Clinical Vignette

Hystrix-like Ichthyosis and Deafness Syndrome in a Toddler

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Abstract

Hystrix-like ichthyosis and deafness (HID) syndrome is characterized by ichthyosis, erythrokeratoderma, alopecia and deafness in varying degrees of severity. The clinical manifestations are present since birth, evolve and gradually worsen. It occurs due to a single known mutation in the *GJB2* gene. Early diagnosis and management and genetic counseling require a high index of suspicion for an underlying genetic basis in such skin disorders.

Introduction

Hystrix-like ichthyosis and deafness (HID) syndrome (OMIM#602540) was first described in a patient in 1977 who presented with icthyosis-hystrix and bilateral hearing loss (Schnyder et al., 1977). Its initial name was 'ichthyosis hystrix gravior, type Rheydt' after the city of origin of the patient, located near Dusseldorf, Germany, with the word 'hystrix' indicating spiky porcupine-like skin changes [Konig et al., 1997]. Traupe H suggested including deafness in the nomenclature, naming it hystrix-like ichthyosis with deafness, or HID syndrome (Traupe, 1989). The molecular basis of the HID syndrome has been found to be a heterozygous pathogenic variant (p.Asp50Asn) in the *GJB2* gene. Pathogenic variants in *GJB2* are more commonly known to cause non syndromic deafness [autosomal recessive (AR) or autosomal dominant (AD)]. A phenotypic variant to the HID syndrome is the keratitis icthyosis deafness (KID) syndrome. KID syndrome patients have keratitis (inflammation of the cornea) that can cause photophobia, scarring and vision loss. They also have palmoplantar keratoderma in addition to erythrokeratoderma, ichthyosis and deafness which is seen in the HID syndrome. About 100 cases of HID have been reported to date in literature (Avshalumova et al., 2014). Here we present a rare case of the HID syndrome.

Case Report

The patient is a 17-month-old girl born to non consanguineous parents. She was born preterm at 36 weeks of gestation, appropriate for gestation with a birth weight of 2.5 kg. She had required admission in the neonatal intensive care unit (NICU) for 4 weeks in view of respiratory distress. Soon after birth she developed redness and peeling of the skin involving the face, arms, trunk and dorsum of hands and feet which persisted at the time of discharge (Figures 1A and 1B). She was treated for congenital pneumonia and seborrheic dermatitis during her NICU stay. However, the skin lesions were persistent and difficult to treat. She received multiple courses of topical steroids, antifungal and antibiotic ointments in view of a possibility of seborrheic dermatitis or atopic dermatitis along with recurrent skin infections. Over a period of time, she developed diffuse thickening of the skin and hyperkeratotic plaques over the arms and legs. The eyebrows were absent and hair on the scalp and body was sparse and lightly pigmented (Figure 1C). There was relative sparing of the skin of the palms and soles. A lack of sweating was also observed. There was no significant developmental delay. Eye evaluation did not reveal any significant finding. Her immunoglobulin profile and blood counts were normal. The patient was the sole affected family member and the only child, with an ongoing pregnancy in the mother. The family desired a definitive diagnosis for the child and genetic counseling for the ongoing pregnancy. With a possibility of congenital ichthyotic disorder or

Figure 1 Clinical photographs of the child, in the neonatal period (A, B) showing facial rash and alopecia, and at 18-months of age (C) showing slight skin rash, and ichthyosis especially on dorsum of hands.

ectodermal dysplasia further definitive genetic testing was planned. Next generation sequencing, for genes related to ichthyosis related disorders revealed the heterozygous pathogenic variant c.148G>A (p.Asp50Asn/ p.D50N) in the *GJB2* gene, which has been previously reported with HID syndrome. Although the parents did not complain of any significant hearing impairment in the child, and her speech appeared appropriate for age, a formal hearing test (auditory steady state responses) showed mild to moderate and moderately profound to severe hearing loss in the right and left ear, respectively. Sanger sequencing further confirmed the presence of the mutation in the child. It was noted to be a de-novo mutation as it was not present in the parents (Figure 2). This confirmed the overall low risk of recurrence for the ongoing pregnancy (~1% due to gonadal mosaicism). The parents chose against prenatal testing of the fetus and continued the pregnancy. For the affected child, the parents were provided with appropriate dermatological referral and antikeratolytic, antibiotic and emollient topical treatment. They were advised to discuss the need for hearing aid or cochlear implant in the future, with an otolaryngologist.

