

# Kindler syndrome

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## Abstract

*Kindler syndrome (KS) is a rare autosomal recessive genophotodermatosis. It combines features of acral blistering and photosensitivity from infancy, which tend to improve through childhood, with progressive poikiloderma and cutaneous atrophy developing later. Phenotypic heterogeneity and variable expression of the condition is known and additional features have been described. It shares some clinicopathologic similarities with dystrophic epidermolysis bullosa and Weary's hereditary acrokeratotic poikiloderma. However, characteristic immunohistochemical, ultrastructural and molecular features have been demonstrated which distinguish KS as a separate entity. Specifically, this condition has recently been shown to result from loss of function mutations in KIND1, the gene encoding kindlin-1, a novel protein involved in attachment of the actin cytoskeleton to the extracellular matrix via focal contacts.*

## Keywords

Genodermatosis, poikiloderma, skin blistering, periodontitis

## Disease name/synonyms

Kindler syndrome

Poikiloderma of Kindler

## Definition/diagnostic criteria

KS is a rare genophotodermatosis described first in 1954 by Theresa Kindler (Kindler, 1954). Its salient features include trauma-induced blistering and photosensitivity usually starting in early infancy. With advancing age, improvement in blistering and photosensitivity usually occurs; a progressive and more persistent poikiloderma and cutaneous atrophy arise. Ultrastructurally, variable planes of cleavage

are seen at the dermal-epidermal junction along with reduplication of the basement membrane. The locus of the disease has been mapped to 20p12.3 (Jobard et al., 2003) and, subsequently, the causative gene identified as KIND1, which encodes kindlin-1, a protein involved in attaching the actin cytoskeleton to the extracellular matrix at focal contacts (Jobard et al., 2003; Siegel et al., 2003; Ashton et al., 2004).

## Differential Diagnosis

A number of other conditions can cause blistering, cutaneous atrophy and / or poikiloderma. Notably, [dystrophic](#)

[epidermolysis bullosa](#) (DEB) and [Weary's hereditary acrokeratotic poikiloderma \(HAP\)](#) may cause confusion with KS (see below). A set of clinical criteria (Table 1) may assist in making a bedside diagnosis until new molecular diagnostic techniques are widely available.

It may also be difficult to differentiate and individually define different congenital poikiloderma syndromes as these rare conditions may have overlapping clinical features (Table 2). Again, delineation of the molecular pathology underlying KS will help confirm this as a distinct entity.

### Etiology

KS has been recently mapped to a locus on chromosome 20p12.3 and pathogenic mutations have been detected in a new gene *KIND1*, encoding a 677 amino acid protein, kindlin-1 (Jobard et al., 2003; Siegel et al., 2003; Ashton et al., 2004). Kindlin-1 is expressed mainly in basal keratinocytes and plays a role in the attachment of the actin cytoskeleton via focal contacts to the extracellular matrix (Ashton et al., 2004). Loss of function mutations in *KIND1* appear to be responsible for the mucocutaneous fragility observed in KS, therefore. However, the precise mechanisms whereby mutations in this gene lead to photosensitivity and poikiloderma are not yet clear.

### Clinical description

KS usually becomes clinically evident by the age of 2-3 years when photosensitivity, acral blistering and poikiloderma are established (Hovnanian et al., 1989). Hair, teeth and nails have no or only mild abnormalities. Endocrine or hematologic abnormalities are not seen, and physical and intellectual development remains unimpaired throughout life (Thappa et al., 2000).

Skin fragility and blistering, mostly over the dorsa of hands and feet, are the most consistent clinical features in KS. Bullae may be present at birth or appear during first few days of life. Blistering follows cutaneous trauma (Fig. 1) or occasionally exposure to sunlight, and may get secondarily infected. Blistering continues to occur in all age groups albeit in a diminished frequency after 10 – 12 years of age (Penagos et al., 2004). Photosensitivity of variable severity is observed by 1 month to 2 years of life. Erythema associated with a burning sensation followed by blister formation is usual after sun exposure. With advancing age and coinciding with diminished blister formation, the photosensitivity, too, tends to

wane in intensity (Penagos et al., 2004). Subsequently a more persistent reticular poikilodermatous pigmentation and cutaneous atrophy ensue.

