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Periodontal Disease in Children

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Periodontal disease among children and adolescents consists mainly of gingivitis.[1] The prevalence of marked periodontal destruction is low in young individuals. In the USA, the prevalence of severe periodontal attachment loss on multiple teeth among children and young adults is between 0.2% and 0.5%. Although periodontitis is more common in adults, it is more aggressive when present in children and adolescents.[2] Periodontal diseases in young individuals can develop as a consequence of a local or a systemic factor. Local factors include plaque, calculus, orthodontic appliances, orthodontic appliances, and dental anomalies (ie, enamel projections, enamel pearls). Systemic factors include malnutrition, systemic diseases, gender, race, hormones, and smoking.[3,4]

Most periodontitis cases among children and adolescents occur as a manifestation of certain systemic diseases with an impaired immune system that compromises their response to microbial plaque and increases the likelihood of periodontal bone loss and premature loss of their teeth.[1,4] Neutrophils play a major role in the human defense system against bacterial infections and any depletion or dysfunction in its adherence and chemotaxis as seen in neutropenia, Down syndrome (DS), Papillon-LeFevre syndrome (PLS), and leukocyte adhesion deficiency (LAD) can result in oral disease. The oral manifestations associated with neutrophils dysfunction are well documented and include oral mucous membrane infection, gingivitis, periodontitis, and premature loss of teeth manifestation.[5,6] This review focuses on these disorders.

Down Syndrome

DS is the most common chromosomal abnormality in humans. For every 10,000 live births in the US, 9.2 babies are born with DS. Studies reported an increased prevalence and severity of periodontal disease in persons with DS and persons younger than 35 years of age; the prevalence varied between 58% and 96%.[7-10] Most investigators agree that oral hygiene is poor but not commensurate with the severity of the periodontal dis-

ease.[10,11] Increased prevalence of acute necrotizing ulcerative gingivitis can result in the progression of periodontal disease.[12] Irregular anatomical morphology of the teeth, including short roots and increased prevalence of fused roots, are thought to be involved.[13] Increased levels of PGE_2, mediator of bone demineralization, and increased matrix metalloproteinases that can degrade type IV collagens, laminin, gelatin, fibronectin, and elastin also have been linked to the tissue destruction associated with periodontal disease.[14] This, together with impaired cell-mediated and humoral immunity, a defective neutrophil chemotaxis and phagocytic ability,[15] reduced number of B lymphocytes in peripheral blood, as well as reduced and immature T lymphocytes, can lead to inadequate reaction to bacteria.[1,15,16]

