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Case Report

An audiological profile of keratitis-ichthyosis-deafness syndrome

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ABSTRACT

Keratitis-ichthyosis-deafness (KID) syndrome is a rare genetic multi-system disorder. It is characterized by defects of the surface of the corneas (keratitis), red, rough thickened plaques of skin (erythrokeratoderma) with sensorineural hearing impairment. The skin of the palms of the hand, soles of the feet and the nails may be affected. Most cases are sporadic caused by mutations in the (GJB2 gene). Most cases are sporadic but familial cases with autosomal dominant inheritance have been reported a rare congenital ectodermal disorder characterized by vascularising keratitis hyperkeratotic skin lesions and hearing loss. The 2-year male child was presented at audiology and speech pathology unit department of ENT at Pt. Jawaharlal Nehru memorial hospital, Raipur, patient came with the complaint of inability to hear since birth. The present report outlined persistent severe sensorineural hearing loss in child with KID syndrome.

Keywords: Keratitis-ichthyosis-deafness, Auditory brain-stem response, Otoacoustic emission, Syndrome

INTRODUCTION

Keratitis-ichthyosis-deafness (KID) syndrome is a rare disorder, its prevalence is unknown. It is characterized by defects of the surface of the corneas (keratitis), red, rough thickened plaques of skin (erythrokeratoderma) and sensorineural deafness or severe hearing impairment. The skin on the palms of the hands and soles of the feet and the nails may be affected. Caused by mutations in the (GJB2gene.). Most cases are sporadic but familial cases with autosomal dominant inheritance have been reported a rare congenital ectodermal disorder characterized by vascularising keratitis hyperkeratotic skin lesions and hearing loss.[1,2] Approximately 100 cases have been reported KID syndrome appears to affect females slightly more often than males the male/female ratio is 32:29.6. The disorder is very rare with fewer than 100 cases reported in the medical literature.[3] Collectively the ichthyosis affect more than 1,000,000 people in the United States, Saudi Arabia, Japan, China, India and other Asian countries.

KID syndrome is a rare congenital multisystem disorder due to the mutation, the gene encoding connexin 26 protein affecting certain tissues of ectodermal origin such as epidermis cochlea and cornea. KID syndrome is usually inherited in an autosomal dominant pattern which means one copy of the altered gene in each cell sufficient to cause the disorder. In some cases, an affected person inherits the mutation from one affected parent. However, most cases result from new mutations in the gene and occurring people with no history of the disorder in their family. A few families have had a condition resembling kid syndrome with an autosomal recessive pattern of inheritance in autosomal recessive inheritance both copies of a gene in each cell have mutations The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene but they typically do not show signs and symptoms of the

conditions The autosomal recessive condition sometimes called demons syndrome. It is unknown whether it is also caused by GJB 2 gene mutations.[4,5]

The cutaneous manifestations include palmoplantar hyperkeratosis with leather grain-like keratoderma nail dystrophy alopecia and ichthyosis forms scaling, slowly progressing keratitis culminates in deafness and blindness respectively before puberty.[6] Most cases have been sporadic but autosomal recessive and dominant cases are reported it is genetically heterogeneous and is caused by missense mutation in the GJB 2 (gap junction β-2) gene encoding for connexin 26 protein which clusters at chromosome 13q12.2 Germinal mosaicism-a mechanism by which some of the germ cells of the gonad are of a form not present in either parent because of mutation in an intermediate progenitor of these cells.[7]

People with KID syndrome have thick hard skin on the palms of the hands and soles of the feet (palmoplantar keratoderma). Affected individuals also have thick reddened patches of skin (erythrokeratoderma) that are dry and scaly (ichthyosis). These dry patches can occur anywhere on the body although they most commonly affect the neck groin and armpit breaks in the skin often occur and may lead to infections. In severe cases these infections can be life-threatening especially in infancy. Approximately 12% of people with KID syndrome develop a type of skin cancer called squamous cell carcinoma which may also affect mucous membranes such as the lining of the mouth partial hair loss is a common feature of kid syndrome and often affects the eyebrows and eye lashes. Affected individuals may also have small abnormally formed nails.[8]

Ophthalmological examination showed bilateral corneal neovascularization with evidence of dry eye. Fluorescein angiography showed no abnormality people with kid syndrome usually have keratitis which is inflammation of the front surface of the eye (the cornea). The keratitis may cause pain increased sensitivity to light (photophobia) abnormal blood vessels growth over the cornea (neovascularization) and scarring. Overtime affected individuals experience a loss of sharp vision (reduced visual acuity) in severe cases the keratitis can lead to blindness.[9]