Poikiloderma, first noticed between 2-3 years of age, becomes persistent for life (Penagos et al., 2004). Although photosensitivity diminishes, the poikiloderma becomes more pronounced and generalized eventually involving both sun exposed and non-sun exposed areas (Fig. 2 & 3). Evidently, photodamage is not the sole cause for poikiloderma.

A characteristic diffuse cutaneous atrophy that involves abdomen, thighs, knees and elbows occurs in all patients. Dry, atrophic, cigarette-paper-thin skin atrophy is more marked over dorsa of hands (Fig. 4) and feet. Webbing of the digits is also a feature as is dystrophy of finger- and toenails.

Mild to moderately severe diffuse, sometimes punctate, hyperkeratosis of palms (Fig. 5) and soles with a characteristic waxy feel is usual. Associated fissuring, wrinkling and scaling may occur. Acral sclerosis, pseudoainhum and loss of dermatoglyphics may accompany sometimes (Kronic et al., 1997; Binder et al., 2002).

Mucosal involvement is frequent in KS. Leukokeratosis of oral mucous membranes (Fig. 6), seen as adherent white patches, is the most frequent finding but may occasionally involve the anal mucosa as well (Fig.7) (Sharma et al., 2003). Restricted mouth opening has been attributed to repeated erosions and scarring of oral commissures (Fig. 6). In addition, atrophy of buccal mucosa and gums, erosions of lips and hard palate and geographic tongue have also been observed (Wiebe et al., 2003). Severe phimosis to the extent that prepuce skin may appear adherent to the glans is another frequent feature (Fig.8) (Thappa et al., 2000). Stenosis of the anal canal, esophagus and urethral meatus may be encountered occasionally (Hovnanian et al., 1989).

Dental abnormalities (Wiebe et al., 2003) include severe periodontal bone loss and periodontitis, swollen, fragile bleeding gums and early exfoliation of deciduous as well as permanent dentition (Fig. 9). Periodontal disease in most cases begins in early adolescence coinciding with eruption of permanent teeth. Patients presenting before the age of 10 years, therefore, may exhibit little or no periodontal disease. The pathomechanism of these defects is not well understood. The inherited defect of

cutaneous fragility is perhaps also expressed in gums and mucous membranes. Spontaneous bleeding from gums suggests it to be due to microblistering and breakdown of periodontal tissues due to minor trauma of normal occlusal function. Occasional stenosis of esophagus/anus also points towards mucosal fragility and subsequent fibrosis (Forman et al., 1989). Many uncommon and less consistent features of this syndrome have also been described (Person et al., 1979; Forman et al., 1989; Hovnanian et al., 1989; Binder et al., 2002; Sharma et al., 2003 and Penagos et al., 2004). Ophthalmic involvement may occur in the form of pigment on lens surface, corneal opacities, thickened corneal nerves, keratoconjunctivitis, bacterial blephritis and ectropion. Isolated abnormalities such as laryngeal webs, imperforate anus, synechia of labia, anhidrosis / hypohidrosis and abnormalities of skeletal maturation manifesting as turricephaly, malformation of ribs, mandible and metacarpals have also been observed.

Development of actinic keratoses and squamous cell carcinoma involving the lower lip and leg in KS (Alper et al., 1978; Karthikaeyan et al., 2003) suggests some predilection for malignant change. Recurrent erosion and regeneration of mucosal surfaces has also been postulated to be responsible for transitional cell carcinoma of bladder in an isolated case (Alper et al., 1978).

### Diagnostic methods

The histopathology of KS is not diagnostic and varies with the type of lesion biopsied. Moreover, due to the sequential appearance of blistering, photosensitivity and poikiloderma, the age at which the patient has been assessed is also important.

On light microscopy, blister formation may be evident within or just beneath basal keratinocytes (Hovnanian et al., 1989). Features of poikiloderma with epidermal atrophy, hyperkeratosis, hyper- or hypopigmentation and telangiectatic vessels may be present. Additionally, there may be disrupted collagen and elastic fibres in the papillary dermis and increased numbers of melanophages (Hovnanian et al., 1989; Patrizi et al., 1996).

With electron microscopy, variable levels of cleavage through basal keratinocytes, the lamina lucida and sub-lamina densa have been observed (Hovnanian et al., 1989; Shimizu et al., 1997; Şenturk et al., 1999). Also, there is a characteristic interruption

and reduplication of the lamina densa which may reflect continuous remodeling of the basement membrane zone (Shimizu et al., 1997; Yasukawa et al., 2002).

