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Case Report

Systematic Audiological Assessment of Individuals with Kallmann Syndrome: In the Indian Population

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Abstract

Kallmann Syndrome (KS) was characterized by hypogonadotropic, hypogonadism (HH) and anosmia/hyposmia with developmental anomalies of the olfactory bulb and hypothalamus. It has a heterogeneous inheritance pattern that can be x-linked autosomal dominant or autosomal recessive disorder. There are currently more than 20 pathogenic genes linked to KS, six of which are quite frequent (KAL1, FGFR1, PROKR2, PROK2, CHD7, FGF8). KS affects approximately 1 in every 10,000 males and 1 in every 40,000 females. Micropenis and cryptorchidism are common in males with KS, as well as the development of secondary sexual characteristics such as deepening of voice and growth of facial hair, while menstruation and breast development are noted in females. Other developmental deficits are also associated with KS, such as hearing impairment, eye related issues, cleft lip or palate, atypical tooth development.

In this study, we have described two case reports of KS, who had hearing loss. Detailed audiological and ENT evaluation were carried out including otoscopic examination, Immittance evaluation, Puretone audiometry, Otoacoustic emissions, Auditory Brainstem implant and Hearing aid trial. Radiological evaluation was lao done and the results were in correspondence with previously published literature. The cruras and footplate of the stapes, as well as the oval window, were absent. The stapes head and neck were made up of a little piece of bone that was linked to the incus' lenticular process. The stapedius tendon was present and connected to the stapes' neck. The facial nerve was lying at a lower position than expected in its tympanic portion.

The implications of the test findings suggest that the early diagnosis of KS is based on multidisciplinary cooperation are important for the treatment process. Puberty development is also important for skeletal, metabolic, and psychological consequences, in addition to sexual health. If KS is detected early, hormone replacement can be started, and secondary sexual development can resume. Adequate genetic counseling can also be provided to family members.

Keywords: Kallmamm Syndrome; Hypogonadotropic Hypogonadism; Conductive Hearing Loss

Abbreviations

HH: Hypogonadotropic Hypogonadism; KS: Kallmann Syndrome; GnRH: Gonadotropin-releasing Hormone; SRT: Speech Recognition Threshold; SIS: Speech Identification Scores; PTA: Pure Tone Average; DPOAE: Distortion Product OtoAcoustic Emission; ABR: Auditory Brainstem Responses

Introduction

In 1944, A German American geneticist, Franz-Josef Kallmann described Kallmann Syndrome (KS). It was characterized by hypogonadotropic, hypogonadism (HH) and anosmia/hyposmia with developmental anomalies of the olfactory bulb and hypothalamus [1]. The main clinical manifestations of KS are hypogonadism and anosmia, which are caused by a disruption in the shared neural migratory pathways of gonadotropin-releasing hormone (GnRH) neurons and olfactory neurons early in embryonic development [2].

It has a heterogeneous inheritance pattern that can be x-linked autosomal dominant [3] or autosomal recessive disorder [4]. There are currently more than 20 pathogenic genes linked to KS, six of which are quite frequent (KAL1, FGFR1, PROKR2, PROK2, CHD7, FGF8). However, only around 30% of the etiology and pathophysiology can currently be explained by recognized genetic abnormalities, with the remaining 70% unclear [5-8].

KS affects approximately 1 in every 10,000 males and 1 in every 40,000 females [9]. The prevalence estimates are limited and inconsistent, but men appear to be 3-5 times more likely than women [10].

Micropenis and cryptorchidism are common in males with KS, as well as the development of secondary sexual characteristics such as deepening of voice and growth of facial hair, while menstruation and breast development are noted in females [11]. Other developmental deficits are also associated with KS, such as hearing impairment, which affects roughly 5% of KS patients [12]. Abnormal eye movements, color blindness, hearing loss, cleft lip or palate, atypical tooth development, movements of one hand mirrored by another hand (binaural synkinesis), anomalies of bones in fingers and toes, and the inability of one kidney to develop (unilateral renal agenesis) are among the other characteristics seen.

Method and Material

Case report

Case 1

A 19-year-old male was referred to the ENT department for a speech and hearing evaluation. He was a recognized case of KS that had been diagnosed in the genetics department. According to his parent's account, he has had hearing loss since childhood but has never had active treatment for it. Specific speech-related difficulties were also reported, including misarticulation of a few words and a borderline intellectual disability. The client is currently enrolled in a Pre-University degree.

