Review Article

Hereditary Palmoplantar Keratoderma: A Practical Approach to the Diagnosis

Abstract

The ridged skin of the palms and soles has several unique features: (i) presence of dermatoglyphics created by alternating ridges and grooves forming a unique pattern, (ii) presence of the highest density of eccrine sweat glands and absence of pilosebaceous units, and (iii) differential expression of keratins compared to the glabrous skin. These features explain the preferential localization of palmoplantar keratoderma (PPK) and several of its characteristic clinical features. PPK develops as a compensatory hyperproliferation of the epidermis and excessive production of stratum corneum in response to altered cornification of the palmoplantar skin due to mutations in the genes encoding several of the proteins involved in it. PPK can manifest as diffuse, focal, striate, or punctate forms *per se* or as a feature of several dermatological or systemic diseases. There is a wide genetic and phenotypic heterogeneity in hereditary PPK, due to which reaching an accurate diagnosis only on the basis of clinical features may be sometimes challenging for the clinicians in the absence of molecular studies. Nevertheless, recognizing the clinical patterns of keratoderma, extent of involvement, degree of mutilation, and associated appendageal and systemic involvement may help in delineating different forms. Molecular studies, despite high cost, are imperative for accurate classification, recognizing clinical patterns in resource poor settings is important for appropriate diagnosis, genetic counseling, and management. This review intends to develop a practical approach for clinical diagnosis of different types of hereditary PPK with reasonable accuracy.

Keywords: *Clinical diagnosis, hereditary palmoplantar keratoderma, keratinization disorders, palmoplantar keratoderma*

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Introduction

Hereditary palmoplantar keratodermas (PPK) are a heterogeneous group of keratinizing disorders characterized by hyperkeratotic thickening of the palms and soles. The molecular basis of PPK has been well established in recent years. The mutations in the genes encoding proteins involved in keratinization process, such as keratins, desmosomes, loricrin, cathepsin C, gap junction proteins, and many others have been implicated in pathogenesis of PPK. The majority of PPK manifests in infancy in isolation or in association with other abnormalities involving nails, teeth, or other organs.[1,2] Traditionally, the diagnosis of hereditary PPKs has been based on history and clinical features combined with histopathology. Although the major histological features of palmoplantar keratosis are usually nonspecific hyperkeratosis, other histopathological characteristics such as epidermolysis may be useful in distinguishing nonepidermolytic and epidermolytic PPK. However, owing to significant clinical heterogeneity, accurate classification of PPK merely on clinical features may be challenging in the absence of molecular studies. On the other hand, recognizing the clinical patterns of keratoderma, extent of involvement, degree of mutilation, and associated appendageal and systemic involvement will help in their management. This review intends to develop a practical approach to diagnose different types of hereditary PPK clinically with reasonable accuracy.

Pathogenesis of hereditary PPK

Most of the types of PPK are inherited as autosomal dominant or autosomal recessive disorders. History of consanguinity in parents may point towards the presence of recessive variants. Medical and occupation details helps in differentiating acquired causes of palmoplantar hyperkeratosis,

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such as manual labor, chronic contact dermatitis, atopic dermatitis, psoriasis, HIV infection, paraneoplstic, metabolic disorders (hypothyroidism, myxedema climacteric), exposure to chemicals (arsenic, hydrocarbons), and drugs (lithium, chemotherapeutics).[3] It will also be prudent here to briefly revisit the structure and functions of various molecules and genetic mutations involved in (molecular) pathogenesis of hereditary PPK.[4,5]

The keratins are members of intermediate filament group that maintain the structural integrity of the cells. Keratins K5 and K14 are expressed in the basal layer, while K1 and K9 are expressed in suprabasal compartment of palmoplantar skin.[6] The other keratins that are expressed in the suprabasal layers include K6a/K16 and K6b/K17. Mutation in the keratin genes results in disruption of keratin assembly leading to compensatory thickening of palmoplantar skin with varying severity depending on the mutation locus. Mutations in the highly conserved region of keratin peptides result in severe PPK, whereas involvement of variable region leads to milder phenotypes.[1,7,8]

Desmosomes are intercellular junctions that integrate intermediate filaments into the cell membrane and provide adhesion between the cells. Desmosomes are larger with increased expression of desmosomal proteins in palmoplantar skin as compared to rest of the skin leading to preferential localization of PPK in some of these desmosomal mutations.[9] Gap junctions are other transmembrane communicating channels between the cells that are made up of connexin proteins. Mutation in connexin protein results in defective gap junctions and intercellular trafficking, leading to accumulation of abnormal proteins and hence PPK.[10,11]

Loricrin is another important protein involved in the formation of cornified cell envelope (CCE). Mutation in the loricrin gene leads to abnormalities in CCE formation and dysfunctional apoptosis of differentiated keratinocytes, resulting in mild ichthyosiform erythroderma and PPK.[12,13]

Various other molecules involved in the pathogenesis of PPK are cysteine lysosomal protease, transient receptor potential vanniloid 3, secreted LY6/urokinase type plasminogen activator receptor (uPAR)-related protein 1), and many others.[14,15]

Classification and clinical features of hereditary palmoplantar keratoderma

Table 1 depicts comparative features of clinically classified four major types of PPK: (i) diffuse, (ii) focal, (iii) striate, and (iv) punctate.[16,17] Diffuse type of PPK characterized by uniform waxy thickening of the palms and soles is the most commonly observed variant of PPK. A contiguous expansion of PPK to the dorsal hands, feet, inner wrists, and Achilles tendons occurs in diffuse PPK with transgrediens. Some forms of PPK also progress/improve with age (progrediens).

Isolated Diffuse PPK

Flow chart in Figure 1 depicts proposed approach for the clinical diagnosis of isolated diffuse PPK.

PPK without transgrediens

This autosomal dominant form includes two clinically similar phenotypes epidermolytic (Vorner) and nonepidermolytic (Unna Thost) PPK.[18,19] Keratoderma begins in early infancy as patchy hyperkeratosis and is well developed by 3–4 years of age manifesting as symmetric, diffuse, thick, yellowish palmoplantar hyperkeratosis with a sharply demarcated erythematous lateral margins that is typically nontransgrediens. Other features include hyperhidrosis, secondary dermatophyte infection, and pitted keratolysis associated with pruritus and malodor.[20-23] Genetically, mutations occur in either K9 or K1 genes. Severe epidermolysis is noted in K9 mutation, while no or minimal epidermolysis occurs with K1 gene mutation.[24] K9 is palmoplantar skin-specific keratin and its mutation results in keratoderma confined to palms and soles. However, K1 is expressed on palmoplantar and glabrous skin as well as coexpressed with K9 in the former and K10 in the later alone.[7] Thus, mutations in both K1 and K10 genes lead to epidermolytic ichthyosis wherein K10 mutation will not have PPK as it is not expressed in the palms and soles and isolated K1 mutation results in generalized epidermolytic ichthyosis with severe PPK. The K1 mutations manifesting as isolated PPK along with hyperkeratosis of the umbilicus, areola, and knuckles too have been described.[22] Mutation in the highly conserved region will result in epidermolysis even in K1 mutations, while that in noncritical region will have less effect on keratin filaments and hence no epidermolysis.

