The Saudi Dental Journal 36 (2024) 682–687

Contents lists available at ScienceDirect

The Saudi Dental Journal

journal homepage: www.ksu.edu.sa
www.sciencedirect.com

Papillon-Lefèvre syndrome in dental pediatric patient: A comprehensive review

Kaminedi Raja Rajeswari [a], Rahaf Almansour [b,*], Farah Alrajhi [b], Alanoud Fahad Binmeqren [b], Maram Shayan Albaqami [b], Raghd abdullah Albarrak [b]

[a] Department of pediatric dentistry, college of dentistry, king Saud university, Riyadh, Saudi Arabia
[b] College of Dentistry, King Saud University, Riyadh, Saudi Arabia

ARTICLE INFO

Keywords:
Papillon–lefevre syndrome
Management papillon–lefevre syndrome
Diagnosis papillon–lefevre syndrome
Clinical manifestations
Etiology papillon–lefevre syndrome

ABSTRACT

Introduction: Papillon–Lefèvre syndrome (PLS) is an autosomal recessive genetic disorder characterized by the presence of palmoplantar hyperkeratosis on the hands and feet, as well as severe periodontal disease affecting both the primary and permanent teeth, which can lead to premature tooth loss

Aims: This review aimed to characterize the etiology, clinical manifestations, diagnosis, and recent dental management strategies of pediatric patients with PLS.

Material and Methods: A comprehensive search of the electronic literature was conducted using specific keywords such as "Papillon–Lefèvre syndrome in dentistry," "Etiology of Papillon–Lefèvre syndrome," "Oral manifestations of Papillon–Lefèvre syndrome," "Management of Papillon–Lefèvre syndrome," and "Papillon–Lefèvre syndrome." A total of 47 publications that provided relevant information and discussed the various aspects of PLS were identified.

Conclusion: The management of PLS necessitates a multidisciplinary approach, including the active involvement of a dental surgeon, dermatologist, and pediatrician to ensure comprehensive care. Extraction of primary teeth and administration of antibiotics is a successful treatment strategy, while placement of removable partial denture is the best option for pediatric patients.

1. Introduction

Papillon–Lefèvre syndrome (PLS), initially described by French physicians Papillon and Lefèvre(Muppa et al., 2011), is a rare genetic condition characterized by widespread palmoplantar hyperkeratosis, which affects the skin on the palms of the hands and soles of the feet, with severe periodontal inflammation that can result in the early loss of primary and permanent teeth. PLS follows an autosomal recessive pattern of inheritance(Saskianti et al., 2020), and is classified as a form of genetically and clinically diverse palmoplantar keratodermas or keratoses (PPKs). These conditions share a common characteristic of hyperkeratotic lesions primarily affecting the palms and soles. However, PLS stands apart from other PPK disorders due to its unique feature of early onset and aggressive periodontitis(Ullbro & Twetman, 2007). The periodontal lesions in PLS manifest at an early stage following the eruption of the primary teeth in the dental arch(Giannetti et al., 2020). The prevalence of this condition is similar in both boys and girls, without any significant racial predominance(Hattab et al., 1995). The cutaneous lesions of PLS can manifest either at birth, or within the first 1–2 months of age. However, the most common timeframe for the appearance of these lesions is between 6 months and 4 years of age, which coincides with the eruption of the primary teeth(Dhanrajani, 2009). Since its initial description, PLS has been consistently linked to a severe and destructive periodontal disease characterized by the premature and extensive loss of teeth and alveolar bone, particularly in young individuals. The oral manifestations of PLS have a profound impact on both the functional and cosmetic aspects of oral health, causing significant challenges. In addition to dermatological lesions, the compromised oral condition can lead to psychological and social difficulties, particularly among young children(Ullbro & Twetman, 2007). Therefore, timely identification and intervention play a crucial role in preventing tooth loss and enhancing the overall quality of life for individuals

Abbreviations: PLS, Papillon–Lefevre syndrome; PPK, palmoplantar keratodermas or keratoses.

* Corresponding author.
E-mail addresses: rchowluru@ksu.edu.sa (K. Raja Rajeswari), r.rahaf.a.almansour@gmail.com (R. Almansour), farah11alrajhi@gmail.com (F. Alrajhi), Alanoudf79@gmail.com (A. Fahad Binmeqren), albaqamimaram422@gmail.com (M. Shayan Albaqami), albarrakraghd@gmail.com (R. abdullah Albarrak).

https://doi.org/10.1016/j.sdentj.2024.02.003
Received 16 December 2023; Received in revised form 10 February 2024; Accepted 12 February 2024
Available online 15 February 2024

affected by PLS. Hence, accurate identification of the clinical manifestations of PLS by dental professionals is crucial, and must be followed by the delivery of suitable treatment and counseling to affected individuals and their families. As such, a high degree of knowledge about the distinctive features of PLS and its oral implications is required(Mangal & Ganapathy, 2023). Consanguineous marriage, a cultural practice deeply rooted in history, is prevalent in communities worldwide, encompassing approximately 20 % of the global population. Notably, Arab countries exhibit the highest rates, with approximately 20–50 %, of marriages being consanguineous(AIBarrak et al., 2016). There have been approximately 250 cases of PLS documented globally, with the majority of cases occurring in Saudi Arabia, among Caucasians. According to estimates, there is one case of PLS for every four million people(Adamski et al., 2020); however, Saudi Arabia has a higher incidence than other regions of the world, which may be related to the cultural phenomenon of cluster marriages(AIBarrak et al., 2016). Consanguineous marriages have been linked to an increased incidence of autosomal recessive diseases(Shawli et al., 2020). For an offspring to have PLS, both parents must carry the autosomal gene. When two carriers have children, the offspring has a 25 % probability of having the disease(Kaustubh et al., 2013). Given that consanguinity is a major risk factor for autosomal recessive diseases, genetic counseling is advised to confirm the diagnosis and educate the family on the disease inheritance pattern(Shawli et al., 2020). This review aimed to characterize the etiology, clinical manifestations, diagnosis, and recent dental management strategies of pediatric patients with PLS.

