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Periodontal disease associated to systemic genetic disorders

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ABSTRACT

A number of systemic disorders increase patient susceptibility to periodontal disease, which moreover evolves more rapidly and more aggressively. The underlying factors are mainly related to alterations in immune, endocrine and connective tissue status. These alterations are associated with different pathologies and syndromes that generate periodontal disease either as a primary manifestation or by aggravating a pre-existing condition attributable to local factors. This is where the role of bacterial plaque is subject to debate. In the presence of qualitative or quantitative cellular immune alterations, periodontal disease may manifest early on a severe localized or generalized basis – in some cases related to the presence of plaque and/or specific bacteria (severe congenital neutropenia or infantile genetic agranulocytosis, Chediak-Higiashi syndrome, Down syndrome and Papillon-Lefèvre syndrome). In the presence of humoral immune alterations, periodontal damage may result indirectly as a consequence of alterations in other systems.

In connective tissue disorders, bacterial plaque and alterations of the periodontal tissues increase patient susceptibility to gingival inflammation and alveolar resorption (Marfan syndrome and Ehler-Danlos syndrome).

The management of periodontal disease focuses on the control of infection and bacterial plaque by means of mechanical and chemical methods. Periodontal surgery and even extraction of the most seriously affected teeth have also been suggested. There are variable degrees of consensus regarding the background systemic disorder, as in the case of Chediak-Higiashi syndrome, where antibiotic treatment proves ineffective; in severe congenital neutropenia or infantile genetic agranulocytosis, where antibiotic prophylaxis is suggested; and in Papillon-Lefèvre syndrome, where an established treatment protocol is available.

Key words: *Periodontal disease, systemic alterations, periodontitis due to genetic alterations, Chediak-Higiashi syndrome, Papillon-Lefèvre syndrome, Down syndrome, Marfan syndrome, Ehler-Danlos syndrome, severe congenital neutropenia, infantile genetic agranulocytosis, hyperimmunoglobulinemia E.*

RESUMEN

Existen condiciones sistémicas que generan una mayor susceptibilidad a la enfermedad periodontal, la cual evoluciona de forma más rápida y agresiva. Los factores involucrados tienen relación, principalmente con alteraciones a nivel inmunológico, a nivel hormonal y del tejido conectivo. Estas alteraciones se asocian a diversas patologías y síndromes, generando la enfermedad periodontal como una manifestación primaria o agravando una condición ya establecida por factores locales. Aquí es donde el papel de la placa bacteriana es discutido. Cuando existe alteración inmunológica celular cualitativa o cuantitativa, la enfermedad periodontal se puede presentar tempranamente de forma severa localizada o generalizada, existiendo en algunos casos relación a la presencia de placa y/o a bacterias específicas (neutropenia severa congénita o agranulocitosis

infantil genética, síndrome de Chediak-Higashi, síndrome de Down y síndrome Papillon-Lefévre). En la alteración inmune humoral el daño periodontal, puede ser generado de forma indirecta por alteración de otros sistemas.
En los desordenes del tejido conectivo, la placa bacteriana y las alteraciones en los tejidos periodontales, aumentan la susceptibilidad a la inflamación gingival y resorción alveolar (síndrome de Marfan y síndrome de Ehler-Danlos)
El manejo y tratamiento de la enfermedad periodontal esta enfocado al control de la infección y de la placa bacteriana, mediante métodos mecánicos y a métodos químicos. También se sugiere la cirugía periodontal e inclusive la exodoncia de los dientes mas afectados. Existen variantes de acuerdo a la alteración sistémica de base, como el caso del síndrome de Chediak-Higashi donde no responde a tratamientos antibióticos, en la neutropenia severa congénita o agranulocitosis infantil genética que sugiere profilaxis antibiótica y en el caso del síndrome de Papillon-Lefévre con un protocolo establecido para el tratamiento.

