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CLINICAL STUDY

Hereditary bilateral sudden sensorineural hearing loss

Varga L[1,2], Jovankovicova A[3], Huckova M[2], Demesova L[1,2], Gasperikova D[2], Sebova I[3], Profant M[1]

Department of Otorhinolaryngology – Head and Neck Surgery, Faculty of Medicine and University Hospital, Comenius University, Bratislava, Slovakia. **profant@fnorl.sk**

ABSTRACT

OBJECTIVES: The aim of our study is to demonstrate a causal link between two distinct diagnoses, the hereditary hearing loss, and the sudden sensorineural hearing loss.

BACKGROUND: Sudden sensorineural hearing loss is an emergency condition in otolaryngology and a rare diagnosis in childhood. Most often it only affects one ear and its cause remains unknown.

METHODS: We present a clinical study of a 10-year-old female patient presenting with bilateral sudden sensorineural hearing loss analyzed by Sanger sequencing of the *GJB2* gene.

RESULTS: The subject was referred to the hospital for bilateral sudden hearing loss which developed 3 days before the admission. Audiometric testing confirmed bilateral asymmetric sensorineural hearing loss. All routine diagnostic procedures including MRI and CT imaging showed normal results. She was treated with intravenous and intratympanic corticosteroids followed by hyperbaric oxygen therapy with partial hearing recovery in one ear. DNA analysis of the *GJB2* gene identified biallelic c.35delG deletion. The subject had no other affected family members and her auditory development to that time was normal.

CONCLUSION: Our finding extends the knowledge on phenotype variability in *GJB2* variants. We suggest considering genetic testing in pediatric cases of bilateral sudden sensorineural hearing loss *(Tab. 1, Fig. 4, Ref. 24)*. Text in PDF *www.elis.sk.*

KEY WORDS: sudden hearing loss, bilateral, DNA analysis, connexin 26, *GJB2.*

Introduction

Sudden sensorineural hearing loss (SSNHL) is characterized by rapid onset (within 72 hours) affecting at least three consecutive frequencies with hearing thresholds of ≥ 30 dB. It is traditionally considered as an emergency condition in otolaryngology and early treatment is known to provide higher rate of hearing recovery (1). According to more recent studies the incidence of SSNHL in adults ranges between 10.2–27 : 100 000 (2, 3). In the vast majority of the cases (95–99 %) it only affects one ear, while bilateral cases are rare (1–5 %) (4, 5). Moreover, bilateral SSNHL is associated with more severe underlying diagnoses, poorer prognosis and higher mortality (6). The epidemiology of SSNHL in children is unknown as most of the available data are based on rather small case series. Nevertheless, it seems that young children with SSNHL have a poorer prognosis than adolescents (7, 8).

Clinical study

A 10-year-old female patient was referred to the Pediatric ENT department at NICD in Bratislava in February 2019 with 3-day clinical history of SSNHL in both ears. About one week prior to hearing loss onset, she complained of sore throat and was prescribed Penicillin for streptococcal tonsillitis based on positive bacterial culture. The subject was otherwise healthy, had normal

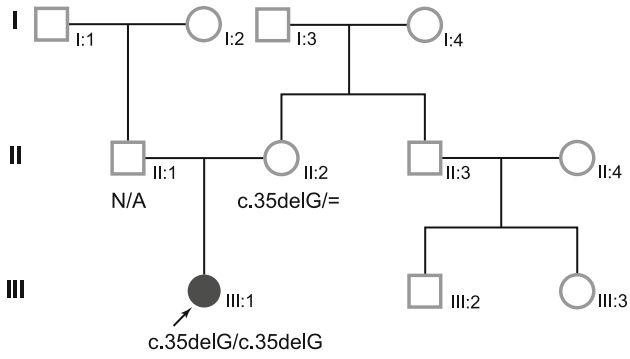

Fig. 1. Pedigree of the proband. Filled symbol- affected individual, empty symbol – normal hearing individual, arrow-proband.