PPK with transgrediens

PPK of Greither

Greither's or transgrediens et progrediens PPK manifests during infancy and develops fully during childhood and is characterized by PPK with contiguous involvement of tendo -achilles [Figure 2a and b]. The severity may vary from mild to severe and hyperhidrosis is frequent, while autoamputation of digits is occasional. Molecular studies show a missense mutation in K1 gene and hence this form is considered a variant of nonepidermolytic PPK. Histologically, orthohyperkeratosis and acanthosis with prominent irregular keratohyaline granules are characteristic.[25] Autosomal dominant Sybert's PPK resembles this phenotype but shows more severe and widespread hyperkeratosis with involvement of natal cleft and groins but exact genetic locus remains unidentified.[26,27]

Mal de Meleda PPK

Mal de Meleda PPK or keratosis palmoplantaris transgrediens of Siemens manifests clinically as bilateral

Table 1: Clinical features of major hereditary palmoplantar keratoderma

Type	Clinical diagnosis	Heredity	Gene mutation	Features of PPK	Transgrediens	Nail changes	Hyperhidrosis	Major histologic features	Other features/Remarks
Diffuse PPK	Vörner (Unna–Thost) PPK	AD	*KRT1, KRT9*	Thick diffuse hyperkeratotic	-	-	–	Epidermolytic hyperkeratosis, perinuclear vacuolization, keratinocytes degeneration in the spinous and granular layer	Acral blistering in infancy (rare), no spontaneous amputation.
	Diffuse PPK with DSG1 mutations	AD	*DSG1*	Thick hyperkeratotic	-	Mild onycholysis with yellow discoloration	–	Enlarged intercellular spaces and partial keratinocyte separation	No spontaneous amputation.
	Nagashima PPK	AR	*SERPINB7* (Serine protease inhibitor)	Mild diffuse hyperkeratotic with redness	+	–	+	Nonepidermolytic hyperkeratosis	Lesion over knees, elbow, Achilles tendon area. Maceration, foul odour, White spongy changes of water soaked skin. No spontaneous amputation.
	Bothnian PPK	AD	*AQP5* (Aquaporin)	Mild to thick diffuse hyperkeratotic	+	Curved nails, ragged cuticles	+	Nonepidermolytic hyperkeratosis	White spongy changes of water soaked skin. No spontaneous amputation. Nonprogressive
	Greither's PPK	AD	*KRT1*	Thick diffuse hyperkeratotic	+ (partly)	–	+	Non-epidermolytic hyperkeratosis	Lesion over flexures, elbows, knees, Achilles tendon area. Onset at infancy, Transient blistering at infancy, Progressive. May regress in 4th-fifth decade. Spontaneous amputation occurs.
	Sybert syndrome	AD	Unknown	Thick hyperkeratotic	+	–	–	Nonepidermolytic hyperkeratosis	Lesions over elbow, knees. Periorbital and perioral erythema. Progressive. Spontaneous amputation occurs.
	Gamborg Nielsen PPK	AR	*SLURP1*	Thick hyperkeratotic	+	–	–	Nonepidermolytic hyperkeratosis	Knuckel pads over dorsal hands. No spontaneous amputation.
	Acral keratoderma	AR	Unknown	Thick, diffuse and striate	+		–	Nonepidermolytic hyperkeratosis	Linear hyperkeratotic lesion over elbows, knees, ankles, Achilles tendon area. Spontaneous amputation occurs.
	Huriez syndrome	AD	Unknown	Diffuse hyperkeratotic	+	Nail dystrophy/hypoplasia	–	Nonepidermolytic hyperkeratosis, thickened dermal collagen, scanty elastic fibers in papillary and reticular dermis, dilated vessels	Scleroatrophy, parchment like dry hyperkeratotic skin over dorsal hands, feet, delayed growth affecting hands, increased risk of SCC,

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Table 1: Contd...

Type	Clinical diagnosis	Heredity	Gene mutation	Features of PPK	Transgrediens	Nail changes	Hyperhidrosis	Major histologic features	Other features/Remarks
	KID (keratitis, ichthyosis, deafness) syndrome	AD	*GJB2* (GJB6) (Cx 26, Cx30)	Diffuse PPK	–	Nail dystrophies	–	Nonepidermolytic hyperkeratosis	Ichthyosiform erythroderma in infants, ichthyosis, alopecia, acrofacial verrusiform hyperkeratosis, sensorineural deafness, kertitis, increased risk of bacterial infections and SCC
	Bart–Pumphrey syndrome	AD	*GJB2* (Cx 26)	Diffuse, focal or punctate PPK	–	Leukonychia	–	Hyperkeratosis, papillomatosis, acanthosis, hypergranulosis	Sensorineual hearing loss, knuckle pads breast/axillary cysts
	Howel–Evans syndrome	AD	*RHBDF2* (rhomboid protease family)	Diffuse yellowish callosities -like	–	–	–	Hyperkeratosis, acanthosis, hypergranulosis	Kertosis pilaris, fissuring and infections, chronic rhinitis, maxillary decalcification, alveolysis/tooth loss. Oral leukoplaka. Esophageal carcinoma in mid or late life.
Diffuse mutilating PPK	Mal de Meleda (Gamborg–Nielsen/ Norrbotten) PPK	AR	*SLURP1* (Ly6/uPAR family)	Severe diffuse, mutilating hyperkeratotic	+ (massive)	Nail dystrophy	+	Nonepidermolytic hyperkeratosis, prominent stratum lucidum, perivascular inflammatory infiltrate	Lesion over flexures, elbows, knees, Achilles tendon area. Digit tapering, joint stiffness/contractures. Fissuring, maceration, foul odor, and infections. Spontaneous amputation occasional.
	Vohwinkel syndrome	AD	*GJB2* (Cx 26)	Diffuse, yellowish, severe mutilating PPK	+	Nail dystrophies	+	Hyperkeratosis hypergranulosis, acanthosis with round retained nuclei	Starfish keratoses on knuckles and wrists. Sensory neural deafness, alopecia, myopathy (spastic paraplegia possible), focal epilepsy,
	Ichthyosiform Vohwinkel syndrome (Camisa disease)	AD	*LOR* (Loricrin)	Diffuse, yellowish, severe mutilating PPK	+	Nail dystrophies	+	Hyperkeratosis acanthosis, focal parakeratosis, papillmatosis, sparse dermal lymphocytic infiltrate, normal appendages	No sensory neural deafness Mild ichthyosis, pseudoainhum
	Olmsted syndrome	AD	*TRPV3* (MBTPS2) *TRPV3* (MBTPS3)	Diffuse, yellow-brown, mutilating PPK, fissures	+	Nail dystrophies	Hyperhidrosis or anhidrosis	Psoriasiform hyperplasia, papillomatosis massive non-epidermolytic hyperkeratosis, hypergranulosis with focal hypogranulosis	Periorificial hyperkeratosis, (neck, upper thorax, abdomen, inguinal folds, thighs, elbows, knees) alopecia, infections, oral leukokeratosis, chronic blepharitis, corneal dystrophies, delayed growth, high tones hearing loss, abnormal dentition, bone deformities, hyper IgE, eosinophilia (rare), foul odor

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Table 1: Contd...

