

# Syndromes that Include both Palmoplantar Keratoderma and Severe Periodontitis: a Review

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## Abstract

Palmoplantar keratodermas (PPK) include a heterogeneous group of disorders with overlapping clinical features. The main aspect of PPK is thickening and hyperkeratosis of the palmar and plantar skin, that may be hereditary or acquired; diffuse, focal, or punctuate; and transgrediens or progrediens. PPKs are further distinguished by their mode of inheritance and by the presence of certain associated clinical features. Periodontitis was reported in association with more than one syndrome characterized by PPK. An extensively reported one is the Papillon-Lefèvre syndrome (PLS) which is characterized by early onset of PPK and periodontitis affecting the primary and secondary dentitions. In addition to PLS, Haim-Munk, HOPP, Variant Carvajal and Weary-Kindler are other syndromes manifested by PPK and reported in association with severe periodontitis. Atypical cases of PLS were also reported, such as partial expression or a late presentation of the syndrome. The aim of this article is to critically review the literature concerned with Papillon-Lefèvre syndrome in its typical and atypical clinical presentation, in addition to other syndromes manifested at the same time by PPK and severe periodontitis.

Thorough history and medical examination, together with periodontal, dermatologic, and genetic counseling, are important to exclude other existing medical conditions or other syndromes that might need special attention and care.

**Keywords:** Papillon-Lefevre syndrome; Palmoplantar keratoderma; Aggressive periodontitis

## Introduction

Periodontal disease is a spectrum of different diseases for which certain individuals are at relatively high risk [1]. Periodontitis is defined as a bacterial disease resulting in inflammation within the supporting tissues of the teeth, progressive attachment and bone loss [2]. Epidemiologic surveys in young individuals have been performed in many parts of the world and among individuals with a widely varied background. For the most part, these surveys indicated that the prevalence of severe attachment loss on multiple teeth among children and young adults are limited. The United States national survey of 11,000 children aged 14-17 years showed that the prevalence of periodontitis was approximately 0.2% to 0.5% [3]. Periodontitis among young individuals is significantly more common in developing than in developed countries, with a significant difference among races and ethnic groups [4].

The nomenclature and classification systems used to describe periodontal disease have changed periodically over the past decades [5-8]. Prepubertal periodontitis is a rare early-onset form of periodontitis that was first described by Page et al. as a distinct clinical entity. It begins with the eruption of the primary teeth and presents in a localized or generalized form. Generalized prepubertal periodontitis (GPP) affects all primary and secondary dentition and is characterized by severe gingival inflammation, rapid destruction of the soft and hard periodontal tissues, mobility, and premature tooth loss [9]. The International Workshop for a Classification of Periodontal Diseases and Conditions held in 1999 established a new classification. According to this classification, the term "prepubertal periodontitis", in particular the generalized form is replaced with the more recent term "periodontitis as a manifestation of systemic diseases" [8]. Systemic disorders that might present as periodontitis were divided into three categories: 1) those associated with acquired hematological disorders such as neutropenia and leukemias; 2) those associated with genetic disorders such as familial and cyclic neutropenia, Down syndrome, leukocyte adhesion deficiency syndromes, Papillon-Lefèvre syndrome, Chediak-Higashi syndrome, Ehlers-Danlos syndrome (Types IV and VIII), hypophosphatasia, and others [8,9]; and 3) disorders not otherwise specified.

