The New York State Dental Journal

Volume 88 | Number 2 Article 5

3-1-2022

Papillon-LeFevre Syndrome: A Case Study of Two Siblings

Babak Bina DMD
NYU, Babak.Bina@NYULangone.org

Boris Zats DDS
NYU, Boris.Zats@nyulangone.org

Tom Rubinstein DMD
Columbia University, Tr2592@cumc.columbia.edu

Papillon-LeFevre Syndrome

A Case Study of Two Siblings

Babak Bina, D.M.D.; Boris Zats, D.D.S.; Tom Rubinstein, D.M.D.

ABSTRACT

Papillon-LeFevre syndrome (PLS) is a rare, autosomal recessive disease associated with palmar-plantar hyperkeratosis and premature loss of both deciduous and permanent teeth. Treatment of this disease continues to be a challenge to the medical and dental professions. The following is a case report of two siblings of Chinese origin diagnosed with Papillon-LeFevre syndrome who were followed for 10 subsequent years.

In 1924, Papillon and LeFevre described a syndrome that was associated with diffuse hyperkeratosis of the palms of the hands and soles of the feet and destruction of periodontium, with premature loss of the primary and permanent dentition.[1]

Papillon-LeFevre syndrome (PLS) is an autosomal, recessive disease with a prevalence of one to three per million and no apparent racial or gender preference.[2] More cases are being reported every year around the world, as physicians and dentists increase their knowledge of this disease.

PLS periodontal involvement manifests itself with the eruption of primary teeth and their subsequent early exfoliation by the age of 4 or 5. Gingival inflammation and breakdown reappear with eruption of the permanent teeth.[3,4]

Mutation of Cathepsin C in the chromosomal region 11q14 has been associated with PLS disease presentation,[5,6] and pathogenesis of the disease has been related to Cathepsin C's capacity to activate neutrophil elastase (NE), Cathepsin G (CG), Proteinase 3 (PR3) and neutrophil serine proteinase 4 (NSP4).[1,7]

The treatment of this disease has remained unsuccessful for decades. Usually, all of the erupted permanent teeth are lost, with patients having full upper and lower dentures by age 13 or 14. A few case presentations have been published regarding the use of dental implants; however, information regarding long-term prognosis is limited.[8-10]

In this paper, we present the cases of two siblings diagnosed with PLS, describe their comprehensive medical and dental care, and discuss possible treatment options based on their clinical and microbiological situation.

Case History

Two siblings of Chinese origin—a 13-year-old boy (Patient B) and a 12-year-old girl (Patient G)—were referred to NYU Langone Health, Brooklyn, NY, by a private general dentist with the diagnosis of localized aggressive periodontitis (AgP), a condition characterized by alveolar bone loss and pocket formation affecting first molars and incisors.[11] Due to limited evidence and lack of pathophysiological uniqueness, AgP is not considered a sepa-

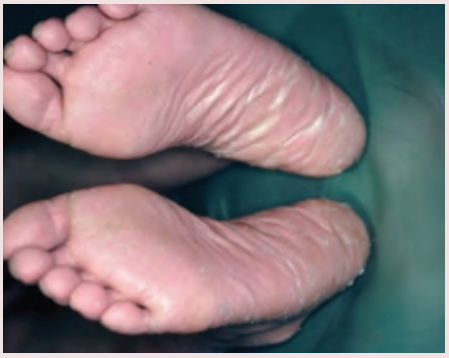

Figure 1. Plantar hyperkeratosis in Patient G.

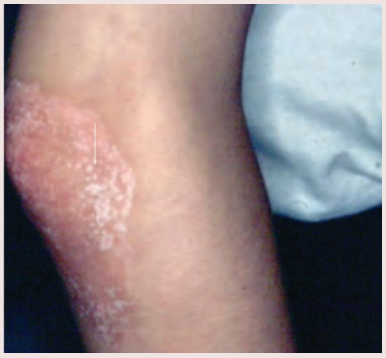

Figure 2. Hyperkeratosis of elbow in Patient B.

