractory" and "early-onset periodontitis" —further including "prepubertal," "juvenile," and "rapidly progressive periodontitis" —are now grouped under a single category ("periodontitis") (2). Genetic predisposition in this context means that an individual has a constitutional susceptibility to develop periodontitis which only becomes manifest in conjunction with other pathogenic factors. Not all persons harboring the genetic risk factors will develop the disease (3).

In contrast, there are a number of specific rare syndromes that are associated with periodontitis in most or all affected individuals irrespective of other risk factors. Many of them are monogenic diseases caused by alterations of specific genes. They are usually rare diseases, i.e., they have a prevalence of <1 case per 2,000 in the population (4). Approximately 8,000 different rare diseases have been identified so far, with up to 14% showing periodontal involvement (5). In the 2017 classification, conditions associated with presentation of severe periodontitis are grouped in the category "Periodontitis as a Manifestation of Systemic Disease." Other systemic conditions that affect the structural integrity of the periodontal apparatus independently of biofilm-induced inflammatory destruction—including neoplastic disorders but also rare genetic diseases—are grouped as "Systemic Diseases or Conditions Affecting the Periodontal Supporting Tissues" (1).

In adolescents, i.e., the age range of 10–19 years (6), the finding of the correct periodontal diagnosis is quite challenging. Slowly advancing multifactorial periodontitis has to be differentiated from rapidly progressing forms with early onset as well as rare systemic diseases and conditions affecting the periodontal supporting structures (**Figure 1**). Incipient loss of periodontal support due to general/multifactorial periodontitis is common in most teenage populations and is causally linked to the presence of local irritants. Usually only minor loss of periodontal attachment is found (8). Botero et al. summarized several clinical studies from Latin America and concluded that periodontitis affects up to 10% of young Latin Americans, with large fluctuations of prevalence and severity within the studies (9). Among Chilean adolescents aged 12–21 years, clinical attachment loss ≥1 mm was seen in 69.2%, ≥2 mm in 16%, and ≥3 mm in 4.5% of cases (10).

Around puberty a subset of otherwise healthy individuals may experience rapidly progressing periodontal destruction, previously called early-onset or aggressive periodontitis, which may be localized or generalized. This has been estimated to affect ∼0.1% of white populations and up to 2.6% of black populations (8).

In some adolescents, periodontal attachment loss is a manifestation of defined monogenic conditions. In case of mild systemic features the underlying cause may not yet been identified, and it may be the task of the periodontist to recognize the abnormality in order to make a tentative diagnosis.

Here we present an overview of rare genetic diseases which still were not be diagnosed in adolescents and are associated with an initial diagnosis of periodontal involvement in this age group (**Table 1**). Genetic diseases that typically present with perpubertal onset of periodontal destruction are excluded or mentioned only briefly.

PERIODONTITIS AS MANIFESTATION OF SYSTEMIC DISEASES

Immunologic Disorders

Many of the systemic disorders that typically present periodontitis at an early age affect immune function. They include primary immune deficiencies with congenital defects of phagocyte number and/or function, diseases of immune dysregulation, and other well-defined immunodeficiency syndromes (19, 35). Severe immune deficiencies are usually diagnosed by pediatricians in early childhood and are not included in this review. Some disorders of immune function—although hereditary—may have their onset in adolescence or youth, and affected individuals may therefore still lack systemic diagnosis. These disorders are described below.

Periodontal Ehlers-Danlos syndrome (OMIM 130080, 617174) is a specific Ehlers-Danlos entity with autosomal-dominant inheritance caused by heterozygous mutations in complement 1 subunits *r* and *s* (*C1S, C1R*). The defining clinical feature is early severe periodontitis diagnosed at a mean age of 14 years (11). Systemic features range from mild or absent to severe with organ or vascular ruptures. Pretibial hyperpigmentation found in 80% of affected individuals is the second defining feature and is caused by hemosiderin deposition (36). Bruising out of proportion to trauma (>90%) and joint hypermobility of mostly distal joints (∼40%) have been reported. The dentist can distinguish periodontal Ehlers-Danlos syndrome from other types of periodontitis by the striking lack of attached gingiva causing oral tissue fragility and predisposing to gingival recession (**Figure 2**). Pattern of alveolar bone loss was described as localized to any region, proceeding in a domino effect from one tooth to the next. Some individuals report on early loss of some primary teeth. For details see (37, 38). The diagnosis of pEDS is reached by molecular genetic analysis with identification of specific heterozygous mutations in the *C1S* or *C1R* genes.

