Kindler Syndrome in Native Americans From Panama

Report of 26 Cases

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Objective: To investigate the clinical, genetic, and laboratory features of 26 patients with Kindler syndrome.

Design: Case series of patients recruited when they were seen at outpatient consultations in the Department of Dermatology at the Changuinola Hospital in Bocas del Toro, Panama, between May 1986 and December 1990.

Setting: Clinical history, physical examination, and laboratory studies were done at a community hospital in Panama. Twelve of the patients had further studies performed at a children's hospital in Costa Rica.

Patients: A total of 26 patients were entered into the study. They were members of the Ngobe-Buglé tribe and resided in isolated villages in rural Panama.

Results: The major findings were skin fragility with blistering (100%), poikiloderma (96%), photosensitivity (92%), severe cutaneous atrophy (89%), hyperkeratosis of the palms and soles (81%), congenital acral blisters (81%), severe periodontal disease (81%), and phimosis (80% of male subjects). In 1 large family with 10 patients, inheritance of Kindler syndrome followed that of an autosomal recessive disease. Karyotypes in 3 patients and 1 unaffected father were normal. Findings from ultrastructural studies showed replication of lamina densa in 10 patients.

Conclusions: To our knowledge, this study represents the largest series to date of patients with Kindler syndrome. The clinical features confirm previously reported cases, and segregation analysis confirms its autosomal recessive inheritance. We also report severe phimosis as a complication, which has not been previously described in this syndrome.

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In 1954, Theresa Kindler described progressive poikiloderma with marked diffuse cutaneous atrophy associated with congenital acral bullae and photosensitivity in a 14-year-old girl. She hypothesized that the syndrome might result from the coincidence in 1 patient of 2 rare congenital conditions (dystrophic epidermolysis bullosa and congenital poikiloderma) or might be due to a previously unidentified genetic disorder. Many subsequent reports have established this syndrome as a distinct clinical entity.

To our knowledge, we describe herein the largest series of patients with Kindler syndrome (KiS) to date—26 cases in 10 families from the Bocas del Toro province of Panama. This kindred was used to identify the gene for KiS (KIND1) on chromosome 20p12.3. These patients all have an identical homozygous loss of function mutation (R271X); therefore, it is likely that the high incidence is due to a founder effect in this genetically isolated population. This genetic locus was also reported by Jobard et al in a group of North African patients. With the genetic basis now established, the present study helps define the clinical characteristics of this disorder.

METHODS

DEMOGRAPHICS AND CULTURAL BACKGROUND

In Panama, 64% of the 194,269 Native Americans belong to the Ngobe-Buglé tribe, 1 of 4 Native American groups. The genetic and geographic isolation of these peoples, who live in remote villages in the mountainous and sunny regions of Bocas del Toro, Chiriqui, and Veraguas provinces, may explain the high rate of this rare, autosomal recessive disorder in this cohort.

PATIENTS

The 15 male and 11 female patients were Native American members of Panama’s Ngobe-Buglé tribe. Age at first diagnosis ranged from...
Clinical Features of Kindler Syndrome in Panama

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Blistering</th>
<th>Poikiloderma Onset</th>
<th>Photosensitivity</th>
<th>Degree of Atrophy</th>
<th>Mucosae</th>
<th>Keratoderma</th>
<th>Ectropion</th>
<th>Leukokeratosis of Labia or Oral Mucosa</th>
<th>Webbing*</th>
<th>Phimosis</th>
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Abbreviations: HBG, hypertrophic bleeding gums; NA, not applicable; UMS, urethral meatal stenosis; −, finding absent; +, finding present; ±, minimal; ++, moderate; ++++, severe.

*Webbing between the third and fourth and fourth and fifth toes.

EXAMINATIONS

Case series of patients were recruited when they were seen at outpatient consults in the Department of Dermatology at the Changuinola Hospital in Bocas del Toro, Panama, between May 1986 and December 1990. Clinical history, physical examination, and laboratory studies were done at a community hospital in Panama. Twelve of the patients had further studies at a children’s hospital in Costa Rica.

RESULTS

PHYSICAL FINDINGS

Blistering

Blistering appeared in all 26 patients, and skin fragility was the most common clinical observation (Table). Blistering were congenital in 21 patients and appeared during the first days of life in the other 5 patients (patients 5, 10, 20, 22, and 23), most frequently on the dorsa of the hands and feet (Figure 1). In each instance, blister formation followed cutaneous trauma or exposure to sunlight. From the clinical follow-up of younger patients, we noted that bullae appeared to diminish in frequency at approximately age 10 to 12 years. Patients who were first seen as adults also reported a decrease in the number of blisters at approximately the same age. Nevertheless, blisters continued to recur in all age groups, and the skin of older patients continued to be fragile and easily injured by mild trauma.

Pyogenic skin infections were common and in 7 patients (patients 5, 6, 19, 20, 21, 23, and 24) were complicated by cases of acute glomerulonephritis. Because no skin cultures were obtained, it was not known whether the precipitating agent in these cases was a glomerulonephritic strain of group A streptococcus or another pathogen.

