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A Meticulous Periodontal Treatment Protocol for Papillon-Lefevre Syndrome

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Abbreviations: PLS: Papillon-Lefevre Syndrome; CTSC: Cathepsin C Gene; SRP: Scaling and Root Planning; OHI: Oral Hygiene Instructions.

Abstract

Background: Papillon-Lefevre Syndrome (PLS) is a condition that results in severe periodontal destruction. Patients suffer from severe inflammation, bleeding of gums, deepening of periodontal pockets, swelling, and tooth mobility, and it ultimately leads to complete loss of primary and permanent dentition. The response of PLS to treatment is unpredictable and often complicated by psychosocial difficulty.

Protocol: A new treatment protocol is presented that meticulously focuses on patients' needs through a team of specialists. A plaque control regimen is focused upon intensively by means of hygiene instructions, scaling and root planning, and subgingival irrigation with 0.2% chlorhexidine and 1.5% H_2O_2. A combination of amoxicillin and metronidazole are given systemically according to the patient's weight. Local delivery of 8.8% doxycycline gel and/or 50 mg doxycycline systemically is given for 3 months in resistant cases. Close monitoring and follow-up appointments are established as close together as 2 weeks to detect any deterioration. Once the periodontal condition is stabilized, referrals to other specialists in the team are then made according to patients' needs. Maintenance visits were established every 4 weeks.

Conclusion: Many patients treated early according to this protocol had positive results with fewer signs of periodontal disease, lost fewer permanent teeth, and had improved quality of life. This protocol is presented to encourage more controlled research in this field.

Introduction

Papillon-Lefevre Syndrome (PLS) is a rare inherited condition that manifests in palmoplantar hyperkeratosis, severe destruction of periodontal structures, and premature loss of both primary and permanent teeth [1]. Increased susceptibility to infection has also been reported in 20% of individuals with additional findings of intracranial calcification and somatic development retardation [1,2].

Hyperkeratosis is the primary skin manifestation associated with PLS that starts as early as the first year of life [1]. PLS expression is reported to vary in range and severity in affected individuals and even in the same individual at different ages [1,3]. Oral manifestations start early after the normal eruption of primary dentition. Severe inflammation, bleeding of the gums, deepening of periodontal pockets, swelling, and tooth mobil-

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ity are all symptoms associated with PLS. These symptoms can result in a completely edentulous child by the age of 4 years [1]. Afterward, gingival tissues may appear to return to their normal status; however, after the eruption of permanent teeth, a similar presentation of the disease re-emerges, which can lead to complete edentulism by the age of 14 years if left untreated [1]. It has been suggested that the most significant degree of hyperkeratosis coincides with the highest severity of periodontal destruction [1]. The genetic defect mapped in individuals with PLS is known to be in chromosome 11q14-q21, which involves mutations of the cathepsin C gene (*CTSC*) [4]. A 90% reduction in cathepsin C activity is reported in PLS [5]. The cathepsin C gene is expressed primarily in epithelial regions, such as the palms, soles, knees, and keratinized oral gingiva, which is explicitly affected in PLS [6]. It also affects immune cells such as neutrophils, macrophages, and monocytes [6]. The detrimental negative impact on the oral health of an affected individual necessitates early and unique management by the dental practitioner [1]. Multiple mechanisms of periodontal destruction have been attributed to PLS, including an altered immune response and tissue pathology, in addition to increased virulence of pathologic bacteria [7]. Neutrophils in PLS individuals have been reported to have a 50% reduction in chemotactic activity, decreased phagocytosis, and intracellular killing of pathologic bacteria [8,9]. Monocytic phagocytotic function has also been found to be reduced [10]. Microbiologically, Van Dyke et al., [9]. reported elevated levels of *Aggregatibacter actinomycetemcomitans* in PLS individuals. Preus et al., [11], hypothesized that infection with *A. actinomycetemcomitans* and hereditary defects in the junctional epithelium seal could cause severe periodontal destruction. The occurrence of PLS is found to be in one to four individuals for every million [12]. Although it is an autosomal recessive trait with worldwide rarity, it is more common in countries where consanguineous marriage is culturally accepted [6]. One-fifth of the world population considers consanguinity a deeply rooted social trend [13]. In Indian Mangalore communities, the frequency of consanguinity varies between different religious groups, where the highest rate (47.6%) is among Hindus from which 43.4% of marriages were first-cousin marriages [14]. The percentage of consanguinity among Cochin Jews is 40% [1]. Some of the highest rates of consanguineous marriages in the world are among Arab countries (50%), particularly through first-cousin marriages (25-30 %) [15]. Hattab and Amin [16] reported that one-third of the total worldwide PLS cases were Arabs (80 of 250 cases) with 75% of the 80 cases having a history of parental consanguinity. The rate among Jordanians was 51.3%, with a first-cousin marriage rate of 33% [17]. In Egypt, it accounts for 35.3% with the majority among first cousins [18]. In Saudi Arabia, the rate of consanguineous marriages was 57.7%, of which 28.4% were between first cousins, 14.6% between second cousins, and 15.2% between distant relatives [19]. Accordingly, a marked increased occurrence of PLS has become obvious [20]. Unfortunately, the response of PLS to treatment is unpredictable and complicated by the psychosocial condition of the child. Historically, treatment has focused on extracting severely affected teeth [21]. Several authors even suggested early extraction of all primary dentition to prevent the periodontal breakdown of permanent dentition [22,23]. Tinanoff et al., [24] suggested a period of edentulousness before the eruption of permanent teeth as a critical element for successful management. Meticulous management of periodontal inflammation through oral hygiene and Scaling and Root Planning (SRP) remains the crucial component of treatment in PLS [25]. Systemic antibiotics have been encouraged in addition to local measures. Tetracycline was supported by Preus and Gjermo [21] to prevent further bone loss; however, several others reported failure of this approach [9,26]. Eronat et al., [27] suggested using amoxicillin/clavulanic acid every six months and showed no tooth loss after two years of follow-up. Umeda et al., [28] reported failure of minocycline and erythromycin in eliminating *A. actinomycetemcomitans*; however, a reduction was observed with ofloxacin. Rüdiger et al., [29] were successful in completely eradicating *A. actinomycetemcomitans* in 3 out of 4 patients using a combination of amoxicillin and metronidazole. Microbiological monitoring is encouraged in the literature, especially for *A. actinomycetemcomitans* [11,28]. Oral retinoids have been used to regulate epithelial cell growth for skin lesions in patients with PLS and are reported to improve periodontal treatment results. Nazzaro et al., [30] reported a marked reduction in hyperkeratosis and periodontitis with treatment with acitretin. Similar results were reported with the use of etretinate [31,32]. However, Lundgren et al., [33] questioned the benefits of oral retinoids in the treatment of periodontitis.