Papillon-Lefèvre syndrome (OMIM 245000) is caused by homozygous or compound heterozygous mutations in the cathepsin C gene (*CTSC*) encoding a cysteine protease involved in a variety of immune and inflammatory pathways. Papillon-Lefèvre syndrome usually presents with severe periodontitis of

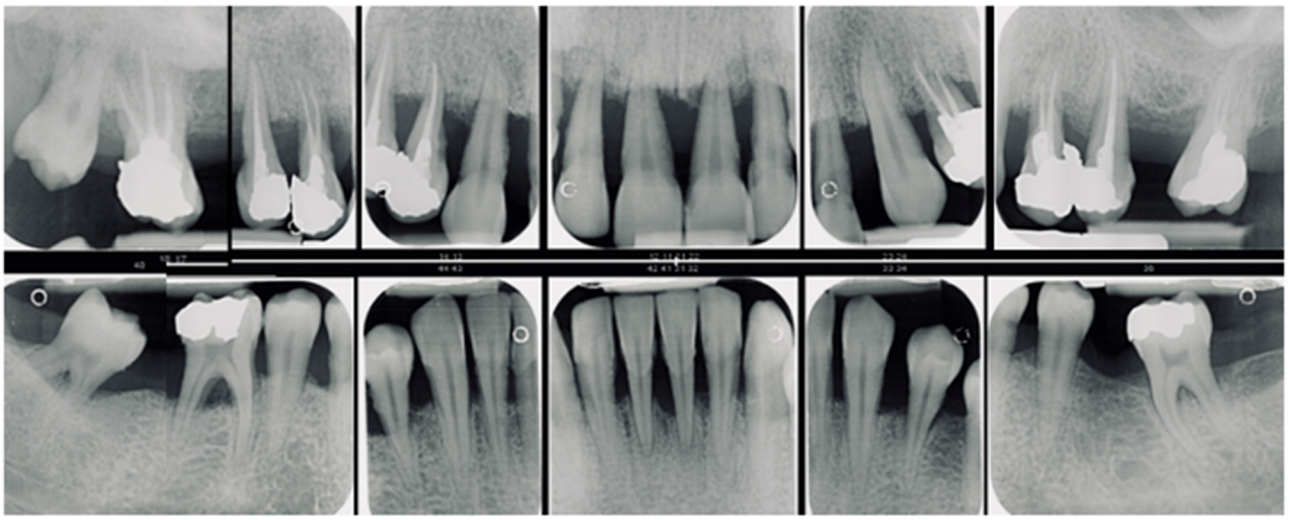

FIGURE 1 | Generalized periodontitis with early onset in a female patient aged 18 years. With a prevalence of 0.1% in white populations it is more likely to see young people with generalized complex periodontitis than an individual with a rare genetic disease. However, the detection of rare diseases increases with physicians awareness (7) and although the prevalence of each individual orphan disease may be low, taken together they affect up to 5% of the general population (7).

primary and secondary teeth in early childhood in association with palmoplantar hyperkeratosis. In a subset of individuals mutations in *CTSC* present as an isolated finding of periodontitis with onset in adolescence (16). The diagnosis is again reached by molecular genetic analysis.

Autosomal-recessive *plasminogen deficiency* (OMIM 217090) is caused by homozygous or compound heterozygous mutations in the gene encoding plasminogen (*PLG*). Plasminogen is not only a complement inhibitor but also a broad-spectrum proteolytic factor either by directly degrading extracellular matrix proteins, e.g., laminin, fibronectin and proteoglycans, and indirectly by activating latent metalloproteinases (39). Plasminogen deficiency is associated with massive fibrin deposition within mucous membranes due to the absence of fibrin clearance by plasmin, leading to a so-called "ligneous" conjunctivitis (80% of patients), ligneous gingivitis (34%) and ligneous periodontitis, characterized by extensive generalized periodontal breakdown in association with pseudomembranous gingival enlargement (12–15). The diagnosis is confirmed by the identification of biallelic pathogenic *PLG* mutations in molecular genetic analysis.

