

CLINICAL REPORT

KID Syndrome: Report of a Scandinavian Patient with Connexin-26 Gene Mutation

Anette BYGUM¹, Regina C. BETZ^{2,3}, Knud KRAGBALLE⁴, Torben STEINICHE⁵, Nils PEETERS², Wim WUYTS² and Markus M. NÖTHEN^{2,3,6}

¹Department of Dermatology, Odense University Hospital, Odense, Denmark, ²Department of Medical Genetics, University of Antwerp, Antwerp, Belgium, ³Institute of Human Genetics, University of Bonn, Bonn, Germany, ⁴Department of Dermatology, ⁵Department of Pathology, Aarhus University Hospital, Aarhus, Denmark, and ⁶Life & Brain Center, University of Bonn, Bonn, Germany

Keratitis-ichthyosis-deafness syndrome is a rare genodermatosis, which has recently been connected with mutations in the connexin-26 gene, GJB2. We present a 15-year-old boy with erythroderma, hyperkeratotic plaques and deafness. Sequencing analysis showed a heterozygous missense mutation D50N (148G > A) in GJB2. The boy has not yet manifested characteristic eye lesions but his case shows that tardy development of eye signs should not preclude a clinical diagnosis of keratitis-ichthyosis-deafness syndrome. Besides the typical clinical features, the patient's height was above the 98th percentile and he displayed a delayed bone age in his hands. Additionally, he suffered from migrainoid headaches and the results of a magnetic resonance scan of the cerebrum showed he had a large cisterna magna which probably occurred independently from the syndrome. This patient is the first Danish patient in whom the keratitis-ichthyosis-deafness syndrome has been verified by mutation analysis.

(Accepted August 16, 2004.)

Acta Derm Venereol 2005; 85: 152–155.

A. Bygum, Department of Dermatology, Odense University Hospital, 5000 Odense C, Denmark. E-mail: anette.bygum@ouh.fyns-amt.dk

The keratitis-ichthyosis-deafness (KID) syndrome (OMIM 148210 and 242150) is a rare congenital disorder of the ectoderm characterized by deafness, erythroderma, hyperkeratotic plaques and often keratitis. Alopecia, susceptibility to infections and squamous cell carcinoma can also occur among a variety of other features. This condition was first reported in 1915 by Burns (1). Senter and co-workers delineated the syndrome in 1978 (2); it has also been named Senter's syndrome (3). In 1981 Skinner et al. reviewed 18 affected patients and proposed the name KID to describe the three main symptoms consisting of diffuse hyperkeratotic erythroderma, vascularizing keratitis, and often profound sensorineural hearing loss (4). Since then approximately 80 cases, the majority of which are sporadic, have been reported in the literature (5–9).

Recently, it has been shown that KID syndrome belongs to the connexin disorders caused by

heterozygous missense mutations in the connexin-26 gene, GJB2 (10, 11) or in the connexin-30 gene: GJB6 (12). Here, we report the first Danish patient where the KID syndrome has been verified by mutation analysis.

CASE REPORT

Clinical course

A 15-year-old boy, the first child of non-consanguineous healthy parents, was seen in our Department of Dermatology in Odense. The patient's skin has been red and dry since birth and was considered, at first, to be ichthyosis. During his first years of life, up to the age of 4, he developed figurate red-brown hyperkeratotic plaques on his face and extremities. These plaques continued to grow in size with him (Fig. 1). The skin lesions and dystrophic nails had often been superinfected with dermatophytes, candida and pyogenic bacteria. Systemic antimycotic treatments had been used with a beneficial effect on skin and nail lesions. Scalp hair, eyebrows, eyelashes and body hair had always been very sparse. A skin biopsy taken from the scalp when he was 4 years old showed a thick epidermis with hyperkeratosis and follicular plugging. The hair follicles were consistent with hairs of normal structure. Several of the following skin biopsies consistently showed the same ichthyosis-like changes. Sensorineural deafness was noted at the age of 1 year. As a result, the boy has been wearing bilateral hearing aids ever since. The same year a tentative diagnosis of KID syndrome was proposed.

No diagnosis of keratitis has been made so far, but he reported photophobia in summertime and has been seen regularly by an ophthalmologist without any secure pathology. During the last 8 years he has complained of stiffness in his lower back, hips and knees and extensive physiotherapy has been necessary. Upon physical examination his height was 187 cm (above the 98th percentile) and his weight was 53 kg (25th to 50th percentile). He wore size 44 shoes but only size 10 gloves. An earlier X-ray showed that the bone age in his hands was delayed by 2 years. His pubertal development appeared normal. Two years ago he had a magnetic



Fig. 1. Development of facial lesions in a patient with KID syndrome. Unmasked pictures with the patient's approval.

resonance scan (MR) of the cerebrum due to intense headaches of migrainoid type. The scan showed a large cisterna magna with a string-shaped communication from the fourth ventricle to cisterna magna. An expert in this field interpreted this condition to be an accidental finding. This condition might have occurred independently from the syndrome as it has never been previously reported in patients with KID syndrome.

