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Lethal Keratitis, Ichthyosis, and Deafness Syndrome Due to the A88V Connexin 26 Mutation

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ABSTRACT

Keratitis-ichthyosis-deafness syndrome is a well-characterized disease that has been related to mutations in the *GJB6* gene. Clinical features such as erythrokeratoderma, palmoplantar keratoderma, alopecia, and progressive vascularizing keratitis, among others, are well known in this entity. In this report we describe a newborn female patient diagnosed with keratitis-ichthyosis-deafness syndrome with a lethal outcome due to sepsis. The patient harbored the mutation A88V that has been previously reported in lethal cases. (REV INVES CLIN. 2016;68:143-6)

Key words: KID syndrome. A88V mutation. Keratoderma.

INTRODUCTION

Keratitis-ichthyosis-deafness syndrome (KID, OMIM #148210) is a very rare genodermatosis with less than 100 cases reported in the literature. This syndrome is characterized by erythrokeratoderma, palmoplantar keratoderma, alopecia, progressive vascularizing keratitis, dry eyes, blepharitis, and conjunctivitis. In addition, non-progressive, congenital, sensorineural hearing loss is consistently present[1]. It has been reported that 64% of cases are sporadic, with a small fraction involving a dominant mutation in the *GJB2* gene[2]. This gene encodes a protein called connexin 26 (Cx26), and it has been shown that its mutations disrupt gap junction in intercellular communications through several mechanisms, such as mislocalization of the encoded protein, alteration of ion conductance, and formation of hemichannels with abnormal function[3]. Alterations at the molecular level in the *GJB2* gene have been related to deafness and skin disorders: Bart-Pumphrey syndrome (BPS), palmoplantar keratoderma (PPK), Vohwinkel syndrome (VS), keratitis-ichthyosis-deafness syndrome (KID), and hystrix-like ichthyosis-deafness syndrome (HID)[4]. The mutations reported in protein Cx26 are

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Figure 1. a) Leonine facies with erythroderma, alopecia, and well-demarcated hyperkeratotic plaques associated to the scalp and frontal regions with deep furrows; b) hyperkeratotic plaques with a verrucous surface; c) hyperkeratotic plaques with ichthyosis-hystrix-like scaling on shoulder; d) scattered follicular hyperkeratosis in the trunk and wrinkled skin; e-f) palmoplantar keratoderma with severe constriction and onychodystrophy.

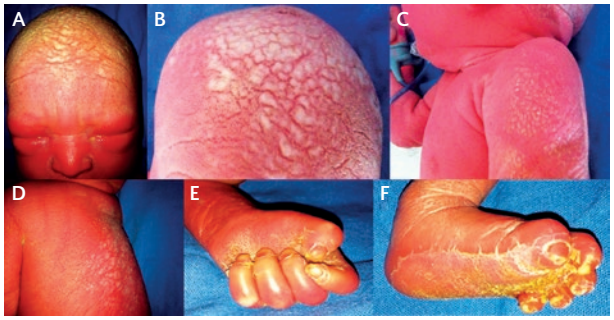
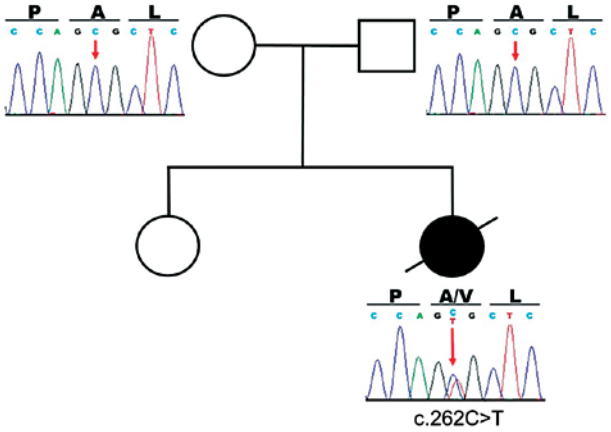


Figure 2. Pedigree of the patient with the *de novo* A88V mutation. The affected child is heterozygous for the c.262C>T (A88V) variant.



G12R, N14K, A40V, G45E, D50N, and A88V[5-7]; all of these increase hemichannel opening. Unfortunately, patients with the mutations G45E and A88V experience skin breakdown and recurrent infection, and eventually die from septicemia during the first year of life[8].

The objective of this study was to report a Mexican female infant with a fatal outcome who harbored the A88V mutation.

MATERIAL AND METHODS

DNA isolation and exome sequencing

After clinical examination and obtaining signed informed consent, blood samples were taken from the patient and both parents in tubes containing EDTA as an anticoagulant (BD Vacutainer®, Franklin Lakes, NJ). DNA was extracted using the Easy-DNA™ kit from Invitrogen (Carlsbad, CA). Samples were sequenced in the MiSeq platform from Illumina Company (San Diego, CA) following the manufacturer's protocols. The procedure was carried out in the Department of Dermatology at Yale University. The mutation detected was validated by Sanger sequencing in the same institution.