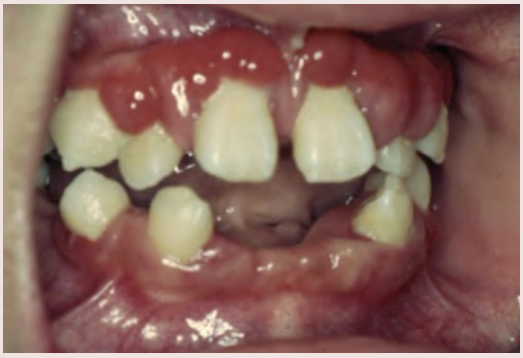

Figure 3. Gingival hyperplasia in Patient G.

rate disease from chronic periodontitis but, rather, an aggressive manifestation in susceptible individuals. Thus, with the publication of the 2017 periodontal classification,[12] the phenotypical presentation of AgP falls under the Grade C modifier.

As for the medical status of the remaining members of the immediate family, out of the four children in the family, the two remaining older siblings exhibit no signs of this syndrome. The parents are not related, and they deny any family history of such a condition.

Upon careful clinical examination, plantar and palmar hyperkeratosis was observed in both siblings, with additional hyperkeratosis on their knees and elbows. (Figures 1, 2). According to their parents, the hyperkeratosis was noted soon after birth and has continued throughout their lives. They said the eruption of the primary teeth was normal; however, soon after eruption, the gingiva became inflamed and exfoliation of teeth began.

Histological analysis of punch biopsies taken from the dorsum of the wrist showed marked hyperkeratosis, with acanthosis of epidermis and hyperplasia of the granular layer. These findings are consistent with palmoplantar keratoderma (PPK) Group. Papillon-LeFevre syndrome is a type of PPK known to be associated with severe periodontal disease.

Further examination revealed hyperkeratosis on the skin in the gluteal region in Patient B. Sonogram of testicles showed that the right testis was localized in the right groin rather than in the scrotal sac and was smaller in size than on the left side. Left testis was in scrotal sac. Both testes were normal in echogenicity.

Cytogenic findings with G-banding showed an apparently normal 46, xx karyotype in Patient G and normal 46, xy karyotype in Patient B. Skull series in both patients were normal, with no signs of abnormal intracranial calcification or fracture.

Hematologic analysis revealed a high level of alkaline phosphatase (pt. B=331 u/l and pt. G=366 u/l) when compared to normal range, which is still considered to be compatible with the patients' age.

IgG, IgM, IgA immunoglobins were in normal range in both patients.

Oral examination and radiographic evaluation of Patient G revealed 80% to 90% bone loss around incisors and first molars, with mandibular central incisors exfoliated on their own. Although premolars and canines were not fully erupted, radiographic bone loss (between 20% and 30%) was apparent. Severe gingival hyperplasia of both buccal and lingual surfaces, with the exception of the mandibular incisor area, was noted; the mandibular-incisor region presented with clinically normal gingival tissue (Figure 3). Suppuration was present around the incisors and maxillary molars.

Oral examination and radiographic evaluation of Patient B revealed more than 90% bone loss around the incisors and molars, with mandibular central incisors exfoliated on their own. Premolars and canines were erupted, presenting 30% to 40% bone loss. Generalized, severe gingival hyperplasia was noted on both buccal and lingual aspects of the dentition, with bleeding upon palpation and probing noted. Gingiva appeared clinically healthy around lower central incisors where teeth were lost. Suppuration was present around incisors and maxillary molars.

An oral microbiological sample was taken from both patients and sent to University of Pennsylvania School of Dental Medicine for microbiological assessment by culture and indirect immunofluorescent.

In Patient G, intraoral plaque sampling was conducted from the mesial palatal surface of the maxillary left second premolar (tooth #13). Microbial analysis revealed elevated levels of *Aggregatibacter actinomycetemcomitans* (A.a.), which

TABLE 1. Laboratory analysis report of patient G: Sample taken from mesial palatal aspect of maxillary left second premolar (13MP). Note high level of *Actinobacillus actinomycetemcomitans, P. intermedia, C. rectus, P. gingivalis* and *B. forsythus* when compared to normal range.

			Antibiotic Susceptibility "S"=Susceptible "R"=Resistant		
Cultivable Species	Normal Range (approximate %)	% of Cultivable Microbiota	Tetracycline-HCl (2 microgram/ml)	Penicillin G (2 microgram/ml)	Metronidazole (4 microgram/ml)
A. actinomycetemcomitans	0-0.01	8.571	R	R	R
P. intermedia/nigrescens	0-2.5	5.714	S	S	S
Eikenella corrodens	0-1.0	0.000			
Campylobacter (Wolinella) rectus	0-2.0	11.714	S	S	S
Capnocytophaga species	0-5.0	0.000			
Fusobacterium species	0-5.0	4.286	S	R	S
Peptostreptococcus micros	0-2.5	2.857	S	S	S
Enteric gram-negative rods	0	0.000			
Enterococcus species	0	0.000			
Staphylococcus aureus	0	0.000			
Other staphylococcus species	No defined range	0.000			
Yeast	0-0.5	0.000			

