Clinical, etiopathogenic and therapeutic aspects of KID syndrome.

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Abstract

Keratitis-ichthyosis-deafness (KID syndrome) is a syndromes ichthyoses that is clinically and genetically heterogeneous requiring early and long-term multidisciplinary monitoring of affected individuals. A review of the clinical, etiopathogenic and therapeutic aspects is presented of this rare congenital ectodermal disorder.

Keywords: syndromes ichthyoses, KID syndrome, clinical, etiopathogenic, therapeutic

Introduction

The ichythyoses consist of clinically and genetically heterogeneous Mendelian disorders of cornification. Inherited ichthyoses are subdivided into non-syndromic ichthyoses with phenotypes that are restricted to the skin and syndromic ichthyoses with defects in skin and other organs (Yoneda, 2016). Keratitis-ichthyosis-deafness (KID syndrome, OMIM 148210 and 242150) (Cheung et al., 2019; Dalamón et al., 2016; Lee et al., 2019; Ogawa et al., 2014; Serrano-Ahumada et al., 2018; Wonkam et al., 2013; Yoneda, 2016), was initially described by Burns in 1915 (Burns, 1915; Cheung et al., 2019; Yoneda, 2016), and the acronym is proposed by Skinner et al., in 1981(Cheung et al., 2019; Skinner et al., 1981; Wonkam et al., 2013; Yoneda, 2016). KID syndrome is a rare congenital disorder characterized by the association of the classic triad of chronic vascularizing keratitis, ichthyosiform erythroderma and moderate to profound bilateral prelingual sensorineural hearing loss (Abdollahi et al., 2007; Cheung et al., 2019; Dalamón et al., 2016; Lee et al., 2019; Ogawa et al., 2014; Patel et al., 2015; Sanchez et al., 2013; Serrano-Ahumada et al., 2018; Taki

et al., 2018; Wang X, et al., 2018; Wonkam et al., 2013; Yoneda, 2016), which often impacts speech (Patel et al., 2015).

Clinical Features

The skin findings are typically noted soon after birth as generalized scaling and extensive erythrokeratodermic, follicular hyperkeratoses, psoriasiform or verrucous plaques with scarring progressive alopecia (Cheung et al., 2019; Dalamón et al., 2016; Lee et al., 2019; Patel et al., 2015; Yoneda, 2016), a typical reticulated pattern that is often defined as leather-like (Dalamón et al., 2016), palmoplantar keratoderma often described as reticulated or pitted, onychodystrophy, and due to the extensive skin involvement there is an increased risk of chronic, opportunistic cutaneous infection (bacterial or fungal) and in severe cases septicemia (Abdollahi et al., 2007; Cheung et al., 2019; Dalamón et al., 2016; Lee et al., 2019; Patel et al., 2015; Taki et al., 2018). Furthermore, some patients develop thick perioral rugae and an aged appearance of the face (Figure 1) (Abdollahi et al., 2007), angular cheilitis and dental abnormalities (Cheung et al., 2019; Patel et al., 2015). Patients present an increased susceptibility of developing both benign and malignant cutaneous tumors, such as trichilemmoma and squamous cell carcinoma of mucous membranes in at least 12% of patients (Dalamón et al., 2016; Lee et al., 2019; Patel et al., 2015; Serrano-Ahumada et al., 2018; Taki et al., 2018), apparently due to p53 loss in the lesions (Dalamón et al., 2016). The development has also been described spinocellular carcinoma from dermal or lingual lesions (Yoneda, 2016). These complications can have a significant impact on life expectancy (Lee et al., 2019).

The ocular manifestations usually are progressive and develop during infancy (Abdollahi et al., 2007). There is significant corneal involvement with corneal epithelial defects, severe punctate keratitis (Abdollahi et al., 2007), progressive neovascularization (Cheung et al., 2019; Dalamón et al., 2016; Lee et al., 2019;

Serrano-Ahumada et al., 2018), which is bilateral but asymmetrical, (over 80% of cases) (Abdollahi et al., 2007), and recurring corneal erosions (Abdollahi et al., 2007; Cheung et al., 2019). There are disturbances of the tear film due to meibomitis and severe dry eye syndrome (Abdollahi et al., 2007). Ultimately pannus formation, corneal leukoma and limbal stem cell deficiency impact significantly on visual function. Other reported ocular manifestations include recurrent conjunctivitis, hypotrichosis of the eyebrows and lashes, and atrophy of secretory glands (Cheung et al., 2019). In one case ocular surface squamous neoplasia was reported (Serrano-Ahumada et al., 2018). Ultimately pannus formation, corneal leukoma and limbal stem cell deficiency impact significantly on visual function (Dalamón et al., 2016).

