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Symmetrical Acral Keratoderma and Ichthyosis Vulgaris: Related or Independent?

Yixiao Huang,[1] Yaping Tang,[1] Chenxi Zhang,[1] Wanhua Yuan,[2] Wenjun Zeng,[2] Changxing Li[1]

[1]Department of Dermatology, the Tenth Affiliated Hospital, Southern Medical University (Dongguan People's Hospital), Dongguan, Guangdong Province, China
[2]Department of Dermatology, The Sixth Affiliated Hospital of Jinan University, Dongguan, Guangdong Province, China

ABSTRACT

Objective: Symmetrical acral keratoderma (SAK) is a rare dermatosis that primarily affects young males and manifests as symmetric, brownish, well-demarcated hyperkeratotic plaques on acral sites, particularly the wrists, dorsal hands, and fingers. Ichthyosis vulgaris (IV), the most common subtype of ichthyosis, is characterized by dry, rough skin with fine, adherent, diamond-shaped or polygonal scales on the extensor surfaces of the limbs and trunk. Clinical evidence frequently links the onset of SAK with the presence of IV. However, systematic analyses of this association remain limited.

Materials and Methods: We searched PubMed, Web of Science, and the China National Knowledge Infrastructure (CNKI) for English- and Chinese-language literature.

Results: The comparative analysis revealed key parallels and distinctions. SAK predominantly affects young males and is exacerbated in hot and humid climates. IV typically manifests in infancy or early childhood, persists lifelong, and worsens during cold, dry winters. Both disorders involve FLG mutations at distinct loci. Clinically, SAK presents as symmetrically distributed, well-demarcated tan-to-dark brown macules or papules on acral sites, excluding the palms and soles. IV is characterized by light-to-dark brown diamond-shaped or polygonal scales with central adhesion and peripheral detachment, primarily on the extensor surfaces of the lower limbs. Histopathologically, SAK shows marked hyperkeratosis, thinning of the granular layer, and increased basal melanocytes. IV demonstrates mild-to-moderate hyperkeratosis with attenuation or absence of the granular layer and follicular keratin plugs. Both conditions are managed symptomatically with topical emollients and salicylic acid. Systemic approaches differ: retinoids are frequently used for IV but are seldom indicated for SAK.

Conclusion: This systematic comparative analysis delineates the salient features of SAK and IV, suggesting that they may be classified as distinct disease entities.

Keywords: Epidermal differentiation disorders, genodermatosis, ichthyosis vulgaris, keratoderma, symmetrical acral keratoderma.

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Address for correspondence:
Changxing Li.
Department of Dermatology, the Tenth Affiliated Hospital, Southern Medical University (Dongguan People's Hospital), Dongguan, Guangdong Province, China
Phone: +8613922499350
E-mail: lilichangxing@163.com

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INTRODUCTION

Symmetrical acral keratoderma (SAK) is a hyperkeratotic disorder that predominantly affects young-to-middle-aged males. Patients present with symmetric, tan, hyperkeratotic papules on acral surfaces. Characteristically, the lesions exhibit transient whitening and wrinkling after immersion in water, which resolves upon drying. The distribution typically involves the wrists, dorsal hands and fingers, ankles, and dorsal feet, occasionally extending to the elbows and knees while sparing the flexural surfaces. SAK demonstrates prominent seasonal variation, worsening in summer and improving in winter, with minimal patient discomfort.[1–5]

Following the seminal report by Jiang et al.[3] on SAK in mainland China in 2008, which detailed the clinical and histopathological features of 11 patients (9 males and 2 females; mean age at onset, 26.5 years), the entity was designated "symmetrical acral keratoderma" because of its distinct presentation. SAK has since been recognized in subsequent literature.[3]

Ichthyosis vulgaris (IV), the most common subtype of ichthyosis, arises from mutations in the filaggrin (FLG) gene. Notably, IV and SAK frequently coexist, with Liu et al.[4] reporting that 67.6% of patients had a personal or family history of IV.[1,2,4–10] This frequent association has prompted discussion regarding their nosological separation. From both clinical and etiological perspectives, the features of SAK and IV appear to overlap, making clear delineation challenging. However, no studies have systematically compared SAK and IV to date. This review comprehensively summarizes both disorders to elucidate their interrelationship and differences.

METHODS

We conducted this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Our methodology comprised the following key steps:

Search Strategy

A comprehensive literature search was performed across three electronic databases: PubMed, Web of Science, and the China National Knowledge Infrastructure (CNKI). The search included all literature published from June 1, 2005, to June 1, 2025, with no restrictions on publication type. The search strategy was designed to encompass all aspects of symmetrical acral keratoderma (SAK) and ichthyosis vulgaris (IV). In PubMed and Web of Science, we used the following key terms combined with Boolean operators:

Population/terms: "Symmetrical acral keratoderma" OR "pigmented carpotarsal hyperkeratosis" OR "symmetrical acrokeratoderma" OR "ichthyosis vulgaris"

Concepts: AND "epidemiology" OR "predisposing factors" OR "pathogenesis" OR "histopathology" OR "clinical manifestations" OR "therapeutic approaches."