ENT examination

The otoscopic examination revealed a normal appearance of the external auditory canal and tympanic membrane in both ears, as well as landmark marks. Pure tone audiometry was performed using a Resonance r37a dual channel audiometer, and the thresholds were tracked using a modified Hughson and Westlake approach. The findings revealed a bilateral moderate conductive flat hearing loss with a 40-45dBHL air bone gap. The audiogram showing the thresholds of the case is represented in figure 1. Speech recognition threshold (SRT) and speech identification scores (SIS) were obtained using speech audiometry, and there was a strong association between speech audiometry and pure tone average (PTA). Tympanometry and acoustic reflex performed with an interacoustic diagnostic (AT 235) middle ear analyzer revealed normal compliance and normal middle ear pressure in both ears suggesting an 'A' type of tympanogram in both ears with the absence of Ipsilateral and Contralateral acoustic reflexes bilaterally. Distortion product OtoAcoustic Emission (DPOAE) done with titan interacoustic was absent in each ear. Auditory brainstem responses (ABR) were recorded in both ears using LABAT MASTER. For air conduction, the ER 3A was used, and for bone conduction, the K71 Radio ear bone vibrator was used. Bone conduction click ABR was present till 30dBnHL, indicating bone conduction hearing sensitivity within normal ranges in both ears. In both ears air conduction click ABR was present till 70dBnHL, which corresponds to 50-55dBHL, indicating a moderate degree of hearing loss in both ears. Widex enjoy 30 BTE digital hearing aid was used for hearing aid trial and aided thresholds were found to be at the upper border of speech spectrum showing subsequent benefit in hearing function. But the client had refused to use a hearing aid as a management option.

Radiological findings

HRCT of the temporal bones was performed after the patient and his family gave their approval to investigate for possible causes of conductive hearing loss. The CT scan revealed that the superior, posterior, and lateral semicircular canals were all normal on both sides. The cochlea's anatomical appearance was unremarkable,

the round window niche was patent bilaterally, and the vestibular aqueduct for both ears was normal. The cruras and footplate of the stapes, as well as the oval window, were absent. The stapes head and neck were made up of a little piece of bone that was linked to the incus' lenticular process. The stapedius tendon was present and connected to the stapes' neck. The facial nerve was lying at a lower position than expected in its tympanic portion.

Figure 1: The audiometric thresholds obtained for case 1 in right and left ears suggesting bilateral moderate conductive hearing loss.

Case 2

A 17-year-old male presented to the ENT department with a complaint of hearing loss, but no complaints of ear pain, ear obstruction, or ear discharge were reported. Since the age of 14, his parents had been aware of his hearing impairment. Parents reported no complaints relating to speech and language.

ENT examination

The external auditory canal (EAC) and tympanic membrane were structurally normal, with all landmark features present in both ears, according to an otoscopic examination. Pure tone audiometry with Resonance r37a dual channel audiometer was used to assess the patients' hearing thresholds, with the modified Hughson and Westlake approach used to monitor the threshold. The findings indicated bilateral moderate conductive hearing loss with a 40-50dBHL air bone gap. The audiogram showing the thresholds of the case is represented in figure 2. Speech recognition threshold (SRT) and speech identification score (SIS) were obtained using speech audiometry, and the scores were found to be highly correlated with the pure tone average (PTA). Interacoustic diagnostic (AT 235) middle ear analyzer tympanometry and acoustic reflex demonstrated normal compliance and middle ear pressure in both ears, indicating an 'A' type of tympanogram in both ears with the absence of Ipsilateral and Contralateral acoustic reflexes bilaterally. Titan interacoustic was used to perform distortion product OtoAcoustic Emission (DPOAE), which was absent in each ear. Auditory Brainstem Responses (ABR) were recorded in both ears using LABAT MASTER and ER 3A insert receivers for air conduction and K71 Radio ear bone vibrator for bone conduction. In both ears, bone conduction click ABR was present until 30dBnHL, indicating hearing sensitivity within normal limits for bone conduction, while air conduction responses were present until 65dBnHL in both ears, correlated with 45-50dBHL suggesting the presence of bilateral moderate hearing loss. A hearing aid trial was done with Starkey aries pro BTE digital hearing aid.

Figure 2: The audiometric thresholds obtained for case 2 in right and left ears suggesting bilateral moderate conductive hearing loss.