Other immunologic disorders described in the literature with onset of severe periodontitis in adolescence are usually associated with typical systemic manifestations diagnosed in early childhood. For example, autosomal-recessive *Cohen syndrome* (MIM 216550) predisposes to periodontitis with early onset in adolesence or youth with alveolar bone loss of up to 10 mm (18). Due to characteristic systemic features—failure to thrive, developmental delay, truncal obesity, early-onset hypotonia, microcephaly, joint hypermobility and characteristic facial features—it is usually diagnosed in early childhood (40). The same is true for *Hermansky-Pudlak Syndrome* (OMIM 203300), comprising a group of rare autosomal recessive disorders with oculocutaneous albinism, bleeding diathesis, and in some individuals, granulomatous colitis, severe chronic neutropenia and immunodeficiency, and sometimes fatal pulmonary fibrosis (41). It is due to defects in lysosome-related organelles and may be caused by pathogenic variants in at least 10 different genes (42). Hermansky-Pudlak syndrome is confirmed by molecular analysis of the candidate genes by massive parallel sequencing.

Some children affected by monogenic diseases associated with severe chronic neutropenia such as glycogen storage disease type 1b, Chediak-Higashi syndrome, and others are typically treated with granulocyte colony stimulating factor (G-CSF) which prevents periodontitis as manifestation of the disease in the permanent dentition. Non-regular administration by the patient or failure to adjust the G-CSF dose to the body weight or the individual response can lead to periodontal destruction in adolescence. For patients with severe chronic neutropenia who do not respond to G-CSF treatment, hematopoietic stem-cell transplantation is currently considered the only treatment available (43).

Genodermatoses

A second category of genetic diseases manifesting with severe periodontitis in adolescence are conditions affecting the structural integrity of periodontal tissues. An example is *Kindler syndrome*, a type of epidermolysis bullosa characterized by impaired adhesion of gingival junctional epithelium to the tooth which predisposes to severe generalized periodontitis in teenage years (44, 45). Due to striking systemic features with acral blisters and skin atrophy the syndrome is usually diagnosed in early childhood. Kindler syndrome is inherited as an autosomal recessive disease caused by mutations in the *FERMIT1* gene.

TABLE 1 | Periodontitis as manifestation of systemic diseases with primary onset in adolescence.

Disease name	Systemic diagnosis in childhood	Frequency of associated periodontal attachment loss	Age of onset (attachment loss)	Further specific oral features	Main manifestations—non-oral	References (first author, year)
Immunologic Disorders						
Periodontal Ehlers-Danlos syndrome	No	99% of affected	Mean age: 14 years	Lack of attached gingiva Gingival recession	Pretibial hemosiderin deposition	(11)
Plasminogen deficiency	No	Single individuals	Range 8–26 years	Chronic mucosal pseudomembranous enlargement	Ligneous conjunctivitis	(12–15)
Papillon-Lefevre syndrome	Usually yes	Almost always	In a subset of individuals: onset in adolescence	None	Palmoplantar hyperkeratosis (maybe mild or missing)	(16)
Glycogen storage disease type Ib	Yes	More prevalent in untreated individuals	Dependent on treatment of neutropenia	None	Hypoglycemia, hepatomegaly, growth failure, recurrent infections	(17)
Cohen Syndrome	Probably	Unclear	Range 20–57 years	None	Failure to thrive, developmental delay, truncal obesity, early-onset hypotonia, microcephaly, joint hypermobility and characteristic facial features	(18)
Hermansky-Pudlak Syndrome	Probably	Unclear	In youth	None	Oculocutaneous albinism, bleeding diathesis	(19)
Genodermatosis						
Kindler epidermolysis bullosa	Yes	Frequent	Teenage years	Thin and fragile gingiva predisposing to gingival recession, ulcers, angular cheilitis, microstomia due to adhesions of mouth corners	Skin fragility and acral blister formation beginning at birth, diffuse cutaneous atrophy, photosensitivity, poikiloderma, diffuse palmoplantar hyperkeratosis, and pseudosyndactyly	(20–23)
Bone Metabolism Disorders						
Hypophosphatemic rickets	Dependent on age of onset	Appr. 60% of affected	Variable age of onset	Spontaneous periapical abscesses and fistulae occurring without any history of trauma or dental decay short roots, large pulp chambers, extended pulp horns and sometimes taurodontism	Short stature, osteomalacia, bone pain, osteoarthritis, pseudofractures, stiffness	(24, 25)
Adult Hypophosphatasia	No	Unclear	Variable age of onset	Non-inflammatory loss of alveolar bone Enlarged pulp chambers Taurodontism	Fractures, pseudofractures, chronic muscle, joint and bone pain, osteomalacia, pseudogut	(26, 27)
Odontohypophosphatasia	Mostly	Always	Variable age of onset	Early loss of primary teeth Impaired development of alveolar bone during vertical growth of teeth	None	(26, 27)