Discussion

HID is a genetic disorder occurring due to a mutation in the *GJB2* gene, which belongs to the family of gap junction proteins. Connexin 26 is a 225- amino acid- long protein encoded by the *GJB2* gene located on chromosome 13. Gap junction channels are made from a family of proteins called connexins. Their main function is to allow passage of small molecules between adjacent cells, coupling them both metabolically and electrically. The function of the various connexin channels is distinct in terms of their gating, conductance and permeability characteristics (Avshalumova et al., 2014). Connexin 26 is involved in intercellular communication and differentiation of cells in the epithelium of cornea, cochlea, palmoplantar epidermis, hair and sweat glands. The *GJB2*

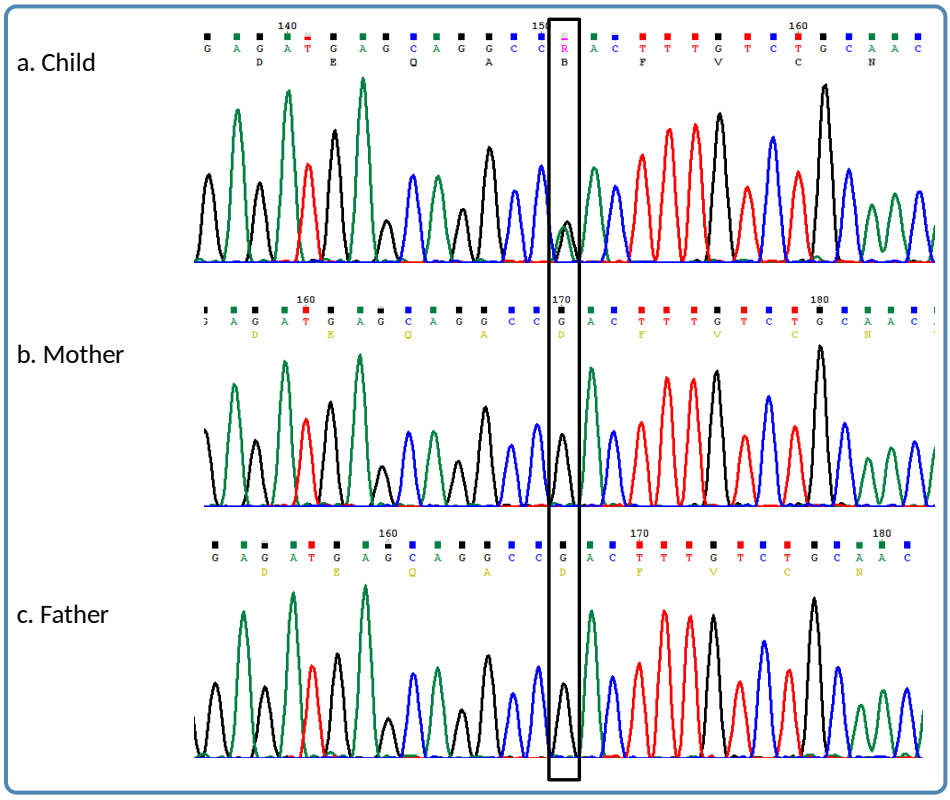

Figure 2 Sanger sequencing analysis of *GJB2* gene (A) child heterozygous for the c.148G>A variant; (B & C) Mother and father negative for the c.148G>A variant.

gene has been more commonly implicated with non-syndromic deafness, both autosomal recessive and autosomal dominant types. It has been identified as the most common cause of non-syndromic deafness – DFNB1 accounting for up to 50% of congenital severe-to-profound autosomal recessive non-syndromic hearing loss in many countries (Smith et al., 2016).