For CNKI, an equivalent search was performed using the Chinese-character term for "symmetrical acral keratoderma."

Eligibility Criteria

Inclusion Criteria

The inclusion criteria were as follows: (a) original studies, including case series and case reports, describing the clinical features, histopathology, pathogenesis, or epidemiology of SAK and/or IV; (b) systematic reviews and meta-analyses providing critical summaries or novel insights into SAK or IV; (c) studies involving human subjects; and (d) articles published in English or Chinese.

Exclusion Criteria

The exclusion criteria were as follows: (a) studies without primary data, such as narrative reviews, editorials, or comments without new cases; (b) articles for which the full text was unavailable despite exhaustive efforts; and (c) duplicate publications involving the same patient cohort.

Study Selection Process

All identified records were imported into reference management software, such as EndNote. After duplicates were removed, two reviewers independently screened the titles and abstracts against the eligibility criteria. The full texts of potentially relevant articles were then retrieved and independently assessed by the same two reviewers for final inclusion. Any disagreements during the selection process were resolved through discussion or consultation with a third senior researcher. This process is summarized in a PRISMA flow diagram (Fig. 1).

Quality Assessment

The methodological quality of the included studies was critically appraised by two independent reviewers using standardized tools appropriate for each study design.

For case reports and case series, we used the corresponding critical appraisal checklists from the Joanna Briggs Institute (JBI). For systematic reviews, we used the AMSTAR-2 checklist.

Any disagreements were resolved through consensus or consultation with a third reviewer. The results of the quality appraisal were narratively summarized and considered when interpreting the findings and determining the strength of the conclusions drawn.

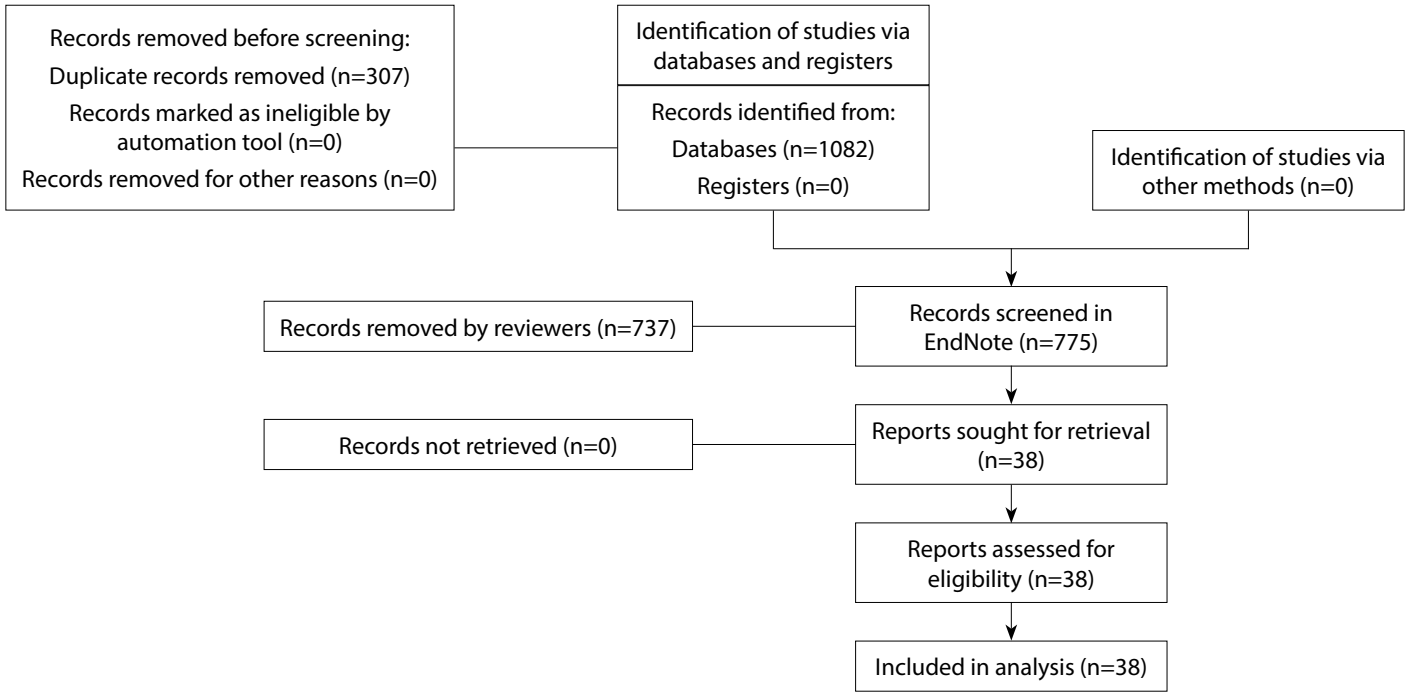

Figure 1. PRISMA flow diagram illustrating the study selection process. The diagram summarizes the identification, screening, eligibility assessment, and inclusion of records from database searches. Of the 1,082 records initially identified, 38 studies were ultimately included in the systematic review.

