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COMMENT

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Pediatric dentistry

Recent developments in the diagnosis, treatment, and management of Papillon-Lefèvre Syndrome

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A COMMENTARY ON
Schnabl D, Thumm F M, Kapferer-Seebacher I, Eickholz P. Subsiding of periodontitis in the permanent dentition in individuals with Papillon-Lefèvre Syndrome through specific periodontal treatment: a systematic review. *Healthcare (Basel)* 2022; https://doi.org/10.3390/healthcare10122505.

PRACTICE POINTS

- Early diagnosis and extraction of all primary teeth before the eruption of permanents, thereby eliminating bacterial reservoirs, was sometimes beneficial.
- Suppression of *A. actinomycetemcomitans* below detection limits, usually achieved with adjunctive amoxicillin/metronidazole, correlated with treatment success. This aligns with evidence that *A. actinomycetemcomitans* plays a key role in PLS-associated periodontitis.
- While challenging due to periodontal defects, orthodontic therapy was successfully performed in a few individuals who maintained strict plaque control and supportive care.
- Maintaining strict compliance with home care and regular visits is crucial, as disease recurrence occurs once compliance lapses.

DATA SOURCES: A systematic search of PubMed, LIVIVO, and Ovid was conducted up to March 2021. These databases were searched for relevant clinical studies on periodontal treatment success in individuals with Papillon-Lefèvre syndrome (PLS).
STUDY SELECTION: Clinical studies reporting successful treatment outcomes defined as the loss of four or fewer permanent teeth due to periodontitis and the arrest of periodontitis or probing depths of 5 mm or less in individuals with PLS followed up for ≥24 months were included, and data extracted.
DATA EXTRACTION AND SYNTHESIS: Twelve studies reporting on nine PLS patients met the inclusion criteria. The extracted main outcomes in the studies reporting successful periodontal treatment in PLS were as follows: (1) clinical and genetic diagnosis of PLS; (2) age at baseline; (3) initial dental, periodontal parameters, and microbiological assessment, if available; (4) description of disease progression and applied therapies; and (5) outcome and follow-up.
RESULTS: Twelve studies reporting nine individuals were included. The timely extraction of affected or all primary teeth, compliance with oral hygiene instructions, supra- and subgingival debridement within frequent supportive periodontal care intervals, and adjunctive systemic antibiotic therapy in most patients affected a halt in disease progression. Suppression of *Aggregatibacter actinomycetemcomitans* below detection limits was associated with periodontal stabilization.
CONCLUSIONS: An intensive, multidisciplinary approach with strict compliance may enable the decelerated progression of PLS-associated periodontitis. The early diagnosis of PLS and the suppression of A. *actinomycetemcomitans* below the detection level might be critical factors for treatment success. It required significant effort and patient compliance. The study emphasized the importance of timely interventions, oral hygiene maintenance, regular professional dental care, and, in some cases, systemic antibiotics.

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GRADE Rating: ●●●○

COMMENTARY

Papillon-Lefèvre Syndrome (PLS) is a rare autosomal recessive disorder characterized by palmoplantar hyperkeratosis and early onset of severe destructive periodontitis, leading to premature loss of both primary and permanent dentitions. PLS prevalence is estimated at ~1/250,000 and 1/1,000,000 in the general population. Specifically, it is reported to occur between 1–4 cases per million. PLS male-to-female ratio is 1:1 and found in all ethnic groups[1–3]. PLS is caused by mutations in the *CTSC* gene (11q14.2)

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that lead to the deficiency of cathepsin C enzymatic activity, a lysosomal protease playing a role in epidermal differentiation and desquamation, and activation of serine proteases expressed in cells of the immune system. The lack of cathepsin C causes impaired neutrophil chemotaxis, phagocytosis, and decreased bacterial clearances. The PLS neutrophils cannot effectively reach the site of infection, allowing the proliferation of bacteria like *Actinobacillus actinomycetemcomitans* that contribute to severe periodontitis[4]. PLS typically becomes apparent between the ages of 2 and 3, as children with this condition experience periodontal infections that cause their primary teeth to be shed prematurely[5]. The periodontal inflammation is severe. If not treated aggressively, there is rapid, widespread destruction of the periodontium, alveolar bone, and subsequent tooth loss. However, even with treatment, most patients lose their permanent teeth by age 14–16[6].

Early diagnosis of PLS is crucial for effective management. Dentists play a significant role in diagnosing PLS, as patients often present with early periodontal destruction. A thorough oral examination and a detailed patient history can help identify the presence of PLS[7]. The dental radiographic examination can reveal alveolar bone atrophy[5]. Histopathological analysis of skin biopsies can demonstrate the presence of hyperkeratosis, focal parakeratosis, moderate perivascular infiltration, hypergranulosis, and acanthosis[8]. Neutrophil function tests can detect abnormalities in chemotaxis and phagocytosis by polymorphonuclear leukocytes. Furthermore, biochemical assessments can indicate reduced cathepsin C (CTSC) activity. Ultimately, genetic testing confirms the diagnosis of PLS[9].