2. Methodology

This review article provides a comprehensive evaluation of published studies that explore and discuss the various aspects of PLS. A systematic search of the electronic literature databases of PubMed and Google Scholar was conducted utilizing specific inclusion criteria to identify systematic reviews, case series, case reports, and previous literature reviews and books. The following articles were excluded from the literature review: articles written in a language other than English and articles not mentioning PLS. The following key terms were searched for: “Papillon–Lefèvre syndrome in dentistry,” “Etiology of

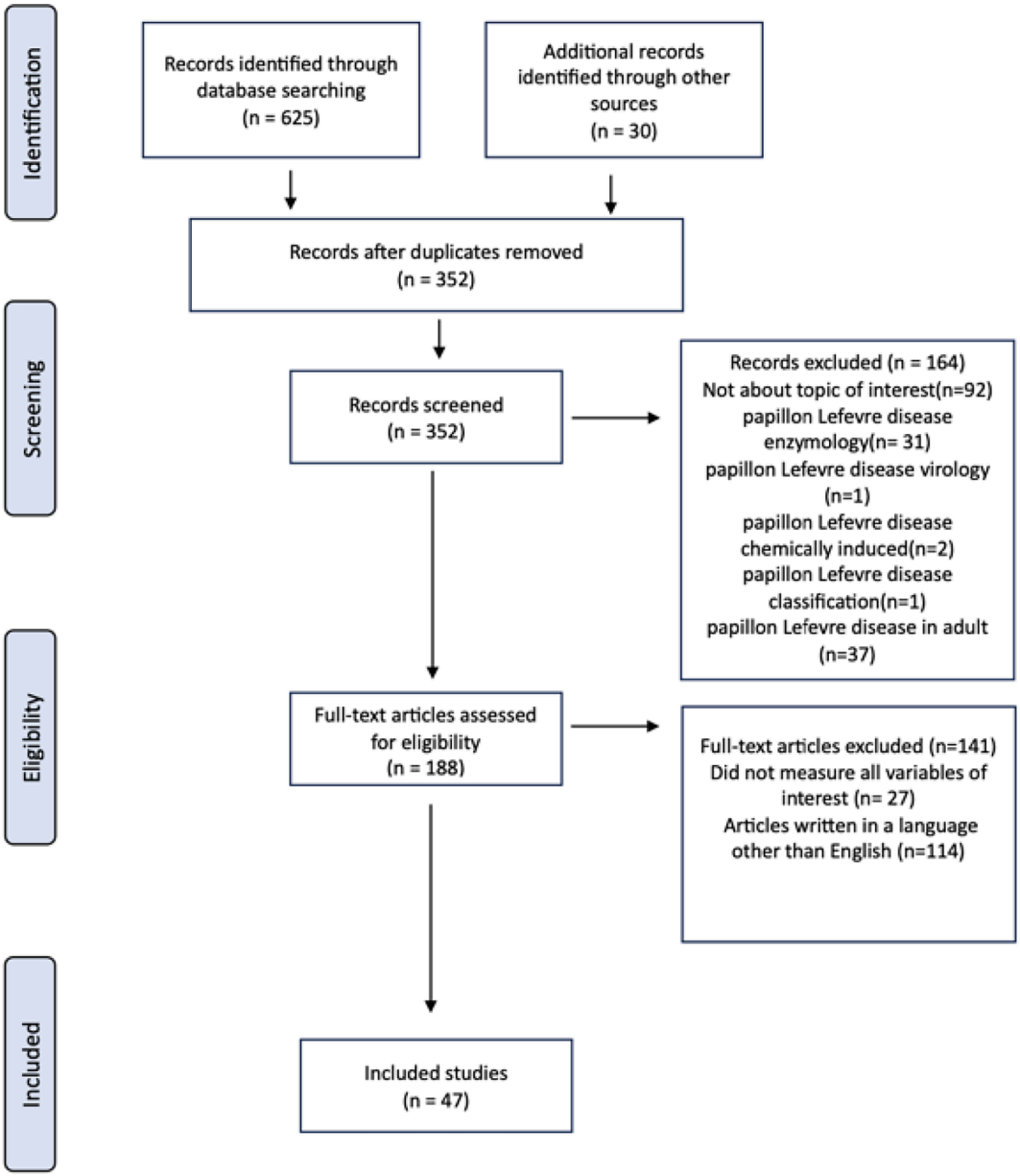

Fig. 1. PRISMA CHART.

Papillon–Lefèvre syndrome," "Oral manifestations of Papillon–Lefèvre syndrome," "Management of Papillon–Lefèvre syndrome" "Papillon–Lefèvre syndrome" and "prosthodontics," from the year 1985 to 2023 in English language. A total of 47 papers specifically related to PLS were finally included in this review]Fig. 1[.