Photosensitivity

Photosensitivity characterized by erythema, burning, and blister formation after sun exposure was observed in 24 patients (Table). This finding was very marked in some patients (patients 5, 8, 9, 11, 12, 17, and 21) and less marked in others (patients 1, 2, 19, 23, and 24). It appeared as early as 1 month of age in 1 patient, but the average age at which photosensitivity developed was 2 years. In some patients, photosensitivity developed af-
ter particularly prolonged sun exposure (Figure 2). The photosensitivity usually decreased over time, coinciding with decreased blister formation by age 10 to 12 years. However, some degree of photosensitivity generally persisted (eg, facial erythema after minimal sun exposure). All patients had type IV-V skin.

Poikiloderma

Poikiloderma was present in 25 of 26 patients, and onset most frequently occurred between ages 2 to 3 years (Table). Poikiloderma developed in patients 9 and 20 on the face at ages 6 and 8 months, respectively, but no cases of truly congenital poikiloderma were observed. Generalized poikiloderma in both sun-exposed and non–sun-exposed areas eventually developed in all of our patients and persisted throughout adult life. The development of poikiloderma in non–sun-exposed areas indicates that it is not solely caused by photodamage. Some patients had axillary freckling.

Atrophy

Diffuse cutaneous atrophy was observed in all cases at the time of first consultation except in patients 10, 17, and 20 (Table). Its main features were thin, wrinkled skin, (cigarette paper skin), most pronounced on the dorsa of the hands and feet (Figure 3). Other affected parts of the body included abdomen, thighs, knees, and elbows. There were frequent sclerodermoid changes distally, with loss of the angle of the proximal nail fold and with tapering of the fingers. The plate of the nails was thin with atrophy and oncolysis in some patients. One patient had sclerodermoid tightening of the perioral skin, but no pa-

tient had sclerodermoid changes on the more proximal limbs or on the trunk.

Hyperkeratosis of the Palms and Soles

Hyperkeratosis of the palms and soles was present in 21 patients, accompanied in some by fissuring or wrinkling, but it was not associated with acrokeratotic papules. The palmar hyperkeratosis often had a glassy appearance, and there was loss of fingerprints. It ended sharply at the volar wrist but extended dorsally onto the hands, wrists, and as far proximally as the distal one third of the forearms. In addition, some patients had ridged, ribbed hyperkeratosis of the lateral and anterior ankles that was reminiscent of epidermolytic hyperkeratosis. Webbing between toes (ie, partial fusion with decreased interphalangeal spaces between the third and fourth and fourth and fifth toes) was found in patients 7, 15, and 22, but required no surgical treatment. This may have been due to the trauma of repeated blistering and scarring in infancy.

Mucosal Involvement

Mucosal involvement was frequent. Urethral meatal stenosis was present in patients 4, 8, 13, 19, 22, and 24 and required dilatation in patients 8, 22, and 24 (Table). Patient 17 was born with an imperforate anus that required surgical repair. Severe periodontal disease, in some cases with premature loss of teeth, was observed in 22 patients (Figure 4). Onset of periodontal disease most
commonly began in early adolescence. Ectropion of the lower eyelid was present in 10 patients.

Phimosis

Phimosis was found in 12 (80%) of 15 male patients, requiring circumcision in 10 (Figure 5). Histopathological studies of the preputial samples were those of poikiloderma: epidermal atrophy, vascular ectasia, and lichenoid tissue reaction. No genital changes were seen in female patients.

Joint Laxity

Joint laxity was present frequently with variable hypermobility of the thumb and fingers, knees, and elbows. Some patients could easily touch the floor with their palms while standing. However, the skin (eg, at the neck) was not hyperextensible. Joint hypermobility was not seen in family members unaffected by KiS.

LABORATORY FINDINGS

Microcytic anemia was found in 23 patients (87%). The microcytic anemia is likely unrelated to KiS, since it is also common in the general population. The most likely causes are malnutrition and parasites. No other hematologic disorders were identified. Other studies performed were entirely within normal limits including serum urea nitrogen, glucose, serum calcium, phosphorus, cholesterol, alkaline phosphatase, total bilirubin, VDRL test for syphilis, immunoglobulins, and aspartate aminotransferase. Urinary uroporphyrin study findings were normal. When performed, endocrine evaluations (thyrotropin, follicle-stimulating hormone, luteinizing hormone, and cortisol) were within normal limits.

RADIOLOGICAL STUDIES

Renal and abdominal ultrasound findings were normal in 12 cases. Two intravenous pyelograms were performed (patients 2 and 8); the results from both were normal except for an anatomically normal kidney present in the pelvis in patient 8. Five patients had delayed ossification of the epiphyses in the hand and wrist. This finding also was common in the general population and likely is due to malnutrition.

PHOTOSENSITIVITY TESTING

We performed photopatch testing in 13 patients at National Children’s Hospital, San José, Costa Rica (patients 1, 2, 5, 6, 8, 9, 11, 12, 17, 19, 21, 23, and 24); the other 14 patients were classified by clinical history and
physical examination. In patients 11 and 12, the minimal erythema dose for UV-B was abnormal, and 2 patients also had an abnormal minimal erythema dose for UV-A. Patients 5 and 6 developed hyperpigmentation 48 hours after the test. Our youngest patients appeared to be the most sensitive in their response to UV-B light in the photosensitivity tests, which may correlate with the clinical observation that the photosensitivity was greatest in children.