GJB2 has also been studied to cause five syndromic forms of deafness that include skin disease. The syndromic deafness disorders are very rare, and can be divided into two broad groups. The first group includes Bart-Pumphrey syndrome, Vohwinkel syndrome, and Palmoplantar keratoderma with deafness, presenting with palmoplantar keratoderma along with deafness. Specifically, patients with the Bart-Pumphrey have nail involvement in the form of leukonychia and growth on the knuckle pads while, constriction bands and auto amputation have been reported in the Vohwinkel syndrome (Srinivas et al., 2018).

Hystrix-like ichthyosis deafness syndrome (HID) and keratitis ichthyosis deafness (KID) syndrome make up the second group. HID manifests shortly after birth with erythematous patches. By the age of 1 year, spiky and cobblestone-like greyish brown to red hyperkeratotic masses involve the entire skin including the scalp and face. The palms and soles are usually mildly affected. Scarring alopecia can also occur. Histopathologic features resemble those of lamellar ichthyosis with reduction of tonofibrils and abundance of mucous granules and are not diagnostic. There is associated bilateral neurosensory hearing loss. Our patient had all the clinical characteristics of HID syndrome.

HID and KID are identical at the molecular level and the difference is mainly clinical. Some basic differences between the two are: KID can present at birth in the form of hyperkeratotic erythroderma which resolves spontaneously only to recur later but never involves the trunk. Scaling typical of ichthyosis (seen in HID) is not seen, so it is not a true ichthyosis. In addition, palms and soles are severely affected and eye manifestations are typically seen in KID, although few case reports have mentioned mild keratitis in patients of HID

(Van Geel at al., 2002; Avshalumova et al., 2014). Both AD (*GJB2* gene) and AR (*AP1B1* gene) types of KID are known (Boyden et al., 2019). In the AD variety of KID, the p.Asp50Asn accounts for ~80% of mutations but other mutations have also been described. KID also has increased morbidity and chance for disfigurement along with the risk for squamous cell carcinoma (SCC) as compared to HID which generally has a good prognosis. KID is the only connexin-related skin disorder described with SCC. HID begins as erythematous patches soon after birth and evolves to ichthyosis involving the scalp and face. Palms and soles are less affected (differentiating it from KID). A mild punctate keratitis has also been described in some HID patients. There is only one known mutation for HID (p.Asp50Asn). The electron microscopy features are now known to not be diagnostic for either disorder, contrary to the previous notion, and include excess formation of mucous-containing granules and reduction of tonofibrils (Avshalumova et al., 2014). Thus, HID and KID may represent a spectrum of the same disorder at the molecular level with HID being less severe. As suspected with other genes with a wide spectrum of disease severity, possible causes include gene-gene interactions, polymorphisms in other genes expressed in the skin, environmental modifiers and other epigenetic mechanisms.

A genotype-phenotype correlation has been suggested among the KID patients. The *GJB2* p.Asp50Asn mutation-associated patients of KID syndrome live into adulthood despite vision loss and high risk for developing squamous cell carcinoma, while the *GJB2* p.Gly45Glu and p.Ala88Val mutation-associated patients have higher chances of dying in childhood due to septic complications (Srinivas et al., 2018).

The other skin disorders reported with connexin mutations are erythrokeratoderma variabilis (EKV), involving mutations in *GJB3* and *GJB4*, Clouston syndrome (a.k.a. hidrotic ectodermal dysplasia), involving mutations in *GJB6*, and oculodentodigital dysplasia (ODDD) caused due to mutations in *GJA1* (Avshalumova et al., 2014). Confirmation of diagnosis in skin disorders has implications for accurate counseling and management. HID syndrome is a condition that requires regular skin care throughout life. Patients with the KID phenotype need to be monitored for possibility of developing life-threatening SCC. Accurate diagnosis helped to pick the additional symptom of hearing loss in our patient, which may have gone unnoticed until significant speech impairment might have appeared.

Although this is an autosomal dominant disorder, one study reported 64% of cases to be sporadic while 36% cases were familial, many with unaffected parents (Mazereeuw-Hautier et al., 2007). Hence, germline mosaicism is high for this disorder, like most skin disorders and this is a challenging point in counselling.

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