Palmoplantar keratodermas (PPKs) is a heterogeneous group of

disorders characterized by thickening or hyperkeratosis of the palmar and plantar skin with or without other associated clinical features. The underlying gene defects for many types of hereditary PPKs have been defined. The involved genes encode intracellular structural proteins, desmosomal proteins, gap junction components, and enzymes [10]. PPKs are classified as hereditary or acquired; diffuse, focal or punctuate; and transgrediens or progrediens. Hereditary type follows autosomal recessive or dominant patterns [11]. Acquired PPKs maybe a result of internal disease, drug-related, malnutrition-associated, chemically-induced, systemic disease-related, malignancy-associated, dermatoses-related, infectious, or idiopathic [12]. Punctuate and focal types of PPK affect localized areas of the palms and soles, whereas the diffuse type affects most of the palms and soles. The latter type is further subdivided into: type I, or classical Vörner type which consists of epidermolytic PPK; type II, or Unna-Thost type, consists of non-epidermolytic PPK; type III, in which the hyperkeratotic plaques are not confined exclusively to the palms and soles, but comprises such entities of erythrokeratodermas Mendes da Costa or keratosis palmoplantaris transgrediens and progrediens, Greither's type (progressive diffuse PPK with hyperhidrosis); and type IV, the palmoplantar ectodermal keratoderm as associated with periodontitis [13]. It is the early onset of periodontal disease component that distinguishes these from the other more common forms of PPK. Therefore, PPKs are further distinguished by the presence of associated features. For example keratoderma may be limited to the volar surface of the palms of the hands and soles of the feet, i.e., transgrediens, or extends onto the dorsal aspect as well, i.e., progrediens [14].

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## Papillon-Lefèvre Syndrome

Papillon-Lefèvre syndrome (PLS) is defined as periodontitis associated with type IV diffuse palmoplantar ectodermal keratodermas. It was first described by two French dermatologists Papillon and Lefèvre in 1924 as “Mal de Meleda” which is characterized by diffuse PPK with disseminated keratotic lesions, in particular on the elbows and knees [15]. PLS, however, is typically associated with premature loss of deciduous and permanent teeth and severe periodontitis which develops shortly after tooth eruption and subsides after exfoliation of the teeth [16]. Consanguinity between parents is a factor in a significant number of PLS cases [17]. No gender or racial predominance was reported for PLS [16]. More recently, PLS is recognized as a rare autosomal recessive disorder caused by mutations in Cathepsin C gene. The exact etiology and pathogenesis of this syndrome are still not fully understood. Several factors were attributed to the etiology of PLS-periodontitis including microbiologic, immunologic, and genetic. Gram-negative anaerobic rods were predominantly found in PLS periodontitis lesions [18]. *Aggregatibacter actinomycetemcomitans* was also reported to have a significant role in the pathogenesis and progression of periodontal involvements in PLS patients. Several patients, however, were positive for other periodontal pathogens [19-21]. PLS-periodontitis was also reported to be associated with human herpesviruses [22].

Dysfunction of polymorphonuclear leukocytes (PMNs) is found to play a role in the etiology of PLS-periodontitis. PMNs released significantly increased amounts of  $O_2$  in PLS patients compared to controls [23]. PMNs chemotaxis, phagocytosis of opsonized *Staphylococcus aureus*, and production of superoxide radicals by PMNs are significantly impaired in PLS patients [24]. These functionally defective PMNs are reported to be inheritable, thus leading to difficulty in coping with periodontitis-associated pathogens [25,26].

Ultrastructural examination of the periodontal lesion in PLS revealed primary defects of cementum or periodontal ligament attachment, and disruption of fibroblast and cementoblast function [27]. Low salivary secretion rate, peroxidase level and buffering capacity are also other reported findings in PLS patients [28].

A gene defect responsible for PPK and periodontitis is thought to be caused by a defect in keratin gene clusters. However, Hart et al. in 1997 suggested that mutations in other genes are the cause [29]. In the same year, the PLS gene was demonstrated to be localized to chromosome 11q14 by homozygosity mapping [17,30]. Later it was found that PLS is caused by mutations in the gene encoding Cathepsin C, a lysosomal cysteine protease of the papain type known as dipeptidyl aminopeptidase (CTSC and DPP1) [31,32]. However, some CTSC mutations are causal for prepubertal periodontitis without PPK, and no relationship has been shown between CTSC mutations and other forms of periodontitis [33]. According to the Human Gene Mutation Database (HGMD), 77 variants of the CTSC gene exist [34].

## Typical Features of Papillon-Lefèvre Syndrome

The two main clinical features of PLS are early onset of palmoplantar keratoderma and severe periodontitis of the primary and permanent dentitions. Dermatological disorders in PLS are manifested with erythema, which progresses within six months to hyperkeratosis of soles, palms, knees, and elbows [35]. The manifestations in the palms and soles vary from mild psoriasi form scaly skin to overt hyperkeratosis that typically develops within the first three years of life. Keratosis may also affect other sites such as the elbows and knees [31]. Although there is a significant correlation between the severities of keratosis in the feet and hands, changes in the feet are more severe [36]. There

also is a positive correlation between the severity of skin lesions and seasonal variations as well as intensified periodontal destruction [37]. Other skin areas involved manifestations of PLS include eyelids, cheeks, thighs, and external malleolus [38].