While many treatment options have been reported in the literature [22,25,26,34], none have reported control over periodontics, orthodontics, endodontics, and restorative treatment for patients diagnosed with PLS. Accordingly, the objective of this article is to present a meticulous controlled periodontal treatment protocol for managing PLS.

Treatment protocol

This treatment protocol was developed by the author (NYA) to provide a comprehensive prevention and treatment program for patients diagnosed with PLS, which includes periodontal, restorative, endodontic, prosthodontic, and orthodontic treatment. Accordingly, a team was formulated in 2012 at the College of Dentistry of King Saud University to provide dental treatment for these patients. The team's objective was to provide quality oral health care for PLS patients through the formulation of a multidisciplinary comprehensive treatment plan. This treatment plan was performed in an orderly collaborative manner, with scheduled follow-up to assure the most significant preservation of the patient's teeth and provide optimum oral health care. The protocol starts with a meticulous periodontal regimen based on mechanical plaque control comprising of Oral Hygiene Instructions (OHI), supragingival and subgingival instrumentation, and root planing with subgingival irrigation of mixed 0.2% chlorhexidine and 1.5% H_2O_2 mouthwash every 2-4 weeks, depending on the oral hygiene status of the patient. If the gingival inflammation was generally aggravated, then combined systemic antibiotics were used, including amoxicillin (20-50 mg/kg/d) plus metronidazole (15-35 mg/kg/d) in divided doses every 8 hours for 2 weeks as an adjunctive treatment with the conventional periodontal treatment. If patients presented with localized inflammation or slight mobility, then 8.8% doxycycline gel was applied locally in the affected area. In situations where patients were at high risk of redeveloping inflammation, systemic use of 50 mg doxycycline for 3 months twice daily was used in adjunct to the clinical observation and periodontal treatment to act as host moderator (Figure 1).

After achieving stable periodontal conditions, if needed, orthodontic treatment was started to enhance the facial skeletal appearance and to maximize future prosthetic appliance retention that may be needed. If patients needed restorative or endodontic treatment, they were referred to the appropriate

specialist in the team. If a tooth was lost, space was maintained by a pedodontist or a prosthodontist to ensure optimal space for permanent tooth eruption and/or a dental implant.

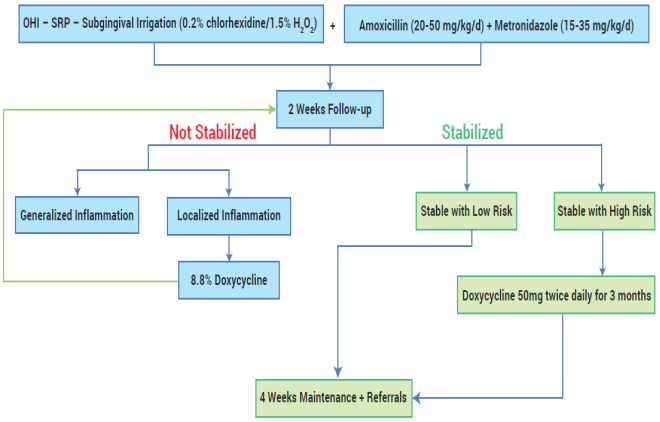

Figure 1: PLS periodontal treatment protocol.