3. Discussion

3.1. Etiology

PLS is an autosomal recessive disorder resulting from loss of function mutations in the *CTSC* gene(Castori et al., 2009). Dipeptidyl-peptidase I, another name for cysteine-lysosomal protease encoded by the *CTSC* gene, is responsible for removing dipeptides from the amino terminus of protein substrates. It also exerts activity against endopeptidases(Angel et al., 2002). This gene encodes cathepsin C, a lysosomal cysteine protease that is essential for the activation of serine proteases associated with granules in immune/inflammatory cells(Castori et al., 2009). Many different immunological and inflammatory reactions are mediated by the *CTSC* gene. For example, it activates serine proteinases produced in the granules of bone marrow-derived cells belonging to the myeloid and lymphoid series. Serine proteinases are involved in many inflammatory and immunological processes, including the activation of T lymphocytes and phagocytic cells and the phagocytic killing of microorganisms. As a result, a lack of *CTSC* function can impair the immune response and increase the risk of infection. According to recent developments, the first immunological dysfunction in PLS that is consistently observed is the reduction of the cytotoxic activity of natural killer cells. This indicates that the pathophysiology of PLS-associated periodontitis may be influenced by the decreased cytotoxicity of natural killer cells(Lundgren et al., 2005).

Cathepsin C is a protein composed of three polypeptide chains linked together through noncovalent interactions. Over 60 mutations in the *CTSC* gene with the potential to disrupt the proper folding and functioning of the encoded protein have been identified. Notably, the expression of the cathepsin C gene is specifically found in epithelial regions, such as the keratinized oral gingiva, in individuals affected by PLS(Giannetti et al., 2020). Impaired neutrophil function is recognized as the primary underlying factor in PLS, leading to the dysregulation of polymorphonuclear leukocyte response to microbial infections(Newman & Takei, 2015). Autophagy machinery and lysosomal degradation, a process in which autophagosome–lysosome fusion plays a crucial role, must cooperate to ensure the normal cellular turnover of proteins and organelles(Bullón et al., 2018; Castejón-Vega et al., 2021). Aberrations in this pathway is a recognized pathologic mechanism that causes significant pathologic abnormalities when undegraded substrates accumulate in autophagolysosomes due to lysosomal enzyme deficiency (Bullón et al., 2018). Autophagic dysfunction in the fibroblasts of patients with PLS is linked to changes in autophagosome and lysosomal permeabilization(Castejón-Vega et al., 2021). Various disruptions in the autophagy and lysosome metabolic machinery may account for the many clinical phenotypic features observed in PLS. As a result, many patients with PLS exhibit increased susceptibility to infections and periodontal disease. This is logical considering that autophagy plays an essential role in the immune response to bacterial infections, and that autophagic malfunction has been linked to infection progression and inflammation(Bullón et al., 2018).

3.2. Clinical manifestations

The oral manifestation in PLS is the Aggressive of periodontal disease, characterized by early and extensive tooth loss, representing a key feature of PLS(Hart & Shapira, 1994). Premature exfoliation of primary teeth in patients with PLS typically occurs around the age of 4–5 years, while premature loss of the permanent teeth is commonly observed between the ages of 13–15 years(Saskianti et al., 2020). In infants and young children affected by PLS, the oral mucosal and gingival tissues initially appear normal. However, following the eruption of primary teeth, the gingival tissues become inflamed and swollen, exhibiting a tendency to bleed easily. These inflammatory changes are subsequently accompanied by the swift deterioration of the periodontal tissues, leading to tooth mobility and the formation of periodontal abscesses (Hart & Shapira, 1994), As such, individuals with PLS may exhibit discomfort while chewing, as well as challenges in food ingestion (Lundgren & Renvert, 2004). Upon the loss of all deciduous teeth in patients, the previously observed gingival inflammation ceases, leading to the resolution of inflammation. Consequently, the oral mucosa exhibits a healthy appearance(Ashri, 2008). In general, no abnormalities related to sequence, timing, shape, or structure are observed in individuals with PLS. However, in certain cases, microdontia and incomplete root formation may be present as observed anomalies(Nagaveni et al., 2008). The oral manifestations in the permanent dentition exhibit similarities to those observed in the deciduous dentition. The eruption of permanent teeth follows a normal physiological timeline, and demonstrates typical developmental patterns and shapes. During tooth eruption, the gingiva becomes red and swollen, and after eruption, it continues to exhibit edema and bleeding. This condition is characterized by severe gingival inflammation, with elevated bleeding indexes, often associated with plaque accumulation. Consequently, deep periodontal pockets begin to form, indicating severe periodontal defects. Significant mobility is observed in the teeth, particularly within the anterior group. Spontaneous tooth loss commonly occurs, consequently leading to patients displaying reduced facial height and a prematurely aged appearance(Giannetti et al., 2020). The diffuse erythematous hyperkeratosis with or without fissuring was the most commonly observed presentation of palmo-plantar hyperkeratosis. This condition predominantly affected pressure areas such as the palms, soles, knuckles, ankles, elbows, and knees. The greater prominence of hyperkeratosis on the feet as compared to the hands can be attributed to the mechanical pressure exerted during walking and standing(Ullbro et al., 2003). The skin lesions in PLS present as plaques with varying colors, including white, light yellow, brown, or red. These plaques undergo a process of crustation, cracking, and deep fissuring. Additionally, there is a potential for secondary infection to occur on the compromised skin, leading to the development of abscesses(Dhanrajani, 2009). The majority of individuals diagnosed with PLS commonly present with hypotrichosis (sparse hair on the scalp and body), discolored skin pigmentation, and fragile nails that are prone to breakage. However, some patients may exhibit an excessive release of keratin within hair follicles, resulting in the formation of rough papules on the skin(Abou Chedid et al., 2019).

