Kindler Syndrome

A New Mutation and New Diagnostic Possibilities

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Background: Kindler syndrome (KS) is a rare genetic disorder that is characterized by blistering in infancy, followed by the onset of poikiloderma and photosensitivity in childhood. The recently elucidated molecular pathogenesis involves mutations in KIND1, a gene encoding the protein kindlin-1, which is involved in the attachment of the actin cytoskeleton to the extracellular matrix in basal keratinocytes.

Observations: We describe a child with the neonatal diagnosis of epidermolysis bullosa simplex who developed poikiloderma and skin fragility at 6 years of age. His skin showed diminished staining with anti-kindlin-1 antibody, and genetic analysis revealed that he was a compound heterozygote with a previously unreported mutation in KIND1. Ultrastructural clues to the diagnosis of KS were present in a biopsy specimen that was obtained when the patient was 10 months old, before he developed poikiloderma and photosensitivity.

Conclusions: In this case, a combination of a known mutation (R271X) and a newly described mutation (1755delT) in the KIND1 gene produced loss of function in kindlin-1, leading to the clinical features of KS. Ultrastructural findings characteristic of KS were evident years before the onset of poikiloderma and sun sensitivity. In infancy, electron microscopy can enable early, accurate diagnosis of KS.

Arch Dermatol. 2006;142:620-624

In 1954, Kindler 1 described a 14-year-old girl with the clinical constellation of acral bullae during infancy, followed by the later development of progressive poikiloderma and photosensitivity. This syndrome had many overlapping features with Weary hereditary acrokeratotic poikiloderma (acral blisters in infancy or early childhood, eczematous dermatitis, development of diffuse poikiloderma, and acral keratoses 2), making specific diagnosis difficult. 3 Early in life, before the onset of the photosensitivity and poikiloderma, Kindler syndrome (KS) is frequently confused with variants of epidermolysis bullosa (EB). Although these 2 entities have clinically similar features in infancy, mutations in the genes involved in the different subtypes of EB have been excluded as a cause of KS. 4

The pathogenesis of KS remained uncertain until recently, when it was discovered that the disease mapped to the short arm of chromosome 20, where several loss-of-function mutations in a gene called KIND1 have been demonstrated. 5 KIND1 encodes a protein, named kindlin-1, which is thought to be involved in actin cytoskeleton-extracellular matrix interactions. 5-7 Patients with KS experience trauma-induced blistering in infancy, similar to patients with EB. Blistering tends to improve with age, and progressive poikiloderma develops, especially on sun-exposed areas. Other features may include nail dystrophy, webbing of the digits, esophageal and urethral stenosis, ectropion, poor dentition, and gingival fragility. 3,8

Our patient was diagnosed as having EB simplex in the first year of life and developed sun sensitivity, poikiloderma, skin atrophy, and multiple keratoses by the age of 6 years. He was found to be a compound heterozygote for a nonsense-frameshift combination of mutations in KIND1 (R271X/1755delT). To our knowledge, the single nucleotide deletion in exon 14, designated 1755delT, has not been previously reported. On review of our patient’s initial diagnostic studies (obtained at 10 months of age), the electron microscopic changes described in KS 9-11 were present well before the onset of the clinical findings that led us to the correct diagnosis when he was 6 years old.
REPORT OF A CASE

The pediatric dermatology service was consulted regarding a 5-day-old white boy who was transferred to the neonatal intensive care unit of Children’s Hospital, Denver, Colo. The patient was born at 42 weeks’ gestation, after labor was induced with oxytocin (Pitocin). Delivery was difficult, requiring forceps assist after a failed attempt at vacuum extraction. At 18 hours of age, the neonate developed seizure activity that responded to phenobarbital. Initial workup was done for herpes simplex virus (HSV) infection, and the results of a toxicology screen were negative. On the second day of life, a “weeping lesion” was noted on the abdomen, at the site of a temperature probe. Then, several vesicles and erosions developed at other sites of previous trauma. These cutaneous sites were also cultured for HSV. The cutaneous and central nervous system workup was negative for HSV.

The patient was seen in follow-up at the pediatric dermatology clinic at 3 weeks of age. He had several intact and crusted vesicles on his hands and feet, and a presumptive diagnosis of EB was made. He underwent a blister-free period between 1 and 3 months, after which he developed mostly acral blisters at sites of trauma. A diagnostic biopsy specimen was sent for routine microscopy, and an immunofluorescence examination was performed. Electron microscopy was not performed.

Hematoxylin-eosin staining of the biopsy specimen obtained at 3 months demonstrated a subepidermal blister that was filled with red blood cells and occasional neutrophils. Immunofluorescence studies revealed C3 and multiple colloid bodies along the basal cell layer, but no blister was present on the specimen submitted for mapping. The type of EB was uncertain.