Type	Clinical diagnosis	Heredity	Gene mutation	Features of PPK	Transgrediens	Nail changes	Hyperhidrosis	Major histologic features	Other features/Remarks
	KLICK syndrome (keratosis linearis with ichthyosis)	AR	*POMP* (POMP)	Diffuse, mutilating PPK	–	–	–	Non epidermolytic hyperkeratosis	Hyperkeratosis plaque, ichthyosis and papules in linear pattern over arm flexors and wrists.
Focal PPK	PPK nummularis	AD	*KRT16*, *KRT6c*, *DSG1*, *TRPV3*	Circumscribed callosities	–	None or minimum (fifth toenail hypertrophy, splinter hemorrhages)	+	Nonepidermolytic hyprkeratosis, acanthosis, hypergranulosis	Childhood onset, may be induced by mechanical stress and become painful. Follicular hyperkeratosis. Plantar blistering. No spontaneous amputation. Minimal oral or orogenital leukokeratosis.
Striate PPK	Striate PPK I (Brünauer–Fuhs–Siemens syndrome) Striate PPK II Striate PPK III	AD	*DSG1* (Demoglein 1) *DSP* (Desmoplakin) *KRT1* (Keratin 1)	Linear skin thickening over flexor aspects of digits and pressure points of soles (diffuse on soles in Striate PPK III)	–	–	+ in type-I	Hyperkeratosis, widening of intercellular spaces, condensed keratin filament network in suprabasal cell layers	Classification of Type I–III is based on the responsible gene mutation. Knee, elbow hyperkeratosis (rare), foul odor, plantar pain in type-I. Improves with age. No spontaneous amputation.
Punctate PPK	Type-IA (Buschke–Fischer–Brauer syndrome) Type-IB	AD	*AAGAB* *COL14A1*	Multiple palmoplantar punctate keratosis	–	None or rare	–	Hyperkeratosis, hypergranulosis with central epidermal depression	Onset at late childhood or adolescence, increase in number and size with advancing age. Worsening with soaking in water. Classification of Type IA and IB is based on the responsible gene mutation. No spontaneous amputation.
	Type-II (Porokeratotic type)	AD	Unknown	Tiny punctate palmoplantar keratosis, pits with kearatotic plugs	–	–	–	Columnar parakeratosis overlying where the granular layer is absent/reduced	Onset at early twenties. Sebaceous hyperplasia in males. No spontaneous amputation.
	Type-III (acrokeratoela-stoidsis	AD	Unknown	Keratotic papules along the margins of hands and feet	Rare (occurs in severe cases only)	Rare nail dystrophy	–	Hyperkeratosis, hypergranulosis, elastorhexis	Onset at adolescence or adult life. No spontaneous amputation.

AD=Autosomal dominant; AR=Autosomal recessive; Cx=Connexin; PPK=Palmoplantar keratoderma; SCC=Squamous cell carcinoma; +=Present; –=Absent

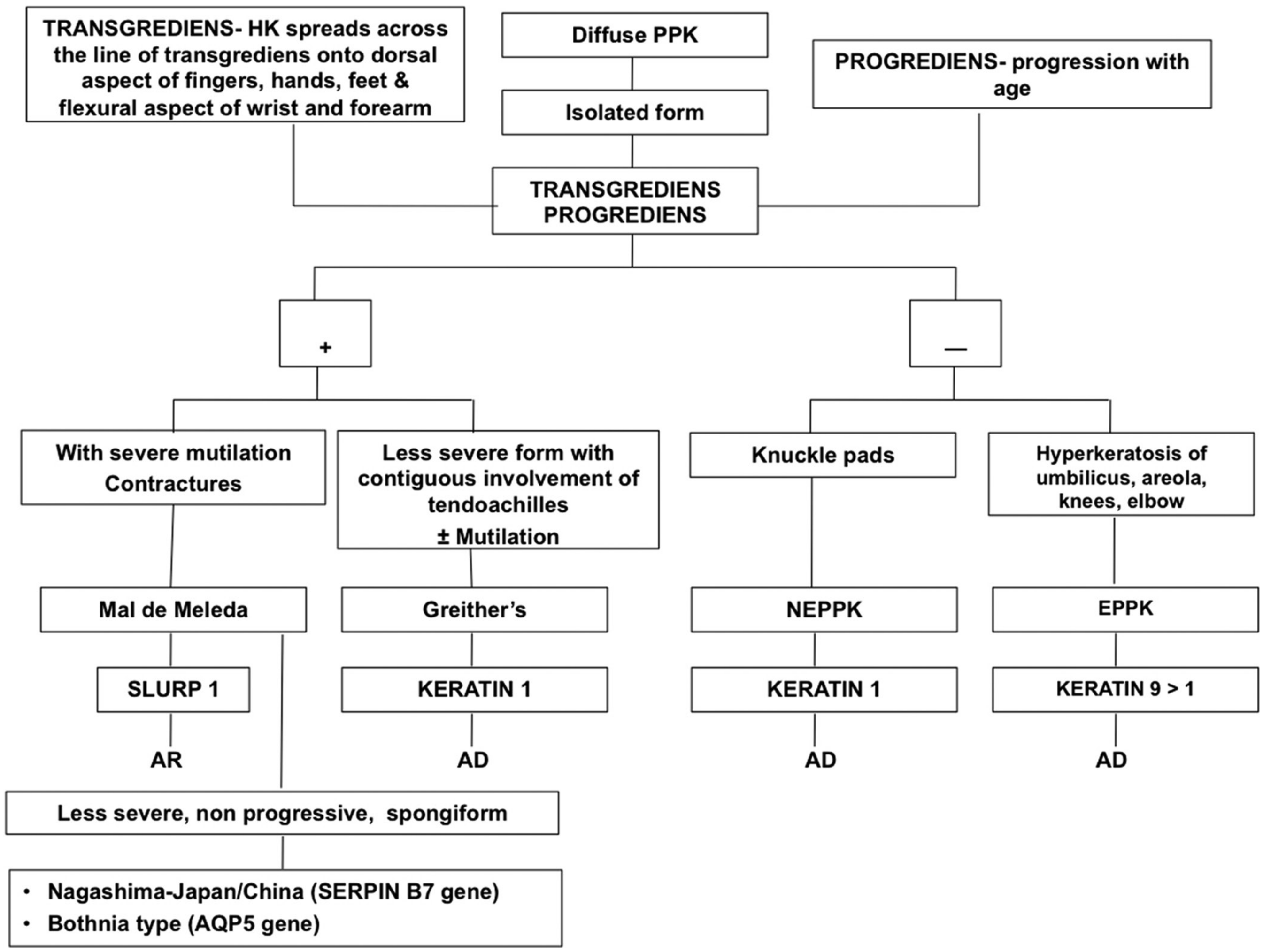

Figure 1: Flow chart showing a practical approach to cases with isolated diffuse PPK. (AD, autosomal dominant; AR, autosomal recessive; EPPK, epidermolytic palmoplantar keratoderms; NEPPK, nonepidermolytic palmoplantar keratoderma; PPK, palmoplantar keratoderma)

