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CASE REPORT

Connexin 26 (*GJB2*) mutation in KID syndrome: An Egyptian patient

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KEYWORDS

Deafness;
Ichthyosis;
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Abstract Keratitis ± ichthyosis ± deafness (KID) syndrome is a rare disorder characterized by the occurrence of localized erythematous scaly skin lesions, severe bilateral keratitis, and sensorineural deafness. Other ocular manifestations include corneal epithelial defects and scarring, which cause progressive decline of visual acuity and may eventually lead to blindness. To our knowledge, few cases have been reported worldwide and none were reported from the Middle East Arab countries. Here we report the first Egyptian patient with this syndrome.

1. Introduction

Skinner et al. [1] proposed that the term KID syndrome be used for an entity that falls under the general heading of congenital ectodermal defects and have the following features in common: (1) a distinctive ichthyosis characterized by a fine dry scale, follicular hyperkeratotic spines, and a reticulated pattern of hyperkeratosis on the palms and soles; (2) a vascularizing keratitis that results in notable visual impairment; and (3) neurosensory deafness. One half of the affected patients also display frequent, severe cutaneous infections.

The term "ichthyosis" is, strictly speaking, not correct, as the skin lesions are more appropriately classified as erythrokeratodermia. A scarring alopecia can be part of the phenotype. The skin lesions occur predominantly on the face, palms, and soles, and have a typical reticulated pattern that is often called leather-like. Squamous cell carcinoma has been reported in 11% of the patients and may probably be considered as a manifestation of the disease [2].

2. Case report

Our patient is a 5-year-old girl, the second in order of birth of a non-consanguineous marriage. She has an older normal sister. The pregnancy and delivery were uncomplicated.

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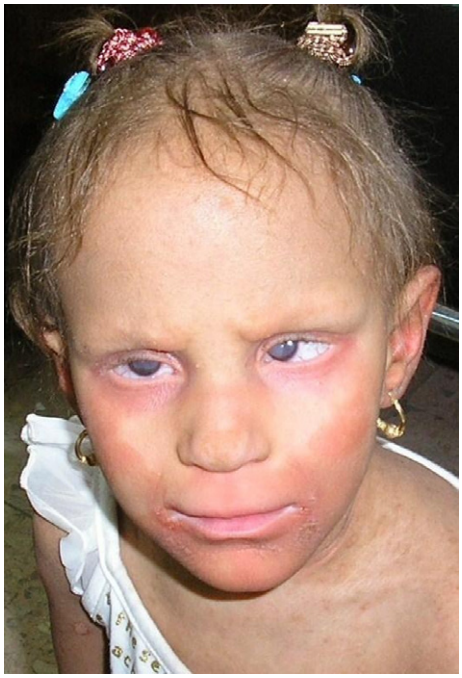

Figure 1 AP view of the patient showing fine sparse hair (hypotrichosis), cataract and erythrokeratodermia of the face and neck.

Family history revealed two paternal cousins with congenital deafness with no skin manifestations.

She presented to the genetic clinic with generalized skin lesions in the form of dryness of skin and red macules and patches especially around the mouth and overlying the large joints (erythrokeratodermia). There was also hyperkeratotic brown-colored plaque on elbows and axillary flexures, the back of the neck and the upper part of the front of chest. Hair of the scalp hair was fine fair and sparse, also that of the eyebrows and eyelashes (hypotrichosis). Thick perioral rugae were noted at the angles of mouth. Her teeth were erupted with no abnormal shape, and her nails were not dysplastic. She had also bilateral corneal opacities and deafness (Figs. 1–3).

Abdominal, chest and heart examination were clinically free. Audiometry revealed bilateral sensorineural hearing loss. Coloured B and A scan ultrasonography of the left eye revealed normal ocular contour with an axial length ± 21.5 cm. Lens was in place and acoustically clear with slightly thickened posterior capsule. Few scattered amorphous vitreous opacities of low amplitude echoes, mobile on kinetic scan. Retina and optic nerve head showed no abnormalities.

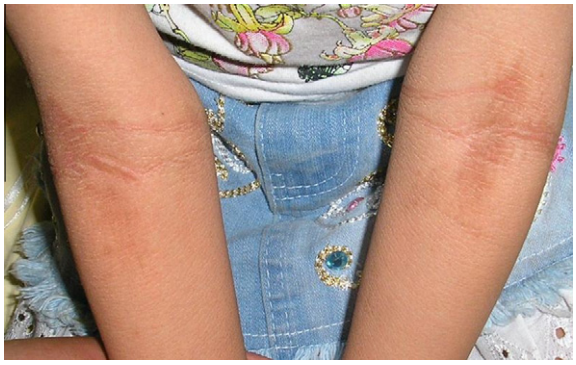

Figure 2 Hyperkeratotic brown-colored plaques on the elbows.