The patient continued to have recurrent blisters on his extremities and face that healed with milia but not scarring. At 10 months of age, another skin biopsy specimen was obtained for electron microscopic diagnosis. The ultrastructural study revealed a cleavage plane passing through the middle epidermis that was judged to be an artifact and of questionable clinical significance. The findings of this biopsy were thought to be supportive of the diagnosis of EB simplex.

When the patient was 4 years old, with continued acral blisters, mild atrophy of the dorsal area of the hands was noted for the first time. At 5 years of age, mild hyperkeratosis of his feet was observed, especially over the heels. Generalized blisters were present, and the epidermal atrophy of the dorsal aspect of the hands was more pronounced. The patient also had poor dentition, chronic constipation, and constriction of the foreskin that was so severe that circumcision was recommended. At 6 years of age, he had diffuse xerosis and erythema of the sun-exposed areas of his face and neck. By 7 years of age, he had developed more widespread epidermal atrophy, poikiloderma on sun-exposed areas, and multiple light-brown keratoses on his arms (Figure 1). At this point, the diagnosis of KS was considered. Biopsy specimens of sun-exposed skin were obtained for routine microscopy, immunofluorescence studies, and electron microscopy. Blood samples were also obtained for genetic analysis. The patient is in the custody of his maternal grandmother, and his parents were not available for genetic analysis.

METHODS

Following informed consent, DNA was extracted from a peripheral blood sample. Polymerase chain reaction amplification of the KIND1 gene was performed using 15 pairs of primers spanning all 15 exons and situated in flanking introns, as described in detail elsewhere. A skin biopsy specimen was processed for immunofluorescence microscopy by the EB diagnostic laboratory at St Thomas’ Hospital, London, England, as described previously.

RESULTS

Examination of hematoxylin-eosin–stained tissue taken from a sun-exposed site showed an attenuated epidermis, vacuolar alteration of the basal layer with early cleft formation, and telangiectasia of the vessels in the superficial dermis, with some areas of fibrosis (Figure 2). A thickened basement membrane was not observed. The results of immunostaining of the tissue with an antibody to kindlin-1 were markedly decreased compared with control tissue (normal breast skin) (Figure 3).
Electron microscopy of the biopsy specimen obtained when the patient was 7 years old showed extensive reduplication of the lamina densa. Abundant collagen deposition filled the cleft between the epidermis and the reduplicated basement membrane. Cells, similar to those previously described as fibroblastlike cells, were also present within the cleft underlying the epidermis (Figure 4). The electron microscopy specimen obtained when the patient was 10 months of age was reexamined and compared with the specimen obtained when the patient was 7 years old. Reduplication of the basal lamina with associated collagen deposition and scattered fibroblastlike cells were also present in this initial biopsy specimen.

Sequencing revealed a previously described heterozygous single nucleotide substitution (C>T) at position 811 in exon 6 (Figure 5A). This transition converts a cysteine residue (CGA) to a stop codon (TGA), the nonsense mutation being designated R271X. Also, a new heterozygous single nucleotide deletion in exon 14, designated 1755delT, was also identified (Figure 5C). The 2 mutations together led to loss of function of the kindlin-1 protein.

**COMMENT**

Kindler syndrome (Online Mendelian Inheritance in Man 173650) is a rare genetic disorder characterized by the following cutaneous findings: neonatal acral blistering, photosensitivity, atrophy of the skin with skin fragility, dyspigmentation, diffuse telangiectasia, hyperkeratosis of the palms and soles, nail dystrophy, digital webbing, and phimosis. Early clinical diagnosis of KS is difficult, as demonstrated by the present case. Many of the early clinicopathologic features closely resemble those of EB.

In 2003, the molecular basis of KS was established. This syndrome is now known to be due to mutations in the *KIND1* gene on chromosome 20. *KIND1* encodes a novel protein, kindlin-1, which is expressed in basal keratinocytes. Homology and expression data suggest that kindlin-1 is a membrane-associated structural and signaling protein that plays a role in the attachment of the actin cytoskeleton via focal contacts to the extracellular matrix. Focal contacts are transmembrane links that play a critical role in directing cell migration, adhesion, and normal growth. Seventeen different loss-of-function mutations in *KIND1* in 41 families from around the world have been determined. Our case introduces a new mutation in *KIND1*, never previously reported (to our knowledge) in a patient with KS.