Palabras clave: *Enfermedad periodontal, alteraciones sistémicas, periodontitis por alteraciones genéticas, síndrome de Chediak-Higashi, síndrome de Papillon-Lefévre, síndrome de Down, síndrome de Marfan, síndrome de Ehler-Danlos, neutropenia severa congénita, agranulocitosis infantil genética, síndrome de hiperglobulinemia E.*

INTRODUCTION

Periodontal disease, which produces lesions in the tooth-supporting tissues, requires a different approach when associated to risk factors secondary to systemic disorders. The alteration of the periodontal tissues may be a primary consequence of such systemic alterations or a secondary effect - causing periodontal disease to progress without any apparent underlying cause, or alternatively maintaining or incrementing the severity of a previously established local condition (1).

The principal causal agent of periodontal disease is bacterial plaque, which induces progressive tissue damage. In the presence of susceptibility to periodontal disease due to systemic conditions, the role of bacterial plaque is debated. Some authors consider that periodontal disease cannot be induced without the presence of plaque and tartar, and suggest that a systemic predisposition simply accelerates the destruction caused by bacterial agents. Others, however, consider that there is no consistent evidence demonstrating that nonspecific bacterial plaque causes processes of this kind, since no cause-effect relationship is established between the type of bacterial plaque and the severity of periodontal damage (2).

The development and evolution of periodontal disease is largely dependent upon the host immune response, the integrity of the tissues, humoral and cellular immunity, and on certain endocrine and nutritional factors. Other factors have also been related to periodontal disease, such as age, locations within the mouth that are more susceptible to infection (incisors and first molars associated to specific flora), and concrete bacterial species (Captosinofaga, Actinomyces naeslundi, Actinobacillus actinomycetemcomitans) (2).

Thus, alterations in this system increase susceptibility to periodontal disease, with signs of a simple or more complex presentation, in accordance with the existing immune alteration. Furthermore, the condition may prove more severe in the presence of associated metabolic disorders, since the latter act in synergy with periodontal damage (2).

The alterations in the immune system may be located at cellular and/or humoral level. In this context, lymphocytes play a key role in immune function, and the congenital or acquired absence of one or more cell lines gives rise to diseases that may prove fatal – such as acute leukemia or AIDS (2). Neutrophil alterations in turn may be of a qualitative (altered chemotaxis and phagocytosis) or quantitative nature (neutropenia, agranulocytosis), and both predispose to rapid and severe periodontal destruction. An increased vulnerability to severe periodontitis can be seen in Down syndrome (trisomy 21), Chediak-Higashi syndrome and Papillon-Lefèvre syndrome. The affected individuals show an increased incidence of infections attributable to the fact that these cells show a diminished expression of surface glycoproteins needed for adhesion to bacteria. In some cases, this kind of disorder has been associated to periodontal damage similar to that of generalized prepuberal periodontitis (2). Alterations in the humoral immune system, fundamentally affecting the immunoglobulins, generates periodontal disease when the humoral disorder in turn affects other systems such as cellular immunity or the metabolic system. Therefore, the alteration of these two systems is the principal mechanism underlying periodontal disease mediated by immunoglobulins (2). It has even been demonstrated that humoral response at this level is specific in each individual – which in turn helps explain the great variety of responses to periodontal treatment (3).

Other disorders, such as those associated to the connective tissues also increase the susceptibility to periodontal alterations, and in some cases, to the presence of plaque; as a result, the destructive effects inherent to inflammatory response are exacerbated, with no adequate reparatory response (2).

The present study reviews the literature on periodontal disease associated to systemic alterations of genetic origin, together with the clinical manifestations associated to these processes. In addition, the odontologic treatment options of these patients are commented.