The majority of KID syndrome cases suffer from profound hearing loss although several cases with mild hearing loss have been reported the sensorineural hearing loss in KID syndrome is generally pre-lingual and profound but occasionally is less severe.[10,11] Although ear structures can be affected ear-related symptoms have never been investigated in patients with ichthyosis for that there is a survey/study had done their aim was to determine the frequency of ear symptoms hearing loss and related medical interventions in patients with ichthyosis. In one of the study reported 135 unique surveys were used for data analysis. Of all participants, 80% reported ear pruritus, 66% reported trouble hearing, 29% reported frequent ear pain, 28% had abnormal hearing test results, and 16% had used hearing aids. Of the 88 participants who reported trouble hearing, 24 (27.3%) had never been to a hearing specialist ear pruritus ear pain and hearing loss are important concerns in patients with all forms of ichthyosis Early diagnosis and intervention may improve the quality of life of patients with ichthyosis.[12]

KID syndrome is caused by mutation in the GJB2 gene. This gene provides instructions for making protein called connexin 26 (amino acids). Connexin 26 protein forms channels called gap junction, Gap junctions made with connexin 26 transport potassium ions and certain small molecules, that permits the transports of nutrient charges (ions) signaling molecules between the neighboring cells that are in contact with each other. In connexin 26 the mutations are thought to result in channels that constantly leak ions which impairs the health of the cells and increases cell death. Connexin 26 is found in cells throughout the body including the inner ear and the skin. Connexin 26 plays a role in the growth and maturation of the outer most layer of skin (the epidermis). The GJB2 gene mutations that cause kid syndrome change single protein building blocks. Death of cells in the skin and the inner ear may underlie the ichthyosis and deafness that occurring in KID syndrome.[13]

In the inner ear channels made from connexin 26 are found in a snail-shaped structure called the cochlea. These channels may help to maintain the proper level of potassium ions required for the conversion of sound waves to electrical nerve impulses. This conversion is essential for normal hearing. In addition, connexin 26 may be involved in the maturation of certain cells in the cochlea. It is unclear how GJB2 gene mutations affect the eye because at least one of the GJB2 gene mutations identified in people with kid syndrome also occurs in hystrix-like ichthyosis with deafness (HID) a disorder with similar features but without keratitis many researchers categorize kid syndrome and HID as a single disorder which they call KID/HID. It is not known why some people with this mutation have eye problems while others do not learn more about the gene associated with keratitis-ichthyosis-deafness syndrome. GJB2.[14]

CASE REPORT

Here in the present study, we tried to explore some ear and hearing related issues in KID syndrome patient reported in the clinic. The 2-year male child was presented at' audiology and speech pathology unit department of ENT at Pt. Jawaharlal Nehru Memorial Hospital Raipur. Patient came with the complaint of inability to hear since birth. The patient's history revealed erythrokera-todermic and mild scaling since birth. In the first months of life the skin became thick and had a leathery appearance with time, erythematous hyperkeratotic plaques developed on elbows, knees, dorsal sides of hands and feet, with marked thickening of

palms and soles. Lesions spread to the face and the concha of the ears. Since the age of 6 month the patient

the patient's whole-body skin was diffusely thickened showing follicular keratosis. Prominent erythema affected the face and furrowing erythematous plaques were present around the mouth. Bilateral keratoconjunctivitis and corneal vascularization were also present. The patient presented with scalp hypotrichosis and scarring alopecia, with thick crusty squamous plaques. The scalp hair was sparse, fine, brittle, pale in colour and slow growing. The eyebrows and eyelashes were thin or absent. Body, pubic and axillary hair was also affected the same time. His parents observed hearing impairment as well. Patient also often suffered from eye inflammations. During hospitalization the patient was treated by a dermatologist, ophthalmologist otorhinolaryngologists and visited a psychiatrist on a regular basis.

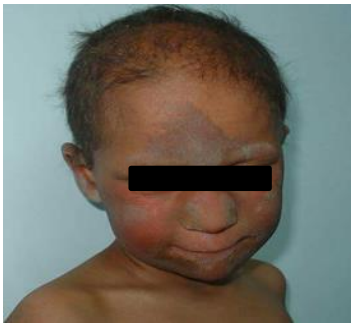

Figure 1: Blindfolded photograph of child.

frequently developed whole body erythema, for which he had been hospitalized after observing skin abnormalities,

Table 1: Laboratory investigation report of child.