Immunohistochemically, a broad reticular labeling pattern of types IV and VII collagen streaking deep into the connective tissue beneath the basement membrane is seen, reflecting the basement membrane reduplication seen ultrastructurally (Shimizu et al., 1997; Wiebe et al., 1999).

With the identification of kindlin-1 pathology in KS, it is now possible to use immunohistochemistry to assist diagnosis (Siegel et al., 2003). Using a polyclonal antibody against kindlin-1, the skin from KS patients shows very reduced or absent staining compared to bright staining in basal keratinocytes and along the dermal-epidermal junction in normal controls. Mutation analysis of *KIND1* in affected families can further confirm diagnosis and also provides the potential for first trimester DNA-based prenatal testing in at risk pregnancies.

### Management including treatment

The treatment of KS is mainly symptomatic. Avoidance of trauma, photoprotection and use of emollients helps prevent blistering. Antibiotics may be needed for bacterial infections and physiotherapy is recommended to prevent contractures. Gingival problems improve with conservative periodontal therapy and by maintaining good oral hygiene (Wiebe et al., 1996). Psychological counseling is important in view of cosmetic disability.

### Kindler syndrome and epidermolysis bullosa

As the characteristic poikilodermatous cutaneous changes appear in later life, the bullous component of KS in infancy may often be misdiagnosed as epidermolysis bullosa. Indeed, Kindler's original case was considered to have incidental co-occurrence of DEB and congenital poikiloderma. Clinical absence of photosensitivity and poikiloderma in DEB, helps differentiate it from KS, but these features may not be apparent for a number of months or years. In contrast, bullae in DEB heal with extensive scarring, milia formation, nail loss, flexural contractures and often marked digital webbing. Although blistering at the dermal-epidermal junction may occur in both KS and different forms of EB, multiple planes of cleavage in an individual patient are more consistent with KS. Also, the extensive

reduplication of the lamina densa seen ultrastructurally is not a feature of EB. Finally, the molecular mechanisms underlying KS and DEB are now understood and separate (Yasukawa et al., 2002): whilst DEB is caused by mutations in the type VII collagen gene, *COL7A1*, KS is caused by mutations in the kindlin-1 gene, *KIND1* (Jobard et al., 2003; Siegel et al., 2003).

#### Kindler syndrome and Weary's hereditary acrokeratotic poikiloderma

In 1971, an autosomal dominant condition named hereditary acrokeratotic poikiloderma (HAP) with clinical features similar to those of KS was described (Weary et al., 1971). Subsequent reports also revealed significant overlapping clinical findings in KS and Weary's HAP. Some workers even adopted the term "Weary-Kindler syndrome" to describe similar cases (Kronic et al., 1997; Kapasi et al., 1993). Weary's HAP is the main differential diagnosis when poikiloderma appears in KS. However, the hallmark photosensitivity, cutaneous atrophy and mucosal lesions of KS are not seen in Weary's HAP and poikiloderma appears before the first year of life in most cases of KS. Palmoplantar keratoderma when present in Weary's HAP is usually of punctuate variety. Keratotic papules over knees, elbows, dorsa of hands and feet and eczematous dermatitis are strikingly exclusive to Weary's HAP. Histologically, also, cleft formation is epidermal in Weary's HAP.

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**Table 1 : Proposed Clinical criteria for bedside diagnosis of Poikiloderma of Kindler**

**Essential Criteria**

- 1) Progressively diminishing photosensitivity since early infancy.
- 2) Traumatic acral bullae since birth or developing during first few days of life.
- 3) Characteristic cigarette-paper-thin cutaneous atrophy, more pronounced over acral areas.
- 4) Diffuse, generalized poikiloderma involving sun exposed and non-sun exposed skin with onset after 1<sup>st</sup> year of birth.

**Minor Criteria**

- 1) Early onset of severe gingivitis/periodontitis.
- 2) Mucosal leukokeratosis.
- 3) Normal physical and mental development.
- 4) Palmoplantar hyperkeratosis with a waxy feel.
- 5) Severe phimosis.
- 6) Webbing of fingers and toes.
- 7) Absence of definite histopathologic features.