3.3. Characteristics of histopathology

The histopathologic characteristics of PLS are often unclear. The gingival epithelium may exhibit psoriasiform hyperplasia, acanthosis, hypergranulosis,hyperkeratosis,and irregular patches of parakeratosis. The periodontal pocket often displays an exocytosis of inflammatory cells,while the underlying connective tissue exhibits enhanced vascularity with a mixed inflammatory cell infiltration that is mostly composed of plasma cells, lymphocytes, histiocytes,and polymorphonuclear neutrophils(Shah & Goel, 2007).The thickened epidermis,hypergranulosis, hyperkeratosis,and some papillary dermal infiltrations of mononuclear cells are all visible on the skin of the palm (Sreeramulu et al., 2015).

3.4. Characteristics of radiograph

Usually during puberty, vertical alveolar bone loss in its limited form is observed around the incisors and first molars. In contrast to the horizontal type of bone loss found in chronic periodontitis, which may include two or the maximum number of teeth, the vertical pocket development associated with periodontitis is characterized by a loss of

bone that is typically more extensive on one tooth than on an adjacent tooth(Rajendran, 2009). In severe cases, the alveolar bone may be severely destroyed, with the teeth subsequently seeming to float in midair. While unerupted teeth usually grow into their bone crypts properly, in some cases, they take an unusual posture and have partially developed roots(Sreeramulu et al., 2015).

3.5. Diagnosis

The diagnostic investigations that may be necessary include:

- Hematological analysis
- Hormone assay
- Anthropometric measurements of height and weight
- Urine analysis
- Alkaline phosphatase assessment
- Radiological examinations, such as orthopantomography, intraoral periapical radiographs, and lateral cephalogram
- Neutrophil function test(Sreeramulu et al., 2015).

However, the diagnosis of Papillon–Lefèvre syndrome relies on the identification of clinical signs and symptoms as the primary diagnostic approach. Genetic testing is often subsequently performed to confirm the diagnosis(Henderson et al., 2009). Clinical examination may further be performed on both the skin and oral tissues (Hart & Shapira, 1994). Periodontal inflammation plays a dominant role in clinical diagnosis (Henderson et al., 2009). Because the periodontium is involved, the dentist is typically the first to diagnose the PLS(Tariq et al., 2022). One prior study showed that patients with PLS exhibit similar bacterial flora, including spirochetes, and populations of Epstein–Barr virus and cytomegaloviruses, as in individuals with chronic periodontitis. Fusobacterium, black-pigmented Bacteroides, *Eikenella corrodens*, *Capnocytophaga gingivalis*, and *Aggregatibacter actinomycetemcomitans* were all found in the gingival pockets of patients with PLS(Adamski et al., 2020). Some researchers have hypothesized that herpes viruses with pathogenic bacteria, such as *A. actinomycetemcomitans*, and underlying abnormalities of the host defense system contribute to the development of PLS periodontitis(Umeda et al., 1990). Numerous virulence factors, including collagenase, endotoxin, leukotoxin, epithelial toxins, and fibroblast-inhibiting factor, are present, indicating a bacterial mechanism for PLS. High immunoglobulin G titers against *A. actinomycetemcomitans* are observed in the serum of affected individuals. Furthermore, a significant proportion of *A. actinomycetemcomitans* colonies were cultivated from the periodontal pocket samples(Albandar et al., 2012). The mode of inheritance can be determined through a pedigree analysis, and mutation analysis using blood or tissue samples enables the identification of specific mutations. PLS follows an autosomal recessive pattern of inheritance, which means that if both parents are carriers of the defective gene, there is a 25 % risk that their child will be affected by the disorder(Hart & Shapira, 1994).

3.6. Differential diagnosis

Acrodynia, hypophosphatasia, and cyclic neutropenia are among the differential diagnoses for PLS. Erythrocyanosis, insomnia, tachycardia, muscular discomfort, mental disorders, and premature eruption of teeth with dystrophic enamel are characteristics that differentiate PLS from acrodynia or mercury poisoning. The symptoms of knock-knee, tibia and femur bending, larger wrists, hypoplastic teeth, and elevated phosphoethanolamine levels in the urine set hypophosphatasia apart from PLS. Furthermore, palmoplantar hyperkeratosis does not present in cyclic neutropenia(Sreeramulu et al., 2012). Greither's syndrome, keratosis punctata, and Howel-Evans syndrome are the additional disorders that might be considered in the differential diagnosis. However, periodontopathy is not observed in any of these conditions, despite the fact that they are all linked to palmoplantar hyperkeratosis(Sreeramulu et al., 2012).