GENERAL CLINICAL CHARACTERISTICS

This group of genetic diseases has been classified according to the principal alteration involved, in order to better understand the most likely mechanism underlying periodontal disease:

a) Connective tissue alterations: Marfan syndrome, Ehler-Danlos syndrome.
b) Immune alterations: severe congenital neutropenia (SCN) or infantile genetic agranulocytosis or Kostmann syndrome (IGA), Chediak-Higiashi syndrome, Down syndrome, Papillon-Lefèvre syndrome, hyperimmunoglobulinemia E syndrome.
In Marfan syndrome it seems that the mutation of a gene encoding for fibril-1 in chromosome 15 generates an alteration in the synthesis of a glycoprotein forming part of the connective tissue matrix. This in turn generates defects in a series of locations such as the ocular lens suspensor ligament, blood vessel walls and, apparently, the periodontal ligament (4). Ehler-Danlos syndrome in turn is characterized by extensible skin, hypermobile joints, tissue fragility and, at oral level, persistent hyperplastic gingivitis (5).
The immune diseases contemplated in the above classification are all primary immune deficiencies caused by a decrease in neutrophil presence (SCN or IGA), or by alterations in the functions of these cells – as in the four above cited syndromes. SCN or IGA predisposes patients to bacterial and fungal infections in childhood, because the decrease in neutrophil presence alters the host defense capacity. Moreover, a decrease is seen in the production of granulocyte colony stimulating factor (6,7). Chediak-Higiashi syndrome is accompanied by leukocyte alterations, fundamentally circumscribed to the lysosomes, which destroy melanosomes producing oculo-cutaneous albinism. Affected patients also present mental retardation, and neutropenia moreover may also be observed – with altered neutrophil chemotaxis associated to recurrent chronic infections (8). Down syndrome or trisomy 21 is caused by a chromosomal aberration that generates peculiar physical characteristics, manifesting with mental retardation and systemic alterations. The immune alterations described in Down syndrome are related to leukocyte function, responsible for the defensive mechanisms in periodontal tissues (9,10). Papillon-Lefèvre syndrome in turn is defined by palmoplantar erythematous hyperkeratosis and periodontal disease. The postulated underlying mechanism is a mutation of the gene encoding for catepsin C, which generates a lysosomal protein implicated in host immune response, inflammatory mediation and extracellular matrix function – with expression in the epithelium of the palms and soles, and at gingival level (11). Hyperimmunoglobulinemia E (HE) consists of an increase in serum IgE. This in turn leads to a series of systemic alterations with involvement of the skin, facial malformations and increased susceptibility to staphylococcal infections (12).

CLINICAL MANIFESTATIONS OF PERIODONTAL DISEASE, MECHANISMS AND ASSOCIATED FACTORS

The mechanism underlying periodontal disease in the group of syndromes characterized by connective tissue alterations is explained by the fact that anomalies at this level generate increased susceptibility to periodontal inflammation and bone resorption (4). Despite the existence of a common background alteration, the manifestations of periodontal disease may differ in each of the syndromes. In the case of Marfan syndrome, periodontitis manifests in a chronic and severe form with patterns of both horizontal and vertical bone resorption, and in accordance to the presence of bacterial plaque. Dental mobility has been shown to be due to periodontitis, and is not attributable to the primary condition of the syndrome (4).
In the case of Ehler-Danlos syndrome, periodontal disease can be associated to syndromes type I, VII, III, or IV (5). Only in relation to type I is a predisposition to periodontal disease described, while type VIII presents as early onset periodontitis, premature loss of permanent teeth, fragility of the alveolar mucosa and gingival bleeding. The postulated mechanism is a defect in type III collagen, present in 16% of the total collagen of the periodontal ligament, affecting the integrity of the periodontal junction. In addition, a relationship has been found to Fusobacterium nucleatum, which is found in the active lesion sites (5).
In SCN or IGA, the decrease in the number of neutrophils alters the host defense capacity, causing periodontal disease to manifest at an early age, with gingival inflammation, aggressive periodontal destruction, edema, periodontal pouches and tooth mobility. This is similar to prepuberal or rapidly progressive periodontitis with premature loss of the deciduous teeth (6,7,13).
The periodontal condition in Chediak-Higiashi syndrome manifests as early onset periodontitis with premature exfoliation of both dentitions. The patterns of bone resorption may be local or generalized, and are related to the gingival inflammation. The disorder is associated to anaerobe flora, due to the abundant presence of purulent processes. Mention has also been made of the abundant presence of spirochetes in the locations with inflammation and high proteolytic activity, which facilitates bacterial adherence. Addition to this situation of lysosomal alterations and defective chemotaxis in neutrophils gives rise to very aggressive periodontitis that tends to be recurrent and is refractory to antibiotic treatment (9).
Down syndrome associated to mental retardation and to the systemic alterations is characterized by aggressive and generalized periodontitis, with the subsequent destruction of the supporting tissues and loss of teeth at an early age. Eight percent of children with Down syndrome suffer periodontal lesions by 12 years of age, versus only 0.5% of the general population of the same age (14). The prevalence of periodontal disease in the population with this syndrome ranges from 60% to 100% in young adults under 30 years of age (9,15). To these factors we must also add immune deficiency, inadequate control of bacterial plaque, deficient masticatory function, early aging and alterations in dental anatomy (short roots)(15). It has been reported that the presence of Actinobacillus actinomicetenconcomitans and of Captocinofaga in bacterial plaque is associated to periodontitis in these individuals. These bacterial colonies appear at an early age and vary according to the latter – increased prevalence being seen in early puberty (15,16).