Differential diagnosis of PLS should consider two rare disorders allelic variants: Haim-Munk syndrome and prepubertal/aggressive periodontitis. In Haim-Munk syndrome, skeletal abnormalities are usually present, which are not seen in PLS[9]. Additionally, several diseases with similar dermatologic features should be considered. These include localized epidermolysis palmoplantar keratoderma (Vörner), mal de Meleda, Howel-Evans syndrome, transgrediens et progrediens palmoplantar keratoderma (Greither's disease), and keratosis punctata[1, 8]. A thorough evaluation of clinical signs, symptoms, and genetic testing can help differentiate PLS from these other conditions and ensure an accurate diagnosis.

A variety of treatment methods have been proposed for PLS. Among them, the review by Schnabl et al. [10] is noteworthy as it offers a glimmer of hope, displaying how specific periodontal treatment can significantly reduce periodontitis in the permanent dentition of these patients. This debunks the past belief of the inevitability of tooth loss in PLS cases, thus bringing a paradigm shift in the approach to PLS treatment. While affirming specific periodontal treatment's success, the review leaves several questions unanswered. It does not delve into the effectiveness of treatment against the severity or subtype of PLS, nor does it ponder on whether the presence of existing systemic conditions could influence the response to therapy. These research gaps reflect the necessity for concerted efforts to understand PLS thoroughly. It also highlights the demand for comprehensive studies to decipher the syndrome's pathogenesis and treatment response. Acknowledging the informative value of the systematic review in light of specific periodontal treatments for PLS, enlightening, the largely anecdotal and case report-based evidence provided in the review makes a compelling case for well-designed clinical studies. Further research should focus on the influences of disease severity, systemic conditions, and potential benefits of adjunctive therapies.

The management of PLS involves a combination of dental and dermatological treatments. The suppression of Aggregatibacter actinomycetemcomitans below the detection limit was correlated with the subsiding of periodontitis. Patients are instructed to brush their teeth frequently with a soft brush and use chlorhexidine mouthwashes. The mainstay of periodontal treatment consists of mechanical plaque control measures like professional scaling and root planing to reduce the bacterial load and halt the periodontal breakdown. Antibiotic therapy, especially amoxicillin with metronidazole, was key for Aa suppression and periodontitis control. Primary tooth extraction to eliminate pathogenic niches was also deemed beneficial[5, 10]. Frequent supportive periodontal care at 1-week to 3-month intervals according to the severity of diseases. With intensive treatment, PLS periodontitis progression may be halted. Patient motivation and compliance are paramount. Prognathic defects and dental abnormalities resulting from extensive bone and tooth loss are managed via prosthetic or surgical rehabilitation to improve esthetics and function. Regarding the replacement of missing teeth with implants, the findings are contradictory. Studies have confirmed the successful placement of extracted teeth with implants after controlling the disease and maintaining good oral hygiene[6, 11].

Management of the dermatological component focuses on treating recurrent palmoplantar keratoderma. Retinoids such as isotretinoin demonstrate efficacy in palliating palmoplantar hyperkeratosis and are considered first-line agents. Acitretin therapy has also shown excellent results in improving palmoplantar skin lesions within four weeks[12]. However, relapses are common after discontinuation due to the lifelong nature of the disease. Topical keratolytic containing urea or salicylic acid help soften thickened skin and reduce fissuring pain. Based on anecdotal case reports, biologic treatments blocking tumor necrosis factor-alpha activity have shown promise for severe, treatment-resistant cases.

More recently, hematopoietic stem cell transplantation (HSCT) has emerged as a promising treatment approach. HSCT allows for replacing the defective immune system with healthy donor cells, thereby correcting the underlying immunologic defect. More recently, HSCT has emerged as a promising treatment approach. HSCT allows for replacing the defective immune system with healthy donor cells, thereby correcting the underlying immunologic defect. Several successful cases of dental implant placement and retention of teeth have been reported following HSCT, though long-term follow-up studies are still lacking.

Patients should be educated about the importance of proper oral care, including brushing, flossing, and using mouthwash. Regular dental visits can help monitor the progression of periodontitis and allow for early intervention if necessary. Dental professionals treating patients with PLS should be aware of the importance of early intervention and the need for a comprehensive, multidisciplinary approach to periodontal treatment. In addition, dental professionals should educate patients and their families about the importance of maintaining good oral hygiene and adhering to prescribed treatment regimens.

In conclusion, the best treatments for Papillon-Lefèvre Syndrome involve a combination of dental and dermatological interventions. Early diagnosis, effective management, and preventive measures can significantly improve the quality of life for patients with PLS. As dentists play a crucial role in diagnosing and managing PLS, it is essential to create awareness among the dental fraternity about this rare condition. This path would undoubtedly pave the way for refining disease management strategies, thereby improving the life quality of PLS patients.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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