Laboratory investigation	Results	Reference value
MCH (pg)	35.9	27-32
Haemoglobin (g/dl)	13.6	13.8-17.2
RCB (cumm)	4.01	4.4 -5.4
Neutrophile (%)	54	40 -70
Platelet (g/dl)	576	150 -400
WBC (g/dl)	15.4	4.0 -12.5
Lymphocyte (%)	40	20 -48
Sodium (mmol/l)	135.9	132 -145
Potassium (mmol/l)	5.58	3.5-5.5
Iron calcium (mmol/l)	1.22	1.1-1.3
Blood group	B +ve	

Prenatal history

The prenatal history revealed that 20-year-old mother had no significant prenatal history as such as reported by patient, there was no history of PIH/UTI/PROM/ hypothyroidism/diabetes/cardiac renal abnormalities. She received calcium iron supplements. There were no uses of illegal drugs, tobacco, alcohol or any other personal and family medical history and there was no history of consanguinity in his family present case was first child of his parents.

Table 2: Audiological tests and its findings.

Test administered	Instrument used	Right ear	Left ear	Impression
BOA behavioral observation audiometry	Intracaustic audiometri ll diagnostic IA AC-40	No response till 120 dB.	No response till 120 dB.	Severe degree of hearing loss.
Immittance audiometer Tympanogram	GSI-Tympstar	"A" type	"A" type	Normal middle ear function
Immittance audiometer Reflexes.	GSI-Tympstar	Absence of ipsi and contra reflexes	Absence of ipsi and contra reflexes	Presumed to be normal functioning of middle ear and reflex tract
OAE oto-acoustic emission	GSI-Audera	REFER	REFER	Indication of bilateral hearing loss (>40 dB)
ABR	GSI-Audera	No peak observed at 90 dBnHL	No peak observed at 90 dBnHL	Bilateral severe degree of hearing loss.

Perinatal history

Patient was born in 39 weeks (post term birth) with birth weight of 3.2 kg with normal vaginal delivery. There was significant history that child cried on 3rd day after birth and also the cry tone, whole body activity and new born reflexes were decreased. The child was admitted in NICU for 7 days. The patient frequently suffered from the neonatal hyperbilirubinemia (jaundice).

Postnatal history

After 1 month of delivery patient had severe respiratory distress. There was gradually change in the skin was observed. In the first months of life the skin became thick and had a leathery appearance the typical symmetrical, erythrokera-todermic non scaling plaques developed. Erythrokera-todermic plaques affected predominantly theverrucous hyper-keratotic coalescent plaques located

on the ears, cheeks, forehead, nose and perioral skin presented in the child. The above sign and symptoms confirmed that the child was an under KID syndrome.

Ear and hearing test findings

Case presented with the complaint of reduced hearing sensitivity neonatal seizures/sepsis with shock/respiratory distress neonatal hyperbilirubinemia was observed since the time of birth. Routine audiological evaluation were carried out in Table 1. First audiological test administered was behavioural observation audiometry (BOA) which revealed severe degree of hearing impairment. Next evaluation administered was immittance audiometric test in which A type of tympanogram was obtained along with the absence of acoustic reflexes (IPSI as well as contra lateral) next audiological test was diagnostic OAE revealed bilateral "refer" which suggested the abnormal functions of outer hair cells (OHC's) which also indicated the hearing loss was more than 40 dB HL. Next objective hearing evaluation that was auditory brainstem evoked response (ABR), which revealed bilateral severe degree of hearing impairment no peak observed even after repeated trail was done at higher intensity till 90 dB HL (Figure 2). The present report outlined persistent severe sensorineural hearing loss in child with KID syndrome.