[1]Department of Otorhinolaryngology – Head and Neck Surgery, Faculty of Medicine and University Hospital, Comenius University, Bratislava, Slovakia, [2]Diabgene Laboratory, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia, and [3]Pediatric ORL Department, Faculty of Medicine and National Institute of Children's Diseases (NICD), Comenius University, Bratislava, Slovakia

Address for correspondence: M. Profant, MD, PhD, Department of Otorhinolaryngology – Head and Neck Surgery, Faculty of Medicine and University Hospital, Comenius University, Antolska 11, SK-851 07 Bratislava, Slovakia.
Phone: +421-2-68672052

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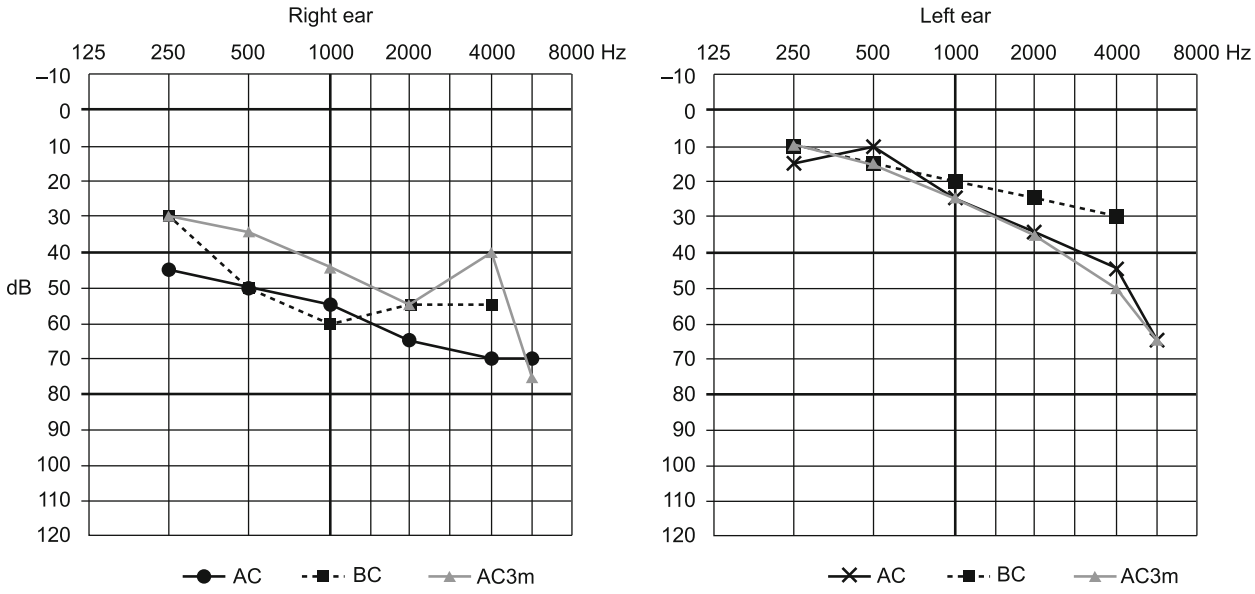

Fig. 2. Pure tone audiogram of the proband showing asymmetric hearing loss (left ear – mild degree, right ear – moderate degree). Colored full lines – initial air conduction thresholds, colored dashed lines – initial bone conduction thresholds, gray lines – air conduction thresholds after three-month follow-up.

language development (bilingual) and attended regular school without learning problems or any other signs suggesting previous hearing loss. Family history of hearing loss was negative (Fig. 1). Physical ENT examination showed normal findings. Audiological evaluation confirmed asymmetric bilateral sensorineural hearing loss (Fig. 2) with absent otoacoustic emissions (DPOAE), normal auditory brainstem response (ABR) latencies, A-type tympanometric curves, and positive recruitment based on acoustic reflex thresholds indicating cochlear damage. Pure tone average (0.5, 1, 2, 4 kHz) thresholds were 28.75 dB for the left ear and 60 dB for the right ear. The subject did not complain of tinnitus or dizziness and basic vestibular investigation demonstrated normal vestibular functions.

The subject was admitted for intravenous therapy and further investigations. All laboratory tests (complete blood count, coagulation, serum biochemistry, urinalysis, serology for CMV and EBV) showed normal results with exception of positive anti-EBV IgG antibodies. Ophthalmologist diagnosed mild hypermetropia, but apart from that, the subject had normal retinal findings. Neurological investigation did not reveal any focal neurological signs. Both CT and MRI of the brain and temporal bone showed normal anatomy of the inner ear and pontocerebellar angle (Fig. 3). Based on routine diagnostic protocol the subject was further treated as idiopathic SSNHL case. Systemic corticosteroids (methylprednisolone) were administered intravenously in a taper dose over 14 days. Because no hearing recovery was observed within 5 initial days after hospital admission the treatment was boosted with 3 consecutive shots of intratympanic methylprednisolone in both ears under propofol anesthesia. Moreover, the patient underwent 20 sessions of hyperbaric oxygen therapy after hospital discharge. Three months after hearing loss onset and treatment the audiogram showed a slight improvement of thresholds in the right ear, while it remained unchanged in the left ear (Fig. 2).

