# Keratitis-Ichthyosis-Deafness Syndrome: Early Death Caused by the *GJB2* Mutation p.Gly12Arg

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Accepted May 16, 2019; E-published May 17, 2019

Keratitis-ichthyosis-deafness (KID) syndrome is a rare disorder caused by mutations in *GJB2* encoding connexin (Cx) 26. Cxs are membrane proteins that are primarily involved in intercellular communication. Six Cx molecules are oligomerized to form a connexon (hemichannel), which docks at cell–cell contact points to form a gap junction intercellular channel that allows exchanges between neighbouring cells. The p.Asp50Asn mutation is a recurrent mutation (80% of patients), but other mutations have also been reported, namely p.Gly12Arg, p.Asp50Tyr, p.Ser17Phe, p.Gly45Glu, p.Gly12Cys and p.Ala88Val (1). KID syndrome is an autosomal dominant condition with some familial cases, but the majority of cases are sporadic. Patients with KID syndrome present with vascularizing keratitis and hearing loss in conjunction with various skin manifestations (erythematous lesions, hyperkeratotic plaques, palmoplantar keratoderma, inflammatory nodules), alopecia and dystrophic nails. Patients also show increased susceptibility to viral, bacterial and mycotic infections and some types of skin cancer. Patients with a life-threatening disease have occasionally been reported. We report here a new case of KID syndrome with early childhood death caused by the *GJB2* mutation p.Gly12Arg.

## CASE REPORT

The patient was the first child of healthy unrelated parents originating from Democratic Republic of Congo. He was born at term (37$^{th}$ week of pregnancy), weighed 2.9 kg and measured 46.5 cm. He has 2 healthy half-sisters. His skin was normal at birth and the first skin abnormality was noticed at the age of 2 weeks in the form of generalized hyperkeratosis. Bilateral sensorineural hearing loss (negative *evoked* oto-acoustic emissions) was diagnosed at the age of 9 months and warranted hearing aids. Bilateral keratitis with ulceration and corneal neovascularization was diagnosed at 2 years of age. The diagnosis of KID syndrome was suspected and confirmed by the sequencing of the *GJB2* gene, showing that the patient was heterozygous for the c.34G>C (p.Gly12Arg) *GJB2* mutation. No parental molecular analysis could be performed. The hyperkeratosis gradually worsened over time and the clinical course was complicated by several episodes of fungal and bacterial cutaneous infections requiring systemic therapy with antibiotics or antifungal drugs. The patient was started on acitretin (1 mg/kg/day) at the age of 5 years. This was deemed ineffective and was discontinued at the age of 7 years. He was then started on alitretinoin (0.5 mg/kg/day). Again, this proved ineffective and was stopped after 6 months. He was first seen in our department at the age of 7 years. Psychomotor development and height were normal, but he was underweight (–1.5 standard deviation (SD)). He presented severe hyperkeratosis, with areas of hypertrophic and inflamed skin over the entire body, which was more pronounced on the feet, legs and mouth. A characteristic "leather grain-like" appearance was seen on his palms and soles, and his nails were dystrophic (**Fig. 1**). The skin was foul-smelling and skin surface swabs repeatedly revealed numerous bacteria (*Streptococcus agalactiae*, *Corynebacterium striatum*, *Klebsiella pneumoniae*, *Providencia stuartii*, *Citrobacter koseri* (*Citrobacter diversus*), *Proteus mirabilis* and *Pseudomonas aeruginosa*), but no human papilloma virus. A few months later, his general condition deteriorated, with severe pain, fever, malnutrition and exacerbation of the skin condition. He was transferred to the intensive care unit, where he was diagnosed with septicaemia (*Corynebacterium* and *Staphylococcus aureus*). He was intubated and put on a ventilator. He received rehydration, transfusions, intravenous antibiotics and antifungal drugs. He died shortly afterwards from septic shock combined with renal failure.