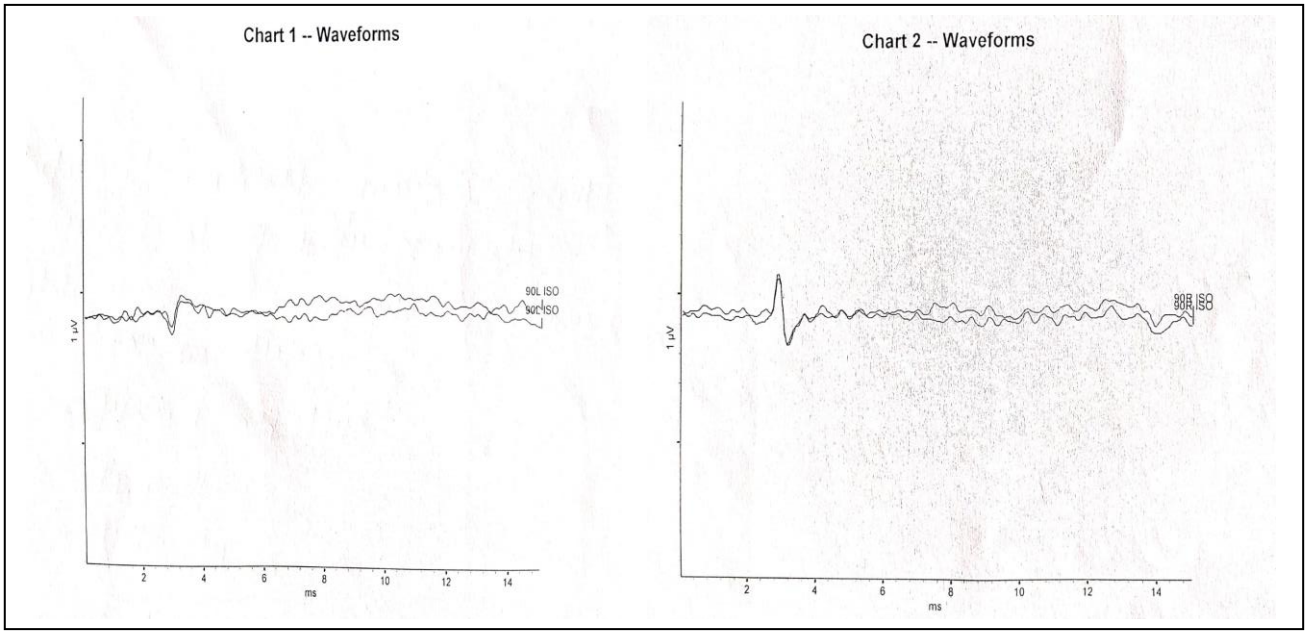

Figure 2: ABR waves for both left ear and right ear.

DISCUSSION

KID syndrome is a disorder of skin tissue, cornea and the inner ear. Generally, it was autosomal dominant inheritance but, in few families, having an autosomal recessive pattern. However, most cases resulted from new mutations in the gene.[6] Because parental genetic analysis was not done in our case, we cannot comment on the exact mode of inheritance.[13,14]

This syndrome was first reported by burns in as a generalized congenital keratoderma with ocular and mucosal involvement, but the term KID syndrome was coined by Skinner et al in 1981 to highlight the main features of the syndrome.[15] Approximately 70 cases were analysed by Caceres-Rios et al most of them were sporadic, had been reported and found all of them showing cutaneous and auditory abnormalities, 90% sensorineural deafness, 89% erythrokeratoderma 79% alopecia, 41% reticulated hyperkeratosis of the palms and soles, and 95% had ophthalmologic defects, most of them (79%) had vascularizing keratitis. The name keratodermatous ectodermal dysplasia proposed by them, as the KID acronym did not accurately define this entity. The skin condition did not always show ichthyosis, but rather keratodermatous skin.[16]

Early diagnosis of KID syndrome was important. Hearing loss was always present with variable degrees of compromise, mainly sensorineural in nature. The hearing loss was congenital it can be detected in infancy or early and had almost always developed by age 7 years. Because of sensorineural deafness, speech development was usually delayed and the timely use of hearing aids and speech therapy can prevent and manages in the development of speech.[17] A good general prognosis but the life-long follow up was required because this syndrome can be associated to malignant tumors.

Eye related symptoms of this syndrome were irritation, photophobia and visual disturbance due to vascularizing keratitis. The eye lesions expressed later than the other alterations and they may not evolve with symptoms until puberty. Bilateral asymmetrical corneal vascularization was very frequent (in more than 80% of cases). An autosomal dominant form and an autosomal recessive

form both inheritances had been described. The differential diagnosis of KID syndrome was ichthyosis follicularis with alopecia and photophobia (IFAP). There was no palmoplantar keratoderma in IFAP and hearing was normal.[18]

CONCLUSION

This case study revealed that the child with KID syndrome showed bilateral severe to profound hearing loss along with erythrokera-todermic and mild scaling since birth. Since the age of 6 month the patient frequently developed whole body erythema. Bilateral keratoconjunctivitis and corneal vascularization were also present. As this is the single case study which required attention of many professionals, so a greater number of cases will be helpful for understanding of hearing problem in children with KID syndrome.