Figure 2: Greither's syndrome in a 20-year-old female showing transgrediens PPK (a), and contiguous involvement of skin over tendo Achilles (b)

thick yellow-brown PPK with prominent erythematous border, trangrediens, and progrediens in a glove and stocking pattern [Figure 3a-d]. Inherited autosomal recessively it becomes evident at birth as palmoplantar erythema that has a progressive clinical course evolving to thick lesions during first 4 years of life. Keratoderma may be complicated by hyperhidrosis and secondary infection leading to malodor. Nails show Beau's line, subungual hyperkeratosis, onycholysis, koilonychia and onychogryphosis. Oral manifestations include high arched palate, perioral erythema, and angular chelitis.[15,28] Psoriasiform lesions occur occasionally over elbows and knees, while severe mutilation, contractures, constricting bands around digits, pseudoainhum and amputation of the digits are the features of progressive form.

Molecular studies show improperly regulated keratinocyte apoptosis from mutation in *SLURP1* protein that is primarily expressed in the stratum granulosum.[15] This protein also inhibits macrophage and keratinocyte release of TNF-α. Thus, uninhibited tumor necrosis factor (TNF)-α release in the epidermis results in inflammation and dermal inflammatory cell infiltrate.

Nagashima PPK

The autosomal recessively inherited Nagashima PPK, reported mostly from Japan and China, is similar to Mal de Meleda but with a milder phenotype manifesting as nonprogressive mild hyperkeratosis and lacks mutilation, constricting bands, spontaneous amputation, and contractures. It usually exhibits perioral erythema,

Figure 3: (a and b) Mal de Meleda PPK (mutilating PPK) showing severe hyperkeratotic, mutilating PPK with several constriction bands with nail dystrophy; (c and d) showing significant improvement in keratoderma and mutilation 6 weeks after treatment with acitretin (2 mg/kg/day). The patient did not improve with acitretin 1 mg/kg/day given for 8 weeks prompting dose escalation

occasional brachydactyly, nail abnormities, and lichenoid plaques. The white spongy appearance of the keratosis on exposure to water is considered to be a diagnostic clue.[29] Molecular studies show mutations in SERPINB7 gene that encodes the serine protease inhibitor superfamily distinguishing it from Mal de Meleda. A similar phenotype is also described in Bothnian PPK and is due to mutation in AQP5 gene that encodes a water channel protein.[30]

Diffuse PPK with associated features

Flow chart in Figure 4 depicts proposed approach for the clinical diagnosis of diffuse PPK with associated features.

PPK with honeycomb pattern

This spectrum includes the deafness-associated Vohwinkel syndrome and the ichthyosis associated loricrin PPK (Camisa's variant). Vohwinkel syndrome or keratoderma hereditaria mutilans is a rare form resulting from mutation in GJB2 gene encoding connexin 26. Inherited in autosomal dominant form it presents at birth and becomes more evident in adulthood. The honeycomb appearance of PPK with a fine discernible superficial pattern replacing normal dermatoglyphics and starfish-shaped keratotic plaques over the knuckles, wrists, elbows, and knees are highly diagnostic. Over time the affected children develop constricting fibrous bands and pseudoainhum and autoamputation of the toes and fingers particularly of the fifth digit. Other features include moderate to severe sensory neural deafness, myopathy, spastic paraplegia, mental retardation, acanthosis nigricans, ichthyosiform dermatitis, alopecia, and nail abnormalities.[31]

The children with loricrin PPK are often born with collodion membrane and present with mild nonerythrodermic ichthyosis.[32] Unlike Vohwinkel PPK they do not exhibit starfish-shaped keratosis and deafness. Alopecia may occur in few cases; however nail, teeth, and mucosae remain normal. Skin biopsy shows the pathognomonic features of marked hyperkeratosis and parakeratosis along with round retained nuclei and intranuclear granules in the upper granular layer. Immunoelectron microscopy has confirmed that these granules are mutated loricrin protein.[12,13]

PPK with severe mutilation and periorifical plaques

Olmsted syndrome is a rare mutilating keratoderma with periorifical plaques. Most cases are inherited sporadically and PPK manifests during infancy as focal lesions, which eventually becomes diffuse and severe with transgrediens. Severe mutilation, contractures, constrictions, and autoamputation of digits occur over time [Figure 5a]. Other distinctive features are severe itching, hyperkeratotic plaques around the mouth, nostrils, ears, anogenital region [Figure 5b], axillae, neck, and groins and histologically inflammatory infiltrate with mast cells. Corneal defects, alopecia universalis, keratosis pilaris, oral leucokeratosis, teeth abnormalities, and sensory neural deafness have been also described.[14,33]

PPK with periodontitis

Papillon Lefèvre syndrome (PLS), an autosomal recessive disorder, is characterized by the triad of symmetrical keratoderma with transgrediens, early onset severe periodontitis with loss of primary and permanent dentitions, and susceptibility to cutaneous and systemic infections.[34] PLS manifests at birth or early infancy with the appearance of the palmoplantar keratoderma, which may be preceded by erythema. Although punctate or striate keratoderma is not uncommon, a diffuse keratoderma with transgrediens is highly characteristic [Figure 6a]. Soles are affected more severely than palms and malodorous hyperhidrosis is frequent. Additionally, there will be scaly psoriasiform plaques over interphalangeal joints, elbows, knees, tendo Achilles, and external malleoli.[35]

Eruption of deciduous teeth is associated with gingival inflammation and severe periodontitis affecting both deciduous and permanent teeth leading to rapid destruction of periodontium and premature loss of teeth and extensive bone resorption [Figure 6b]. Once the primary teeth are lost at the age of 4–5 years, the gingiva becomes normal. However, periodontitis recurs with the eruption of permanent teeth and the child is edentulous by 14–15 years of age and gingiva becomes normal. Radiologically, there is loss or resorption of both maxillary and mandibular alveolar