## DISCUSSION

We report here a new case of fatal childhood KID syndrome. In the literature, we found 21 other patients (from 19 families) with KID syndrome with a fatal outcome (1–7). The characteristics of these patients (and our patient) are reported in Table SI[1]. Of these 21 patients, 19 died in the neonatal period (before reaching the age of 18 months), none during late infancy and 2 in early adulthood (death at

[1]https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-3218

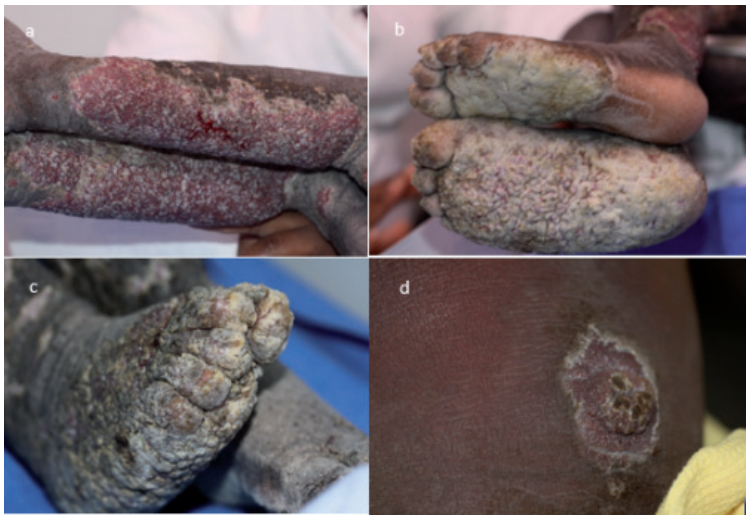


**Fig. 1. Massive hyperplasia and hyperkeratosis.** On (a) the legs, (b and c) extremities, and (d) umbilicus.



doi: 10.2340/00015555-3218
Acta Derm Venereol 2019; 99: 921–922

33 or 29 years of age, respectively (3, 7)). Molecular analysis was performed for 17 of these 21 patients. The most frequent mutations were the p.Gly45Glu mutation (n:8) (1, 5) and p.Ala88Val (n:6) (4, 6). The other mutations were as follows: p.Ser17Phe mutation (n:2) (2, 7) or pAsp50Asn mutation (n:1) (3). None of these 17 patients carried the p.Gly12Arg mutation that has also been reported in 3 patients with KID syndrome, albeit without fatal outcome (8–10). The first patient was reported as having unusual clinical symptoms including follicular occlusion syndrome, porokeratotic eccrine ostial and dermal duct naevus and persistent oral mucosal papules (9). The second patient had limited cutaneous involvement occasionally linked to cystic acne (10). The clinical aspect of the third patient is not clearly described (8). This p.Gly12Arg mutation has also been reported in patients with non-syndromic deafness (11).

Although the causative genetic defect of KID syndrome has been identified, the molecular mechanisms leading to skin phenotypes of variable severity via gap junction dysfunction are poorly understood. Cell death induced by *GJB2* mutations may be associated with more severe disease (12).

With regard to p.Gly12Arg mutation, the studies by Taki et al. may help to clarify the consequences of p.Gly12Arg and provide some explanation for the fatal outcome in our patient. The authors have shown that the murine Cx26 mutant p.Gly12Arg is responsible for high extracellular $Ca^{2+}$ conditions, leading to the closure of gap junction hemichannels, resulting in prohibition of Cx-26 mutant-induced cell death (13).

Nevertheless, this does not explain why the other 3 reported cases with the identical mutation displayed milder phenotypes. The effect of modifying factors/genes has not been elucidated to date.

All but 1 of the 21 patients with early death reported in the literature died from infectious complications (septicaemia or pneumonia). The remaining patient died from congenital abnormality of the brainstem (6). The causes of these cutaneous infections are not well known and there are no underlying immunological anomalies. A defective skin barrier may have contributed to these infections. In addition, the severity of the hyperkeratosis could be responsible for bacterial proliferation in areas not accessible to therapy. Taki et al. (13) have also shown a down-regulated expression of immune response-related genes in keratinocytes expressing Cx26 mutations. Taking different forms of ichthyosis with barrier defect into account, this may explain why bacterial and fungal infections are more frequent and severe in KID syndrome (14).

Lilly et al. (6) also reported that abnormalities in organs other than skin, cornea and inner ear may contribute to infant death in KID syndrome. For example, epithelial involvement of the oesophagus can be severe. This could explain why our patient was malnourished.

To date, no therapy has been effective in improving disease prognosis or preventing skin infections. Improvements in skin condition, especially erythema, have been reported with oral retinoids (acitretin, isotretinoin, alitretinoin, or etretinate). Prophylactic antibiotics do not appear to prevent death (6, 12). This outcome appears to be unavoidable despite intensive medical interventions, often in modern intensive neonatal care units in tertiary academic centres.

In conclusion, we report here a case of KID syndrome due to p.Gly12Arg mutation, where the patient died from infectious complications in early infancy. This mutation has not been reported previously in fatal KID syndrome. This case illustrates the severity of the disease and the complexity of the cell biology of connexins. It may also help to better understand the phenotype-genotype correlation.

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