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REFERENCES

1. National Organization for Rare Disorders (NORD). Fact sheet: Keratitis ichthyosis deafness syndrome, 2006. Available at: https://rarediseases.org/rare-diseases/keratitis-ichthyosis-deafness-syndrome. Accessed on 14 May 2022.
2. Medline. Fact sheet: Keratitis-ichthyosis-deafness syndrome. Genetics Home Reference, 2012. Available at: https://medlineplus.gov/genetics/condition/keratitis-ichthyosis-deafness-syndrome. Accessed on 14 May 2022.
3. Binder B, Hennies HC, Kraschl R, Smolle J. Connexin-26-Mutation bei, keratitis-ichthyosis-deafness-syndrom (KID-Syndrom) Connexin 26 mutation and keratitis-ichthyosis-deafness (KID) Syndrome. J der Deutschen Dermatologischen Gesellschaft. 2005;3(2):105-8.
4. Mazereeuw-Hautier J, Bitoun E, Chevrant-Breton J, Man SY, Bodemer C, Prins C, et al. Keratitis-ichthyosis-deafness syndrome: disease expression and spectrum of connexin 26 (GJB2) mutations in 14 patients. Br J Dermatol. 2007;156(5):1015-9.
5. Richard G, Rouan F, Willoughby CE, Brown N, Chung P, Ryynänen M, et al. Missense mutations in GJB2 encoding connexin-26 cause the ectodermal dysplasia keratitis-ichthyosis-deafness syndrome. Am J Human Genet. 2002;70(5):1341-8.
6. Enei ML, Cassettari A, Córdova S, Torres O, Paschoal F. Do you know this syndrome?. Anais brasileiros de dermatologia. 2011;86:819-21.
7. Iossa S, Marciano E, Franzé A. GJB2 gene mutations in syndromic skin diseases with sensorineural hearing loss. Curr Genomics. 2011;12: 475-85.
8. Steensel MA. Gap junction diseases of the skin. Am J Med Genet C Semin Med Genet. 2004;131(1):12-9.
9. Messmer EM, Kenyon KR, Rittinger O, Janecke AR, Kampik A. Ocular manifestations of keratitis-ichthyosis-deafness (KID) syndrome. Ophthalmology. 2005;112(2):1-6.
10. Bygum A, Betz RC, Kragballe K, Steiniche T, Peeters N, Wuyts W, et al. KID syndrome: report of a Scandinavian patient with connexin-26 gene mutation. Acta Dermato Venereolog. 2005;85(2):152-5.
11. Bondeson ML, Nyström AM, Gunnarsson U, Vahlquist A. Connexin 26 (GJB2) mutations in two Swedish patients with atypical Vohwinkel (mutilating keratoderma plus deafness) and KID syndrome both extensively treated with acitretin. Acta Dermato Venereolog. 2006;86(6):503-8.
12. Huang JT, Mallon K, Hamill S, Ohlms LA, Liang MG. Frequency of ear symptoms and hearing loss in ichthyosis: a pilot survey study. Pediatr Dermatol. 2014;31(3):276-80.
13. Lee JR, White TW. Connexin-26 mutations in deafness and skin disease. Expert Rev Molecul Med. 2009;11.
14. Xu J, Nicholson BJ. The role of connexins in ear and skin physiology-functional insights from disease-associated mutations. Biomembranes. 2013;1828(1):167-78.
15. Skinner BA, Greist MC, Norins AL. The keratitis, ichthyosis, and deafness (KID) syndrome. Arch Dermatol. 1981;117(5):285-9.
16. Caceres-Rios H, Tamayo-Sanchez L, Duran-Mckinster C, Orozco MD, Ruiz-Maldonado R. Keratitis, ichthyosis, and deafness (KID syndrome): review of the literature and proposal of a new terminology. Pediatr Dermatol. 1996;13(2):105-13.
17. Langer K, Konrad K, Wolff K. Keratitis ichthyosis and deafness (KID)-syndrome: report of three cases and a review of the literature. Br J Dermatol. 1990;122(5):689-97.
18. Traboulsi E, Waked N, Mégarbané H, Mégarbané A. Ocular findings in ichthyosis follicularis-alopecia-photophobia (IFAP) syndrome. Ophthalm Genet. 2004;25(2):153-6.

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