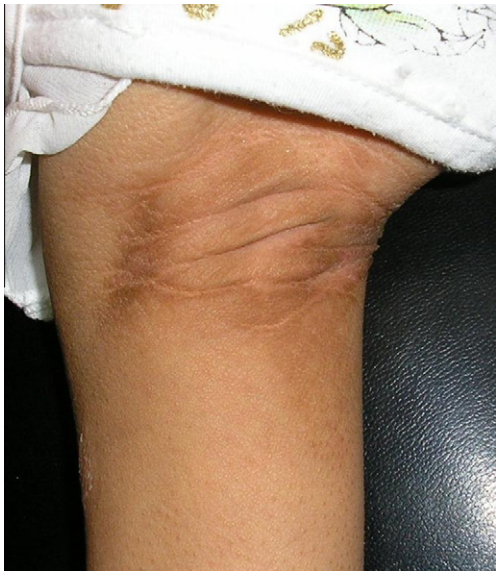

Figure 3 Hyperkeratotic brown-colored plaque on the axilla.

3. Molecular analysis

Genomic DNA was prepared from peripheral blood of the patients and her parents. The coding region of exon 2 of the *GJB2* gene on chromosome 13q12.11 was amplified by the polymerase chain reaction and sequenced. The resulting sequence data was compared with the reference gene ID ENSG00000165474. Results revealed a heterozygous *GJB2* mutation c.148G > A (p.D50N) in the present patient. Both parents did not have this mutation.

4. Discussion

Our patient has typical features of KID syndrome consisting of keratitis, ichthyosis and deafness that was also confirmed by molecular testing. Manifestations of the disease usually appear in neonates as generalized erythema, sometimes with diffuse scaling and leathery skin. Typical skin changes gradually develop during infancy and include linear and spiny hyperkeratosis of the flexures, and ichthyosis-hystrix-like scaling on the limbs [3].

Scattered follicular hyperkeratosis may also appear on the trunk. A typical feature is the evolution of fixed, orange, symmetrical, well-demarcated, hyperkeratotic plaques on the scalp, ears and face. Like the present patient, some develop thick perioral rugae and may evolve into an aged or leonine appearance of the face [4].

Increased susceptibility to mucocutaneous infections is common and sometimes fatal in the neonatal period. Squamous cell carcinoma of the skin and oral mucosa (carcinoma of tongue) is a rare but serious complication that can shorten life expectancy [5].

Other manifestation includes corneal epithelial defects, scarring, and neovascularization (‘keratitis’) which cause progressive decline of visual acuity and may eventually lead to

blindness. Congenital sensorineural hearing loss is generally severe and bilateral, although unilateral or moderate hearing impairment has been observed [6]. Cochlear implant can be effective in these patients [7].

Rare manifestations include Dandy–Walker malformation which has been reported few times with KID syndrome, but thought to be coincidental. However, some authors suggested the possibility that this is an association and not a coincidental finding [8].

Differential diagnosis includes erythrokeratodermia variabilis*** of Mendes da Costa, in which patients have erythrokeratodermia and deafness but no keratitis. It is caused by mutations in the connexin genes 30 and 31. In erythrokeratodermia variabilis, keratitis is not part of the syndrome but the skin lesions and sensorineural deafness are similar to those found in KID syndrome [9–11] .

KID syndrome is genetically heterogeneous and may be caused by mutations in connexin 26 or connexin 30 genes. Our patient was heterozygous for p.D50N mutation which affects an evolutionarily highly conserved residue and represents the most prevalent mutation of the KID syndrome [12].

Inheritance is usually sporadic but autosomal recessive and dominant cases are reported [13]. Germinal mosaicism has also been reported [5]. The autosomal recessive form is characterized by hepatic disease, growth failure, and mental retardation [14]. The present patient had a mutation in the connexin 26 gene that is not present in her parents which indicates the de novo nature of the mutation.

A rare lethal form of the disease with a fatal course in the first year of life due to severe skin lesion infections and septicaemia has been only observed in two Caucasian sporadic patients with the GJB2 mutation, with the p.Gly45Glu (G45E) arising de novo. Later Jonard et al. [15] reported an African family with dizygotic twins suffering from a lethal form of KID and are heterozygous for the G45E mutation of GJB2, whereas the mutation was not detected in the two parents. This confirms the possibility of germinal mosaicism in KID syndrome.

5. Disclosure statement

We declare that there is no conflict of interests.

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