3.7. Management

In cases where early diagnosis occurs during the deciduous or permanent dentition period, the treatment approach for PLS may involve non-surgical methods. This includes conventional periodontal treatment such as scaling and root planing. In addition, oral hygiene instructions are provided, and mouth rinses containing 0.2 % chlorhexidine gluconate are recommended. Antibiotic treatment may also be administered to effectively manage active periodontitis, aiming to preserve the teeth and prevent bacteremia(Ullbro et al., 2003). One prior study recommended antibiotics such as amoxicillin or amoxicillin with clavulanic acid. The suggested dosage was 20–50 mg/kg/day or 20–40 mg/kg/day, respectively, administered in divided doses every 8 h. It is advised to administer antibiotics for a duration of two weeks following tooth extraction to prevent postoperative complications(Tariq et al., 2022). In the book, Pediatric Dentistry Infancy through Adolescence, successful treatment outcomes in children were also documented through the implementation of antibiotic therapy(Casamassimo et al., 2012). Moreover, in Carranza's book it is noted that there are limited case reports documenting the successful retention of teeth in individuals diagnosed with PLS. The ability to preserve permanent teeth is likely influenced by the timing of treatment, specifically the administration of antibiotics and the extraction of the primary erupted teeth, in relation to the severity of syndrome symptoms(Newman & Takei, 2015). In their literature review, Wiebe et al. observed that the symptoms of Papillon–Lefèvre syndrome tended to decrease with age, while teeth that erupted later in life may have a lower likelihood of being lost(Wiebe et al., 2001). The occurrence of pyogenic liver abscess, a complication associated with PLS due to immune system impairment, can be mitigated. It is crucial to educate patients regarding proper dental care practices and schedule monthly follow-up visits for dental scaling and assessment of their oral health status(Ullbro et al., 2003).

Conventional periodontal therapy has proven to be ineffective in patients with PLS, primarily due to the rapid and aggressive nature of periodontitis, leading to severe loss of alveolar bone(Shapira et al., 1985). Due to early severe alveolar bone resorption, prosthetic management presents a notable challenge in these patients. Certain studies have proposed an alternative approach(Saskianti et al., 2020) involving the extraction of all primary teeth at least six months before the eruption of the first permanent tooth(Tariq et al., 2022) as a means to preserve alveolar bone height and facilitate subsequent prosthodontic rehabilitation. This may include the utilization of osseo-integrated implants to address the functional and aesthetic needs of these patients(Etöz et al., 2010).

Further, the study families and affected individuals may benefit from genetic counseling. The entire family should receive psychosocial support. The comprehensive care of patients with PLS requires a multidisciplinary strategy combining teams of pediatricians, dermatologists, and pediatric dentists. In the treating children with PLS who are still growing, removable partial dentures are the best option, as they allow for easy maintenance, good aesthetics, and the recovery of mastication and aesthetic functions(Saskianti et al., 2020). A systematic review provided evidence indicating that dental implants exhibit ankylosed teeth and are contraindicated in teenagers and individuals who are still in the growth phase due to the potential risk of implant infrapositioning (Atarbashi-Moghadam et al., 2020). Further, Behrents speculated that during bone growth, the implant fixture would remain fixed in its initial position, leading to a new and inferior position of the implant in relation to the alveolar crest. This is referred to as infrapositioning(Behrents, 1985). Two studies have previously demonstrated that young patients with PLS can benefit from implant therapy. In this study, the alveolar bone that supported the two titanium implants was maintained in addition to the implant's excellent osseointegration. Because of their attachments and the preservation of the underlying bone structure, these

implants contributed to an increase in the stability and retention of the mandibular denture(Woo et al., 2003; Ullbro et al., 2000). Dental implants can be used to help maintain complete dentures in place during adolescence, and implant-supported fixed prostheses can be placed through the end of growth(Millet et al., 2020). The presence of movable teeth complicates the dental impression procedure, and may result in unintentional tooth extraction(Lampraki et al., 2016). Intraoral scanning and computer-aided design and manufacturing have also been utilized in the production of complete and removable dentures in recent times. Intraoral scanning is a helpful tool for preventing loose teeth from moving while creating impressions(Bilgin et al., 2016). Digital scanning methods have also been found to be more comfortable for younger patients than traditional methods, as they prevent the gag reflex from being triggered(Burhardt et al., 2016). As such, the care of young patients with special needs can be positively impacted by implementing an entirely digital approach through an effective collaboration strategy (Crighton, 2017). The standard treatment for the dermatological symptoms of PLS is emollients; topical steroids and salicylic acid might be used to increase their effectiveness. Oral retinoids, including isotretinoin, acitretin, and etretinate, have been shown to be effective in treating PLS cutaneous and oral lesions(Ullbro et al., 2005). When the successor teeth erupt, retinoid therapy is often initiated and continued until the natural developmental process is completed(Al-Khenaizan, 2002). These retinoids, which are metabolites of vitamin A, are known to have a significant impact on keratinization by lowering the keratin content of keratinocytes. They are also implicated in the control of epithelial cell development and differentiation. Synthetic retinoids used in systemic medicine have also recently shown potential in improving cutaneous lesions in patients with PLS(Sreeramulu et al., 2015). Additionally, it is believed that retinoid stimulates humoral and cellular immunity, which in turn affects inflammation. Indeed, one study noted a noticeable improvement with a significant decrease in keratodermas after 8 weeks of oral acitretin(Lundgren et al., 1996). The detrimental consequences associated with retinoid usage include lip dryness, minor pruritus (itchiness), temporary alopecia (hair loss), increased levels of serum triglycerides and liver enzymes, hypervitaminosis A (excessive vitamin A levels), teratogenicity (ability to cause birth defects), and hepatotoxicity (liver toxicity)(Sreeramulu et al., 2015). Prolonged administration of retinoids for the treatment of keratosis can induce bone toxicity, which may subsequently disrupt growth patterns in pediatric patients, cause premature closure of epiphyses (growth plates), and increase the risk of traumatic fractures(Sreeramulu et al., 2015).