(Continued)

TABLE 1 | Continued

Disease name	Systemic diagnosis in childhood	Frequency of associated periodontal attachment loss	Age of onset (attachment loss)	Further specific oral features	Main manifestations—non-oral	References (first author, year)
Hereditary Hyperparathyroidism	No	Varying frequency and severity	May occur at any age	Loosening and drifting of teeth, widened periodontal ligament spaces, alveolar bone loss, partial loss of lamina dura, obliteration of pulp chambers by pulp stones, alterations in dental eruption, malocclusion, spacing of teeth, teeth become sensitive to percussion and mastication, soft tissue calcifications, caries, sialolithiasis, mandibular tori, and jaw bone pain	Fatigue, exhaustion, weakness, polydipsia, polyuria, nocturia, joint pain, bone pain, constipation, depression, anorexia, nausea, heartburn, nephrolithiasis, hematuria	(28, 29)
Neoplastic Disorders						
Neurofibromatosis type 1	Maybe	Rarely	May occur at any age	Localized periodontal destruction due to neurofibromas invading the alveolar ridge	Neurofibromas and/or café au lait macules	(30)
Langerhans cell histiocytosis	Maybe	Mandibula is involved in 40% of cases	Particularly frequent in children aged 5–15 years	Painful erythematous swelling along with tooth mobility, sometimes non-healing gingival ulcers	In some cases accompanied with fever	(31)
Gorham-Stout-Syndrom	Maybe	In mandibular and maxillofacial GSD always	Any age group, but has mainly been reported in children and youth	Pain, loose teeth, sense of floating teeth upon biting and occlusal disorder, fractures	Facial deformity	(32, 33)
Others						
Primary hyperoxaluria	Maybe	Always	7–55 years of age	Destruction of the periodontal tissues, root resorption	Renal failure	(34)

Others

Primary hyperoxaluria (MIM 259900) is an autosomal-recessive deficiency of peroxisomal alanine glyoxylate aminotransferase encoded by the *AGXT* gene resulting in reduced or absent conversion of glyoxylate to glycine and leading to accumulation of calcium oxalate in various bodily tissues, especially the kidney. Inflammatory periodontal destruction with primary hyperoxaluria has been attributed to a foreign body reaction caused by deposition of calcium oxalate crystals in periodontal tissues (46–48). External root resorptions were common in all case reports. Reported age of onset ranges from 7 to 55 years (34). The diagnosis is confirmed by increased urinary concentrations of oxalate and glycate or by molecular genetic studies.

RARE DISEASES OR CONDITIONS AFFECTING THE PERIODONTAL SUPPORTING TISSUES

Some systemic conditions mimic the clinical presentation of periodontitis although breakdown of periodontal tissues is independent of dental plaque biofilm-induced periodontitis (1, 49). Some may manifest in adolescence.

Disorders of Bone Metabolism

Hypophosphatasia (MIM 146300) is a rare genetic disorder caused by mutations in *ALPL* encoding tissue-non-specific alkaline phosphatase. It is usually inherited as an autosomal-recessive trait, some mutations may cause an attenuated late onset form. The disease is characterized by mineralization defects of bone and teeth. Early tooth loss is not caused by inflammatory bone loss but rather by cement dysplasia resulting in compromised periodontal attachment (50). In most cases, the reduced height of the bony alveolar attachment in the first dentition and early mixed dentition is a consequence of the absence of alveolar process development during the vertical growth of the teeth. The severity and age of onset is highly variable ranging from severe intrauterine onset skeletal hypomineralization and deformities to *odontohypophosphatasia*, i.e., isolated tooth loss without skeletal alterations that may present at any age (51). Independent of the highly variable clinical presentation, most affected individuals show premature loss of