Upon physical examination he had universal dry skin with palms and soles showing glove-like keratoderma with a grainy, pitted surface (Fig. 2a). His face had a mask-like appearance with symmetric well-circumscribed infiltrated reddish-brown plaques around his eyes, mouth and ears (Fig. 2b). Dirty-looking ridged and verrucous plaques on an erythematous base were seen on his buttocks and extremities, accentuated around elbows (Fig. 2c), knees and ankles. Paronychia with nail dystrophy affected most of his fingers and all his toes (Fig. 2d). He had a near universal alopecia. The intraoral examination was normal with unremarkable teeth.

Local treatment with calcipotriol, corticosteroids and tar had been tried earlier in his childhood without any effect. Pulsed dye laser had also been tried without success. Etretinate orally 10 mg per week was used for 4 months without effect when he was 1 year of age. From the age of 5 to 7 he was treated with acitretin 10 mg daily with some improvement. However, the treatment had to be stopped after 1 year because of erosive skin lesions in his auditory canals.

Today he uses plenty of moisturizers (Locobase LPL[®] containing propylene glycol and lactic acid, and Locobase Repair[®], Yamanouchi, Denmark) as well as soothing baths with wheatbran. Occasionally he needs potassium permanganate baths and antibiotics because of erosive infected skin. Recalcitrant fungal infections with dermatophytes and candida affecting skin and nails need frequent treatments with topical and systemic antifungal drugs which improve skin and nails. The family has also noticed the therapeutic effect of sun exposure.

There was no family history of KID and his younger brother showed no signs of this disease.

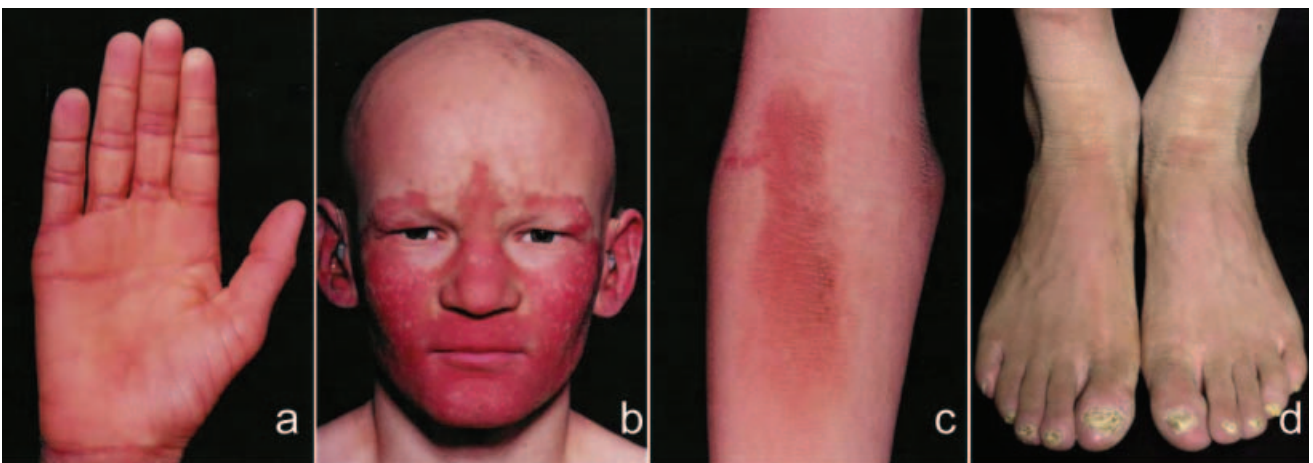


Fig. 2. Clinical features showing palmar keratoderma with a grainy pitted surface (a), face with mask-like appearance (b), ridged and verrucous plaque around an elbow (c) and dystrophic toenails (d).