4. Conclusion

PLS is a rare genetic condition characterized by widespread palmoplantar hyperkeratosis, affecting the skin on the palms of the hands and soles of the feet, with severe periodontal inflammation that can result in the early loss of primary and permanent teeth. Mutations in the cathepsin C gene have been identified as the causative factor for PLS. Dentists are typically the first to diagnose PLS due to the involvement of the periodontium. The management of PLS necessitates a multidisciplinary approach involving the active involvement of a dental surgeon, dermatologist, and pediatrician to ensure comprehensive care. Extraction of primary teeth and administration of antibiotics constitutes a successful treatment strategy, and removable partial dentures are the best option for pediatric patients. The implementation of prosthetic interventions offers psychological and social advantages to patients by reinstating both functional abilities and aesthetic appearance, thus contributing to their overall well-being. As Saudi Arabia has a greater incidence of PLS than other regions of the world, which may be related to the societal practice of consanguineous marriages. As this incidence represents a concern, genetic counseling and mass education programs could be implemented to spread awareness among the population and to advise families of the risk of disease inheritance. Growing children must also be counseled to equip them with better disease-handling skills. Unfortunately, there are currently only a few studies addressing the impact of psychosocial factors on pediatric patients with PLS; thus, further studies are needed in this field.

CRediT authorship contribution statement

Kaminedi Raja Rajeswari: Conceptualization, Project administration, Supervision, Validation. **Rahaf Almansour:** Resources, Writing – review & editing, Writing – original draft. **Farah Alrajhi:** Resources, Writing – review & editing, Writing – original draft. **Alanoud Fahad Binmeqren:** Resources, Writing – review & editing. **Maram Shayan Albaqami:** Resources, Writing – review & editing. **Raghd abdullah Albarrak:** Resources, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abou Chedid, J.-C., Salameh, M., El-Outa, A., Noujeim, Z.E.F., 2019. Papillon-Lefèvre Syndrome: diagnosis, dental management, and a case report. Case Reports in Dentistry. 2019, 1–7. https://doi.org/10.1155/2019/4210347.

Adamski, Z., Burchardt, D., Pawlaczyk-Kamieńska, T., Borysewicz-Lewicka, M., Wyganowska-Świątkowska, M., 2020. Diagnosis of Papillon-Lefèvre syndrome: review of the literature and a case report. Adv. Dermatol .Allergol. 37 (5), 671–676. https://doi.org/10.5114/ada.2020.100480.

AlBarrak, Z.M., Alqarni, A.S., Chalisserry, E.P., Anil, S., 2016. Papillon-Lefèvre syndrome: a series of five cases among siblings. J Med Case Reports. 10 (1) https://doi.org/10.1186/s13256-016-1051-z.

Albandar, J.M., Khattab, R., Monem, F., Barbuto, S.M., Paster, B.J., 2012. The subgingival microbiota of Papillon-Lefèvre syndrome. J. Periodontol. 83 (7), 902–908. https://doi.org/10.1902/jop.2011.110450.

Al-Khenaizan, S., 2002. Papillon-Lefevre syndrome: the response to Acitretin. Int. J. Dermatol. 41 (12), 938–941. https://doi.org/10.1046/j.1365-4362.2002.01664_3.x.

Angel, T.A., Hsu, S., Kornbleuth, S.I., Kornbleuth, J., Kramer, E.M., 2002. Papillon-Lefevre syndrome: a case report of four affected siblings. J. American Academy of Dermatology, 46(2 Suppl Case Reports). S8–10 https://doi.org/10.1067/mjd.2002.104968.

Ashri, N.Y., 2008. Early diagnosis and treatment options for the periodontal problems in Papillon-Lefèvre syndrome: a literature review. J. Int. Acad. Periodontol. 10 (3), 81–86. https://pubmed.ncbi.nlm.nih.gov/18714933/.

Atarbashi-Moghadam, F., Atarbashi-Moghadam, S., Kazemifard, S., Sijanivandi, S., Namdari, M., 2020. Oral rehabilitation of Papillon-Lefèvre syndrome patients by dental implants: a systematic review. J. Korean Assoc. Oral Maxillofac. Surg. 46 (4), 220–227. https://doi.org/10.5125/jkaoms.2020.46.4.220.

Behrents, R., 1985. Growth in the aging craniofacial skeleton | WorldCat.org. In Search. worldcat.org. Center for Human Growth and Development, University of Michigan.

Bilgin, M., Baytaroglu, E., Erdem, A., Dilber, E., 2016. A review of computer-aided design/computer-aided manufacture techniques for removable denture fabrication. European J. Dentistry. 10 (2), 286. https://doi.org/10.4103/1305-7456.178304.

Bullón, P., Castejón-Vega, B., Román-Malo, L., Jiménez-Guerrero, M., Cotán, D., Forbes-Hernández, T.Y., Varela-López, A., Pérez-Pulido, A.J., Giampieri, F., Quiles, J.L., Sánchez-Alcázar, J.A., Cordero, M.D., 2018. Autophagic dysfunction in patients with Papillon-Lefèvre syndrome is restored by recombinant cathepsin C treatment. J. Allergy Clin. Immunol. 142 (4), 1131–1143.e7. https://doi.org/10.1016/j.jaci.2018.01.018.