Immunofluorescence			
		____ % of microscopic counts	Note: The pathogenicity of individual species is affected by presence of other bacteria, as well as host-parasite interactions
Porphyromons gingivalis	0-0.5	13.9	
Bacteroides forsythus	0-1.0	4.2	
Morphotypes			
Spirochetes	0-5.0	24.0	
Motile Rods	0-5.0	14.0	
Nonmotile Rods	No defined range	15.0	
Coccoid Cells	No defined range	47.0	
		___	
		TOTAL: 100%	

showed resistance to tetracycline-HCl, penicillin G and metronidazole. Elevated levels of *P. intermedia, C. rectus, P. gingivalis (P.g.)* and *T. forsythia* were also noted (Table 1).

In Patient B, intraoral plaque sampling was acquired from the buccal aspect of the maxillary right central incisor (tooth #8). Microbial analysis revealed high levels of A.a that was resistant to tetracycline-Hcl and metronidazole. The sample from patient B also showed high levels of *Peptostreptococcus micros, T. forsythia* and Gram-negative rods species. (Table 2).

High levels of A.a, *P. intermedia, C. rectus, T. forsythia*, P.g., and Gram-negative rods species are indicative of severe periodontal disease. Furthermore, antibiotic sensitivity testing revealed lower antibiotic efficacy, suggesting that conventional antibiotic therapy might not be successful in these patients (Tables 1,2).

Treatment

Right orchiectomy was performed on Patient B under general anesthesia to address the undescended right testicle. Both patients initially received full-mouth scaling and root planing, and they continued to receive periodontal maintenance approximately every other month.

Initially, hopeless teeth in both upper and lower arch (incisors and first molars) were extracted in both patients, with fabrication of upper and lower transitional partial dentures replacing missing teeth.

After two years, all of the remaining teeth were extracted due to severe bone loss, and upper and lower complete dentures were fabricated.

Both patients were placed on isotretinoin, which produced significant improvement in palmar and plantar hyperkeratosis. All risks and benefits were explained to the patients prior to oral retinoid treatment (Figure 6).

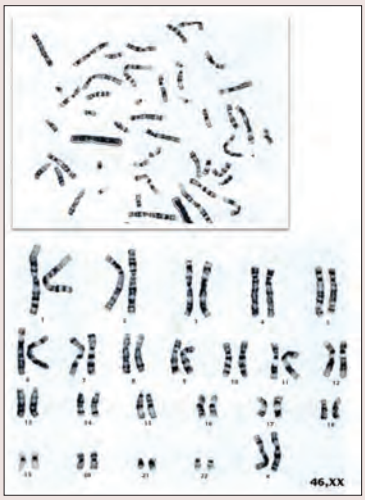

Figure 4. Normal XX karyotype in patient G.

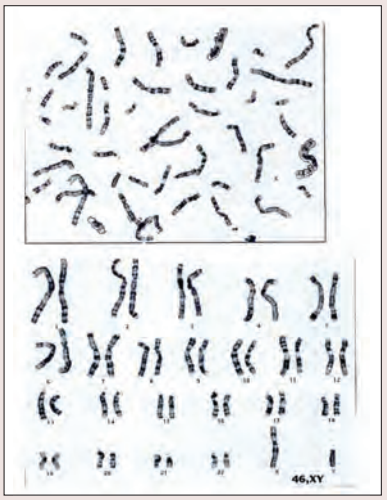

Figure 5. Normal XY karyotype in patient B.

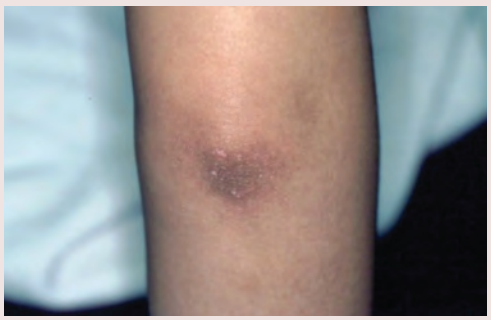

Figure 6. Resolution after treatment on Isotretinoin.

