

## SHORT COMMUNICATION

Lethal Form of Keratitis–Ichthyosis–Deafness Syndrome Caused by the *GJB2* Mutation p.Ser17Phe

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Keratosis–Ichthyosis–Deafness (KID) syndrome is a rare form of ichthyosis caused by mutations in the gene *GJB2* encoding the gap junction protein connexin 26 (Cx26). Connexins are a family of integral membrane proteins forming gap junction channels that control and coordinate a variety of cellular activities through the exchange of small ions, metabolites and signalling molecules.

The most frequent mutation associated with KID syndrome arises from the missense mutation p.Asp50Asn (1). Other mutations have been reported, namely p.Ser17Phe, p.Asp50Tyr, p.Gly45Glu, p.Gly12Arg, p.Asn14Tyr, p.Ala40Val and p.Ala88Val (1–3).

Generally, KID syndrome occurs sporadically in the population but familial cases have been reported suggesting autosomal dominant inheritance (4). Titeux et al. (5) reported such a case of KID syndrome in a child who inherited the *GJB2* mutation (p.Asp50Asn) from his mother, who had displayed a segmental form of the disease.

Patients with KID syndrome present with vascularising keratitis and hearing loss in association with various skin manifestations (erythematous lesions, hyperkeratotic plaques, palmoplantar keratoderma, inflammatory nodules), alopecia and dystrophic nails. They also show increased susceptibility to viral, bacterial and mycotic infections and some type of cancers.

A total of 9 families with a lethal form of KID syndrome have been reported in the literature. Only 5 were characterized by molecular analysis: 4 had the mutation p.Gly45Glu (6–10) and one had the mutation p.Ala88Val (3). We report a new case of lethal KID syndrome associated with a different Cx26 mutation, p.Ser17Phe.

## CASE REPORT

The patient was born following an uncomplicated pregnancy and was the first child of healthy unrelated parents originating from North Africa. There was no prior history of skin disease in the family. Skin lesions appeared at the age of one month in the form of erythema and erosions on the diaper area and scalp. The patient's condition progressively worsened and he had failure to thrive. He was therefore, at the age of 15 months, transferred to France.

He presented with a generalised and thick hyperkeratosis with deep fissures (Fig. 1). The underlying skin was erythrodermic, oedematous, painful and smelly. Palms and soles displayed a "leather grain-like" aspect, nails were dystrophic and he had complete atrichia. Skin surface swabs revealed *Candida albicans*,



Fig. 1. Generalised and thick hyperkeratosis with skin fissures, palmoplantar keratoderma, dystrophic nails and complete atrichia. A written permission from the parents was given to publish this photo.

*Staphylococcus aureus* and *Pseudomonas aeruginosa*. Histological examination of the skin showed an epidermis with mild regular acanthosis, large keratotic plugs located within hair follicles and follicular and perifollicular parakeratosis. In the upper dermis, capillaries were hyperplastic and surrounded by a dense infiltrate of lymphocytes and neutrophils (Fig. S1<sup>1</sup>). Serial sections showed a follicular spongiform pustule with spores and hyphae corresponding to candida with the PAS (periodic acid-Schiff). Laboratory investigations showed normal immunological work-up.

Due to the continuing deterioration, he was quickly transferred to the intensive care unit where he was intubated and put on respiratory support, as well as enteral and parenteral nutrition. He was treated with intravenous antibiotics and antifungal agents and was put on a skin care regimen of emollients and acitretin. Deafness could not be evaluated (unconscious patient and complete obstruction of the external ear). Eye examination revealed unilateral keratitis. Despite adequate care, his condition continued to deteriorate. Several episodes of uncontrollable septicaemia (*P. aeruginosa* and *C. albicans*) led to death at the age of 16 months.

Sequencing of the *GJB2* gene confirmed the diagnosis of KID syndrome and revealed that he was heterozygous for c.50C>T (p.Ser17Phe) mutation (formerly called NM\_004004.5:c.50C>T), occurring in exon 2 and leading to a substitution of serine to phenylalanine (Fig. S2<sup>1</sup>). No other mutation or polymorphism were identified. The parents did not carry the *GJB2* mutation.

## DISCUSSION

The characteristics of reported patients with lethal KID syndrome are summarized in Table S1<sup>1</sup> (3, 6–14). There

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were 2 familial cases, otherwise parents were not related and of no particular geographic origin. All cases were *de novo*, except for 2 families in which a mosaic inheritance was suspected (6, 10). Skin abnormalities started at birth except for 2 patients (disease began at 1 or 2 months). All presented with atrichia and palmoplantar keratoderma. A majority had dystrophic nails. Keratitis and hearing defects were not always found. Other abnormalities were reported for 5 families: small or absent foreskin (6, 10, 11), facial dysmorphism (3, 6) and abnormal fingers (6, 10–12). All cases died in the first year of life except our patient who died at 16 months of age. All patients died due to bacterial septicaemia. One also had systemic cytomegalovirus infection (14).

Histological findings were reported for all patients and showed follicular plugging, psoriasiform hyperplasia, alternating parakeratosis and orthokeratosis without Munro abscesses and mild superficial infiltrate. Our case was peculiar because of the presence of a spongiform pustule.