Leukocyte Adhesion Deficiency

LAD1

LAD1 is a rare inherited autosomal-recessive immunodeficiency disorder caused by deficiency of the leukocyte beta 2 integrin receptor CD11/CD18.[17] CD11/18 integrins are selectively expressed by leukocyte and are essential for leukocyte adhesion and transendothelial migration, and phagocytosis. The severity of the disease among patients with LAD1 is directly related to the degree of CD18 deficiency.[18] The phenotypes of LAD are described as severe patients, expressed as <1%, and moderate, expressed as 1% to 5% of normal surface values of the CD18. Patients affected with the severe form of the disease tend to have more severe recurrent life-threatening systemic infections and often die in infancy, whereas in the moderate phenotypes, such life-threatening infections are infrequent and patients' survival rate is prolonged.[19] Patients with LAD have recurrent bacterial and fungal infections of the skin, oral and genital mucosa, respiratory and intestinal tract, delayed separation of the umbilical cord, diminished pus formation, impaired wound healing, leukocytosis, and irregularities of adherence dependent leukocyte functions.[18,19] Oral manifestations of LAD include generalized periodontitis with rapidly progressive alveolar bone loss (primary and permanent dentitions), premature tooth loss, and severe gingival inflammation with an onset during or following the eruption of the primary dentition. Gingival biopsies in these patients showed a marked peripheral blood leukocytosis with minimal or no infiltration of neutrophils into the inflamed extravascular periodontal areas.[20,21]
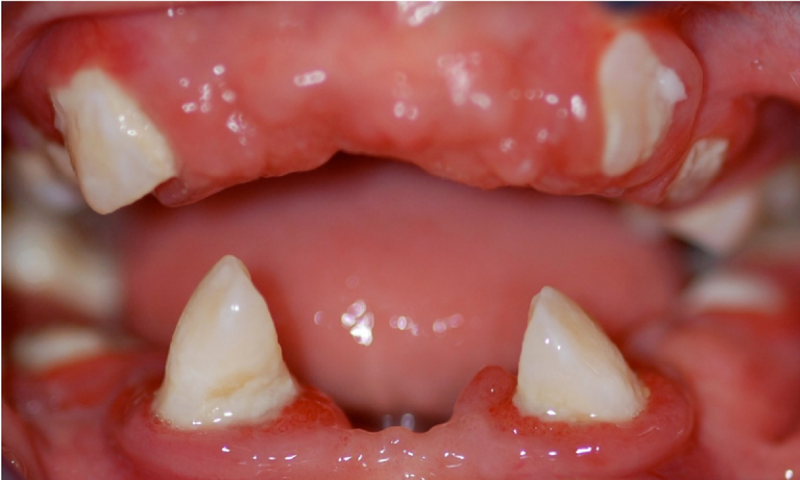
FIG 1. Permanent dentition showing significant plaque accumulation and severe periodontal destruction. (Color version of figure is available online.)

LAD2

The clinical characteristics of LAD2 (OMIM 266265) resemble the classic LAD syndrome (LAD1); however, the infections are not life-threatening and there is no delay in the umbilical cord separation. Furthermore, patients with LAD2 present other abnormal features, such as growth and mental retardation. The leukocytes of patients with LAD2 have normal levels of CD11/CD18 but are found deficient in SLeX, a fucose-containing carbohydrate and a ligand necessary for selectin-mediated neutrophil adhesion to the endothelial cell.[22]

Papillon-Lefevre

PLS was first described in 1924.[23] PLS is a rare autosomal recessive genetic syndrome characterized by hyperkeratotic skin lesions and severe periodontitis that begins in early childhood. Hyperkeratosis typically affects the palms and soles of the feet, with involvement of the elbows and knees in ~ 80% of cases. Periodontitis occurs soon after eruption of the primary teeth, with dramatic gingival inflammation accompanied by rapid destruction of alveolar bone and periodontium, leading to premature loss of both primary and permanent dentitions (Figs 1 and 2). It affects both genders equally and has no racial predominance, and is found in racial and ethnic populations worldwide. The prevalence of PLS is greater in ethnic groups with high incidence of consanguineous marriages.[23,24]
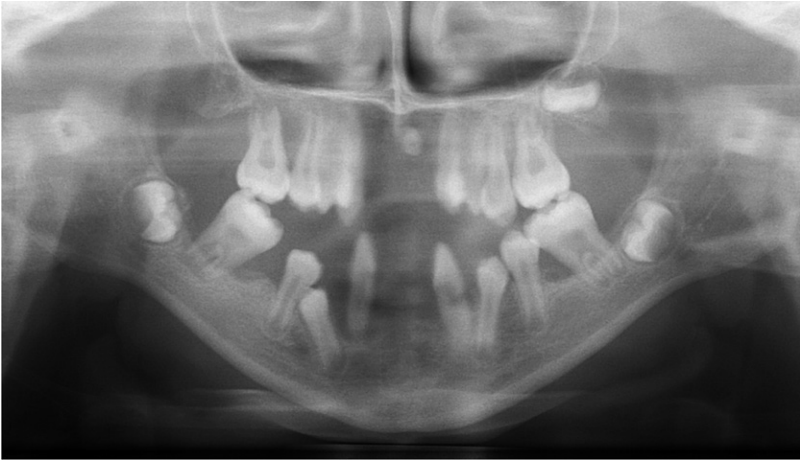
FIG 2. Panoramic radiograph reflecting bone loss in a Papillon LeFevre case.