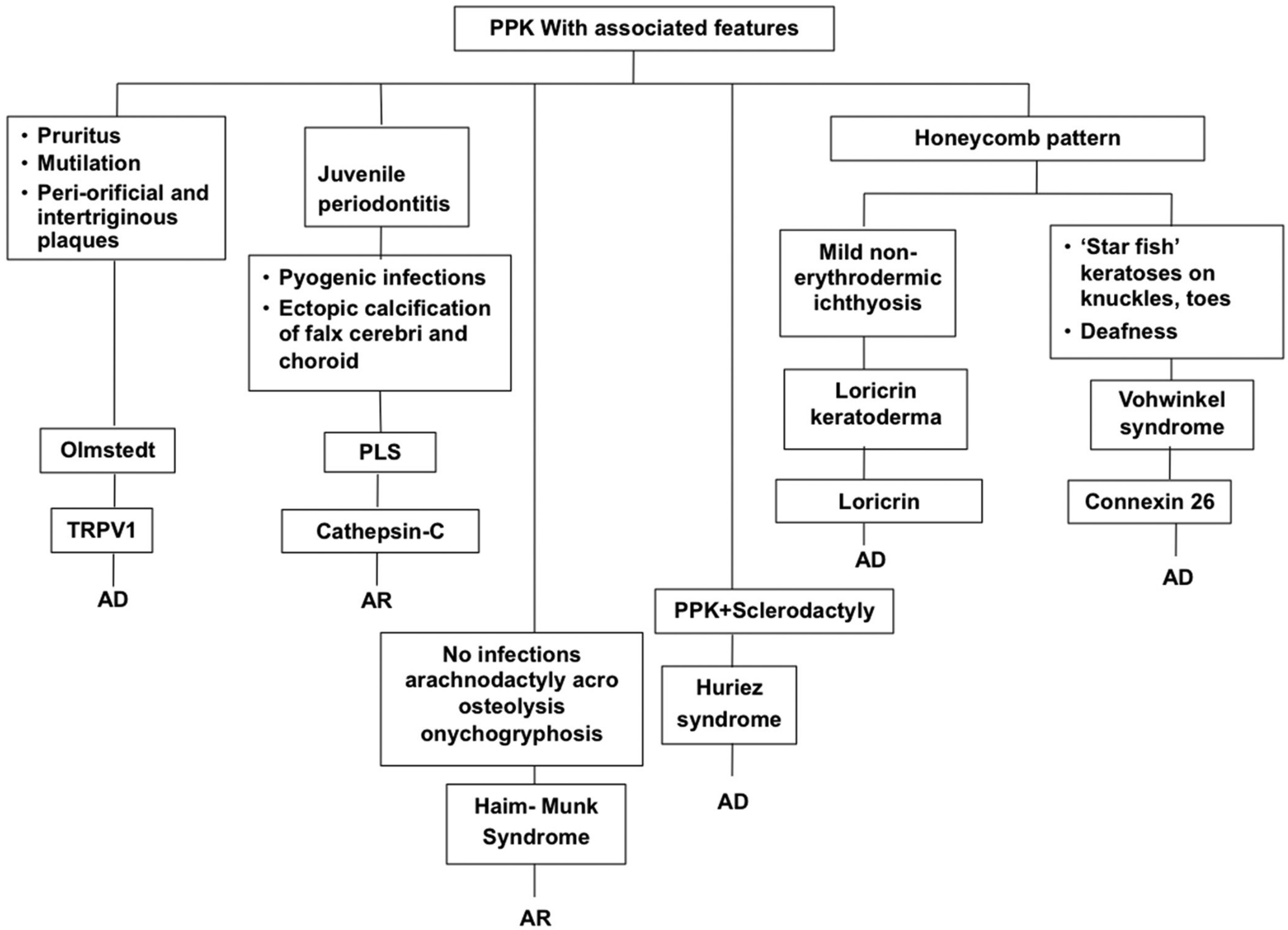

Figure 4: Flow chart showing a practical approach to cases with diffuse PPK and associated features. (AD, autosomal dominant; AR, autosomal recessive; PPK, palmoplantar keratoderma; PLS, Papillon–Lefèvre syndrome)

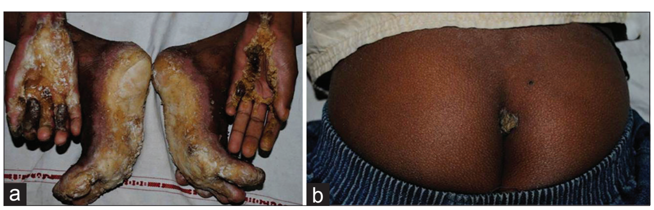

Figure 5: Olmsted syndrome in a 12-year-old boy: Severe mutilating PPK (a), intertriginous keratotic plaque involving natal cleft (b)

ridges [Figure 6c]. Another remarkable clinical feature of PLS is increased susceptibility to pyogenic skin and liver infections mostly due to *Staphylococcus aureus*. Ectopic calcifications of falx cerebri and choroid plexus, and mild mental retardation are also reported. Haim–Munk syndrome resembles PLS but additional features of arachnodactyly, acroosteolysis, and atrophic nail changes are present.[36]

PLS is due to loss-of-function mutation in CTSC gene for cathepsin C mapped to chromosome 11q14-q21, which is expressed in palms, soles, knees, and keratinized gingiva. The cathepsin C protein, a lysosomal protease, is essential for activation of serine proteinase, neutrophil serine protease, proteinase 3, and elastase. Deficiency of CTSC leads to dysregulation of host immune response which in turn predisposes to infections in gingiva, skin, and liver.[34,37]

PPK with scleroatrophy

Huriez syndrome, an autosomal disorder, is characterized by a triad of PPK, congenital scleroatrophy of extremities, and hypoplastic nail changes with onset in infancy. The keratoderma is mild and diffuse with involvement of palms more than soles. The sclerodactyly is progressive and nail changes include ridging, koilonychia, fissuring, and hypoplasia. The atrophic skin plaques have an increased risk of squamous cell carcinoma in approximately 15% cases by third-fourth decade with a tendency for early metastasis. The gene for this rare syndrome has been mapped to chromosome 4q.[38]

Focal PPK

Keratosis palmoplantaris nummularis

Keratosis palmoplantaris nummularis or hereditary painful callosities is associated with mutation in *KRT* 6C genes encoding keratin 6c expressed predominantly on plantar skin.[39] It is autosomal dominant and manifests clinically within first 2 years of life as painful, nummular-shaped keratotic plaques located mainly over pressure points. Blistering and minor nail abnormalities may also be seen. Oral leukokeratosis or gingival keratosis as leukoplakic lesions of the labial mucosa or attached gingival surface may occur. Histologically, it is characterized by focal epidermolytic hyperkeratosis.

Pachyonychia congenita

Pachyonychia congenita (PC), an autosomal dominant disorder, is due to mutations in one of the four keratin genes, *KRT6A*, *KRT6B*, *KRT16*, or *KRT17*. Based on the specific keratin mutation, it has been classified into PC-6a, PC 6b, PC-16, PC-17, and PC-unknown. It affects skin, nails, oral mucosa, and teeth. Plantar keratoderma, plantar pain, and thickened toenails, the cardinal features [Figure 7], develop in >90% cases before 5 year of age.[40,41] Of 254 reviewed cases, 98% had toenail thickening and 87% showed fingernail involvement.[40] The average reported age for onset of toe nail dystrophy in all types was 2.8 years with earliest average age at onset being 4 months in PC-6a, 9.5 years in PC-6b, and late in PC-17. The average number of toenail involved was 8.8 and both toenail and fingernail involvement occurred in all PC-6a cases. Whereas fewer fingernails are affected in PC-6b cases compared to other types. Plantar keratoderma was found in 91–96% cases and callosity-like thickening being the most common manifestation.[40,41] The other features included were fissuring, blisters, and ulceration. These manifestations never resolved completely. The associated plantar pain seen in 89% significantly affects the quality of life.[40]