RESULTS

Study Selection, Characteristics of Included Studies, and Critical Appraisal

Study Selection

The initial search identified 1,082 records. After duplicate removal and a tiered screening process, 38 studies were ultimately included in this systematic review. The detailed selection process is illustrated in Figure 1, the PRISMA flow diagram.

Characteristics of Included Studies

A total of 38 studies were included in this systematic review. The literature comprised 19 studies on SAK and 19 on IV. The SAK studies included 16 case reports or case series and 3 review articles. The IV studies consisted of 11 case reports or case series and 8 review articles. The publication dates of the included studies ranged from 2006 to 2024, and the studies originated from multiple countries across Asia, Europe, and North America. The reported SAK cases were primarily from China.

Critical Appraisal

Overall Findings: Critical appraisal using the JBI checklists demonstrated high methodological quality across the 16 SAK and 11 IV case reports or case series.

Strengths: Most case reports provided clear and comprehensive descriptions of clinical presentations and diagnostic processes.

Limitations: Commonly identified limitations included inadequate reporting of adverse events, a lack of standardized diagnostic criteria, and insufficiently defined follow-up duration. Notably, the relatively recent introduction of the term "SAK" may objectively explain the observed inconsistencies in reporting, a challenge that will likely be resolved as the disease entity becomes more established in the literature.

SAK

Epidemiology of SAK

First reported in Taiwan in 1991 but misdiagnosed as acral acanthosis nigricans, SAK has since been documented predominantly in Southern China, with sporadic cases reported in India, Japan, Europe, and the United States.[2,5–9,11–13] SAK predominantly affects young male individuals. In 2014, an analysis of 71 patients with SAK (64 males and 7 females) reported by Li et al.[1] determined a mean age at onset of 27±8.9 years (range, 20-40 years; male-to-female ratio, 9.1:1). However, no consensus exists regarding the contribution of occupational factors to SAK pathogenesis.

Predisposing Factors of SAK

Current studies report conflicting data on familial and occupational contributions to SAK. Patients frequently report symptom exacerbation after chemical exposure. Notably, occupational analyses have shown a disproportionate prevalence of SAK among workers in the dyeing and finishing industries. Chemical agents are therefore implicated as potential predisposing or exacerbating factors in the pathogenesis of SAK.[1,4]

SAK demonstrates distinct seasonality, with symptom exacerbation in summer and remission in winter. Disease incidence peaks during warm months, consistent with clinical observations that warm, humid climates may potentiate SAK manifestations.[2–4,7–9]

Pathogenic Mechanisms Underlying SAK Manifestations

SAK is an autosomal dominant disorder caused by FLG mutations, with dysregulation of the OVOL1-FLG axis driving epidermal barrier dysfunction through the downregulation of differentiation complex proteins. Environmental factors, such as high temperature and humidity, increase skin hydration and perspiration, while FLG loss-of-function mutations impair barrier integrity. Together, these factors induce cutaneous microbiome dysbiosis, which underlies the clinical phenotypes of SAK.[14–17]

FLG, IVL, and OVOL1 expression is downregulated in SAK lesions compared with healthy controls. FLG loss-of-function mutations reduce the expression of FLG and IVL through the OVOL1 pathway, impairing skin barrier function. As components of the epidermal differentiation complex, FLG and IVL are essential elements of the cornified envelope.[17] FLG plays a critical role in cutaneous microbiome homeostasis, barrier formation, and UV photoprotection.[18] During the movement of cornified cells from the granular layer to the inner cornified layer, FLG promotes the collapse of cornified cells into an impermeable barrier. In addition, FLG is enzymatically metabolized in the upper stratum corneum and undergoes extensive degradation, releasing free amino acids that are essential for the synthesis of natural moisturizing factors (NMFs), a complex mixture of hygroscopic substances.[19] FLG deficiency can impair skin barrier function and decrease NMFs, leading to hyperkeratosis and dry skin.[19]

Environmental factors contribute critically to SAK pathogenesis, with elevated temperature, humidity, and enclosed occupational microenvironments promoting cutaneous microbiome dysbiosis.[1] Bacterial communities from SAK lesions demonstrated greater beta-diversity dispersion than those from healthy controls on principal coordinate analysis. The dominant phyla included Actinobacteria, Proteobacteria, Firmicutes, Bacteroidetes, and Thermi, and the key genera comprised Propionibacterium, Staphylococcus, Corynebacterium, Acinetobacter, Enhydrobacter, and Streptococcus. Patients with SAK exhibited decreased abundance of Actinobacteria, Streptococcus, Propionibacterium, and Neisseria, along with increased abundance of Proteobacteria, Acinetobacter, and Staphylococcus, compared with controls.[17]

SAK pathogenesis involves FLG loss-of-function mutations. Downregulated OVOL1-FLG axis activity reduces the expression of skin barrier proteins (FLG, IVL, and LOR) in lesional skin. Environmental factors that increase skin hydration and perspiration induce cutaneous microbiome dysbiosis, which synergizes with genetic defects to drive the clinical phenotype of SAK.