The genetic basis for PLS is due to mutations that affect both alleles of the cathepsin C gene (CTSC) which is located on chromosome 11q14.[25] In addition to PLS, cathepsin C gene mutations are also etiologic for Haim-Munk syndrome as well as some cases of aggressive periodontitis and prepubertal periodontitis in children.[26] The CTSC gene encodes a proteinase enzyme that functions to cleave and activate other proteins. Through its ability to activate other proteins, cathepsin C plays a role in the development and maintenance of the skin, the regulation of immune and inflammatory responses.[26] Disease associated mutations of the cathepsin C gene cause the cathepsin C protein product to lose its enzyme activity. As a result, mutated cathepsin C is enzymatically inactive and patients cannot activate the neutrophil serine proteases: cathepsin-G, elastase and proteinase 3, which are secreted in tan inactive, proenzyme form, and must be cleaved by cathepsin C to become functionally active.[27] The severe periodontal disease that manifests in PLS and related conditions is a result of deregulation of the inflammatory and immune response in the periodontal tissues surrounding the teeth. The microflora in the gingival sulci surrounding the teeth trigger a host response in patients that is deregulated due to the patients lack of functional cathepsin C.[26,27,28] As such, the periodontal tissues surrounding the teeth are destroyed by the deregulated inflammatory and immune response. After the teeth are exfoliated and the microbial trigger is removed, the gingival tissues heal and appear normal. Genetic testing can be performed to confirm the diagnosis of PLS may be performed by direct sequencing of

the CTSC gene or by determining CTSC enzyme activity.[29] Various treatment modalities have been suggested, including early extraction of primary teeth to eliminate all pathogens involved and allowing the remaining teeth to erupt without infection, a combined approach using systemic and topical antimicrobial therapy as an adjunct to nonsurgical periodontal therapy; and the use of synthetic retinoids for the skin lesions.[30]

Neutropenia

Neutropenia is an absolute reduction in the number of circulating neutrophils that result in one or more defects in the differentiation or proliferation in the bone marrow, or increased peripheral destruction. It can be transient and not lasting for more than 2 weeks as seen with viral infections, severe generalized infection, such as septicemia in neonates, or due to drugs, such as cytotoxic agents and nonsteroidal anti-inflammatory drugs. Neutropenia can also occur in babies born to mothers with pregnancy-induced hypertension.[31] It also can be chronic when neutropenia lasts for more than 6 months, as seen in children with severe chronic neutropenia and cyclic neutropenia.

Neutrophils play a major role in host defense against bacteria; as a result, neutropenia patients suffer from frequent episodes of opportunistic bacterial infections.[32] Children with neutropenia commonly present with malaise and lethargy, skin infections, mucosal and respiratory infections, and septicemia and oral manifestation, including oral mucous infection, gingivitis, and periodontitis.[31]

Hypophosphatasia

Hypophosphatasia is a rare inherited disorder caused by a deficiency of tissue nonspecific alkaline phosphatase (TNSALP). One of the major functions of TNSALP is the hydrolysis of inorganic pyrophosphate, a potent natural inhibitor of hydroxyapatite crystal growth.[33] The deficiency in TNSALP results in extracellular pyrophosphate accumulation, which inhibits skeletal and dental mineralization.[34]

Hypophosphatasia has several recognized clinical forms classified according to the age of the patient at diagnosis and the degree of severity: perinatal, infantile, childhood, adult, and odontohypophosphatasia, where its manifestation ranges from absence of skeletal mineralization and stillbirth to loss of teeth in adult life.[35]