Table 1. Summary of clinical manifestations of periodontal disease due to genetic alterations.

Systemic disorder	Type of periodontal disease	Associated factors	Treatment
Marfan syndrome	Chronic-sever	Local factors Bacterial plaque	Chemical and mechanical control of bacterial plaque
Ehler-Danlos syndrome	Type I: predisposes to localized periodontitis. Type VIII: early-onset periodontitis	Related to *Fusobacterium nucleatum*	Chemical and mechanical control of bacterial plaque
Severe congenital neutropenia or IGA	Severe, loss of teeth in both dentitions (rapidly progressive)	Bacterial plaque	Chemical and mechanical control of bacterial plaque Antibiotic prophylaxis advised (clindamycin)
Chediak-Higiashi syndrome	Early onset, premature loss of teeth in both dentitions	Bacterial plaque: refractory type, anaerobes, spirochetes	Rigorous bacterial plaque control Unresponsive to antibiotics
Down syndrome	Similar to juvenile periodontitis Similar to early onset periodontitis. Severe	Associated to external factors such as bacterial plaque. Associated to ABAMC. Hormone changes	Rigorous bacterial plaque control
Papillon-Lefevre syndrome	Early onset, premature loss of teeth in both dentitions	Associated to ABAMC	According to protocol (see Table 2)
Hyperimmunoglobulinemia E syndrome	Generalized, advanced	Associated to plaque (no relation to magnitude of damage)	Chemical and mechanical control of bacterial plaque

In patients with severe mental retardation, difficulties are obviously found in ensuring correct autonomous tooth brushing and plaque control. In this context, oral hygiene is essential to avoid the organization of plaque and prolongation of the disease (16). Bactericidal dysfunction results from defective neutrophil chemotaxis, which leads to progressive periodontal disease as in juvenile periodontitis. Likewise, it has been reported that the B and T cells, and monocytes, also exhibit functional defects. The periodontal damage is related to the degree of alteration in chemotactic function. It has even been shown that the neutrophil chemotactic depression rate reaches 59% in generalized juvenile periodontitis, 44% to 60% in localized juvenile periodontitis, and 50% in the case of rapidly progressing periodontitis (9). The mechanism accounting for such dysfunction is related to a decrease in the number of cell surface receptors, and diminished levels of zinc and certain vitamins in serum.

Papillon-Lefèvre syndrome in turn is characterized by aggressive periodontal inflammation implicating the premature loss of both dentitions. The mechanisms involved are related not only to immune alterations but also to alterations in the gingival tissues and the presence of Actinobacillus actinomycetemcomitans (11). In hyperimmunoglobulinemia E syndrome an increased susceptibility to infections is observed – this contributing to the development of periodontal disease.