Mutation analysis of *GJB2* gene

After informed consent, blood was taken from the patient and DNA was extracted from peripheral blood leukocytes according to standard methods. PCR was performed using standard conditions with the following primers for *GJB2*: cx26F 5' AGACTCAGAGAAGTCTCCCTG 3', cx26R 5' GGGCAATGCGTTAAACTGGC 3'. The PCR product was purified by the enzymatic ExoI-SAP purification method and sequenced using the Terminator Cycle Sequencing Kit (Amersham Pharmacia Biotech). Sequencing products were analysed on an ABI 3100 genetic analyser (Applied Biosystems). The sequencing analysis showed a heterozygous 148G→A transition in connexin 26 (Cx26) resulting in substitution of aspartic acid with asparagine in codon 50 (D50N).

DISCUSSION

The diagnosis of KID syndrome has been confirmed in our patient by using molecular genetic analysis, although the boy has not yet manifested characteristic eye lesions. In fact, in a recent review of 61 patients with KID syndrome only 18 patients developed eye symptoms before the age of 15 and it appears that some patients will never develop keratitis (5). Tardy development of eye abnormalities should not preclude an early diagnosis of the syndrome. Alopecia can be part of the phenotype in KID syndrome and has been reported in about 80% of patients (5). It is probably related to the follicular plugging confirmed by histopathology in our patient. In fact, he also presented with hypotrichosis on skin areas which were seemingly unaffected, which suggest a role for Cx26 in hair follicle differentiation. It has been shown that Cx26 upregulates E-cadherin expression which is probably involved in the regulation of hair growth and therefore can be the background of hypotrichosis in KID syndrome (11). A recent article suggests a close association of Cx26 and Cx43 with hair follicle morphogenesis (13). Our patient was above the 98th centile in height but slim and with a delayed bone age in his hands. Growth delay has been described in 16% of patients (5), with verification of delayed skeletal age in some of them (14, 15). The limited mobility of several joints in our patient can also be associated with the syndrome as these features have been reported earlier (2, 16).

Different mutations in connexin genes can disturb the gap junction system of one or several ectodermal epithelia but the precise phenotype depends on the nature and location of the mutation, and on the connexin gene involved. The connexin mutations are associated with an increasing number of other human pathologies including the X-linked form of Charcot-Marie-Tooth disease (Cx32) (17), sensorineural hearing loss (Cx26)

(18), congenital cataract (Cx50) (19), and the skin disorders erythrokeratoderma variabilis (Cx31) (20), palmoplantar keratoderma (Cx26) (21) and autosomal dominant hidrotic ectodermal dysplasia (Cx30) (for review see 22). Richard et al. (10) and van Steensel et al. (11) were the first to detect connexin-26 mutations in patients with KID syndrome. The 148G→A transition (D50N) in Cx26 is very common in KID patients and has been observed in 11 sporadic cases as well as one family with vertical transmission of KID syndrome (10, 11, 23–26) which confirms the autosomal dominant inheritance of this disorder.

Cx26 is a 26-kDa protein consisting of 226 amino acids, and is encoded by two exons of the *GJB2* gene localized on chromosome 13q12.11. Connexins assemble into hexameric hemichannels (connexons) that dock with a neighbouring hemichannel in an adjacent cell forming gap junctions. These inter-cytoplasmic channels mediate the direct exchange of ions, metabolites and secondary messengers to coordinate cellular activities crucial for tissue homeostasis, cell growth, differentiation, and response to stimuli. Gap junctional inter-cellular communications have tissue-specific functions and are important for normal development and differentiation of human epidermis. Cx26 is expressed in the skin most commonly on the palms and soles and there is a high expression of Cx26 in hair follicles and eccrine sweat glands (27). Cx26 is the major connexin expressed in the cochlea. Most cell types and tissues express more than one connexin protein and the epidermis, its appendages, and other ectoderm-derived epithelia of inner ear and cornea utilize up to 10 different connexin proteins.

Decreased host defence with a tendency to fungal and bacterial infections combined with an increased carcinogenesis are described in KID patients and illustrate that gap junction communication also plays a crucial role in immune response and epidermal carcinogenesis (28).

It is quite interesting that KID syndrome at the molecular genetic level is associated more with ectodermal dysplasia and erythrokeratoderma than with ichthyosis. This supports the view that the eponym KID should be abandoned (29) and reclassified as ectodermal dysplasia (5, 9).

Considering the broad clinical scope of Cx26 defects detected to date, in the future, it seems reasonable to search for *GJB2* mutations in any congenital disorder of cornification associated with hearing loss and perhaps also in potential syndromes with congenital cataract and hereditary polyneuropathy (28).

ACKNOWLEDGEMENTS

We thank Dr Hans Pedersen for reviewing and commenting on the magnetic resonance scanning of the cerebrum. R.C.B. is supported by a postdoctoral fellowship from the Fund for Scientific Research-Flanders (FWO).

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