Etiopathogeny

This hereditary cornification disorder is of unknown prevalence, and to date, approximately 100 cases of KID syndrome have been reported in the literature (Dalamón et al., 2016; Patel et al., 2015; Serrano-Ahumada et al., 2018; Wang X, et al., 2018; Wonkam et al., 2013). Inheritance is usually sporadic, but some familial forms have been reported with autosomal dominant and recessive transmission pattern (Abdollahi et al., 2007; Dalamón et al., 2016; Lee et al., 2019; Serrano-Ahumada et al., 2018; Wang X, et al., 2018; Wonkam et al., 2013; Yoneda, 2016). KID syndrome is genetically heterogeneous and in the most cases are caused by heterozygous germline missense mutation in *GJB2* gene (Cheung et al., 2019; Dalamón et al., 2016; Lee et al., 2019; Ogawa et al., 2014; Patel et al., 2015; Serrano-Ahumada et al., 2018; Wonkam et al., 2013; Yoneda, 2016), which encode the closely related gap junction β-2 protein (connexins 26) (Lee et al., 2019; Serrano-Ahumada et al., 2018; Yoneda, 2016;). Additionally, two heterozygous non-synonymous mutations p.Asp50Asn in *GJB2* and p.Glu162Asp in *TTC9* gene were

identified in two affected family members proposing new etiological cause (Wang X, et al., 2018).

Connexins are integral membrane proteins forming gap junction channels for diffusional exchange of ions and other metabolites between cells (Serrano-Ahumada et al., 2018), and play part in a variety of biological functions that allow for intercellular communication between epithelial cells, cell growth and development (Cheung et al., 2019; Dalamón et al., 2016; Patel et al., 2015), and an expressed in keratinocytes and in support cells of the inner ear (Sanchez et al., 2013).

Connexins present a common structure consisting of four transmembrane domains, linked by one cytoplasmic, and two extracellular loops (namely, EC1, and EC2, respectively), with both cytoplasmic N-terminal and C-terminal (Dalamón et al., 2016; Wonkam et al., 2013). The membrane spanning and the extracellular domains are highly conserved and the main differences between connexin are found in their C-terminal tails. In the case of KID syndrome, all pathogenic mutations were described clustering in regions coding for the first extracellular domain and the N-terminal of connexin 26, implying common functional defects (Dalamón et al., 2016).

Mutations in *GJB2* gene were identified in several autosomal recessive non-syndromic sensorineural deafness pedigrees (Dalamón et al., 2016; Sanchez et al., 2014), and represent one of the most common causes of inherited deafness. More than 100 mutations have been identified and produce loss of function as a result of premature stop codons, deletions, insertions and frameshifts (Taki et al., 2018). The resultant loss of channel function produce the alteration of cochlear intercellular communication (Dalamón et al., 2016). However, mutations at 18 positions in connexin 26 have been identified in several syndromic deafness with varying phenotypes that alter epidermal differentiation, such as KID syndrome, palmoplantar keratoderma with deafness, Bart-Pumphrey syndrome and Vohwinkel syndrome.

Genetically, all of these disorders result from mutations in *GJB2* gene, but the nature of each disease depends on the particular mutation detected (Dalamón et al., 2016; Sanchez et al., 2013; Sanchez et al., 2014). In contrast to non-syndromic deafness, syndromic deafness is characteristically cause by missense mutations of single residues, and behave in an autosomal dominant manner (Patel et al., 2015; Sanchez et al., 2014).