In PLS aggressive periodontal destruction begins with the primary dentition, leading to premature loss of deciduous teeth by age 6 years; until the eruption of the permanent dentition, where periodontitis reappears and the teeth are prematurely lost by the age of 16-years [35,39]. Ullbro et al. analyzed 47 patients with PLS and found, with no exception, that both skin and oral changes developed early in life in all the patients studied. Dermatologic involvement showed no correlation with age, whereas periodontal disease was significantly worse in young children with deciduous teeth [36]. No significant correlation, however, was demonstrated between the severity of the periodontal and of skin affections [36]. There was an early eruption of the permanent teeth, which were caries-free with no sign of root resorption [37].

## Secondary Features associated with PLS

In addition to palmoplantar keratoderma and early periodontal destruction of primary and permanent dentition, other features may be associated with PLS, i.e., increased susceptibility to infection [16], increased risk of pyogenic liver abscess [40-43], calcification of the falx cerebri of the dura mater [44], excessive sweating (hyperhidrosis), and growth of fine body hair with the development of dirty-colored skin on the affected areas [45]. Recently, the first case of multiple brain abscesses in a child with PLS was reported [46]. The association between pyogenic liver abscess and PLS may be related to neutrophil dysfunction [41]. PLS was also reported to be associated with type-1 oculocutaneous albinism (OCA). Seven cases (six males and one female) from Egypt and Jordan were described. All of the affected individuals exhibited the typical clinical features of PLS and type-1 OCA, in addition to increased susceptibility to infection [47-50]. The co-occurrence of these two rare recessive genetic conditions was investigated by Hewitt et al. who concluded that the causative genes (CTSC and tyrosinase, respectively) shared their chromosomal location (11q14.2-14.3), but not their pathogenic mechanism [48,49].

PLS was reported to be associated with pseudoainhum of the toes, i.e., formation of constricting bands around the fingers leading to autoamputation [51]. Mental retardation is another feature that is reported [38,52]. Xanthogranulomatous pyelonephritis, which is a rare, serious, chronic inflammatory disorder of the kidney characterized by a destructive mass that invades the renal parenchyma, has also been reported in a patient with PLS [53]. A patient with PLS associated with acroosteolysis and bone loss of the fingers and the toes was described for the first time [54]. Dystrophy and transverse grooving of the nails are another feature reported in PLS patients [55].

## Atypical PLS

The term “syndrome” is derived from the Greek syn (together) and dromos (running) and refers to a running together or concurrence of symptoms. Its use for a single symptom or sign is incorrect [56]. However, a number of atypical PLS cases had been reported, including those with late presentation or partial expression of the syndrome, milder form of periodontitis or mild dermatological features. These features increase the ambiguity in understanding this syndrome and cause more confusion for the clinician to diagnose PLS-periodontitis.

Two atypical cases of familial Papillon-Lefèvre syndrome were reported, one of which had only late onset of mild skin lesion, the other had severe skin lesions and relatively mild periodontal disease [57].

Syndrome	# patients & county of origin	Main clinical features			Comments
		Dermal	Periodontal	Other	
Haim-Munk [67]	18 cases from India 1 case from Brazil 1 case from Turkey	PPK	Early onset periodontitis affecting deciduous and permanent dentitions	Onychogryphosis Acroosteolysis Pesplanus Heat intolerance Lever abscess	Autosomal recessive inheritance Causative gene CTSC Variant of PLS or distinct clinical entity
PLS/H.M? [70]	2 sisters from Jordan	PPK hyper-keratosis of knees and elbows Psoriasiform lesion around the lips	Early onset periodontitis affecting both dentitions	Onychogryphosis Acroosteolysis Pesplanus Bilateral distal interphalangeal joint contracture	Uncertain diagnosis No genetic testing
*HOPP [72,73]	Dutch mother and daughter Venezuelan male	Striate palmoplantar keratoderma	Periodontitis	Hypotrichosis, Onychogryphosis, Acro-osteolysis, Lingua plicata, Psoriasis	Mode of inheritance is uncertain
Weary-Kindler [74-76]	1 case from Afghanistan	PPK	Early onset periodontitis of primary and part of permanent dentitions Gingival fragility	Congenital poikiloderma Epidermolysis Bullosa Photosensitivity	Short-term favorable response to periodontal therapy
Variant Carvajal [77]	one female from England	Liner palmar and diffuse plantar keratoderma with episodic plantar fissures	Prepubertal periodontitis, Premature root resorption of primary teeth Missing permanent teeth, enamel defects	Wiry hair, Abnormal finger nails Cardiomyopathy	Potential risk for cardiac abnormalities