Light microscopic findings in patients with KS include epidermal atrophy, vacuolar alteration with cleft formation of the epidermis, and only nonspecific autofluorescence in the stratum corneum is present. In contrast, in control skin there is pan-epidermal labeling, which is maximal in basal keratinocytes and at the dermoepidermal junction.
formation, and colloid bodies. The dermis contains dilated capillaries, with dermal edema or mild fibrosis. The gene mutations in KS cause loss of function of the protein kindlin-1, which is involved in the binding of actin to the extracellular matrix. Prior studies of the skin ultrastructure in KS have described cleavage planes in variable locations. The most frequently encountered cleavage plane is through the lowermost portion of the basal keratinocyte layer of the epidermis.10,12,13 This finding correlates with structural defects in the anchoring of the actin filaments, which are localized to the lower portion of the keratinocyte. Cleavage planes have also been reported within the basement membrane, both through the lamina lucida and beneath the lamina densa.3,9-12 Extensive reduplication of the basement membrane and associated collagen deposition within the clefts are the unique ultrastructural findings in KS.3,9-12 These findings suggest that there was prior cleavage through the basal epidermis or basement membrane, followed by attempted tissue remodeling and repair. The presence of fibroblast-like cells within the cleft beneath the basal keratinocytes3 and clumping of tonofilaments3,13 surrounding the nucleus have been reported. Hemidesmosomes, desmosomes, and anchoring fibrils are normal.9,13

Ashton et al17 performed immunofluorescence microscopy studies with the carboxy-terminal anti–kindlin-1 antibody as a potential diagnostic probe and demonstrated marked reduction or complete absence of immunostaining in patients with known mutations in KIND1. They concluded that anti–kindlin-1 antibody was a consistent and reliable marker in KS skin.

In the present case, skin immunostaining with this new antibody against the carboxy-terminal part of the kindlin-1 protein showed markedly reduced labeling in the patient’s skin compared with control skin (which showed kindlin-1 staining in basal keratinocytes and at the dermoeipidermal junction). This new antibody probe now offers a simple and quick means of diagnosing KS in early life. The light microscopic findings when our patient was 7 years old were consistent with reported findings in other patients with KS: epidermal atrophy, vacuolar alteration with many colloid bodies, and early cleft formation as well as dilated capillaries in the superficial dermis, with some fibrosis.

Molecular genetic analysis found our patient to be a compound heterozygote for a nonsense-frameshift combination of mutations in KIND1 (R271X/1755delT), leading to the clinical syndrome described in the case report. He had a new, previously unreported mutation involving a single nucleotide deletion in exon 14, designated 1755delT, in addition to the previously described mutation, R271X.8

Figure 4. Electron microscopy at 10 months of age. Characteristic ultrastructural features of Kindler syndrome are present. There is reduplication of the basal lamina (arrows) with interspersed zones of collagen deposition. At fresh sites of disruption (arrowhead), there are fibroblast-like cells (FB) lying within the clefts beneath the exposed keratinocytes (Ker) (bar=1 µm).

We were able to compare tissue obtained for electron microscopy when our patient was 10 months old with that obtained when he was 7 years old. The findings that are described in the literature in patients with KS have been present in our patient at the age of 10 months, before the onset of skin atrophy, wrinkling, and telangiectasia. The early presence of these electron microscopic findings raises the possibility of correctly diagnosing this disorder in early infancy, before the full constellation of symptoms and clinical findings is evident. Electron microscopic findings suggestive of KS were present in our patient at 10 months of age, before his clinical findings suggested the diagnosis. Therefore, screening of tissue specimens from young patients should be considered. The presence of these suggestive findings may indicate the need for early genetic analysis to confirm the diagnosis. Clinicians will then be able to diagnose this syndrome accurately, to counsel parents and patients regarding strict sun protection and warn them of the expected poikilodermatosus skin changes, and to reassure families that the blistering will likely improve with age, as it does in patients with KS.

Our patient presented with blistering in a predominantly acral distribution shortly after birth. He was initially diagnosed as having Koebner EB simplex. He subsequently developed skin atrophy, telangiectasia, palmar-plantar hyperkeratosis, phimosis, nail dystrophy, periodontitis, and multiple caries, calling this diagnosis into question. The underlying molecular defect in EB is found in the keratin-intermediate filament-hemidesmosome complex network of proteins at the basement membrane. Kindler syndrome is the first genodermatosis caused by a defect in the structural link between the actin cytoskeleton, focal contacts, and extracellular matrix. This actin-extracellular matrix disruption seen in KS initially produces a phenotypic mimic of the keratin extracellular matrix mutations seen in EB.

This case retrospectively demonstrates that it is possible to diagnose KS in infancy using electron microscopy before the onset of poikilodermia and sun sensitivity, even if antibodies to KIND-1 are not readily available. Early, accurate diagnosis of this disorder in infancy will allow early intervention with photoprotection to potentially decrease the cutaneous affects of the photosensitivity. Early accurate diagnosis will also influence surveillance for extracutaneous issues such as chronic gingival inflammation; esophageal, urethral, and urethral stenosis; and mucocutaneous malignancy. Early, accurate diagnosis of the underlying disorder will also enable accurate genetic counseling for the families of children with KS and EB.

Accepted for Publication: July 16, 2005.
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Financial Disclosure: None.

Acknowledgment: We thank Alan Arbuckle, MD, who was involved in the clinical care of our patient and obtained specimens and arranged for their transport to London.

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