Discussion

Papillon-LeFevre syndrome is known to be associated with premature loss of both deciduous and premature teeth. Other diseases in children that are involved in early alveolar bone loss are: agranulocytosis; cyclic neutropenia; juvenile diabetes; leukemia; actalasia; hypophosphatasia; histocytosis x; and Haim-Munk syndrome.[13] From all of the above conditions, the only other disorder that is associated with diffuse palmoplantar hyperkeratosis in addition to Papillon-LeFevre syndrome is Haim-Munk syndrome. In contrast to Papillon-LeFevre syndrome, in patients with Haim-Munk disorder, the periodontium is less affected and hyperkeratosis is accompanied by arachnodactyly and deformity of the terminal phalanges.[14]

Although the palmoplantar keratosis and destruction of periodontal disease are always present in Papillon-LeFevre syndrome, some of these patients have a variety of other conditions, such as susceptibility to infections,[15] intracranial calcifications[16] and retardation of somatic development.[10,17]

The PLS locus has been mapped to chromosome 11q14, where the gene (CTSC) encoding for lysosomal protease cathepsin C lies.[4,18] A dysfunctional CTSC message will yield a deficiency in Cathepsin C, an important proteinase responsible for intracellular degradation of proteins and activation of serine proteases in inflammatory cells.[19] NE, CG, PR3, NSP4 are granular-associated serine proteinases of neutrophils that are activated by Cathepsin C via N-terminal trimming during biosynthesis. Very small quantities or absence of these serine proteinases has been reported in patients with PLS.[1,7] Without these serine proteinases, the host's ability to kill periodontal bacteria is diminished.[20] It is important to note that the total number of neutrophils in individuals with PLS are not elevated, but these neutrophils are considered hyperactive, releasing increased amounts of pro-inflammatory cytokines. Thus, neutrophils in PLS will arrive to answer a bacterial challenge but they are unable to kill the periodontal bacteria effectively therefore exacerbating local inflammation even further by signaling for the recruitment of more, equally deficient neutrophils to the site.[21]

Previous studies have reported an increased presence of gram-negative anaerobic pathogens, such as P.g, *Capnocytoph-*

aga, *Spirochetes*, and A.a in individuals with PLS.[22,23] Microbiome assessment of the two patients presented in this report is consistent with previously published data. While these are common periodontal pathogens, their increased presence in PLS patients can be compared to that microbiome previously described in individuals historically diagnosed with AgP. Furthermore, comparisons can be made due to the similar neutrophil dysfunction[24,25] found in both conditions and a possible AgP-specific microbiome profile.[26,27]

It is important to note, however, that periodontitis found in individuals with PLS is thought to be a systemic manifestation of the disease, as described by Albandar,[13] where individuals diagnosed with Grade C periodontitis (or an AgP phenotype) often respond positively to periodontal therapy, which aims to eliminate or reduce the amount of periodontal pathogens positively; individuals with PLS do not.

Treatment of PLS is a challenge to the medical and dental profession. Multiple therapeutic approaches have been proposed over the years; none has been consistently successful. Cases have been reported in which stringent plaque control and recall periods as frequent as two weeks were enacted, yet periodontal degradation often continued.[23] Complete extraction of deciduous teeth has also been attempted, in hopes that a complete edentulous period before eruption of permanent teeth would decrease the rate of periodontal breakdown, but that, too, has yielded inconsistent results.[28] Patients are often left with complete maxillary and mandibular dentures by their late teens; however, severely atrophic and thin alveolar ridges make the stability of complete upper and lower dentures very difficult in these patients.

Advancements in implants in the past 20 years have opened another treatment option for these patients. Implant osseointegration does not seem to be affected by the deficiency of cathepsin C in PLS,[8-10] yet information is limited regarding the complication rate in these individuals. Clinicians should proceed with caution. Even with different etiology, individuals with AgP and LPS appear to share a defective immunological response and retarded ability to answer to a bacterial challenge. AgP has been shown to increase risk of future peri-implantitis by 14-times[29] and a four-fold increased risk for implant failure.[30] It would be prudent to believe that implants in LPS patients would see a similar if not higher risk.

Table 2. Laboratory analysis report of Patient B: Sample taken from buccal aspect of maxillary right central incisor (8B). Note high level of *Actinobacillus actinomycetemcomitans*, *Fusobacterium* species and *Peptostreptococcus micros* when compared to normal range.