The key characteristic of all forms is premature loss of dentition, with the incisors being the most frequent teeth to be lost. Premature loss of deciduous teeth and periodontal involvement is not due to deficiency in

the immune system as presented in the previous conditions but rather to aplasia, hypoplasia, or dysplasia of the dental cementum that anchors the tooth root within the surrounding alveolar bone via the periodontal ligament.[36] Odontohypophosphatasia is diagnosed when the only clinical abnormality is dental disease. Dental radiographs show reduced alveolar bone and enlarged pulp chambers and root canals.[37] These individuals can have only mildly reduced serum ALP levels.[35] This milder clinical form of hypophosphatasia suggests that tooth development is the most sensitive developmental process dependent on TNSALP function.

Conclusions

Periodontal disease among children and adolescents most frequently indicates an underlying systemic or immunologic disorder. Early diagnosis is essential to the success of treatment and prevention of infection. To combat the severity and progression of periodontal disease among persons with these systemic diseases, a preventive strategy should be implemented that includes more frequent than 6 months dental recall visits, chlorhexidine mouth rinse, antibiotic therapy when indicated, fluoride gel, and/or professionally applied fluoride varnish. Every effort should be made to decrease the severity and progression of periodontal disease in these patients.

REFERENCES

1. Meyle J, Gonzáles JR. Influences of systemic diseases on periodontitis in children and adolescents. Periodontol 2000 2001;26:92-112.
2. Löe H, Brown LJ. Early onset periodontitis in the United States of America. J Periodontol 1991;62:608-16.
3. Cabanilla L, Molinari G. Clinical considerations in the management of inflammatory periodontal diseases in children and adolescents. J Dent Child 2009;76(2): 101-8.
4. Albandar JM, Rams TE. Risk factors for periodontitis in children and young persons. Periodontol 2000 2002;29:207-22.
5. Page RC, Beatty P, Waldrop TC. Molecular basis for the functional abnormality in neutrophils from patients with generalized prepubertal periodontitis. J Periodont Res 1987;22(3):182-3.
6. Van Dyke TE, Hoop GA. Neutrophil function and oral disease. Crit Rev Oral Biol Med 1990;1(2):117-33.
7. López-Pérez R, Borges-Yáñez SA, Jiménez-García G, et al. Oral hygiene, gingivitis, and periodontitis in persons with Down syndrome. Spec Care Dentist 2002;22(6):214-2.
8. Morgan J. Why is periodontal disease more prevalent and more severe in people with Down syndrome? Spec Care Dentist 2007;27(5):196-201.
9. Amano A, Kishima T, Akiyama S, et al. Relationship of periodontopathic bacteria with early-onset periodontitis in Down's syndrome. J Periodontol 2001;72:368-73.