HISTOPATHOLOGY

Light Microscopy

Histologic features of the poikilodermic skin from all 10 KiS patients who underwent biopsy showed orthokeratotic hyperkeratosis, epidermal atrophy, and focal vacuolization of the basal layer. In the papillary dermis, numerous melanophages and rare colloid bodies were seen. There was also vascular ectasia and lymphohistiocytic infiltrate. In 8 patients with bullous lesions, vacuolization of the basal layer with intraepidermal cleft formation was present. Subepidermal clefts were not seen.

Electron Microscopy

In the 10 patients who underwent biopsy, nontraumatized poikilodermic skin and bullous lesions showed interruption and reduplication of the basal lamina. Colloid bodies were present in the upper dermis. The epidermis and the keratinocytes of the basal layer were normal. We were not able to determine the level of the blister split on electron microscopic studies.

OTHER STUDIES

Additional tests included audiometric, ophthalmoscopic, and psychiatric evaluations in the 12 patients evaluated at the National Children’s Hospital. Findings from all audiometric tests were normal except for patients 19 and 24, who both had mild conductive hearing loss at the time of testing. Findings from all eye examinations were normal except for patient 8, who was found to have a posterior subcapsular cataract. Psychometric test results were normal in all instances.

COMMENT

In a socially and geographically isolated population of Native Americans in Panama characterized by a high degree of consanguinity,14 we have identified 26 cases of KiS. In this case series—the largest reported to date to our knowledge—the principal clinical features were skin fragility and acral blister formation beginning at birth or in early infancy, photosensitivity (which is most prominent during childhood), diffuse cutaneous atrophy, poikiloderma, and palmoplantar hyperkeratosis without punctate lesions. Mucosal manifestations were also very common and included hemorrhagic mucositis, hemorrhagic gingivitis, periodontal disease, and premature loss of teeth, similar to other recent reports.7,13,16 Other mucosal findings included labial leukokeratosis, urethral ste-nosis, ectropion, and in 12 cases, severe phimosis requiring surgical correction.

Our histopathological studies showed a lichenoid tissue reaction and splitting at the lamina densa level. We were not able to determine the level of bullae on electron microscopic studies, and, similar to other reports to date, we found no definitive ultrastructural feature.6 However, several articles report a pattern regarding KiS and ultrastructural findings such as marked duplication of the lamina densa,3,17 basal layer separation,18 and blistering with trauma above the level of the lamina densa.16

Several conditions can cause blistering, cutaneous atrophy, and/or poikilodermalike skin changes. Weary et al19 described a similar syndrome with an autosomal dominant pattern of transmission named “hereditary acrokeratotic poikiloderma,” and a subsequent report by Larregue et al20 proposed the name “Weary-Kindler syndrome” to describe patients with this constellation of findings. However, our findings suggest that both the clinical features and inheritance patterns of these syndromes are distinctive enough to warrant separation. In KiS, blisters are often congenital, photosensitivity is frequent, and the poikiloderma typically has its onset after age 1 year and involves both sun-exposed and non–sun-exposed skin. In addition, marked diffuse skin atrophy in areas of skin not exposed to the sun and mucosal involvement is also present. In contrast, the blisters in Weary syndrome are not usually congenital, photosensitivity is generally absent, keratotic papules develop on the dorsal hands, elbows, and knees, and there is no mucosal involvement. The group of patients described in the present study were used for linkage studies and molecular analysis, which were crucial to the identification of the gene KIND1 for KiS.22 This gene appears to function as actin-extracellular matrix linker protein, and is a homologue of the Caenorhabditis elegans protein UNC-112.21 The discovery of the gene will aid in the confirmation of the diagnosis in new cases and may eventually lead to the development of new treatments. Our findings demonstrate that KiS is a distinctive entity that can be differentiated from similar conditions such as Weary syndrome, on the basis of clinical and histologic features and genetics.

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REFERENCES


Board Certification in Dermatopathology

The International Board of Dermatopathology will organize under the auspices of the International Committee for Dermatopathology (www.icdpath.org) the Second Certifying Examination in Dermatopathology (Diploma in Dermatopathology) in Frankfurt/Main, Germany, on December 11, 2004. Participating societies are the International Society of Dermatopathology, the European Society for Dermatopathology, and the Ibero-Latin American Society of Dermatopathology. For further information about this examination contact Helmut Kerl, MD, Department of Dermatology, Medical University of Graz, Auenbruggerplatz 8, 8036 Graz, Austria; phone: +43-316-385-2358; fax: +43-316-385-3424; e-mail: helmut.kerl@meduni-graz.at or Guenter Burg, MD, Department of Dermatology, University Hospital Zurich, Gloriastrasse 31, 8091 Zurich, Switzerland; phone: +41-1-255-2550; fax: +41-1-255-4403; e-mail: burg@derm.unizh.ch.