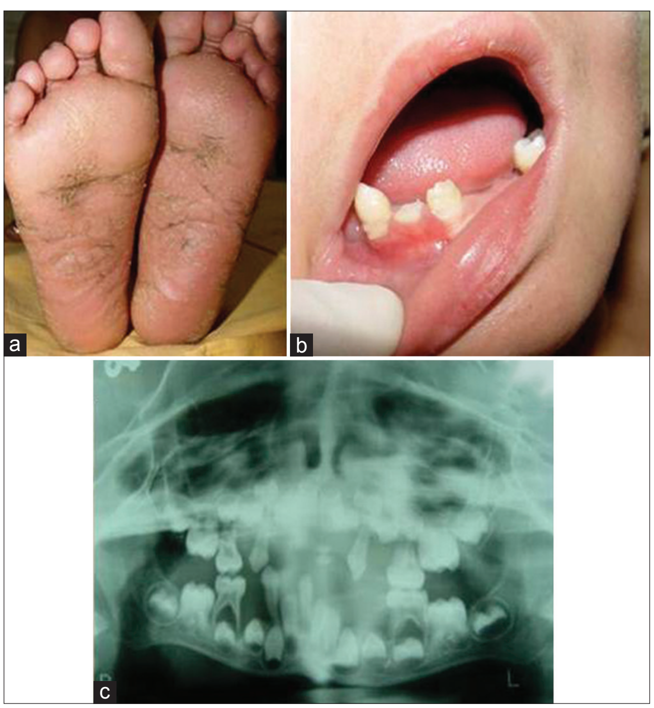

Figure 6: Papillon–Lefévre Syndrome showing: diffuse plantar keratoderma (a), Periodontitis and loss of teeth (b), panoramic radiograph showing hypodontia, alveolar bone resorption, and a "floating in the air" appearance of teeth (c)

Mucosal changes present at birth in 54% cases, while their onset is by 1 year of age in 73% cases.[40,41] Oral leucokeratosis develops in 70% cases at an average age of 5.1 years. Pilosebaceous and steatocysts develop in 41% patients and chances are higher by 88% in PC-17 cases compared to other types who also tend to have natal teeth more frequently.[40]

Recently, co-occurrence of filaggrin gene mutation has been described as a genetic modifier increasing the phenotypic severity of PC in a parent–child trio where both mother and the son had PC, carrying K16 mutation (p.Leu132Pro) and the father had ichthyosis vulgaris. The son was affected more severely than the mother as he additionally had heterozygous filagrin mutation (p.R2447X) inherited from father.[42]

Linear or striate PPK

Also known as PPK striata, Wachter-type focal nonepidermolytic palmoplantar keratoderma, or Brünauer–Fuh–Siemens syndrome, is an autosomal dominant disorder. It follows mutations in desmoglein 1 gene mapped to chromosome 18q1-12 (striate PPK 1), desmoplakin gene on chromosome 6p21 (striate PPK 2), and keratin 1gene (striate PPK 3) involved in maintaining epidermal integrity that is important for friction-bearing areas.[2] Clinically, onset is in early infancy or first few years of life with marked phenotypic variability. Woolly hair and left ventricular dilated cardiomyopathy (in recessive form) may occur. In manual workers, palmar keratoderma may have linear pattern (islands of linear hyperkeraosis) and increased skin fragility from occupational friction/trauma, while others may have no or minimal changes. Histologically, hyperkeatosis, acanthosis, and hypergranulosis occur without epidermolysis.

Punctate PPK

Punctate PPK or Buschke–Fischer syndrome, an autosomal dominant disorder, presents between 12 and 30 years of age as multiple asymptomatic punctate hyperkeratotic

Figure 7: Pachyonychia congenita showing focal plantar keratoderma with heaped up tented nails in a 10-year-old female child

papules involving whole or part of palms and soles. Hyperhidrosis is not a feature. Nails may show longitudinal ridging, notching, trachyonychia, onychoschizia, and onychorrhexis. Ankylosing sponylitis, spastic paralysis, sebaceous hyperplasia, and association with gastrointestinal or pulmonary malignancy can be seen. Two mutations in PPK loci have been mapped to chromosome 15q22-24 and 8q24.13-8q24.21.[43,44] Histologically, presence of compact hyperkeratosis, hypergranulosis, cornoid lamella absence of epidermal dykeratosis, or hydropic changes differentiates it from porokeratosis.

Dermatoses and syndromes with diffuse or punctate PPK as an associated feature

The diffuse or punctate keratoderma, small rounded papular keratosis on the palms and soles with tendency to coalesce over pressure points, can be a presenting feature of many dermatoses [Tables 2 and 3].[4,16,17,45-64] Flow chart in Figure 8 depicts proposed approach for the clinical diagnosis of PPK as a feature of common dermatological conditions of diagnostic significance.

PPK associated with systemic abnormalities

Table 4 lists the PPK with associated major systemic diseases.

Treatment of PPK

Hereditary PPK persists lifelong and significantly affecting quality of life. There is no presently available therapy that is specific and curative. Apart from genetic counseling, patient needs to be educated for taking care of hyperkeratotic hands and feet. Mechanical debridement with blade or dental drill and liberal use of topical keratolytic agents as first-line treatment will provide temporary relief. Secondary infection needs require appropriate treatment. Systemic treatment with retinoids improves symptoms of hyperkeratosis in most patients [Figure 3c and d]. A significant improvement in PPK and gingivitis with oral retinoids in PLS has been reported.[65] However, only low-dose retinoids therapy is preferred in epidermolytic palmoplantar keratoderma (EPPK) as it might trigger epidermolysis, while adverse effects associated with prolonged retinoid therapy remain