***Presence of all essential and four of minor criteria is diagnostic***

**Table 2 : Differential Diagnosis of major Hereditary Bullous Poikiloderma syndromes**

S.No.	SYNDROME	INHERITANCE	BULLAE	PHOTO SENSITIVITY	POIKILODERMA	KERATOTIC LESIONS	ECZEMA	NAIL CHANGES	PALMO-PLANTAR KERATODERMA	MUCOSAL LESIONS	REMARKS/ISOLATED ADDITIONAL FEATURES
1	KINDLER SYNDROME	AR/AD	Acral with onset before 1yr of age	Since infancy	Widespread. Involves Sun exposed & Non-sun exposed body areas.	Absent	Absent	Mild or none	Diffuse	Leukokeratosis	Defective gene mapped to chromosome 20p12.3. Stenosis of Oesophagus, Anus & Urethra, Webbing of digits, Dental Abnormalities Anhidrosis
2	WEARY'S HEREDITARY ACROKERATOTIC POIKILODERMA	AD	Acral with onset after 1 yr of age	Absent	Limited to neck & upper chest. Onset within 1 <sup>st</sup> year of life	Present in Acral distribution	Present	None	Punctate or absent	Absent	Poor dentition, Enteropathy
3	HEREDITARY SCLEROSING POIKILODERMA	AD	Absent	Absent	Accentuated in flexors with sclerotic bands	Absent	Absent	Clubbing is occasional	Sclerosis	Absent	Poor dentition, Calcinosis cutis
4	DYSKERATOSIS CONGENITA	XR or AD	Absent (or occasional)	Absent	Poikiloderma is more of dyschromatic variety	Absent	Absent	Present	Absent	Premalignant leukokeratosis	Blood dyscrasias, Growth retardation, Poor dentition
5	ROTHMUND – THOMSON SYNDROME	AD	Occasional (over photo exposed skin)	Present	Present (in Photo distribution)	Absent	Absent	None or Occasional	Absent	Absent	Cataract, Dwarfism, Hypogonadism, Bone abnormalities
6	XERODERMA PIGMENTOSA	AR	Occasional (over photo exposed skin)	Present	Present (in Photo distribution)	Present (not limited to Acral areas)	Absent	Absent	Absent	Absent	Cutaneous malignancies, Neurologic changes, Photophobia/Corneal opacities
7	MENDES DA COSTA SYNDROME	XR	Present (Acral bullae)	Absent	Present (spares the trunk)	Absent	Absent	Occasional	Absent	Absent	Acrocynosis, Scarring alopecia, Dwarfism, Micro cephal, Mental retardation, Short conical digits, Bone abnormalities
8	DERMATOPATHIA PIGMENTOSA – RETICULARIS	AD	Present (Acral bullae)	Absent	Dyschromatic (Trunkal)	Present (scattered Keratotic lesions)	Absent	Dystrophy or Hypoplasia	Hyperkeratosis	Absent	Corneal opacities, Alopecia, Axillary papillomatosis Pseudoainhum, Flexion contractures, Hypertrophic scars
9	FRANCESCHETTI – JADASSOHN SYNDROME	AD	Absent	Absent	More of Reticulated hyperpigmentation	Absent	Absent	Absent	Present	Absent	Hypo/Anhidrosis, Poor dentition
10	DEGOS – TOURAINE SYNDROME	?	Present (Acral or facial)	Absent	Photo distributed	Present in Acral distribution	Absent	Absent	Absent	Absent	Enteropathy

(Modified after Forman et al., 1989). Few isolated reported cases of poikiloderma syndromes and reviewed by Person et al., 1979 are not included (AD = Autosomal Dominant, AR =Autosomal Recessive, XR =X-linked Recessive)



**Fig. 1. Multiple infected crusted lesions of acral bullae over lower limbs. Note: Characteristic atrophic skin over dorsa of feet and dystrophic toe nails.**



**Fig. 2. Poikiloderma of left side of neck extending over face**



**Fig. 3. Poikiloderma of abdominal skin.**



**Fig. 4. Characteristic atrophic skin over dorsa of hands.**



**Fig. 5. Mild palmar hyperkeratosis. Note: Unusual shape of fingers.**



Fig. 6. Leukokeratosis of oral mucosa near angle of mouth. Note: Erosions and scarring at oral commissures



Fig. 7 Leukokeratosis of anal mucosa.



**Fig. 8. Severe phimosis.**



Fig. 9. Severe periodontitis and loss of teeth



**Fig.10.Turricephaly. Premature obliteration of transverse sutures causes upward growth via sagittal sutures resulting in a dome shaped skull. Note: Loss of mandibular angle.**