RESULTS

The patient was the second child of healthy, unrelated parents. Their first pregnancy was a non-affected child. The patient was born after 35 weeks of an uneventful pregnancy, weighed 2 kg, and measured 48 cm. She presented alopecia totalis, leonine facies, a wizened forehead, a scowl with deep furrows, and well-demarcated hyperkeratotic plaques on the scalp. Erythroderma and verrucous plaques covered her trunk and back. Her limbs showed ichthyosis-hystrix-like scaling and severe palmoplantar keratoderma that caused fixed flexion of the digits, which were tapered and had hyperconvex nails (Fig. 1). The external auditory canals were blocked by scale, and auditory brain stem potentials were not performed. Exams of the heart, brain, and kidney were normal. She developed sepsis at day 3 and was treated with cefotaxime (150 mg/kg/day) followed by fluconazole (3 mg/kg/day) and meropenem (120 mg/kg/day), without improvement; the patient died at nine days of age.

The DNA obtained from the patient was analyzed by exome sequencing; a heterozygous mutation (c.262C>T; p.A88V) located at exon 2 of the *GJB2* gene was found. Neither parent presented any genetic alteration in the *GJB2* sequence (Fig. 2).

DISCUSSION

We present a clinical case of sporadic KID syndrome harboring a *de novo* A88V mutation. Fatal KID syndrome has previously been described in eight families (Table 1)[8-15]. These cases were related to infection and sepsis, which complicated about half of the cases,

Table 1. Findings of the fatal form of keratitis-ichthyosis-deafness syndrome

Cases	Mallory, et al. 1989[13]	Helm, et al. 1990[10]	Berker, et al. 1993[11]	Gilliam, et al. 2002[14]	Janneke, et al. 2005[8]	Sbidian, et al. 2010[12]	Koppelhus, et al. 2011[15]	Haruna, et al. 2010[9]	Present case
Mutation	NE	NE	NE	G45E‡	G45E	G45E§	A88V	A88V	A88V
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Angola/African	Caucasian	Japanese	Mexican
Prematurity	34 weeks	38 weeks*	33 weeks	36 weeks	36 weeks	1/4	33 weeks	–	34 weeks
Alopecia	+	+	+		+	4/4	+	+	+
Ichthyosiform erythroderma	+	+	+	+	+	4/4	+	+	+
Palmoplantar keratoderma	–	–	+	+	+	4/4	+	–	+
Nails	–	–	Small	Thick	–	Dystrophy	Dystrophy	–	Brittle
Deafness	+	+	NE†	+	+†	NE	+	+	NE†
Eyes	–	+	–	+	+	0/4	–	+	–
Additional findings	Inguinal hernia Hirschsprung	–	–	–	–	–	Hydrocephalus	–	Fixed flexion digits
Death due to sepsis	+	+	+	+	+	4/4	+	+	+
Age at death	3 m	3 m	2 m	6 m	12 m	30 d, 5 m, 30 d, 10 d	3 m	3 y 5 m	9 d

*Premature labor at 34 weeks; †External auditory canals blocked by desquamation; ‡Griffit, et al. 2006; §Four siblings are described.
NE: not evaluated; y: years; m: months; d: days.

with bacteria and fungi being the most recognized agents, although a case with disseminated cytomegalovirus infection has been also described[10]. The underlying causes for increased susceptibility to infection remain unclear, but they can be related to extensive skin damage, resulting in the loss of the protector barrier and an increased amount of scaling. It is debatable if early and aggressive antibiotic prophylaxis could modify the lethality of this disorder or improve survival. Other measures, such as antiseptic baths and emollients, are useful at least in the less aggressive variants.

The case reported herein presented a severe palmoplantar keratoderma that produced tight skin in the palms and soles, causing flexion contractures in all digits (hands and feet). Some of these congenital findings resemble those found in Vohwinkel syndrome, which is another entity related to *GJB2*; however, digital involvement in Vohwinkel syndrome is an acquired feature and is always associated to pseudoainhum[16].

Connexins have conserved structural domains that include four transmembrane, two extracellular, and three cytoplasmic domains[17]. To date, 12 mutations in the gene encoding CX26 have been described as causative of KID syndrome, all located in the first transmembrane helix, the first extracellular loop, or the N terminal domain[18]. Interestingly, the mutations G45E (p.Gly45Glu) and A88V (p.Ala88Val) are linked to the fatal phenotype, and cases harboring these mutations suffer recurrent infections, eventual septicemia, and breathing problems[8]. Regarding the mutation found in this neonate female (A88V), it has been previously reported in two other cases with a fatal course and the mutation is located in the second transmembrane helix of CX26[9,15].

It is been reported that the A88V mutation produces enhanced hemichannel activity compared to the wild-type genotype, resulting in accelerated cell death that explains the etiology of the KID syndrome[3,19]. *In vitro* assays have shown that the magnitude of the hemichannel currents produced by the genotype D50A (a mutation present in a non-severe version of KID syndrome) was less than the currents produced by the genotype A88V, suggesting that the severity of the syndrome may correlate with the relative increase in hemichannel activity caused by the respective mutation[3,20].

Fatal cases are related to G45E or A88V mutations and represent about 10% of all KID syndromes, which shows a strong genotype-phenotype correlation in terms of survival. The case reported here harbored the A88V mutation and, consequently, the patient died during the second week of life.

Finally, caregivers must be aware of the lethal nature of some KID syndromes, with sepsis being a key factor of this lethality. Therefore, early and aggressive antibiotic treatment and other isolation measures should be used immediately after birth in order to improve survival.

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