Radiological finding

HRCT of the temporal bones was performed after getting the patient's and his family's consent to check for potential reasons of conductive hearing loss. The CT scan revealed that all inner ear structures, including the superior, posterior, and lateral semicircular canals, were normal on both sides, the cochlea was normal anatomically, the round window niche was patent, and the vestibular aqueduct was adequate on both sides. The stapes footplate and cruras were missing from the middle ear structures, but the stapes head and neck were there, linked to the lenticular process of the incus, with a typical stapedius tendon. The tympanic part of the facial nerve was lying at the bottom.

Discussion

The case presented in our current study was diagnosed in adulthood. This delay in diagnosis may seriously affect patient care and recurrence risk counseling. Nonetheless, before maturation, the diagnosis may be extremely difficult to make. The diagnosis is generally delayed until the patient seeks medical treatment for delayed puberty and hypogonadism in their third decade, as was the case in the current case report. To link all of the symptoms of KS to one syndrome, several pediatric doctors from various medical disciplines should be aware of them. The main distinguishing characteristic of KS is anosmia, which is why otorhinolaryngologists are familiar with it; nevertheless, this is often neglected because its most visible feature is hypogonadism [13]. It's caused by a problem with the olfactory bulb, which causes the neuroendocrine gonadotropin releasing hormone (GnRH) cells to migrate too slowly into the preoptic and hypothalamic areas [14].

Although the basic defects in KS are HH and anosmia or hyposmia, patients with KS can also have several non-reproductive malformations, such as deafness. The lack of secondary sexual features is a common presentation of KS to an endocrinologist. When anosmia and hypogonadism are present, the diagnosis is usually obvious. On the contrary, some of these individuals may report to an otolaryngologist as a youngster with a variety of ENT-related symptoms.

A small number of individuals with KS have been observed to have hearing loss [15-17]. Hearing loss in KS has been linked to some different genetic mutations. Mutations in KAL1, FGFR1, FGF8, IL17RD, CHD7, and the transcriptional factor SCX 10 that regulates neural crest cell development, deletion in Xp22.3 where the gene for X linked Kal S is located, or a single amino acid loss of KAL1 are all possibilities [12,15-18]. The majority of patients, however, have an unknown cause. Hearing inability in the currently reported patient stopped his family to admit him to the school for education which subsequently implied the quality of his life. As a result, we agree with pediatricians who recommend hearing screening in male children with micropenis or undescended testes, two features commonly linked with KS [15].

Although most authors correlate sensorineural hearing loss with KS, conductive and mixed hearing loss have been documented as well [19,20]. Two examples of KS presenting with conductive hearing loss were reported by Coatesworth., *et al*. 2002. These two patients had undergone tympanotomies, which revealed the same findings: nonexistent stapes footplate and crura, as well as an absent oval window.

Our patient's aberrant CT temporal bone findings are quite remarkable. We describe the same findings in both the cases with KS and conductive hearing loss in this publication. The oval window, stapes footplate, and crura were all missing, along with a low-lying tympanic section of the facial nerve in all cases. An absence of an oval window has been linked to a facial nerve that is abnormally low-lying. This link is thought to have formed as a result of the growth of oval windows being halted [21].

If patients with KS and conductive deafness are seen in the future, it should be assumed that they have similar abnormalities. Before a tympanotomy, they might be taught about the benefits and drawbacks of a cochleostomy. Lambert reported the findings of ossicular repair in six patients with conductive hearing loss and 13 congenital oval window absences. In four of the six cases, there was an initial hearing improvement of 20 to 45 decibels. However, with time, most of the improvements were reversed.

The limitation of this case study is the lack of genetic screening. However, mutations in any of the six genes linked to Kal S were found in only 30% of the cases (2.7), while mutations in SOX10 were found in 38% of the cases. This means that the inability to detect any gene mutation does not rule out KS as a diagnosis. As a result, the diagnosis of KS in the reported patient was completely clinical, based on the combination of anosmia and delayed puberty.

Conclusions

The early diagnosis of KS based on multidisciplinary cooperation is important for the treatment process. Puberty development is also important for skeletal, metabolic, and psychological consequences, in addition to sexual health. If KS is detected early, hormone replacement can be started, and secondary sexual development can resume [22]. Adequate genetic counseling can also be provided to family members.

Ethical Statement

The hospital ethics committee has approved the study, and the written informed consent for publication of their clinical details was obtained from the patient and his family members.

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