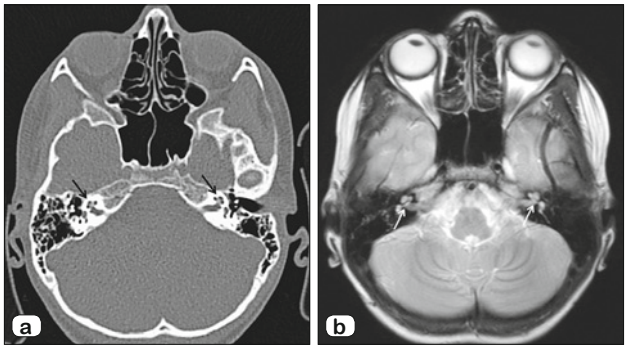

Fig. 3. Brain and temporal bone CT (a) and T2 weighted MRI (b) scans in axial plane demonstrating normal inner ear anatomy (arrows).

However, since bilateral SSNHL cases are rare, peripheral blood and buccal swab were also taken during hospital stay for DNA analysis of hereditary hearing loss despite negative family history and postlingual onset of hearing loss. The non-coding (exon 1) and coding region (exon 2) of the *GJB2* gene were amplified and analyzed by Sanger sequencing as the first step in our otogenetic diagnostic pipeline. Surprisingly, the subject turned out to be a homozygous carrier of c.35delG deletion (Fig. 4), which was confirmed by repeated analysis of two independent samples. The only other family member available for genetic testing was her mother who was detected to be a c.35delG heterozygous carrier. We further retrospectively analyzed the phenotypes in other 163 individuals with biallelic c.35delG variant from our DNA repository of sensorineural hearing loss, but we did not find any other subject with sudden postlingual onset of hearing loss.

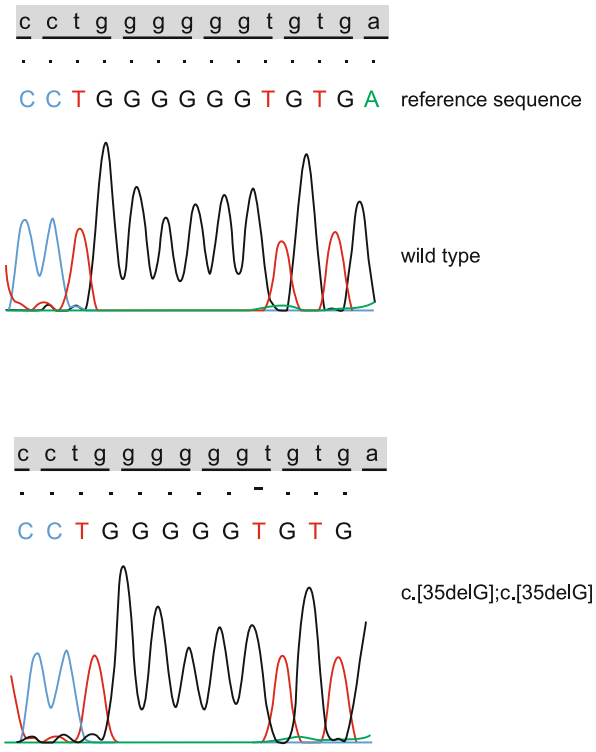

Fig. 4. Sanger sequencing electropherogram of the proband showing homozygous c.35delG deletion compared to wild type. The deletion of one guanine nucleotide is depicted by the arrow.

Discussion

Despite adequate clinical investigation, distinct etiological diagnosis could only be established in about 10-30% of SSNHL cases. The remaining majority is regarded as idiopathic. The most prevalent known causes of this heterogenic disease include infectious and ear diseases, trauma, vascular or hematologic disorders, tumors, ototoxic agents and autoimmune diseases (1, 9). In pediatric population the two most frequently identified etiologies involved infectious (viral) causes and inner ear malformations, particularly the enlarged vestibular aqueduct (EVA) (10–12). The subject presented in this report did not show any signs of acute infection at the time of hospital admission although an episode of acute tonsillitis few days before the hearing loss onset was noted in her clinical files. Similarly, the imaging studies (CT and MRI) excluded any inner ear or intracranial malformations.