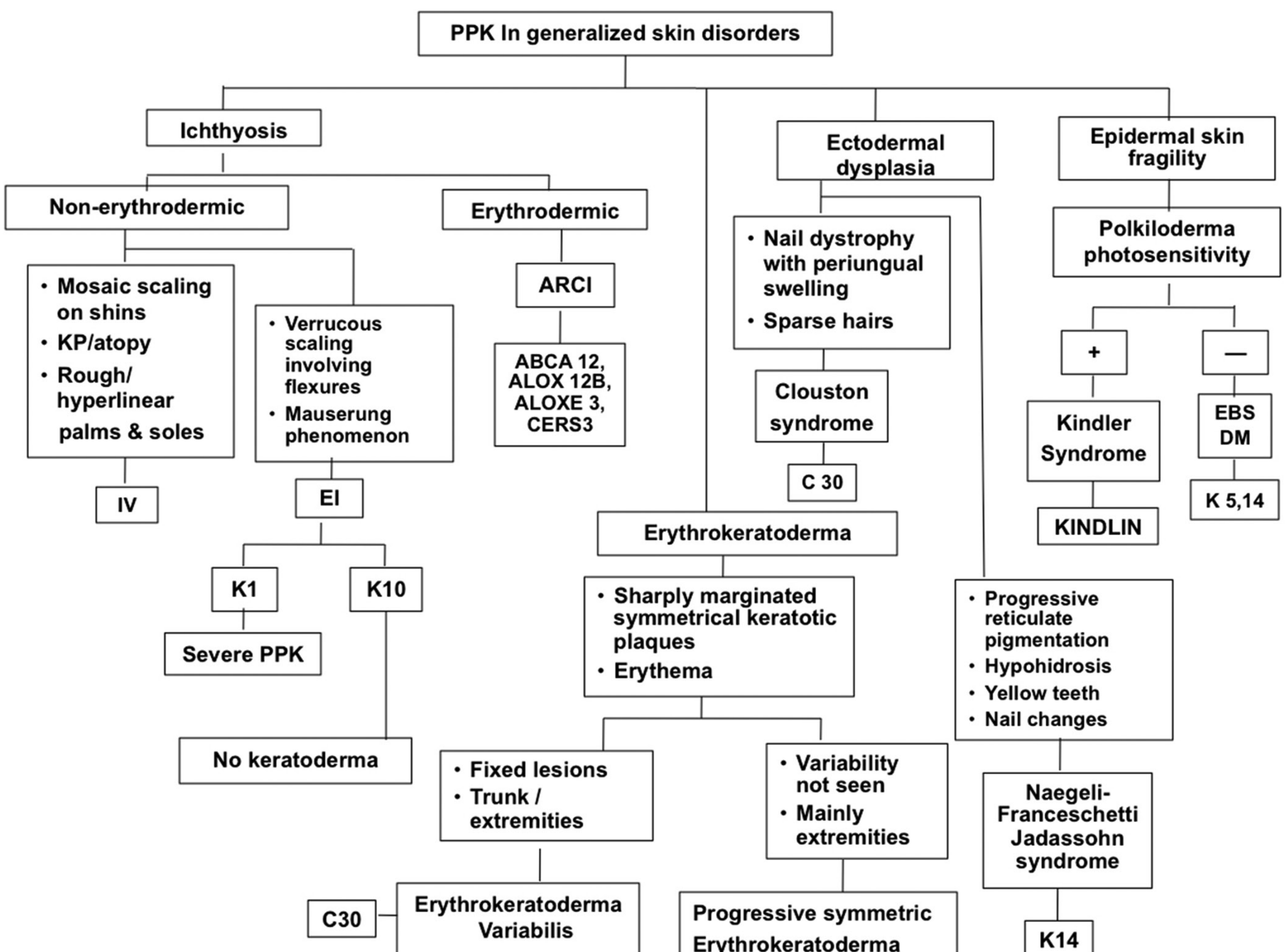

Figure 8: Flow chart showing a practical approach to cases with PPK as a feature of other dermatological conditions. (ALOXE, arachidonate lipoxygenase; C 30; connexin 30; CERS3, ceramide synthase-3; EBS-DM, Epidermolysis Bullosa Simplex-Dowling Meara type; EI, epidermolytic ichthyosis; IV, ichthyosis vulgaris; KP, keratosis pilaris)

Table 2: Syndromes and dermatoses with diffuse or punctate palmoplantar keratoderma (PPK) as an associated feature

Syndrome/dermatoses	PPK type	Other lesions and Remarks
Erythrokeratoderma variabilis and progressive symmetrical erythrokeratoderma	Diffuse bilateral symmetrical PPK in 50% cases	Symmetrical circumscribed, migratory erythematous and hyperkeratotic plaques occur over extensor aspects of extremities, buttocks, and face.
Pityriasis rubra pilaris	Sharply demarcated reddish-orange, diffuse thick PPK with fissuring (PRP sandal)	Nutmeg follicular papules with surrounding erythema over back of fingers, elbows, and wrists are typical. Widespread circumscribed follicular keratoses with orange-red erythema and brany scales with interspersed normal skin (islands of sparing).
Congenital ichthyosis[45-48]	Rough palms and soles and hyperlinearity in ichthyosis vulgaris. Diffuse PPK is more severe in autosomal recessive congenital ichthyosis due to ALOX12B mutation compared to that in ALOXE3 mutation. Diffuse yellowish PPK in NIPAL4 mutation. Mild PPK with hyperlinearity in CERS3 mutation.	Epidermlytic ichthypsis due to heterozygous mutations in K1 and K10 genes and K1 mutation is associated with keratoderma. Superficial epidermolytic ichthyosis usually does not have PPK.
Epidermolysis bullosa[49-51]	Palmoplantar hyperkeratosis in Kindler syndrome. Diffuse PPK in Dowling Mears type (Generalized severe form).	Photosensitivity, acral blistering, progressive poikiloderma, atrophic scarring and pseudo webbing of hands and feet are typical of Kindler syndrome.
Darrier's disease[52]	Punctate keratoses or tiny pits are present over palms and soles	Crusted and greasy dirty yellow-brown-skin colored papules present over seborrhoeic areas. Discrete warty papules occur over dorsal hands and feet.
Acrokeratosis verruciformis of Hopf[53]	Diffuse thickening, small keratosis, and punctiform breaks in dermatoglyphic	Skin colored warty, keratotic papules over dorsal hands and feet.
Cowden disease or multiple hamartoma syndrome[54]	Translucent punctate keratosis and acrokeratosis veruciformis-like lesions occur over the dorsal hands and feet	–
Basal cell nevus syndrome or Gorlin's syndrome[55]	Puntate hyperkeratosis or the characteristic palmoplantar circular pits	–
Acrokeratoelastoidosis or marginal keratoderma	Small discrete keratotic papules that often occur in linear distribution over margins of palms and soles	Autosomal dominant or sporadic inheritance. Begins at puberty or later. Rarely spread to the dorsum of hands and feet
Spiny keratoderma[56]	Discrete keratotic plugs arising from the palms, soles, or both	Unknown status; familial (autosomal dominant), ectopic hair formation. May or may not be associated with neoplastic disorders.
SASH1 variants[57]	PPK, alopecia, nail dystrophy, recurrent SCC, abnormal acrofacial pigmentation	Autosomal dominant dyschromatosis.
PPK and woolly hair (KANK2, KN motif and ankyrin repeat domains) gene mutation[58]	Striate keratoderma, woolly hair, leukonychia, pseudoainhum.	Autosomal recessive. Follicular papules over extensors, cheeks. Sparse scalp and body/eye hairs. Nephrotic syndrome
Oudtshoorn disease (keratolytic winter erythema, erythrokeratolysis hiemalia)[16]	Diffuse palmoplantar thickening preceded by erythema, dry blister and centrifugal peeling with recurrences in winter. Onset at infancy to early adulthood.	Migratory annular erythema on extremities and buttocks. Hyperhidrosis, itching, malodour. Autosomal dominant, *CTSB* gene mutation, Nonepidermolytic PPK, hyperkeratosis, focal parakeratosis, acanthosis, hypergranulosis, spongiosis
Tyrosinemia type II (keratosis palmoplantaris with corneal dystrophy, Richner–Hanhart syndrome)[17]	Yellowish-white, hyperkeratotic papules and plaques, painful, friction-related. No transgrediens	Autosomal recessive, developmental/growth delay onset at early infancy or adolescence. hyperhidrosis, cornea ulcers/dystrophy/opacities. Elevated serum tyrosine levels.
Cystic fibrosis (*CFTR* gene mutation)[59]	Aquagenic PPK in 40–84% cases (transient palmoplantar whitish papules after water exposure)	Autosomal recessive, abnormal levels of sodium and chloride in sweat, lung mucous plugs, infections, and difficult breathing, sinus infection, poor growth, fatty stool, clubbing, infertility,