With regards to *GJB2* molecular analysis, the p.Gly45Glu mutation (also linked to recessive non-syndromic deafness in the Japanese population (15)) was identified in 4 families. In one family, a new mutation, p.Ala88Val, was identified (3). The p.Ser17Phe mutation we report here has been previously reported in the literature for 3 patients. The first patient was described as demonstrating the cardinal features of KID syndrome but a detailed clinical description was not given (1). The 2 other patients were reported by us in 2007 and presented with a skin involvement that seemed to be more severe than in patients with the recurrent p.Asp50Asn mutation (4). They reached adult age but died early in their twenties: one had a rapidly progressive tongue carcinoma; the other died due to bacterial septicaemia.

The severe clinical course of lethal KID syndrome suggests a defective cutaneous barrier to microorganisms but the exact mechanisms remain to be elucidated. To date, *in vitro* experiments suggest that the mutations induce abnormal hemichannels. Indeed p.Gly45Glu and p.Ala88Val mutant Cx26 contribute to the formation of high conductance hemichannels that could induce cell death (16) and the p.Ser17Phe mutation was demonstrated to result in a complete loss of hemichannel activity (1).

The patient we report here strengthens the hypothesis that different modes of action of the same *GJB2* mutation are dependent on the genetic background (7). Further studies are necessary to determine whether other modifying genes or epistasis factors are involved. Correlating genotype-phenotype is difficult because of the rarity of patients with a mutation different from p.Asp50Asn. Nevertheless, p.Gly45Glu, p.Ser17Phe and p.Ala88Val mutations seem to predict a poor prognosis of the disease.

## REFERENCES

- Richard G, Rouan F, Willoughby CE, Brown N, Chung P, Ryyänänen M, et al. Missense mutations in *GJB2* encoding connexin-26 cause the ectodermal dysplasia keratitis-ichthyosis-deafness syndrome. *Am J Hum Genet* 2002; 70: 1341–1348.
- Lai-Cheong JE, Arita K, McGrath JA. Genetic diseases of junctions. *J Invest Dermatol* 2007; 127: 2713–2725.
- Koppelhus U, Tranebjaerg L, Esberg G, Ramsing M, Lodahl M, Rendtorff ND et al. A novel mutation in the connexin 26 gene (*GJB2*) in a child with clinical and histological features of keratitis-ichthyosis-deafness (KID) syndrome. *Clin Exp Dermatol* 2011; 36: 142–148.
- Mazereeuw-Hautier J, Bitoun E, Chevrant-Breton J, Man SY, Bodemer C, Prins C, et al. Keratitis-ichthyosis-deafness syndrome: disease expression and spectrum of connexin 26 (*GJB2*) mutations in 14 patients. *Br J Dermatol* 2007; 156: 1015–1019.
- Titeux M, Mendonça V, Décha A, Moreira E, Magina S, Maia A. Keratitis-ichthyosis-deafness syndrome caused by *GJB2* maternal mosaicism. *J Invest Dermatol* 2009; 129: 776–779.
- Sbidian E, Feldmann D, Bengoa J, Fraitag S, Abadie V, de Prost Y, et al. Germline mosaicism in keratitis-ichthyosis-deafness syndrome: pre-natal diagnosis in a familial lethal form. *Clin Genet* 2010; 77: 587–592.
- Janecke AR, Hennies HC, Günther B, Gansl G, Smolle J, Messmer EM. *GJB2* mutations in keratitis-ichthyosis-deafness syndrome including its fatal form. *Am J Med Genet A* 2005; 133: 128–131.
- Gilliam A, Williams ML. Fatal septicemia in an infant with keratitis, ichthyosis, and deafness (KID) syndrome. *Pediatr Dermatol* 2002; 19: 232–236.
- Griffith AJ, Yang Y, Pryor SP, Park HJ, Jabs EW, Nadol JB, et al. Laryngoscope 2006; 116: 1404–1408.
- Jonard L, Feldmann D, Parsy C, Freitag S, Sinico M, Koval C, et al. A familial case of Keratitis-Ichthyosis-Deafness (KID) syndrome with the *GJB2* mutation G45E. *Eur J Med Genet* 2008; 51: 35–43.
- de Berker D, Branford WA, Soucek S, Michaels L. Fatal keratitis ichthyosis and deafness syndrome (KIDS). Aural, ocular, and cutaneous histopathology. *Am J Dermatopathol* 1993; 15: 64–69.
- Mallory SB, Haynie LS, Williams ML, Hall W. Ichthyosis, deafness, and Hirschsprung's disease. *Pediatr Dermatol* 1989; 6: 24–27.
- Tsuzuku T, Kaga K, Kanematsu S, Shibata A, Ohde S. Temporal bone findings in keratitis, ichthyosis, and deafness syndrome. Case report. *Ann Otol Rhinol Laryngol* 1992; 101: 413–416.
- Helm K, Lane AT, Orosz J, Metlay L. Systemic cytomegalovirus in a patient with the keratitis, ichthyosis, and deafness (KID) syndrome. *Pediatr Dermatol* 1990; 7: 54–56.
- Oguchi T, Ohtsuka A, Hashimoto S, Oshima A, Abe S, Kobayashi Y, et al. Clinical features of patients with *GJB2* (connexin 26) mutations: severity of hearing loss is correlated with genotypes and protein expression patterns. *J Hum Genet* 2005; 50: 76–83.
- Mhaske PV, Levit NA, Li L, Wang HZ, Lee JR, Shuja Z, et al. The human Cx26-D50A and Cx26-A88V mutations causing keratitis-ichthyosis-deafness syndrome display increased hemichannel activity. *Am J Physiol Cell Physiol* 2013; 304: 1150–1158.