\* Hypotrichosis, Acro-Osteolysis, Palmoplantarkeratoderma, Periodontitis syndrome.

Table 1: Summary of reported Syndromes manifested by Palmoplantar Keratoderma (PPK) and Periodontitis other than Papillon-Lefèvre(PLS).

Partial and late presentation of PLS also were reported within the same family in which only late involvement of the permanent dentition with periodontitis in two daughters who showed periodontal breakdown and hyperkeratotic skin lesions. The deciduous dentition however, was not affected, although their two brothers have partial expression of the syndrome manifested only by skin lesions [24].

Partial expression of PLS was also reported in two families with several affected members of each family; they are from distantly separated areas in India and Germany. In each family, one individual has hyperkeratotic lesions with complete absence of periodontal lesions. Further, the difference in severity of the hyperkeratotic lesions between the two families is clear. One sibling in the German family expressed rapid, early onset periodontitis in the absence of PPK [58].

Kothiwale and Mathur in 2008 reported a different case of partial expression of PLS for a 35 year-old male with early onset PPK, but the eruption and exfoliation of the deciduous dentition was normal along with normal eruption of the permanent teeth. The periodontium is relatively healthy, with the exception of presence of moderate localized periodontal pockets [59]. The diagnosis of PLS in this case is questionable. In contrast, Kamalpreet et al. reported a late presentation of PLS in a 20-year-old female with marked early onset PPK but with a history of normal eruption and exfoliation of the primary teeth and normal eruption of permanent dentition. When the patient reached 19 years, she noticed mobility and migration of teeth, family history indicated that her mother had lost all her teeth at a young age and one of her sisters had severe periodontal disease but no history of hyperkeratosis [60]. In our opinion, this is a case of PPK associated with aggressive periodontitis with a family history of severe periodontitis.

Another case of PLS in association with aggressive periodontitis of a 28-year old male with PPK was reported by Reenesh et al. [61] In this case, no genetic analysis was performed. The authors reported a successful outcome with oral retinoid and periodontal therapy including surgical and non-surgical therapy with antibiotics [61]. Because the authors reported the restoration of the periodontium to a healthy status with conventional periodontal therapy, we question whether this case is a true PLS, or a rapidly progressive form of periodontitis.

A more clear illustration of these different cases was reported by Fardal et al. as “PPK and unusual periodontal findings in a family” where the father has marked PPK and very late onset of destructive periodontitis. The son also has palmoplantar hyperkeratosis, and did not develop periodontal disease over a seven-year observation period after improved oral hygiene and professional tooth cleaning were instituted [62]. Pilger et al. also reported a 46-year-old woman with late-onset PPK and a 10-year history of severe periodontal disease. There was no mutation in the cathepsin C gene. The authors suspect a different genetic cause responsible for this late-onset forms of PLS [63]. In some cases, the reason for considering late presentation of PLS is not clear as in the case of a 25-year-old Iranian edentulous woman who presented originally at 7 years of age with PPK and started to lose her permanent teeth at the age of 12 years [42]. Kobayashi et al., however, explained the late presentation of PLS periodontitis with atypical clinical feature of retention of all the permanent teeth at over 40 years of age by identifying a novel CTSC homozygous nonsense mutation, p.Lys106X, which leads to a deficiency of the mutant mRNA because of nonsense-mediated mRNA decay [64]. Therefore, the phenotypic variability of the PLS associated with identical genetic background may reflect the influence of additional genetic and/or environmental factors on disease characteristics [65].