To date, 12 missense *GJB2* mutations have been reported to KID syndrome, and c.148G>A (p.Asp50Asn), is the most common; it has been reported in patients worldwide from different ethnic groups. This mutation is located in the first extracellular loop domain, E1, and thus, it has been suggested that Asp50Asn could alter gap junctions channel gating and/or affect hemichannel interactions (Dalamón et al., 2016; Lee et al., 2019; Sanchez et al., 2013). In addition to this recurrent mutation, others *GJB2* mutations have been described in KID patients, such as p.Gly11Arg, p.Gly12Arg, p.Asn14Tyr, p.Ser17Phe, p.Ala40Val, p.Gly45Glu, p.Asp50Tyr and p.Gly54Glu (Dalamón et al., 2016). At least 10 out of the 12 identified mutations, including c.148G>A (p.Asp50Asn), have been associated with aberrant hemichannel behavior, resulting in elevated membrane currents, enhanced permeability to small-molecule tracers, and/or enhanced ATP release in response to a specific stimuli (Lee et al., 2019). The mutations p.Gly45Glu and p. Ala88Val are associated with uniform early lethality so early genotyping of KID syndrome births will inform prognostic discussion (Lilly et al., 2019).

The mutation c.148G>A (p.Asp50Asn) is also supported by the crystal structure of the connexins 26 gap junctions channel. These properties include a substantially reduced unitary conductance, increased open-state outward rectification, and strongly shifted voltage-dependent activation. Application of using the substituted Cys accessibility method confirmed this mutation as a pore-lining residue in connexin

26 hemichannels. Interestingly, the connexin 26 crystal structure suggests that p.Asp50Asn not only lines the pore, but also participates in inter-subunit interactions (Sanchez et al., 2013). In the epidermis, gap junctions appear to play a role in the coordination of keratinocyte growth and differentiation, whereas in the sensory epithelia of the inner ear they mainly regulate potassium recycling during auditory transduction. Several observations suggest that changes in the proliferation and differentiation pathway of keratinocytes correspond with a switch of the pattern of connexin expression in skin (Dalamón et al., 2016).

KID syndrome autosomal recessive

This entity is clinically characterized by ichthyosiform erythroderma, profound sensorineural deafness, vascularizing keratitis, developmental delay and failure to thrive. There are also reports of other ocular, dental, hepatic and metabolic defects (Alsaif et al., 2019; Boyden et al., 2019; Cremers et al., 1977; Desmons et al., 1971; Jurecka et al., 1985; Wilson et al., 1991).

This subtype is caused by homozygous mutation in the *AP1B1* gene at chromosomal region 22q12.2, as p.Glu14Argfs*5, and a deletion of 75 kb that removes the tentative promoter as well as the first two exons of *AP1B1* gene, so it is predicted to be a null at the protein level (Alsaif et al., 2019) and other homozygous mutation as p.Glu792* (Boyden et al., 2019), or compound heterozygous in a male patient as p.Cys144Arg inherited from his unaffected mother and p.Leu779Serfs*26 inherited from his unaffected father (Boyden et al., 2019).

Differential diagnosis

The differential diagnosis, are shown in the Table 1 (Elsayed et al., 2011; Yoneda, 2016). Hystrix-like ichthyosis with deafness syndrome (OMIM 602540) was initially considered a differ entity from the KID syndrome, however, the phenotypes are similar, and both present cancer predisposition with an increased incidence of squamous cell carcinoma. Subsequently, these entities were associated with an identical connexin 26 missense mutation (van Geel et al., 2002). This entity was not included in the classification of inherited ichthyoses, results of the first ichthyosis consensus conference (Oji et al., 2010)

Examination and treatment

There is an unmet need for targeted treatment of KID syndrome (Lee et al., 2019). Management is challenging for dermatologists as conventional treatments often lack efficacy and currently, there are no therapeutic guidelines for pediatric patients (Patel et al., 2015). Cutaneous treatment is limited to symptomatic management, including retinoid therapy, to attempt to improve the skin barrier, the application of keratolytic drugs and antifungal and antibacterial agents for the risk of infection (Yoneda, 2016; Lee et al., 2019).

Keratitis, photophobia and low vision appear during childhood. Bilateral corneal pannus and neovascularisation is observed (Yoneda, 2016). Medical and surgical ocular interventions have demonstrated limited success in KID syndrome. Therapies have included artificial tears, corticosteroids, cyclosporine A, antibiotics (Cheung et al., 2019), subconjunctival bevacizumab in early stages could prevent corneal neovascularization (Caye et al., 2010; Cheung et al., 2019), penetrating keratoplasty, superficial keratectomy, removal of corneal pannus, corneal grafts, ocular surface stem cell transplantation, and keratoprosthesis implantation (Cheung et al., 2019).