10. Johnson NP, Young MA. Periodontal disease in Mongols. J Periodontol 1963;34: 41-7.
11. Cohen M, Winer RA, Shklar G. Periodontal disease in a group of mentally subnormal children. J Dent Res 1960;39:745.
12. Brown RH, Cunningham WM. Some dental manifestations of mongolism. Oral Surg Oral Med Oral Pathol 1961;14:664-76.
13. Cutress TW. Periodontal disease and oral hygiene in trisomy 21. Arch Oral Biol 1971;16:1345-55.
14. Page RC. The role of inflammatory mediators in the pathogenesis of periodontal disease. J Periodontal Res 1991;26:230-42.
15. Whittingham S, Pitt DB, Sharma DL, et al. Stress deficiency of the T-lymphocyte system exemplified by Down syndrome. Lancet 1977;1:163-6.
16. Yavuzyilmaz E, Ersoy F, Sanal O, et al. Neutrophil chemotaxis and periodontal status in Down's syndrome patients. J Nihon Univ Sch Dent 1993;35:91-5.
17. Harlan JM. Leukocyte adhesion deficiency syndrome: insights into the molecular basis of leukocyte emigration. Clin Immunol Immunopathol 1993;67(3 Pt 2): S16-24.
18. Etzioni A, Doerschuk CM, Harlan JM. Of man and mouse: leukocyte and endothelial adhesion molecule deficiencies. Blood 1999;94(10):3281-8.
19. Anderson DC, Schmalstieg FC, Feingold MJ, et al. The severe and moderate phenotypes of heritable Mac-1, LFA-1, pi50,95 deficiency: their quantitative definition and relation to leukocyte dysfunction and clinical features. J Infect Dis 1985;152:668.
20. Meyle J. Leukocyte adhesion deficiency and prepubertal periodontitis. Periodontol 2000 1994;6:26-36.
21. Waldrop TC, Anderson DC, Hallmon WW, et al. Periodontal manifestations of the heritable Mac-1, LFA-1, deficiency syndrome. Clinical, histopathologic and molecular characteristics. J Periodontol 1987;58(6):400-16.
22. Etzioni A, Frydman M, Pollack S, et al. Brief report: Recurrent severe infections caused by a novel leukocyte adhesion deficiency. N Engl J Med 1992;327:1789.
23. Papillon MM, Lefèvre P. Deux cas de kératodermie palmaire et plantaire symetrique familiale (maladie de Meleda) chezle frère et la soeur: coexistence dans les deux cas d'altérations dentaires grave. Bull Soc Fr Derm Syphiligr 1924;31: 82-4.
24. Gorlin RJ, Cohen MM, Levin LS. Syndromes of the Head and Neck, 3rd edn. Oxford: Oxford University Press; 1990. p. 853-855.
25. Hart TC, Hart PS, Bowden DW, et al. Mutations of the cathepsin C gene are responsible for Papillon-Lefèvre syndrome. J Med Genet 1999;36(12):881-7.
26. Hart TC, Hart PS. Genetic studies of craniofacial anomalies: clinical implications and applications. Orthod Craniofac Res 2009;12(3):212-20.
27. de Haar SF, Jansen DC, Schoenmaker T, et al. Loss-of-function mutations in cathepsin C in two families with Papillon-Lefèvre syndrome are associated with deficiency of serine proteinases in PMNs. Hum Mutat 2004;23(5):524.
28. Ryu OH, Choi SJ, Firatli E, et al. Proteolysis of macrophage inflammatory protein-1alpha isoforms LD78beta and LD78alpha by neutrophil-derived serine proteases. J Biol Chem 2005;280(17):17415-21.
29. Zhang Y, Hart PS, Moretti AJ, et al. Biochemical and mutational analyses of the

cathepsin C gene (CTSC) in three North American families with Papillon Lefèvre syndrome. Hum Mutat 2002;20(1):75.

30. Patel S, Davidson LE. Papillon–Lefèvre syndrome: a report of two cases. Int J Paediatr Dent 2004;14(4):288-94.
31. Lakshman R, Finn A. Neutrophil disorders and their management. J Clin Pathol 2001;54(1):7-19.
32. Berliner N. Lessons from congenital neutropenia: 50 years of progress in understanding myelopoiesis. Blood 2008;111:5427-32.
33. Terkeltaub RA. Inorganic pyrophosphate generation and disposition in pathophysiology. Am J Physiol Cell Physiol 2001;281:C1-11.
34. Fedde KN, Blair L, Silverstein J, et al. Alkaline phosphatase knock-out mice recapitulate the metabolic and skeletal defects of infantile hypophosphatasia. J Bone Miner Res 1999;14(12):2015-26.
35. Mornet E. Hypophosphatasia. Orphanet J Rare Dis 2007;2:40.
36. Van den Bos T, Handoko G, Niehof A, et al. Cementum and dentin in hypophosphatasia. J Dent Res 2005;84(11):1021-5.
37. Brittain JM, Oldenburg TR, Burkes JR, et al. Odontohypohypophosphatasia: Report of two cases. J Dent Child 1976;43:106-11.