Clinical Features of SAK

Patients with SAK are often characterized by the following features:

1. Symmetrically distributed, hyperkeratotic brown papules on the extremities, typically involving the wrists, dorsal hands and feet, knees, and ankles, while sparing the palms and soles. These lesions exhibit xerotic, rough surfaces with accentuated skin markings and grooves (Fig. 2a).
2. Lesions exhibit transient aquagenic whitening after immersion in water and return to baseline after drying.
3. Lesions are typically asymptomatic.
4. The disease shows winter remission and summer exacerbation.
5. No underlying systemic comorbidities are present.[1,3–5,8]

Histopathological Morphology of SAK

The histopathological features of the skin lesions include the following:

1. Epidermal reticular basket-weave hyperkeratosis;
2. Acanthosis;
3. Papillomatosis;
4. Loosening of the stratum corneum after immersion, with the underlying epidermis unaffected;
5. Superficial dermal telangiectasia;
6. Lymphocytic infiltration at the dermoepidermal junction; and
7. Multiple variably sized vacuoles at the stratum corneum–granulosum junction, along with increased basal melanocytes containing abundant melanosomes.[1,3–5,7,9,13]

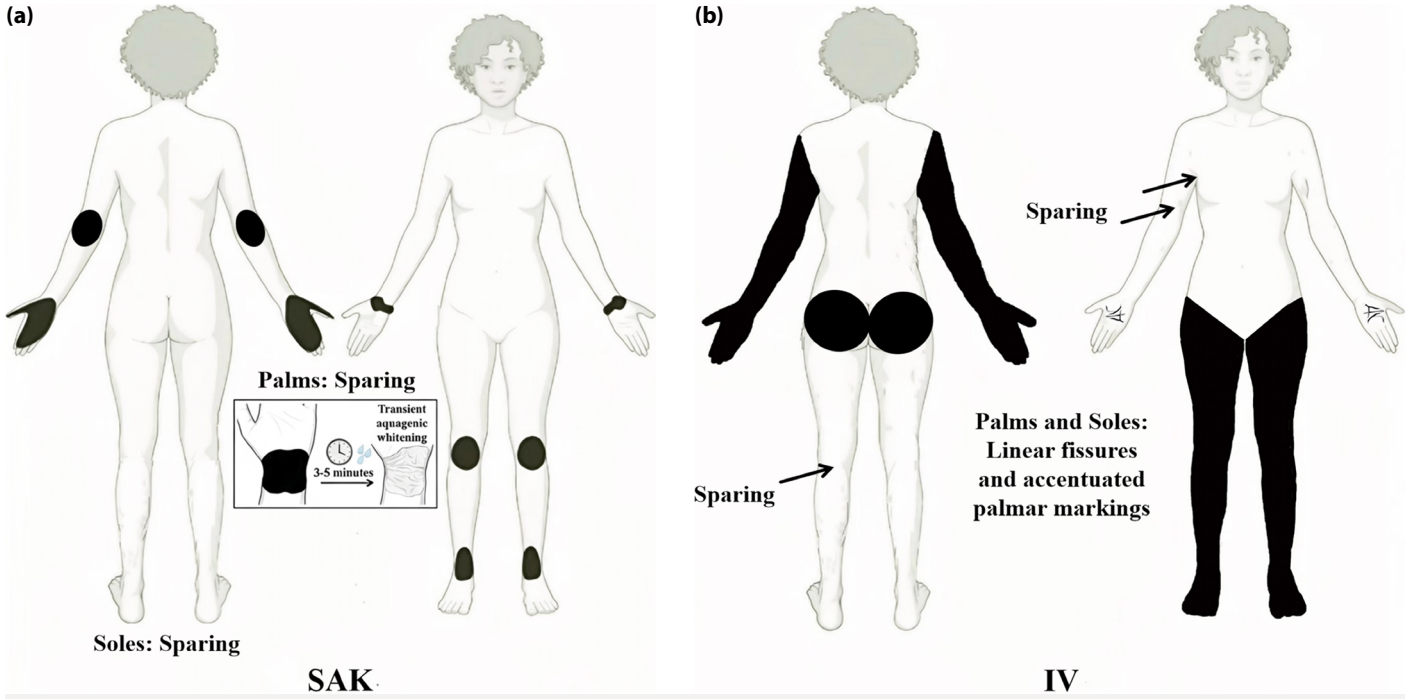

Figure 2. Schematic illustration of the characteristic clinical distribution patterns of symmetrical acral keratoderma (SAK) and ichthyosis vulgaris (IV). **(a)** SAK: The diagram highlights the symmetric involvement of acral regions (black shading), including the dorsal hands, fingers, feet, wrists, knees, elbows, and ankles, with characteristic sparing of the palms and soles. A key diagnostic feature is transient aquagenic whitening after immersion in water. **(b)** IV: The diagram shows the predominant involvement of the extensor surfaces of the limbs, with additional lesions possible on the palms, soles, and buttocks (black shading). Flexural and moist areas, such as the axillae and antecubital and popliteal fossae (indicated by the arrow), are typically spared.