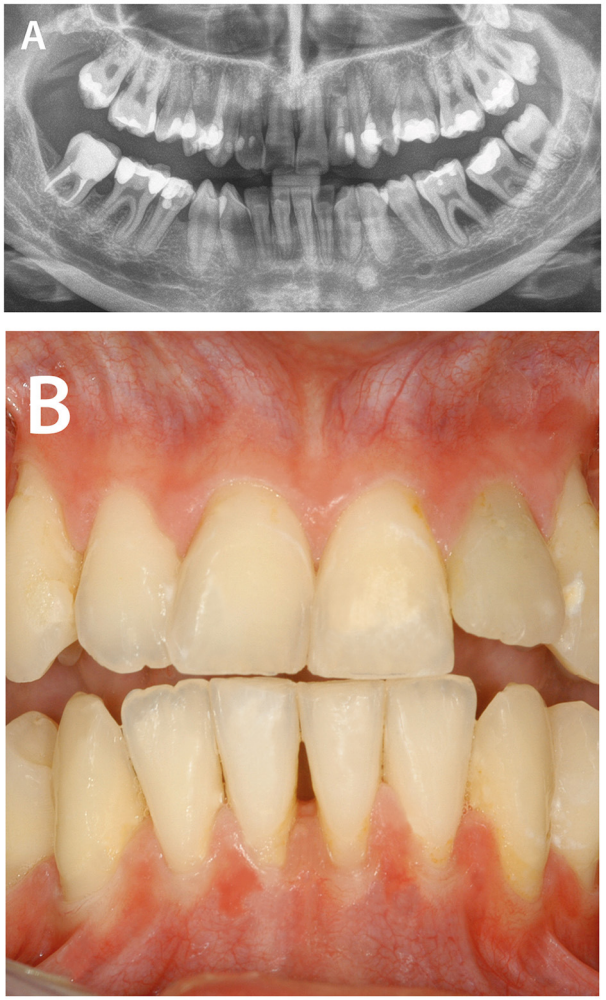

FIGURE 2 | Periodontitis as manifestation of systemic diseases. Periodontal Ehlers-Danlos syndrome is caused by heterozygous mutations in complement 1 subunit genes *C1R* and *C1S* leading to hyperactivation of the classical complement pathway. The defining clinical feature is early severe periodontitis diagnosed at a mean age of 14 years. **(A)** Pattern of alveolar bone loss was described as localized to any region, proceeding in a domino effect from one tooth to the next. **(B)** The clinician can distinguish periodontal Ehlers-Danlos syndrome from other types of periodontitis by the lack of attached gingiva causing oral tissue fragility and predisposing to severe gingival recession.

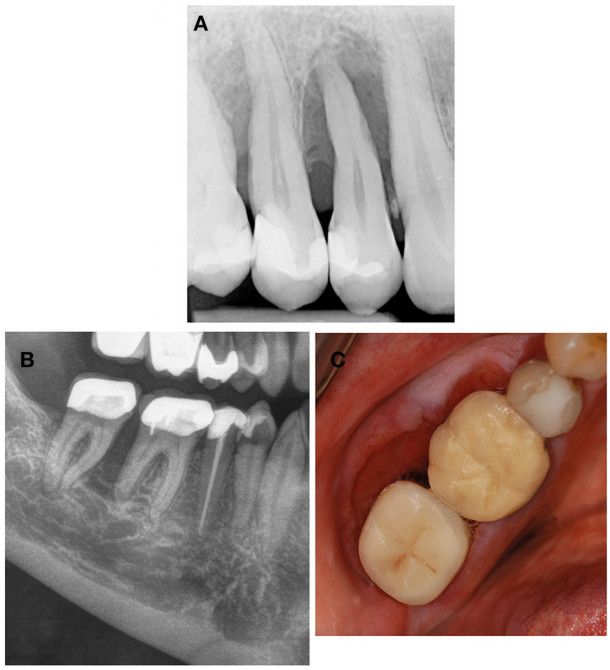

FIGURE 3 | Systemic diseases and conditions affecting the periodontal supporting tissues—neoplastic disorders. **(A)** Neurofibromatosis type 1 is a neurocutaneous disorder caused by mutation or deletion in the *NF-1* gene and affecting the cell growth of neuronal tissues. Plexiform neurofibromas can also invade the alveolar ridge mimicking localized periodontitis. **(B,C)** Squamous cell carcinoma invading the alveolar bone is a differential diagnosis to benign neoplastic disorders but also to localized periodontitis.