Audiography is required to investigate the presence or absence of hearing disorder. For this control, hearing aids and cochlear implants are used. If malignant tumors of the skin develop, surgery should be performed (Yoneda, 2016).

The urgent ophthalmologic and otolaryngologic measures and simple topical therapies may improve skin condition precluding the possible risk of systemic therapy (Abdollahi et al., 2007). Recent work has shown that mefloquine, an FDA-approved anti-malarial drug, potently suppresses aberrant hemichannels in primary keratinocytes from a transgenic mouse model with heterozygous p.G45E mutation in *GJB2*. Very recently, the monoclonal antibody abEC1.1 was developed, which specifically suppressed hemichannels formed by connexins 26-wildtype, p.Gly45Glu or p.Asp50Asn mutants. However, it is unclear whether those strategies can discriminate mutant *GJB2* allele from the wildtype. This concern is particularly important given the context that most KID syndrome mutants exert dominant effects on co-expressed wildtype connexins. In the last decade, allele-specific small interference RNA (AS-siRNA) technology has shown strong therapeutic potential in treatment of dominant genetic disorders and brought clinical (Lee et al., 2019).

Although the general prognosis of KID syndrome appears to be favorable (Caye et al., 2010; Yoneda, 2016), but exanthema may persist over the lifetime (Yoneda, 2016), early and long-term multidisciplinary monitoring of affected individuals is necessary (Caye et al., 2010). Attention should be paid to increased susceptibility to infections and increased risk of developing malignant tumors (Caye et al., 2010; Yoneda, 2016), particularly squamous cell carcinoma.

Conclusions

KID syndrome is a rare syndromic ichthyoses which is clinically and genetically heterogeneous but characterized by the association of the classic triad of chronic vascularizing keratitis, ichthyosiform erythroderma and sensorineural hearing loss.

Inheritance is usually sporadic, but some familial forms have been reported with autosomal dominant and recessive transmission pattern. Most cases are caused by heterozygous germline missense mutation in *GJB2* gene that encode the connexins 26, identified in several autosomal recessive non-syndromic sensorineural deafness as the most common causes. Mutations at 18 positions in the *GJB2* gene have been identified in several syndromic deafness with varying phenotypes as KID syndrome, among others. Early and long-term multidisciplinary monitoring of affected individuals is necessary to manage clinically challenging complications.

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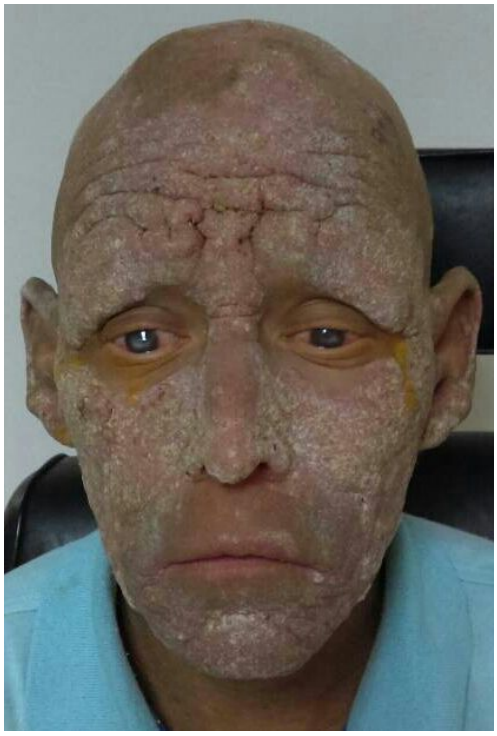

Figure 1. Facial appearance of a 37-year-old male patient with KID syndrome.

Table 1. Differential diagnosis of KID syndrome.

Entity	OMIM	*Gene*	Location	Inheritance	Characteristic
Ichthyosis hystrix Curth-Macklin	146590	*KRT1*	12q13.13	AD	Intermediate filaments of keratin surrounding a nucleus like a shell are detected on electron microscopy
Erythrokeratodermia variabilis	*133200*	*GJB3* *GJB6*	1p34.3 13q12.11	AD, AR	Not cause keratitis

AD: autosomal dominant, AR: autosomal recessive.