Ultrastructural Morphology of SAK

Ultrastructurally, perinuclear keratin tonofilament aggregates and partial desmosomal cleavage were observed in the stratum spinosum. Notably, the layers of the stratum corneum were increased.[5,13,14,16]

Treatment and Prognosis of SAK

No disease-specific therapies exist; therefore, management remains symptomatic. Preventive measures include avoiding hot and humid environments and chemicals, minimizing sweating and water exposure, and maintaining local dryness with appropriate emollients.[1,2,4,6,7,11] For medical intervention, topical tretinoin monotherapy or corticosteroids have shown limited efficacy in some patients, although relapse is common.[1] Transient improvement may occur with systemic agents, including ketoconazole, isotretinoin, or certain vitamins.[8] Intradermal botulinum toxin type A (BT-A) injections have demonstrated efficacy in affected areas. As a potent inhibitor of acetylcholine release, BT-A has been shown to significantly improve lesion severity and alleviate symptoms in treated areas compared with untreated regions. Chiang et al.[20] suggested that BT-A may be used as monotherapy or in combination with adjunctive treatments, such as emollients, particularly in cases of suboptimal therapeutic response.

IV

Epidemiology of IV

Ichthyosis encompasses hereditary or acquired keratinization disorders characterized by defective keratinocyte differentiation and barrier dysfunction.[21] Although epidemiological data suggest a high prevalence, comprehensive population-based studies remain limited, and most reports may overrepresent severe phenotypes. IV, the predominant hereditary form, accounts for more than 95% of all cases.[21–24] The incidence of hereditary ichthyosis is likely underestimated because symptoms may improve with age and mild cases may be underreported. The current prevalence of both hereditary ichthyosis and IV remains undetermined.[21,25] IV typically presents at birth, becomes fully manifest by age 5 years, and persists lifelong. IV shows no racial or sex predilection, but it is exacerbated in cold and dry climates, where its prevalence increases.[10,22,24,26,27]

Predisposing Factors of IV

Adverse mood and neurodevelopmental comorbidities are common across dermatological conditions. Notably, patients with mood disorders show a higher lifetime prevalence of IV than the general population.[27] In addition, the disease exhibits seasonal variation: symptoms tend to worsen during cold or dry winter periods and improve during warm or humid summer periods. This pattern may be associated with FLG hydrolysis, which is necessary for the formation of natural moisturizing factor (NMF) and occurs predominantly within a specific humidity range of 70%-95%.[18,25,27]

Pathogenic Mechanisms Underlying IV Manifestations

IV is a semidominant disorder caused by heterozygous FLG loss-of-function mutations, with 83%-96% penetrance. Classified as retention hyperkeratosis due to impaired desquamation, IV lesions demonstrate epidermal barrier disruption, aberrant cornification, and elevated transepidermal water loss (TEWL), indicating compromised skin homeostasis.[10,21,25,27–30]

McLean et al.[29] established IV as a semidominant disorder because of the high frequency of FLG mutations in European populations, such as approximately 9% heterozygosity in British and Irish cohorts, in which mild signs manifest under triggering conditions such as cold and dry weather.[30,31] Studies have attributed incomplete penetrance to compensatory mechanisms, including partial rescue of NMF deficiency mediated by FLG-2. FLG-2 shares precursor sequence homology and expression patterns with FLG and converges on NMF formation. Experimental data from atopic dermatitis models, which similarly exhibit NMF deficiency, show reduced FLG-2 expression in both lesional and nonlesional skin. Analogously, FLG-2 contributes to NMF generation through similar proteolytic processing.[18,25]

The spectrum of FLG mutations differs across ethnicities. In Europeans, R501X and 2282del4 predominate, whereas 3321delA is the most frequent among more than 30 identified mutations in Asians, although with a lower population prevalence.[10,21] R501X and 2282del4, which are predicted to yield a truncated or aberrant protein or its complete absence because of nonsense-mediated mRNA decay or degradation of an aberrant protein, occur within the large (>12 kb) exon 3. This exon encodes most of the profilaggrin polypeptide.[10] Despite current challenges in amplifying FLG genes by polymerase chain reaction (PCR) because of their repetitive structure, the identification of FLG mutant genotypes, including nonsense and frameshift variants, through next-generation sequencing supports further exploration of exon 3.[10,30,32–34]