The possible role of genetic factors in SSNHL had been largely overlooked in the past, despite sporadic records of familial SSNHL cases (13). In general, genes and variants with autosomal recessive inheritance cause congenital or early onset (prelingual) deafness, whereas genes with autosomal dominant inheritance lead to progressive hearing loss often with delayed onset. However, about one-half of patients with bilateral and about 10 % with unilateral EVA harbor biallelic *SLC26A4* mutations associated with autosomal recessive nonsyndromic deafness or Pendred syndrome (14, 15). These patients may suffer from sudden hearing loss even after minor head trauma (16). This is in contrast with *GJB2* variants, which are typically associated with nonsyndromic autosomal recessive bilateral sensorineural hearing loss with congenital or prelingual onset. The degree of hearing loss in *GJB2* related deafness is variable and depends on specific genotype. In c.35delG deletion, the most frequent pathogenic *GJB2* variant in Caucasians, which was also detected in the presented subject, about 90% of homozygotes demonstrate early onset severe to profound deafness (17).

Reports on episodes of apparently sudden hearing loss in biallelic *GJB2* mutations are scarce with only 6 cases described in the literature (18–21) (Tab. 1). However, half of them were observations from deaf families with several affected family members where genetic etiology of hearing loss could be expected. With one exception (19) they also occurred in association with those *GJB2* variants which generally cause hearing loss of mild to moderate degree, such as c.269T>C, c.235delC and c.109G>A. Additionally, patients homozygous or compound heterozygous for the variant c.109G>A have often delayed hearing loss onset and rarely they may even have normal hearing, which led to past concerns regarding its pathogenicity (22, 23). Moreover, SSNHL episodes in previously published cases did not occur in normal hearing individuals, but as a rapid worsening of previously diagnosed hearing loss. Based on normal auditory behavior in the past, there was no suspicion of hearing loss in the presented subject and thus premorbid audiogram was not available. Similarly, no data are available from neonatal hearing screening (NHS), because she was born in another country, where universal NHS has not yet been established. However, it is assumed that *GJB2* associated deafness is not always congenital and that an early window of functional hearing may exist in some cases before its final deterioration (24). This is also supported by several own observations of children who initially passed NHS and were diagnosed with *GJB2* related deafness later during the

Tab. 1. Causative *GJB2* genotypes detected in association with SSNHL.

Case number	Genotype	Laterality of SSNHL	Age at SSNHL episode	Known HL prior to SSNHL episode	Family history of HL	Resource
1	c.35delG/c.269T>C	N/A	adolescence	yes	familial	Janecke et al (18)
2	c.35delG/c.269T>C	unilateral	13 years	yes	familial	Janecke et al (18)
3	c.35delG/c.35delG	unilateral	23 years	yes	familial	Kokotas et al (19)
4	c.109G>A/c.109G>A	simultaneous bilateral	6 years	N/A	sporadic	Chen et al (20)
5	c.109G>A/c.109G>A	unilateral	41 years	yes	sporadic	Chen et al (20)
6	235delC/ 235delC	unilateral	N/A	yes	sporadic	Wang et al (21)
7	c.35delG/c.35delG	simultaneous bilateral	10 years	no	sporadic	this paper

prelingual period (unpublished data). Thus the presented case may represent an example of extremely extended functional window. Her clinical manifestation clearly fulfilled the diagnostic criteria for SSNHL and without genetic testing, it would be classified into the idiopathic subgroup. Mechanisms leading to these extreme but also rare phenotypes are not yet fully understood. It is hypothesized that overexpression of *GJB6* (connexin 30) or presence of modifier genes may at least partially explain this phenomenon (21).

Conclusion

SSNHL is a rare condition in pediatric population. Bilateral cases may be regarded as extremely rare and require extensive diagnostic workup as they may represent the first symptom of potentially life-threatening underlying disease. We provide further evidence, that SSNHL may be associated with genetic etiology and that genetic testing should be considered in diagnostic protocol for bilateral SSNHL. Moreover, this is the first report of simultaneous bilateral SSNHL in postlingual period in a presumably normal hearing subject homozygous for c.35delG deletion in *GJB2* gene which extends the knowledge on phenotypes in this most frequently affected deafness gene.

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