Discussion

Papillon-Lefevre syndrome is a rare autosomal recessive condition that manifests primarily with palmoplantar hyperkeratosis, severe destruction of periodontal structures, and early loss of teeth. The condition affects 1 to 4 people per million without any sex bias. Consanguineous marriage plays a major part in increasing the number of affected individuals in certain countries. In Saudi Arabia, where this protocol was developed and applied, the rate of consanguineous marriages is 57.7%, of which 28.4% are between first cousins, 14.6% between second cousins, and 15.2% between distant relatives, which has led to a marked increased occurrence of PLS [20].

Periodontal treatment in individuals with PLS remains a challenge. In this article, a new treatment protocol is described that has been applied to multiple patients since its conception with a positive response and maximum retention of permanent dentition. This protocol is patient-centered and can be tailored to individual needs. Periodontal inflammation is the main concern for treatment in individuals with PLS. Periodontitis is an inflammatory disease of the periodontium where progressive destruction of the tissues supporting the tooth is observed [35]. Dental plaque constitutes the primary etiology of periodontitis [35]. This protocol provides extensive care to eliminate inflammation as soon as it is detected. Rounds of oral hygiene instructions and SRP were done thoroughly for each patient to control dental plaque. Lindhe et al., [36] stated that plaque-free tooth surfaces were frequently associated with a lack of recurrent periodontal disease over a period of 5 years. Subgingival irrigation with chlorhexidine or H_2O_2 was added to further control periodontal pathologic microbiota. Southard et al., [37] reported further reduction of *Porphyromonas gingivalis* and enhanced attachment levels with subgingival irrigation of 2% chlorhexidine. Wennström et al., [38] reported improvement in clinical parameters with subgingival irrigation with either chlorhexidine or H_2O_2; however, they considered this as temporary improvement. To ensure the patient is maintaining optimum oral hygiene and a plaque-free environment, close follow-ups every 2 weeks were performed until the goal was reached. This close supervision of plaque control is one of the main reasons for the success of the presented protocol.

Altering pathologic microbiology is mandatory in controlling the aggressiveness of the periodontal destruction. Haffajee et al., [39] reported greater improvement in clinical attachment levels in addition to SRP when systemic antibiotics were administered. The apparent involvement of *A. actinomycetemcomitans* in individuals with PLS requires specific targeting as reported by Van Dyke et al., [39]. The systemic combination of amoxicillin and metronidazole is known to eliminate *A. actinomycetemcomitans* as shown by Van Winkelhoff et al., [40]. Sgolastra et al., [41] demonstrated, in a systematic review, effective treatment of generalized aggressive periodontitis with combined amoxicillin and metronidazole. Other studies have tested this combination on PLS patients and similar results were reached [7,29,42]. Similarly, arrest of periodontal destruction was achieved in our patients with the combination of mechanical debridement and systemic antibiotics. Further recommendation of baseline microbiological analysis and follow-up analyses to provide objective values of treatment progression have been illustrated by Pacheco et al., [7]. In cases of localized inflammation, 8.8% doxycycline gel was used in addition to systemic administration. In a systematic review, Hanes et al., [43] found a statistically significant improvement in clinical attachment level with adjunctive use of doxycycline gel combined with SRP. When patients at considerable risk of disease instability, 50 mg doxycycline was administered systemically for 3 months. This sub-antimicrobial dose blocks the collagenase enzymes responsible for tissue destruction when challenged by periodontal pathogens. Preshaw et al., [44] reported significantly greater clinical benefits from sub-dose doxycycline than with SRP alone in the treatment of periodontitis.

Patients treated strictly according to this protocol from their early years showed fewer signs of periodontal disease and lost fewer permanent teeth than patients who started the protocol at an older age. This was especially true if signs of periodontal disease had emerged when the treatment started. Therefore, it is vital to refer the patient to a periodontist as soon as a diagnosis of PLS is discovered. Compliance with the treatment protocol had a significant impact on the presence of plaque, bleeding surfaces, periodontal pockets, and number of lost permanent teeth. Parents should be well-educated regarding the sequalae of PLS in order to increase treatment compliance. A team approach in managing PLS cases including multiple specialists provided a major positive impact on the outcome of treatment with satisfactory results, minimal tooth loss, and improved quality of life. This team approach is highly advised for treating any PLS patient.

Conclusion

In conclusion, the aforementioned protocol showed, in addition to starting treatment early, a positive result of preserving permanent teeth in many PLS patients for long periods of time that lasted more than 15 years of follow-up in multiple patients. The authors would highly encourage more controlled clinical investigations in this field to develop a consensus with a high degree of evidence in periodontal treatment for PLS patients.

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