Kindler's Syndrome: A Report of Five Cases in a Family
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ABSTRACT
Kindler's Syndrome (KS) is a rare genodermatosis with autosomal recessive mode of inheritance. The disease results from homozygous mutations on both alleles of the FERMT-1 gene (also known as KIND-1 gene) that encodes the protein Kindlin-1 (kindlerin). Clinical features include a constellation of early infantile skin blistering and mild photosensitivity, which improves with age, and progressive poikiloderma with widespread cutaneous atrophy. The differential diagnosis of Kindler syndrome include other congenital poikilodermatous and photosensitive conditions including Bloom syndrome, Cockayne syndrome, dyskeratosis congenita, epidermolysis bullosa, Rothmund-Thomson syndrome and xeroderma pigmentosum. We herein, report the presence of the Kindler's syndrome in 5 out of 7 children of consanguineous parents. To authors' knowledge, this is the first report of Kindler's syndrome involving 5 members of a family.


INTRODUCTION
Kindler's syndrome (KS) is an autosomal recessive disorder, characterized by the presence of early infantile trauma induced blistering, progressive generalized poikiloderma, mild degree of photosensitivity, extensive cutaneous atrophy, abnormal pigmentation and a myriad of other clinical features. It was originally described by Theresa Kindler in 1954 in a young girl with acral blistering, photosensitivity and poikiloderma. In 2003, a loss of functional mutation was first elaborated in the KIND-1 gene which was mapped to chromosome 20p12.3. Later on, more than 20 mutations of KIND-1 gene were described, which codes for a focal adhesion protein known as Kindlin-1 protein. Kindlin-1 plays a role in the attachment of the actin cytoskeleton via focal contacts to the extracellular matrix. This protein is expressed in the basal keratinocytes of epidermis, periodontal tissue and colon. Its loss in basal keratinocytes leads to abnormal fragility with defects in actin extracellular matrix linkage. Thus, Kindler's syndrome is the first genodermatosis caused by a defect in actin-extracellular matrix linkage rather than the keratin-extracellular matrix linkage underlying the pathology of other inherited blistering disorders like epidermolysis bullosa. KS had been included within the spectrum of epidermolysis bullosa based on the presence of blistering and mechanical fragility at sites of trauma. According to new classification, EB includes four subtypes: EB simplex, junctional EB, dystrophic EB and KS.

This report describes the occurrence of KS in 5 members of a family.

CASE REPORT
Five siblings including three sons and two daughters, born to consanguineous parents, presented with history of recurrent blistering, since the first month of life. The family belonged to lower socio-economic class and reported in a free medical camp in a remote area of Pakistan. According to mother, blisters were developing all over the body but predominantly over the acral areas and in the oral cavity. Recurrent blistering episodes used to heal with scarring and although blistering was still going on, it was predominantly at the lower back at the time of presentation. Two out of three brothers gave history of marked burning in sun, but rest of the siblings denied symptoms of photosensitivity. Recurrent diarrhea was complained by two of the siblings and the elder brother was having dysphagia to solid food for few months.

Clinical examination of the patients revealed marked poikiloderma of the neck, face and upper torso in all siblings (Figures 1 - 3). There were generalized hypo and hyper pigmented patches over most of the body areas, along with generalized xerosis. There was extensive cutaneous atrophy, predominantly over the dorsum of hands and feet (Figure 1). The dorsum of hands also showed atrophic scarring with cigarette paper like wrinkling. Hemorrhagic crusted plaques were present in all the male siblings over the lower back (Figure 2). All were having chelitis, periodontitis with gum hypertrophy and buccal ulceration. All had a normal IQ and were studying in school with good performance. No nail and hair abnormalities were seen in siblings.

Diagnosis was made on clinical ground because of the lack of laboratory facilities in remote areas, but all patients were fulfilling the diagnostic criteria of Kindler's
Kindler’s syndrome is an autosomal recessive genodermatosis. The disorder results from loss of function mutations of the KIND-1 gene which encodes the protein kindlin-1. Its loss in basal keratinocytes leads to abnormal fragility with defects in actin-extracellular matrix linkage. The clinical characteristics of KS include congenital skin blistering, photosensitivity, which improve with age, and progressive poikiloderma with extensive atrophy. Other features include webbing of the fingers, palmoplantar keratoderma, nail abnormalities, involvement of the oral cavity with periodontitis, loss of teeth, gum hypertrophy, esophageal and urethral strictures. Involvement of esophageal and genital mucosa is common, and clearly increases with age. Early development of actinic keratoses, squamous cell carcinoma of the lips and transitional cell carcinoma of the bladder have also been reported. In addition, recurrent colitis is also described.

Angelova-Fischer et al. proposed diagnostic criteria for Kindler’s syndrome, with major and minor criteria. The major criteria include acral blistering in early infancy, progressive poikiloderma, skin atrophy, abnormal photosensitivity, gingival hyperplasia and fragility. The minor criteria includes pseudosyndactyly and mucosal involvement (anal, esophageal and urethral stricture/stenosis). A number of other associated findings have been described in these patients like abnormal nail changes, ectropion, leukoplakia, squamous carcinomas, skeletal deformities, periodontitis and tooth abnormalities. The presence of four major criteria makes the diagnosis of KS certain. The presence of three major and two minor criteria makes the probable diagnosis and the presence of two major criteria and two minor criteria or associated symptoms makes the likely diagnosis. These patients had all five major criteria along with few features of minor criteria.

KS must be differentiated from other congenital blistering and photosensitive conditions. Acrokeratotic poikiloderma or Weary syndrome is a close differential diagnosis of KS and few cases have even been reported in literature as Kindler-Weary syndrome. However, there are many clinical differences between Kindler and Weary syndrome. Photosensitivity, a feature of KS, is usually absent in patients with Weary syndrome and blisters appear within the first 6 months of life in Weary syndrome as compared to Kindler syndrome, where blistering is seen soon after birth. Skin atrophy in Weary syndrome is not as remarkable as in KS. Similarly, an important differential diagnosis is epidermolysis bullosa, specially at or soon after the birth, although the development of photosensitivity and poikiloderma are useful features to delineate the disorder from various form of epidermolysis bullosa. However, the presence of scarring, mucosal ulceration and squamous cell carcinoma may make it difficult to differentiate from dystrophic epidermolysis bullosa. Syndrome must also be distinguished from other poikilodermatous conditions like Bloom syndrome and dyskeratosis congenita, where recurrent blistering at trauma prone areas are not witnessed.

Management of patients with Kindler’s syndrome requires detailed education about photoprotection and close monitoring for mucosal complications like malignancies and esophageal, anal and urethral stenosis. Genetic counselling and family screening can be provided and mutation analysis can be done using PCR, if available and desired.

REFERENCES