Burhardt, L., Livas, C., Kerdijk, W., van der Meer, W.J., Ren, Y., 2016. Treatment comfort, time perception, and preference for conventional and digital impression techniques: a comparative study in young patients. Am. J. Orthod. Dentofac. Orthop. 150 (2), 261–267. https://doi.org/10.1016/j.ajodo.2015.12.027.

Casamassimo, P.S., Fields, H., McTigue, D.J., Nowak, A.J., 2012. Pediatric Dentistry: Infancy through Adolescence, 5/e. In Google Books, Elsevier India https://books.google.com.sa/books/about/Pediatric_Dentistry_Infancy_through_Adol.html?id=4VShjGL_QWMC&redir_esc=y.

Castejón-Vega, B., Battino, M., Quiles, J.L., Bullon, B., Cordero, M.D., Bullón, P., 2021. Potential role of the mitochondria for the dermatological treatment of Papillon-Lefèvre. Antioxidants. 10 (1), 95. https://doi.org/10.3390/antiox10010095.

Castori, M., Madonna, S., Giannetti, L., Floriddia, G., Milioto, M., Amato, S., Castiglia, D., 2009. NovelCTSCmutations in a patient with Papillon-Lefèvre syndrome with recurrent pyoderma and minimal oral and palmoplantar involvement. Br. J. Dermatol. 160 (4), 881–883. https://doi.org/10.1111/j.1365-2133.2008.08878.x.

Crighton, A., 2017. Oral medicine in children. Br. Dent. J. 223 (9), 706–712. https://doi.org/10.1038/sj.bdj.2017.892.

Dhanrajani, P.J., 2009. Papillon-Lefevre syndrome: clinical presentation and a brief review. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 108 (1), e1–e7. https://doi.org/10.1016/j.tripleo.2009.03.016.

Etöz, O.A., Ulu, M., Kesim, B., 2010. Treatment of patient with papillon-lefevre syndrome with short dental implants: a case report. Implant Dent. 19 (5), 394–399. https://doi.org/10.1097/id.0b013e3181ed0798.

Giannetti, L., Apponi, R., Dello Diago, A.M., Jafferany, M., Goldust, M., Sadoughifar, R., 2020. Papillon-Lefèvre syndrome: Oral aspects and treatment. Dermatol. Ther. 33 (3) https://doi.org/10.1111/dth.13336.

Hart, T. C., Shapira, L. (1994). Papillon-Lefèvre syndrome. Periodontology 2000, 6(1), 88–100 10.1111/j.1600-0757.1994.tb00029.x.

Hattab, F. N., Rawashdeh, M. A., Yassin, O. M., Al-Momani, A. S., Al-Ubosi, M. M. (1995). Papillon-Lefévre Syndrome: A Review of the Literature and Report of 4 Cases. 66(5), 413–420 10.1902/jop.1995.66.5.413.

Henderson, B., Curtis, M., Seymour, R., Donos, N., 2009. Periodontal Medicine and Systems Biology. John Wiley & Sons, In Google Books https://books.google.com.sa/books/about/Periodontal_Medicine_and_Systems_Biology.html?id=qcRAI7NdALgC&redir_esc=y.

Lampraki, E., Chochlidakis, K.M., Rossopoulos, E., Ercoli, C., 2016. An alternative impression technique for mobile teeth. J. Prosthet. Dent. 116 (4), 492–495. https://doi.org/10.1016/j.prosdent.2016.04.006.

Lundgren, T., Crossner, C.G., Twetman, S., Ullbro, C., 1996. Systemic retinoid medication and periodontal health in patients with Papillon-Lefèvre syndrome. J. Clin. Periodontol. 23 (3 Pt 1), 176–179. https://doi.org/10.1111/j.1600-051x.1996.tb02073.x.

Lundgren, T., Parhar, R.S., Renvert, S., Tatakis, D.N., 2005. Impaired cytotoxicity in papillon-lefèvre syndrome. J. Dent. Res. 84 (5), 414–417. https://doi.org/10.1177/154405910508400503.

Lundgren, T., Renvert, S., 2004. Periodontal treatment of patients with Papillon-Lefevre syndrome: a 3-year follow-up. J. Clin. Periodontol. 31 (11), 933–938. https://doi.org/10.1111/j.1600-051x.2004.00591.x.

Mangal, S., Ganapathy, D., 2023. Awareness of Papillon-Lefèvre Syndrome among dental students. J. Survey in Fisheries Sci, 10 (1S), 3891–3899. https://doi.org/10.17762/sfs.v10i1S.1037.

Millet, C., Virard, F., Lienhart, G., Ducret, M., 2020. Digital prosthodontic management of a young patient with Papillon-Lefèvre syndrome: a clinical report. J. Prosthet. Dent. 123 (4), 548–552. https://doi.org/10.1016/j.prosdent.2019.03.013.

Muppa, R., Duddu, M., Prameela, B., Dandempally, A., 2011. Papillon-lefevre syndrome: a combined approach from the dermatologist and dentist - a clinical presentation. Indian J. Dermatol. 56 (6), 740. https://doi.org/10.4103/0019-5154.91843.