			Antibiotic Susceptibility "S"=Susceptible "R"=Resistant		
Cultivable Species	Normal Range (approximate %)	% of Cultivable Microbiota	Tetracycline-HCl (2 microgram/ml)	Penicillin G (2 microgram/ml)	Metronidazole (4 microgram/ml)
A. actinomycetemcomitans	0-0.01	0.286	R	S	R
P. intermedia/nigrescens	0-2.5	0.102	S	R	S
Eikenella corrodens	0-1.0	0.000			
Campylobacter (Wolinella) rectus	0-2.0	1.225	S	S	S
Capnocytophaga species	0-5.0	0.000			
Fusobacterium species	0-5.0	9.184	S	S	S
Peptostreptococcus micros	0-2.5	3.061	S	S	S
Enteric gram-negative rods	0	0.000			
Enterococcus species	0	0.000			
Staphylococcus aureus	0	0.000			
Other staphylococcus species	No defined range	0.000			
Yeast	0-0.5	0.000			

Immunofluorescence			Note: Pathogenicity of individual species is affected by presence of other bacteria, as well as host-parasite interactions.
		____ % of microscopic counts	
Porphyromons gingivalis	0-0.5	0.0	
Bacteroides forsythus	0-1.0	1.4	
Morphotypes			
Spirochetes	0-5.0	4.0	
Motile Rods	0-5.0	1.0	
Nonmotile Rods	No defined range	37.0	
Coccoid Cells	No defined range	58.0	
		—	
		TOTAL: 100%	

For the treatment of skin lesions, limited success has been achieved with oral retinoids with etretinate, a second-generation retinoid commonly used to treat severe psoriasis. Typically, clearance of skin lesions starts within 8 to 10 weeks of onset of etretinate course, with complete clearance of palmoplantar keratoderma after 10 to 12 weeks.[4] Oral retinoids only suppress and do not revert the keratinization. They should be given in long-term, full doses until complete resolution of the lesions has been obtained. Less than half a dose should be given for maintenance for periods up to three years.[4,11] Prior to start of therapy, it is important to ensure the patient is not pregnant, as exposure to retinoids during pregnancy can result in fetal retinoid syndrome. Patient G completed a pregnancy test before onset of her retinoid therapy.

In this study, though intracranial classification and increased susceptibility to infection were not present, somatic retardation was noticed in Patient B. Also, due to the resistance of some bacteria to tetracycline-Hcl, metronidazole and penicillin G, antibiotic therapy was not used. Therefore, the treatment approach was extraction of hopeless teeth, professional scaling, fabrication of dentures and use of oral retinoids. Significant improvement in palmar and plantar hyperkeratosis was noticed after use of isotretinoin (Figure 8). Both patients eventually lost all of their teeth and had maxillary and mandibular complete dentures fabricated. Although the option of implants at no cost was given, both patients refused.

Queries about this article can be sent to Dr. Bina at Babak.Bina@NYULangone.org.