deciduous teeth at <3 years of age, affecting all primary teeth or just those in the incisor–canine region (26). The condition may be recognized by reduced serum concentrations of alkaline phosphatase (AP) and is confirmed by mutation studies. For reviews see (26, 27).

Genetic disorders of bone metabolism like *hypophosphatemic rickets* and *primary hyperparathyroidism* are associated with varying frequency, severity, and age of onset of periodontal involvement, depending on etiology, systemic treatment, and as yet unknown factors (52). Increased risk for severe periodontal breakdown in hypophosphatemic rickets is probably caused by cementum hypoplasia and altered alveolar bone repair (53, 54). The most frequent type is X-linked hypophosphataemia due to mutations in the X-chromosomal *PHEX* gene, with manifestation in both males and females, but hypophosphatemic rickets can also be caused by mutations in a range of autosomal genes with dominant or recessive inheritance. For primary hyperparathyroidism the evidence is somehow contradictory. Hyperparathyroidism *per se* does not seem to be associated with a higher prevalence of periodontitis (55, 56). However, high serum levels of Ca^{2+} ($\geq$1.51 mmol/L) are associated with an increased probability of tooth extractions (56). Loosening and drifting of teeth due to widened periodontal ligament spaces and partial loss of lamina dura may be misdiagnosed as periodontitis (28). Other intraoral manifestations of hyperparathyroidism include pulp calcifications, dental sensitivity to percussion and mastication, soft tissue calcifications, mandibular tori, and jawbone pain (28, 29). Primary hyperparathyroidism is associated with pathogenic variants in a range of genes.

Neoplastic Disorders

Rare genetic disorders causing neoplastic proliferation may present in adolescence as alveolar osteolysis mimicking localized periodontitis or other neoplastic processes like squamous cell carcinomas (**Figure 3**).

Neurofibromatosis type 1 (MIM 162200) (Von Recklinghausen disease) is an autosomal-dominant neurocutaneous disorder affecting the cell growth of neuronal tissues. It is caused by heterozygous mutations in the *NF1* gene. Typical skin features

include café au lait macules that increase in number and size, axillary and/or inguinal freckles, and the development of dermal neurofibromas which usually have led to the diagnosis before adolescence. There is a range of other manifestations but individuals with only mild neurocutaneous features may escape diagnosis in childhood. Oral manifestations are found in about 72% of the patients; they include impacted or ankylosed teeth, abnormalities in form or number of teeth, as well as oral plexiform neurofibromas (30). The latter commonly affect the tongue, palate, buccal mucosa, floor of the mouth, gingiva or lips, and can also invade the alveolar ridge mimicking localized periodontitis (30) (**Figure 3**).

Langerhans cell histiocytosis is a benign but locally destructive entity that represents true neoplastic proliferation of bone marrow-derived immature myeloid dendritic cells but lacks malignant changes histologically. It is a non-hereditary disorder associated with somatic Langerhans cell mutations that activate the cellular MAPK/ERK signaling pathway and is particularly frequent in children aged 5–15 years (57). The mandibula is involved in 40% of cases, presenting as painful erythematous swelling along with tooth mobility, in some cases accompanied with non-healing gingival ulcers and fever (31). From a radiographic point of view, a similarity of bone lesions to a wide spectrum of diseases was described, such as odontogenic cysts, certain benign and malignant tumors, periapical lesions, and alveolar bone loss (58).