## Other Syndromes Reported PPK in Association with Periodontitis (Table 1)

### Haim and munk syndrome

Haim and Munk reported findings similar to Papillon-Lefevre syndrome in four sibs of a Jewish religious isolate from Cochin, India, on the Malabar Coast who later migrated to Israel [66]. Hence, the name Haim-Munk syndrome (HMS) was introduced. Since then, it is considered by some clinicians as a variant of PLS [35,67,68]. However, other clinicians distinguished HMS as a separate disorder owing to the presence of additional features different from PLS [29]. Features that are similar in both PL and H.M syndromes include palmoplantar keratosis and progressive early onset periodontal destruction. There are, however, a number of additional features in HMS that include arachnodactyly (long, thin, pointed fingers); acroosteolysis (bone loss in the fingers or



toes); onychogryphosis (overgrowth of the fingernails and toenails and a claw-like deformity); Pesplanus (flat foot), and psoriasiform lesions. Two Jordanian girls with symptoms similar to Haim-Munk syndrome were recently documented [69]. Shah et al. pointed out the need to differentiate PLS from other diseases that show severe periodontitis and dermatological lesions, like Haim Munk syndrome [70].

A combination of findings that are not previously reported including congenital atrichia and mental retardation in addition to palmoplantar hyperkeratosis and early loss of teeth was documented in four siblings, and considered to be a new genetic entity [71].

### Hypotrichosis, Acro-Osteolysis, Palmoplantar keratoderma and Peridontitis Syndrome (HOPP)

This syndrome was first reported in a Dutch mother and daughter. The PPK followed a highly unusual reticular pattern and both the mother and daughter have a lingua plicata (fissured tongue). This new syndrome is not related to mutations in cathepsin C gene [72]. A third, unrelated, 24-year-old patient from Venezuela suffering from what appears to be HOPP syndrome confirms the existence of this syndrome as a unique entity and further delineates the phenotype [73].

### Weary-Kindler and kindler syndromes

These are two different syndromes, but sharing similar features [74]. Kindler syndrome is an autosomal recessive disorder characterized by epidermolysis bullosa, congenital poikiloderma, PPK, photosensitivity, skin atrophy, and mucosal lesions [75] whereas Weary-Kindler syndrome is a dominantly inherited disorder with features similar to those reported in the Kindler syndrome except for skin atrophy, photosensitivity, and mucosal lesions [76].

### Variant carvajal syndrome

This syndrome was reported in a 13-years old girl who had been under long term dental care for prepubertal periodontitis, premature root resorption of primary teeth, soft tissue and dental anomalies, and angular cheilitis [77].

### Conclusion

1. PPK as well as periodontitis include many types. Genetic syndromes may be manifested by PPK or by periodontitis, but Papillon-Lefèvre syndrome is the most recognized syndrome sharing these two features.
2. Although the exact etiology, pathogenesis and clinical manifestation are not clearly understood in the many cases of atypical PLS that have been reported, the genetic etiology is properly identified to Cathepsin C (CTSC) gene on chromosome 11q14. Genetic testing therefore, may be used to confirm the diagnosis of this syndrome.
3. Typical types of PLS include: 1) the two features of PPK and periodontitis; 2) early onset of both skin and oral changes during the first three years of life, 3) both the deciduous and permanent dentitions are affected and the patient loses the permanent teeth by the teen age; 4) calcification of the falx cerebri of the dura mater; and 5) development of pyogenic liver abscess are additional specific associated features.
4. Atypical PLS cases include partial expression of the syndrome (PPK or periodontitis); or late presentation instead of early onset, or periodontitis affecting only the permanent dentition; or associated with additional features such as pseudoainhum of the fingers and toes.

5. The establishment of definitive diagnosis for PLS or PLS-periodontitis seems uncertain in cases of atypical presentation, especially without genetic testing. In case of doubtful diagnosis, "PPK associated with aggressive or chronic periodontitis", instead of "late presentation of PLS" is more appropriate at the present time.
6. The term "partial expression of PLS" seems inappropriate for a syndrome that is manifested by no more than two features, i.e., PPK and periodontitis.
7. Most of the periodontal findings appeared in the literature are not described in detail. Genetic testing also is unrecorded.
8. For better understanding and management of patients with PLS, a team of specialists in dermatology, periodontics, and genetics is necessary to rule out the possibility of other medical conditions.

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