REFERENCES

1. Papillon M, Lefevre P. Two cases of symmetrically familial palmar and plantar hyperkeratosis (Meleda disease) within brother and sister combined with severe dental alterations in both cases. Bull Soc Fr Dermatol Syphiligr 1924;31(2): 82-87.
2. Haneke E. The Papillon-Lefèvre syndrome: keratosis palmoplantaris with peiodontopathy. Report of a case and review of the cases in the literature. Hum Genet 1979;51(1):1-35.
3. Fischer J, et al. Mapping of Papillon-Lefevre syndrome to the chromosome 11q14 region. Eur J Hum Genet 1997;5(3):156-60.
4. Hart TC, et al. Mutations of the cathepsin C gene are responsible for Papillon-Lefèvre syndrome. J Med Genet 1999;36(12):881-7..
5. Rao NV, Rao GV, Hoidal JR. Human dipeptidyl-peptidase I. Gene characterization, localization, and expression. J Biol Chem 1997; 272(15):10260-5.
6. Gelmetti C, et al. Long-term preservation of permanent teeth in a patient with Papillon-Lefèvre syndrome treated with etretinate. Pediatr Dermatol 1989;6(3):222-5.
7. el Darouti MA, Al Raubaie SM,, Eiada MA. Papillon-Lefèvre syndrome. Successful treatment with oral retinoids in three patients. Int J Dermatol 1988;27(1):63-6.
8. Etöz OA, Ulu M, Kesim B. Treatment of patient with Papillon-Lefevre syndrome with short dental implants: a case report. Implant Dent 2010;19(5):394-9.
9. Quirynen M, Van Assche N. Microbial changes after full-mouth tooth extraction, followed by 2-stage implant placement. J Clin Periodontol 2011;38(6) 581-9.
10. Senel FC, et al. A 3-year follow-up of the rehabilitation of Papillon-Lefèvre syndrome by dental implants. J Oral Maxillofac Surg 2012;. 70(1):163-7.
11. Adbulwassie H, Dhanrajani PJ, Jiffry A. Papillon-Lefèvre syndrome. Reappraisal of etiology, clinical features and treatment. II. Oral rehabilitation using osseointegrated implants. Indian J Dent Res 1996; 7(2):63-70.
12. Papapanou PN, et al. Periodontitis:consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Clin Periodontol 2018;45 Suppl 20:S162-S170.
13. Jepsen S, et al. Periodontal manifestations of systemic diseases and developmental and acquired conditions: Consensus report of workgroup 3 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol 2018;89 Suppl 1:S237-S248.
14. Ullbro C, et al. Osseointegrated implants in a patient with Papillon-Lefèvre syndrome: a 4½-year follow-up. Journal of Clinical Periodontology: Case Report 2000;27(12):951-954.
15. Woo I, et al. Dental implants in a young patient with Papillon-Lefevre syndrome: a case report. Implant Dent 2003;12(2):140-4.
16. Global Burden of Disease (GBD) 2015 Mortality and Causes of Death Collaborators, Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1459-1544.
17. Bergman R, Friedman-Birnbaum R. Papillon-Lefèvre syndrome: a study of the long-term clinical course of recurrent pyogenic infections and the effects of etretinate treatment. Br J Dermatol 1988;119(6): 731-6.
18. Toomes C, et al. Loss-of-function mutations in the cathepsin C gene result in periodontal disease and palmoplantar keratosis. Nat Genet 1999; 23(4):421-4.
19. Bullon P, et al. Late onset Papillon-Lefèvre syndrome? A chromosomic, neutrophil function and microbiological study. J Clin Periodontol 1993;20(9):662-7.
20. Eick S, et al. Lack of cathelicidin processing in Papillon-Lefevre syndrome patients reveals essential role of LL-37 in periodontal homeostasis. Orphanet J Rare Dis 2014;9:148.
21. Roberts H, et al. Characterization of neutrophil function in Papillon-Lefevre syndrome. J Leukoc Biol 2016;100(2):433-44.
22. Van Dyke TE. Neutrophil receptor modulation in the pathogenesis of periodontal diseases. J Dent Res 1984;63(3): 452-4.
23. De Vree H, Steenackers K, De Boever JA. Periodontal treatment of rapid progressive periodontitis in 2 siblings with Papillon-Lefèvre syndrome: 15-year follow-up. J Clin Periodontol 2000;27(5):354-60.
24. Van Dyke TE, et al. Neutrophil chemotaxis in families with localized juvenile periodontitis. J Periodont Res 1985;20(5):503-14.
25. Gronert K, et al. A molecular defect in intracellular lipid signaling in human neutrophils in localized aggressive periodontal tissue damage. J Immunol 2004;172(3):1856-61.
26. Haubek D, et al. Risk of aggressive periodontitis in adolescent carriers of the JP2 clone of Aggregatibacter (Actinobacillus) actinomycetemcomitans in Morocco: a prospective longitudinal cohort study. Lancet 2008;371(9608):237-42.
27. Chahboun H, et al. Bacterial profile of aggressive periodontitis in Morocco: a cross-sectional study. BMC Oral Health 2015;15:25.
28. Glenwright HD, Rock WP. Papillon-Lefevre syndrome. A discussion of aetiology and a case report. British Dental Journal 1990;168(1):. 27-29.
29. Swierkot K, et al. Mucositis, peri-implantitis, implant success, and survival of implants in patients with treated generalized aggressive periodontitis: 3- to 16-year results of a prospective long-term cohort study. J Periodontol 2012; 83(10):1213-25.
30. Monje A, et al. Generalized aggressive periodontitis as a risk factor for dental implant failure: a systematic review and meta-analysis. J Periodontol 2014. 85(10):1398-407.


Dr. Bina


Dr. Zats


Dr. Rubinstein

Babak Bina, D.M.D., is director of the GPR program at NYU Langone Health, Brooklyn, NY.

Boris Zats, D.D.S., is cochair of oral maxillofacial surgery at NYU Langone Health, Brooklyn, NY.

Tom Rubinstein, D.M.D., is a periodontics resident at Columbia University College of Dental Medicine, New York, NY.