Gorham-Stout disease (synonyms: diffuse cystic angiomatosis of bone; disappearing / vanishing / phantom bone disease) (OMIM 123880) is a rare disorder with unknown etiology, characterized by progressive osteolysis associated with angiomatous proliferation and dilation of lymphatic vessels. It can affect any bone of the human body leading to partial or complete resorption (59). Gorham-Stout disease may start at any age but is most commonly diagnosed in children and young adults (average age of diagnosis is 25 years) (33). Mandibular or maxillofacial involvement is associated with pain, loose teeth, sense of floating teeth upon biting and occlusal disorder, spontaneous fractures, and facial deformity (32, 33, 60).

DISCUSSION

Due to the rarity and diversity of genetic disorders manifesting in the oral and maxillofacial region, even specialist dentists find it difficult to remember and diagnose them (61). In youth, severe multifactorial periodontitis may be difficult to differentiate from rare genetic diseases with sometimes only mild systemic manifestations. Using a systematic approach—as discussed below for adolescents aged 10–19 years—may assist in finding the correct periodontal diagnosis.

An adolescent with severe periodontal destruction should first of all receive detailed clinical and radiologic periodontal diagnostics followed by a critical assessment of the oral soft tissue quality. Thin, translucent and fragile gums or missing frenula may point to connective tissue disease like Ehlers-Danlos syndromes. Pseudomembranous gingival hypertrophy is a typical sign of plasminogen deficiency. Missing inflammatory signs in association with generalized periodontal destruction points to cement dysplasia. Radiologic analysis may elucidate further dental features giving a hint to the underlying systemic diseases, e.g., taurodontism has been reported as additional feature of *CTSC* mutations (16), pulp calcifications are associated with renal disorders and connective tissue diseases like Ehlers-Danlos syndromes (62, 63).

Histologic analysis of extracted teeth or soft-tissues and in case of osteolytic processes bone marrow biopsies will point to the right diagnosis.

Periodontists have to take a detailed medical history with special focus on immunologic diseases, systemic manifestations of bone metabolism disorders like bone, joint or muscle pain, features of connective tissue diseases like bruising out of proportion to trauma and joint hypermobility, and dermatologic problems. An accurate family health history as well as drawing a pedigree are valuable tools to illustrate how conditions are passed down through generations and to define the pattern of inheritance (autosomal-recessive, autosomal-dominant, X-linked, and mitochondrial).

Inspection of hair and skin may give a hint to ectodermal syndromes, connective tissue diseases or genodermatoses like Papillon-Lefèvre and Haim-Munk syndrome. Specialized pediatricians, dermatologists and/or geneticists may be helpful with the further clarification of the diagnosis. However, the periodontist has to be aware of that competent genetic analysis relies on precise clinical diagnosis.

Conditions that increase the risk of complex and biofilm-associated periodontitis were not included in the present review. For example, it was previously shown that systemic lupus erythematosus and familial scleroderma are associated with an increased risk of biofilm-induced periodontitis, with a risk ratio of 1.76 (95% CI 1.29–2.41) and 1.84 (95%CI 1.29–2.41), respectively (64, 65). In the authors' opinion the diagnosis in these cases should be (multifactorial) "periodontitis" as the systemic disease represents a risk factor for periodontitis rather than a specific monogenic cause. In the end this is a purely semantic discussion which neglects the fact that monogenic and multifactorial conditions represent a pathogenetic spectrum which cannot be forced into simple clearly separated categories. The majority of clinical phenotypes are due to a variety of (often as yet unknown) genetic variants of variable penetrance and population frequencies in conjunction with various non-genetic influences in the individual case.

This does not negate the need to make a rapid, precise diagnosis in individuals with a specific monogenic disease. Most of these conditions can now be confirmed with widely available massive parallel (next generation) DNA sequencing approaches. Nevertheless, surveys of patients and physicians found that it takes more than a decade to reach a diagnosis for a rare disease after onset of symptoms (66, 67). Specialist dentists have to be aware of their responsibility in diagnosing rare diseases as young people with orphan diseases may still be undiagnosed especially when systemic features are mild. With precise clinical descriptions of oral features and basic knowledge on pathomechanisms they can provide valuable information to pediatricians and geneticists for finding the right systemic diagnosis.

AUTHOR CONTRIBUTIONS

IK-S designed and directed the project, did the primary analysis of the results, and wrote the first version of the manuscript. LF and JZ substantially contributed to the literature search and revised the manuscript. RS aided in interpreting the results and worked on the manuscript. All authors contributed to the article and approved the submitted version.

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