Nagaveni, Suma, R., Shashikiran, ND., Reddy, S., 2008. Papillon-Lefevre syndrome: Report of two cases in the same family. J. Indian Society of Pedodontics and Preventive Dentistry. 26 (2), 78. https://doi.org/10.4103/0970-4388.41622.

Newman, M., & Takei, H. (2015). Newman and Carranza's Clinical Periodontology THIRTEENTH EDITION. https://s1.papyruspub.com/files/demos/products/ebooks/academicbooks/Medicine/Dentistry-and-Orthodontics/Preview-Newman-and-Carranzas-Clinical-Periodontology.pdf.

R. Rajendran Shafer'S Textbook Of Oral Pathology 6Th Edition 2009 In Google Books Elsevier India https://books.google.com.sa/books?id=Spk0V6TrCggC&newbks=1&newbks_redir=0&printsec=frontcover&redir_esc=y#v=onepage&q&f=false.

Saskianti, T., Ramadhani, K., Ainayah, A.N., Dewi, A.M., 2020. Use of removable partial denture in child with papillon-lefevre syndrome: case report. Indonesian J. Dental Medicine. 2 (2), 25. https://www.academia.edu/52676730/Use_of_Removable_Partial_Denture_in_Child_with_Papillon_Lefevre_Syndrome_Case_Report.

Shah, J., Goel, S., 2007. Papillon-Lefevre syndrome: Two case reports. Indian J. Dent. Res. 18 (4), 210. https://doi.org/10.4103/0970-9290.35834.

Shapira, J., Eidelman, E., Fuks, A., Hacham-Zadeh, S., 1985. Treatment of Papillon-Lefevre syndrome with chemotherapy: report of cases. Spec. Care Dentist. 5 (2), 71–74. https://doi.org/10.1111/j.1754-4505.1985.tb00389.x.

Shawli, A., Almaghrabi, Y., AlQuhaibi, A.S., Alghamdi, Y., Aboud, A.M., 2020. A mutation in cathepsin C gene causing papillon-lefèvre syndrome in a saudi patient: a case report. Cureus. https://doi.org/10.7759/cureus.6546.

Sreeramulu, B., Haragopal, S., Shalini, K., Sudha, M.D., Kiran, G., 2012. The prosthodontic management of a young edentulous patient with the papillon lefevre syndrome-A rare case report. J. Clin. Diagn. Res. 1808–1811 https://doi.org/10.7860/jcdr/2012/4884.2607.

Sreeramulu, B., Shyam, A., Suman, 2015. Papillon-Lefèvre syndrome: clinical presentation and management options. Clin. Cosmet. Investig. Dent. 75 https://doi.org/10.2147/ccide.s76080.

Tariq, M., Maknojia, M., Saurabh, S., Amarnath, Rajbhoj, S., Arya, S., 2022. Papillon-Lefevre syndrome with arachnodactyly and associated aggressive periodontitis. Int. J. Health Sci. 1984–1994. https://doi.org/10.53730/ijhs.v6ns3.5913.

Thakare, K.S., Bhongade, M.L., Charde, P., Kale, S., Jaiswal, P., Somnath, B.K., Pendor, S., 2013. Genetic mapping in papillon-lefèvre syndrome: a report of two cases. Case Reports in Dentistry. 2013, 1–4. https://doi.org/10.1155/2013/404120.

Ullbro, C., Crossner, C.-G., Lundgren, T., Stålblad, P.-Å., Renvert, S., 2000. Osseointegrated implants in a patient with Papillon-Lefèvre syndrome. J. Clin. Periodontol. 27 (12), 951–954. https://doi.org/10.1034/j.1600-051x.2000.027012951.x.

Ullbro, C., Crossner, C.-G., Nederfors, T., Alfadley, A., Thestrup-Pedersen, K., 2003. Dermatologic and oral findings in a cohort of 47 patients with Papillon-Lefèvre syndrome. J. Am. Acad. Dermatol. 48 (3), 345–351. https://doi.org/10.1067/mjd.2003.197.

Ullbro, C., Brown, A., Twetman, S., 2005. Preventive periodontal regimen in Papillon-Lefèvre syndrome. Pediatr. Dent. 27 (3), 226–232. https://pubmed.ncbi.nlm.nih.gov/16173228/.

Ullbro, C., Twetman, S., 2007. Review paper: dental treatment for patients with papillon-lefèvre syndrome (PLS). Eur. Arch. Paediatr. Dent. 8 (S1), 4–11. https://doi.org/10.1007/bf03262602.

Umeda, M., Zhang, Y.J., Koseki, T., Ishikawa, I., 1990. Clinical, bacteriological, and immunological examination and treatment of two Papillon-Lefevre syndrome patients. Kokubyo Gakkai Zasshi. J. Stomatological Society, Japan. 57 (3), 430–440. https://doi.org/10.5357/koubyou.57.430.

Wiebe, C.B., Häkkinen, L., Putnins, E.E., Walsh, P., Larjava, H.S., 2001. Successful periodontal maintenance of a case with papillon-lefévre syndrome: 12-year follow-up and review of the literature. J. Periodontol. 72 (6), 824–830. https://doi.org/10.1902/jop.2001.72.6.824.

Woo, I., Brunner, D.P., Yamashita, D.-D.-R., Le, B.T., 2003. Dental implants in a young patient with papillon-lefevre syndrome: a case report. Implant Dent. 12 (2), 140–144. https://doi.org/10.1097/01.id.0000041223.08656.a7.