Clinical Features of IV

Lesions typically affect the extensor surfaces of the limbs (Fig. 2b) and present as polygonal or diamond-shaped "scales," as reflected by the term "ichthyosis," which is derived from "ichthys," an ancient Greek root meaning fish.[25] These white-to-gray scales exhibit central attachment with upturned edges and show variable distribution across and within anatomical regions.[24,25,32] The distribution of lesions follows a dichotomous pattern: lower limbs > upper limbs and extensor surfaces > flexor surfaces. Palmoplantar involvement manifests as hyperkeratosis and scaly desquamation. On the trunk, the dorsal surfaces are more severely affected than the ventral regions. However, lesions are milder in warm, moist areas, such as the axillae, antecubital and popliteal fossae, and groin.[10,24,25,27,28] Facial involvement is typically minimal. Disease severity ranges from subtle xerosis and roughness to prominent plate-like scaling, with scale coloration reflecting the underlying skin pigmentation.[25]

Palmoplantar skin exhibits hyperkeratosis with fissure-prone plaques, causing xerosis-induced pain.[24,25,28,32]

Follicular keratotic papules typically occur on the extensor surfaces, particularly the upper arms and thighs, and occasionally on the cheeks, appearing as either follicular prominences or hyperpigmented macules depending on severity.[24,25,32]

Histopathological Morphology of IV

The main histopathological features of IV include the following: 1) moderate orthohyperkeratosis or basket-weave hyperkeratosis; 2) focal parakeratosis with follicular plugging; 3) sebaceous and eccrine gland atrophy; and 4) unremarkable sweat glands and hair follicles.[10,25,28,35,36]

Ultrastructural Features of IV

The ultrastructural features of IV include the following:

1. Reduced corneodesmosome density with defective secretion;[10]
2. Diminished or absent friable or spongy keratohyalin granules in the granular layer;
3. Normal keratinization in the hyperkeratotic stratum corneum;[25]
4. Perinuclear keratin retraction within granular cells;[28]
5. Increased layers of the stratum corneum;
6. Uniform keratin density, a continuous keratin capsule, and reduced or absent keratohyalin granules in the granular layer; and
7. Reduced lipid granules.[36]

Treatment and Prognosis of IV

General management involves hydrating baths, stress reduction, and mood optimization.[23,26,28] Dietary modification guided by food-sensitivity testing, with adjunctive supplementation such as fish oil, vitamin D, and probiotics, has demonstrated efficacy in patients with IV.[37]

Pharmacotherapy focuses on promoting hydration and preventing evaporation. Alpha-hydroxy acids provide hydration and induce keratolysis through corneocyte disaggregation, whereas moisturizers prevent evaporation but do not alter FLG gene expression, regardless of genotype.[25,38] Topical tretinoin and retinoids suppress keratin synthesis, as do 70% glycolic acid peels.[25,32]

Potentially Shared Therapeutic Elements in SAK and IV

The pathogenesis of SAK remains poorly understood, and limited therapeutic options are currently available. As previously discussed, a significant proportion of patients with SAK present with concomitant IV, and these two conditions share overlapping pathogenic mechanisms. Although no curative treatments exist for IV, several effective disease-controlling approaches have been established. Consequently, repurposing IV therapeutics for SAK management holds considerable promise.

FLG protein deficiency is a well-documented pathogenic factor common to both SAK and IV and clinically manifests as prominent xerosis. Therefore, maintaining appropriate environmental humidity and using topical moisturizers, such as vitamin E cream, as part of IV therapy may also be effective in managing SAK, as demonstrated in previous studies.[1–7,23–26,38–40]

Tretinoin cream, a topical therapeutic agent for IV, has long been integrated into clinical practice. In addition to its well-documented ability to induce epidermal hyperplasia, promote the differentiation of epidermal granular layer cells into the stratum corneum, and regulate abnormal keratinization in the follicular sebaceous gland epithelium to eliminate keratin plugs, emerging studies suggest that tretinoin may modulate melanogenesis within melanocytes. Notably, it inhibits enzymatic activities, including tyrosine hydroxylase and dihydroxyindole oxidase, thereby attenuating melanin synthesis and mitigating cutaneous hyperpigmentation. This pharmacological mechanism may provide optimal control of pigmentary manifestations in SAK, although no studies have confirmed this to date.[1–7,23–26,38–40]

Alpha-hydroxy acids (AHAs) are widely used in topical therapy for IV because of their potent moisturizing effects. At higher concentrations, AHAs induce desquamation and keratolysis, significantly improving xerosis, fine wrinkles, and hyperpigmentation while enhancing skin smoothness, suppleness, and elasticity. In addition, studies have demonstrated the efficacy of AHAs in ameliorating dyspigmentation and increasing dermal glycosaminoglycan content. Their substantial therapeutic effects on hyperkeratosis and pigmentation disorders suggest promising applicability for SAK management.[41–45]

In conclusion, some medications already used for IV therapy may also be potentially effective for the treatment of SAK.