The postulated mechanism in this case is a deficient host cellular and humoral immune response, with a decrease in neutrophil chemotaxis secondary to an alteration in the regulation of T cell cytokines. The increase in IgE leads to a reduction in the production of gamma-interferon, which intervenes in anti-inflammatory and in bone resorption-inhibiting processes. Consequently, the inflammatory and resorptive phenomena are increased in these patients, giving rise to advanced periodontitis at an early age. Likewise, the disorder is related to bacteria that produce severe periodontal damage in adults and in pediatric immune deficiencies (P. gingivalis, T. denticola, E. corrodens). Contradictorily, however, this immune alteration induces a delay in dentition turnover, since the deciduous teeth exhibit scant physiological root resorption (12). The clinical characteristics of periodontal disease associated to systemic alterations of a genetic nature, the associated factors, and the corresponding treatment options are summarized in Table 1.

ODONTOLOGIC TREATMENT

The management of periodontal disease in these patients centers on the control of infection and bacterial plaque. This is done by chemical methods such as the use of antiseptics and antibiotics, and also mechanical methods such as tartar removal and the rasping of affected teeth. Periodontal surgery is sometimes advised to improve cleaning of certain zones, and even removal of the most severely affected teeth has been suggested.

Table 2. Standardized odontologic management protocol in patients with Papillon-Lefèvre syndrome (11).

Deciduous dentition	Permanent dentition
Instructions for oral hygiene and prophylaxis every three months	
Extraction of teeth with advanced periodontal disease. Extraction of all deciduous teeth 6 months before eruption of permanent first molars. Two weeks of antibiotic treatment to avoid complications after extractions	0.2% chlorhexidine rinses twice a day. Teeth with moderate periodontal disease (bone loss < 30% of root length, periodontal pouch depth < 5 mm): ultrasound and dental prophylaxis once a months, systemic antibiotics for 4 weeks.
Recommended antibiotic treatment: amoxicillin or amoxicillin + clavulanate 20-50 mg/kg/day or 20-40 mg/kg/day, respectively divided into doses every 8 hours.	Recommended antibiotic treatment: amoxicillin 20-50 mg/kg/day + metronidazole (15-35 mg/kg/day) divided into doses every 8 hours.

There are variations in treatment according to the background systemic disorder involved, as in the case of Chediak-Higiashi syndrome, which fails to respond to antibiotics; severe congenital neutropenia or IGA where antibiotic prophylaxis with clindamycin is recommended; and Papillon-Lefèvre syndrome, where the recommendations center on hygiene, antibiotics and programmed extractions as management approach (11)(Table 2). In Down syndrome, the immune defect with alterations in chemotaxis, defects in neutrophil phagocytosis, and the consequent production of free oxygen radicals pose no threat to patient response to conventional treatments (10). As postulated in the recent literature, the results of surgical and non-surgical periodontal treatments are related to control of the bacterial plaque, which can be maintained either by the patient or by the caretakers (17,18). As maintenance treatment, reinforcement of the tooth brushing technique is advised, with regular plaque removal and rigorous oral examination to control and maintain healthy and stable periodontal tissue status (10).

When dealing with periodontal problems, it is advisable to establish a differential diagnosis of periodontal disease due to systemic conditions (18), considering the individual factors that produce the clinical manifestations. In this context, it must be taken into account that response to treatment is not always as expected, and that sometimes the progression of periodontal disease is inevitable despite adequate maintenance treatment (19).