ALOXE=Arachidonate lipoxygenase; CERS3=Ceramide synthase-3; CFTR=Cystic fibrosis transmembrane conductance regulator; NIPAL4= NIPA-like domain containing 4; SCC=Squamous cell carcinoma; SASH 1=SAM and SH3 domain-containing protein 1

Table 3: Syndromes of ectodermal dysplasia associated with PPK

Disorder	Inheritance, Genetic defect	PPK type	Other features
Pachyonychia congenita	AD, *KRT6A/6B/16/ KRT16/17* gene (Keratin 6a/b/16/17)	Diffuse PPK	Nail changes, hyperhidrosis, oral leukokeratosis, steatocystoma
Clouston syndrome[60]	AD, *GJB6* gene encoding Cx30	Progressive diffuse PP with transgradiens with punctiform accentuation, pebbled appearance on dorsum	Hypotrichosis, alopecia Nails: milky white in infancy, gradually thicken with short easily shed nail plates Oral leukoplakia Other: cataract, strabismus, tufted terminal phalanges Teeth: normal Sweating: normal
Papillon–Lefévre syndrome	AR, *CTSC* gene (Cathepsin C)	Diffuse PPK	Periodontitis and tooth loss
Haim–Munk syndrome	AR, *CTSC* gene (Cathepsin C)	Diffuse PPK	Periodontitis and tooth loss, pes planus, arachnoactyly, deformities of digits, acroostelysis
Oculo-dento-digital dysplasia (ODD syndrome)[61,62]	AD, *GJA1* gene encoding Cx43	Diffuse PPK	Typical facies: narrow, pinched nose with hypoplasticalaenasi, hyper/hypotelorism, Eyes: microophthalmia, microcornea, glaucoma Digit: complete syndactyly of 4th, 5th fingers, brittle nails Hypotrichosis, dental abnormality, neurologic defects, lymphedema
Odonto-onycho-dermal dysplasia[62]	AR, *WNT-10A* gene (Wnt-10a)	Diffuse PPK with hyperhydrosis	Oligodontia, peg teeth Onychodysplasia Hair- may be sparse Facial lesions: atrophic, erythematous, reticulate Benign adnexal tumors (eccrineporoma, apocrine hydrocystoma, syringofibroadenoma)
Schö–Schulz–Passarge syndrome	AR, WNT-10A gene (Wnt-10a)	Diffuse PPK with hyperhidrosis	Features of odonto-onycho-dermal dysplasia (as above) and eyelid cysts, increased risk of skin cancer
Naegeli–Franceschetti–Jadassohn or dermatopathia pigmentosa reticularis syndrome[63]	AD, *K14* (nonhelical E1/ V1 domain)	Diffuse PPK Other patterns are localized, punctate keratosis of palmar crease, linear	Adermatoglyphia, reticulate pigmentary abnormality, hypohydrosis, hyperpyrexia, early loss of teeth, hair abnormality
Ectodermal dysplasia with skin fragility[64]	AR, *PKP1* (Plakophillin-1)	Severe disabling Focal PPK	Superficial erosions (generalized), perioral and tongue fissures, abnormal nails, hypotrichosis, esophageal strictures, constipation, sparse eyelashes, blepharitis
Christ–Siemens–Touraine syndrome	XLR, (females are carriers) Ectodysplasin A	Mild diffuse PPK	Anhydrosis with hyperpyrexia Teeth: conical, pointed, spaced Nails: dystrophic (50%) Hair: madarosis, alopecia Abnormal facies- saddle nose, prominent frontal ridge and chin, sunken eyes, large lips

GJA=Gap junction; Cx=Connexin; AD=Autosomal dominant; AR=Autosomal recessive; XLR- X-linked recessive; PPK=Palmoplantar keratoderma

Table 4: Congenital diffuse PPK associated with systemic abnormalities

PPK with associated systemic abnormalities	Syndrome	Genetic defect/inheritance
Cardiac defects	Naxos disease	Plakoglobin/AR
	Carvajal–Huerta syndrome	Desmoplakin/AR
Hearing defects	Vohwinkel syndrome	*GJB2* mutation encoding Cx30/AD
	Bart–Pumphery syndrome	
	Keratitis ichthyosis deafness (KID) syndrome	
	Ichthyosis hysterix	
	(ichthyosis Curth–Macklin)	
Neuropathy	CEDNIK	*SNAP29*
	MEDNIK	*AP1S1*
	Tyrosinemia type 2	Tyrosine aminotransferase/AR
	(Richner–Hanhart syndrome)	
	Oculo-dento-digital dysplasia	*GJA1* gene encoding Connexin 43/AD
Ophthalmic defects	Olmsted syndrome	*TRPV3* (MBTPS2) gene, AD, X-ch
	Schö–Schulz–Passarge syndrome	*WNT-10A* gene
		(Wnt-10a)/AR
	KID syndrome, oculo-dento-digital dysplasia	As above
Malignancy	Howel–Evans syndrome	*RHBDF 2* gene encoding epidermal growth factor receptor (EGFR) signaling
Esophageal cancer	Huriez syndrome	
Squamous cell carcinoma		Mapped to Chromosome 4q/AD

CEDNIK=Cerebral dysgenesis, neuropathy, ichthyosis, keratoderma; MEDNIK=Mental retardation, enteropathy, deafness, neuropathy, ichthyosis, keratoderma, AD=Autosomal dominant; AR=Autosomal recessive

a concern. Vitamin D therapy reportedly had improved hereditary PPK.[66] Erlotinib, an epidermal growth factor inhibitor, in a dose of 100 mg/day escalated to 150 mg/day improved palmoplantar and perioral keratoderma that could be maintained for over 2 years without significant adverse effects.[67] Topical gentamicin for the treatment of Nagashima-type palmoplantar keratosis appears promising but needs clinical evaluation.[68,69]

Conclusion

Hereditary PPK develops as a result of compensatory hyperproliferation of the skin due to mutations in the genes involved in palmoplantar keratinization and has a significant genetic and phenotypic variability. It can manifest in diffuse, focal, striate, or punctate forms. The diffuse forms may be associated with transgrediens and/or progrediens. PPK can occur in isolation or in association with other cutaneous and extracutaneous features. The choice of treatment needs to be individualized combined with prophylactic topical antibacterial and antifungal therapies. Regular hydration and skin care remains primary therapy. Molecular studies, despite high cost, are imperative for accurate classification. However, recognizing clinical patterns especially in resource poor settings is important for appropriate diagnosis, genetic counseling, and management.

For patient information

Patients can check with various organizations and self-help groups, such as pachyonychia.org, ichthyosis.org.uk, rarediseases.info.nih.gov (Genetic and Rare Diseases Information Center) for available genetic testing and management guidelines.

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Conflicts of interest

There are no conflicts of interest.

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