DISCUSSION

Overall, SAK and IV are hyperkeratotic disorders associated with genetic and environmental factors. Both manifest as increased transepidermal water loss (TEWL) due to epidermal barrier dysfunction.[46]

SAK predominantly affects young and middle-aged males, with a significant male predominance, whereas IV typically presents in infancy, often after birth, with overt symptoms manifesting by age 5 years. The prevalence of IV decreases over time, and no racial or sex predilection has been reported. Environmental triggers also differ: SAK is exacerbated by chemical exposure and warm, humid environments, whereas IV worsens in cold, dry conditions and with psychological stressors. Thus, SAK and IV demonstrate distinct onset patterns, age distributions, and opposing environmental susceptibilities.

Pathogenetically, SAK arises from a multifactorial cascade initiated by FLG loss-of-function mutations, leading to cytokeratin disorganization within epidermal keratinocytes, pathological melanosome aggregation in the basal and suprabasal layers, and consequent barrier dysfunction, as evidenced by elevated TEWL measurements. IV arises from profilaggrin deficiency caused by FLG loss-of-function mutations and reduced FLG mRNA expression. Although both disorders involve FLG loss-of-function, there is insufficient evidence to establish mutation site-specific causality.

Clinically, SAK manifests as symmetrically distributed, hyperkeratotic brownish maculopapular eruptions predominantly affecting acral surfaces. It is characteristically asymptomatic, shows diagnostic palmoplantar sparing, exhibits a predilection for the dorsal extremities, and notably spares the volar regions. Characteristic aquagenic whitening occurs after immersion and resolves upon drying. IV presents with polygonal or diamond-shaped scales with central attachment and upturned edges, along with keratosis pilaris, with greater involvement of the lower limbs than the upper limbs and possible palmoplantar involvement. Although both disorders demonstrate hyperkeratosis, SAK uniquely exhibits immersion-induced whitening. Palmoplantar involvement patterns further differentiate these entities.

Table 1. Comparison of characteristics between SAK and IV

Characteristic	SAK	IV
Gender	More common in males, with a male-to-female ratio of 9.1:1.[1,3,4]	No significant sex difference.[10,23]
Age at onset	Mainly affects young and middle-aged individuals.[1]	Usually begins in infancy and presents with distinctive manifestations by age 5 years.[10,23]
Geographical characteristics	Generally more common in coastal areas with hot and humid climates, with a tendency toward sporadic onset.[1–5,8]	More common in regions with cold, dry climates.[28]
Seasonal characteristics	Develops in summer and improves in winter.[1,2,4]	Develops in winter and improves in summer.[28]
Race	Mainly reported in Han Chinese individuals from Southern China, with a small number of cases reported from India, Japan, Europe, and the United States to date.[2,5–9,11,12]	No significant racial difference.[10,23]
Predisposing factors	Chemical exposure and hot, humid climates.[1,3,4]	Cold and dry climates.[17,26,28]
Clinical manifestations	1) Primary lesions: Well-demarcated, brownish hyperkeratotic plaques. 2) Key characteristics: Aquagenic whitening, with lesions turning white after water exposure; smooth surface with fissures in chronic cases. 3) Subjective symptoms: Typically asymptomatic; mild pruritus may occur if fissures are present.[1,3–5,8]	1) Primary lesions: Polygonal scales measuring 1–10 mm and resembling fish scales. 2) Key characteristics: Hyperlinear palms and soles; keratosis pilaris on the arms and thighs. 3) Subjective symptoms: Pruritus secondary to xerosis; painful fissures in severe cases.[25,26,29,34]
Key distribution characteristics	Acral predominance, involving the wrists, dorsal hands and feet, knees, and ankles, with sparing of the palms and soles.[1,3,4]	Preference for extensor surfaces: lower limbs > upper limbs and extensor surfaces > flexor surfaces. The palms and soles may show hyperkeratosis and scaling.[10,25,26,28,29]
Typical histopathological morphology	1) Hyperkeratosis; 2) Mild elongation of the rete ridges; 3) Acanthosis; 4) Hypergranulosis; 5) Increased basal layer melanocytes with abundant cytoplasmic melanosomes; 6) Dermal papillary edema; 7) Capillary dilation; and 8) Mild perivascular lymphocytic infiltration in the superficial dermis.[1,3–5,7,9,13]	1) Basket-weave hyperkeratosis; 2) Adherent scales; 3) Hypogranulosis or agranulosis; 4) Follicular plugging; 5) Shortening of the rete ridges; and 6) No significant dermal changes.[10,26,29,38]
Key ultrastructural alterations	1) Stratum spinosum: Tight perinuclear aggregates of keratin tonofilaments and partial cleavage of desmosomes. 2) Stratum corneum: Increased number of layers.[5,13]	1) Granular layer: Reduction or absence of keratohyalin granules and perinuclear keratin retraction in keratinocytes. 2) Stratum corneum: Decreased corneodesmosome density with defective loading, increased number of layers, uniform keratin density, and a continuous cornified envelope. 3) Lipid metabolism: Decreased lipid granules.[10,26,29,38]
Genetic model	Autosomal dominant inheritance.[16]	Autosomal semidominant inheritance.[28]