REFERENCES

1. Bullon-Fernandez P, Machuca-Portillo G. Tratamiento odontológico en pacientes especiales. Madrid: Edita Laboratorios Normon; 2004. p. 131-8.
2 .Wilton JMA, Griffiths GS, Curtis MA, Maiden MFJ, Gillett IR, Wilson DT, et al. Detection of high-risk groups and individuals for periodontal diseases. J Clin Periodontol 1988;15:339-46.
3. Kinane DF, Lappin DF. Immune processes in periodontal disease: A review. Ann Peridontol 2002;7:62-71.
4. Straub AM, Grahame R, Scully C, Tonetti MS. Severe periodontitis in Marfan's Syndrome: A Case Report. J Periodontol 2002;73:823-6.
5. Perez LA, Al-Shammari KF, Giannobile WV, Wang H. Treatment of periodontal disease in a patient with Ehlers-Danlos Syndrome. A Case Report and literature review. J Periodontol 2002;73:564-70.
6. Hakki SS, Aprikyan AAG, Yildirim S, Aydinbelge M, Gokalp A, Ucar C, et al. Periodontal status in two siblings with Severe Congenital Neutropenia: Diagnosis and Mutacional Analisis of the Cases. J Periodontol 2005;76:837-44.
7. Saglam F, Atamer T, Oman U, Soidinç M, Kiraç K. Infantile Genetic Agranulocitosis (Kostmann Type). A Case Report. J Periodontol 1995; 66:808-10.
8. Delcourt-Debruyne EMC, Boutigny HRA, Hildebrand HF. Features of severe periodontal disease in a teenager with Chediak-Higashi Syndrome. J Periodontol 2000;71:816-24.
9. Izumi Y, Sugiyama S, Shinozuka O, Yamazaki T, Ohyama T, Ishikawa I. Defective neutrophil chemotaxis in Down's Syndrome patients and its relationship to periodontal destruction. J Periodontol 1989;60:238-41.
10 Zaldivar-Chiapa RM, Arce-Mendoza AY, De La Rosa-Ramírez M, Caffesse RG, Solis-Soto JM. Evaluation of surgical and non-surgical periodontal therapies, and immunological status, of young Down's Síndrome patients. J Periodontol 2005;76:1061-5.
11. Ullbro C, Brown A, Twetman S. Preventive periodontal regimen in Papillon-Lefevre Syndrome. Pediatr Dent 2005;27:226-32.
12. Tsang P, Derkson G, Priddy R, Junker AK, Slots J, Larjava H. Severe periodontitis in a 5-years-old girl with hiperimmunoglobulin E Syndrome. Pediatr Dent 2005;27:68-73.
13. Carlsson G, Wahlin YB, Johansson A, Olsson A, Eriksson T, Claesson R et al. Periodontal disease in patients from the original Kostmann family with severe congenital neutropenia. J Periodontol 2006;77:744-51.
14. Borea G, Magi M, Mingarelli R, Zamboni C. The oral cavity in Down syndrome. J Pedodont 1990;14:139-40.
15. Amanao A, Kishima T, Akiyama S, Nakagama I, Hamada S, Morisaki I. Relationship of periodontopathic bacteria with early-onset periodontitis in Down's Syndrome. J Periodontol 2001;72:368-73.
16. Amanao A, Kishima T, Akiyama S, Nakagama I, Hamada S, Morisaki I. Periodontopathic bacteria in children with Down Syndrome. J Periodontol 2000;71:249-55.
17. Emingil G, Atilla G, Sorsa T, Savolainen P, Baylas H. Effectiveness of adjunctive low-dose doxycycline therapy on clinical parameters and gingival crevicular fluid laminin-5 gamma2 chain levels in chronic periodontitis. J Periodontol 2004;75:1387-96.
18. Sollecito TP, Sullivan KE, Pinto A, Stewart J, Korostoff J. Condiciones sistémicas asociadas con periodontitis en la infancia y la adolescencia. Una revisión de las posibilidades diagnósticas. Med Oral Patol Oral Cir Bucal 2005;10:142-50.
19. Diz P, Ocampo A, Fernández J. Alteraciones cuantitativas y funcionales de los neutrófilos. Med Oral 2002;7:206-21.