Table 1 (cont). Comparison of characteristics between SAK and IV

Characteristic	SAK	IV
Reported pathogenic genes and mutations	FLG, RBP3, BRCA2, and epidermal aquaporin-3. Reported mutations include c.3321del, c.7945del, and c.6950_6957delCATCCCAT in China; and c.3320del, c.4909del, c.3099C>G, c.4544C>A, c.6950_6957del, c.7264G>T, c.7945del, c.8117C>G, and c.12064A>T.[6,11,14,16,42,43]	FLG. Reported mutations include c.2282del" with "c.2282del4, mainly in individuals of Northern European descent, and c.3321del, which is prevalent in Japan and China.[28,29]
Therapy and prognosis	Topical treatments: 1) 3%–5% salicylic acid ointment to soften thickened keratin and mitigate posthydration whitening; 2) Retinoids, such as tazarotene, to inhibit hyperkeratosis, with cautious application to minimize irritation; and 3) Moderate-potency corticosteroids, such as mometasone cream. Systemic treatments: 1) Retinoids, which are rarely used and limited to short-term oral administration for severe cases, such as acitretin; 2) Immunomodulators, which may be considered, such as low-dose glucocorticoids; and 3) Antihistamines, such as cetirizine, for pruritus relief.[1,2,4,6,7,13,21]	Topical treatments: 1) Moisturizing and repair with ceramide-, glycerin-, or petrolatum-based formulations; 2) Gentle exfoliation with α-hydroxy acids, such as lactic acid; and 3) Low-concentration urea (<10%) to achieve mild desquamation while avoiding irritation associated with higher concentrations. Systemic treatments: 1) Retinoids, which are commonly used, especially in winter, including acitretin and isotretinoin; 2) Immunomodulators, which are very rarely used; and 3) Antihistamines, which are seldom used unless complicated by urticaria.[24,26,27,29]

SAK: Symmetrical acral keratoderma; IV: Ichthyosis vulgaris.

Histopathological examination reveals a defining divergence. Although both entities exhibit characteristic basket-weave hyperkeratosis and compact orthokeratotic thickening of the stratum corneum, IV distinctively demonstrates a marked reduction or absence of keratohyalin granules accompanied by irregularly distributed parakeratotic foci within the stratum granulosum. Conversely, SAK demonstrates papillomatosis, acanthosis, and increased melanin or melanocytes. Ultrastructural analysis enables further differentiation.

Therapeutic management principles differ significantly. SAK lesions clinically require strict avoidance of environmental humidity, whereas IV requires proactive prevention of xerosis through targeted barrier repair strategies. Symptomatic treatment controls disease progression in both conditions. Prognostically, SAK shows a tendency to relapse in summer, whereas IV symptoms attenuate with age. Neither disorder affects life expectancy, although both compromise quality of life (Table 1).

Key aspects of the SAK-IV association remain unclear. Although FLG mutations represent a shared etiology, their differential clinicopathological expression requires further mechanistic investigation. Cutaneous microbiota and metabolites represent an emerging research focus, particularly with regard to comparative lesional microbiome signatures between these disorders. These research priorities warrant systematic investigation. Future studies should elucidate the pathogenesis of SAK and its relationship with IV and related disorders. A comprehensively integrated multiomics analytical framework, strategically incorporating whole-exome sequencing (WES), whole-genome sequencing (WGS), mitochondrial genome profiling (mtDNA-seq), intronic region interrogation, proteomic characterization, metabolomic mapping, epigenome-wide methylation mapping, and high-resolution immunophenotyping, will help delineate the molecular pathophysiology underlying SAK and IV. This paradigm may enable the following: (1) deciphering multidimensional cross-omics regulatory networks; (2) identifying critical pathophysiological nodes; and (3) establishing evidence-based foundations for precision therapeutic development through advanced multimodal data integration.

Limitations

This systematic review has several limitations that should be considered when interpreting the findings. First, the available literature on SAK primarily consists of observational studies, such as case series and case reports, with an inherent lack of high-quality controlled cohorts. This limits the strength of

causal inferences that can be drawn regarding its pathogenesis and association with IV. Second, our search was limited to articles published in English and Chinese, which may have introduced language bias and omitted relevant studies published in other languages. Furthermore, heterogeneity in reporting standards and data completeness across the included studies posed challenges for direct, standardized comparisons of all clinical and histopathological parameters. Finally, as with any systematic review, the possibility of publication bias cannot be entirely ruled out, as studies with positive or significant findings are more likely to be published.

CONCLUSION

In conclusion, this systematic comparative analysis provides a comprehensive multidimensional characterization of SAK and IV, elucidating their shared epidemiological patterns, etiological triggers, pathogenic mechanisms, histomorphological features, clinical presentations, therapeutic approaches, and prognostic trajectories. Critically, their distinct clinicopathological profiles and divergent reporting patterns support their nosological distinction as independent dermatological entities.

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