Auris Nasus Larynx xxx (xxxx) xxx

Contents lists available at ScienceDirect

Auris Nasus Larynx

journal homepage: www.elsevier.com/locate/anl

Case Report

HDR syndrome, detected in the neonatal period by newborn hearing screening

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ARTICLE INFO

Article history:
Received 2 August 2023
Accepted 21 August 2023
Available online xxx

Keywords:
HDR syndrome
Newborn hearing screening
Congenital hearing loss
Auditory brainstem response
Hypoparathyroidism
Autosomal dominant disorder

ABSTRACT

Hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome is an autosomal dominant disorder. Because HDR syndrome is caused by haploinsufficiency in GATA3, it exhibits variation in the onset and progression of hearing loss. In previous reports, the automated auditory brainstem response (AABR) was considered insufficient to detect sensorineural hearing loss caused by HDR syndrome. We report a case of HDR syndrome whose congenital hearing loss was detected by newborn hearing screening (NHS) using AABR. In this case, HDR syndrome was suspected due to hearing loss, hypocalcemia, and her family history. Genetic testing confirmed the diagnosis of HDR syndrome at 5 months of age. Because the phenotype of hearing loss due to HDR syndrome is variable and includes progressive hearing loss, these cases may not be detected by the HNS. However, most of the previous reports were published before the NHS became common and given the frequency of hearing loss complications in HDR syndrome. We consider that there is a reasonable number of HDR syndrome cases with abnormalities on the NHS. We believe that the NHS may also be useful for early detection of hearing loss due to HDR syndrome.

1. Introduction

Hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome is a rare autosomal dominant disorder first reported by Bilous et al [1]. This disorder is known to be primarily caused by the haploinsufficiency of the zinc-finger transcription factor GATA 3 gene, located on chromosome 10p15 [2]. GATA3 plays an important role in the development of the parathyroid gland, inner ear, kidney, thymus gland, and central nervous system during embryonic development [3].

Sensorineural hearing loss associated with HDR syndrome is often reported as bilateral, moderate to severe high-frequency deafness [4]. Because this disorder is caused by the haploinsufficiency of this gene, the onset and progression of the hearing loss caused by this disorder varies [1,4–6]. Despite the potential risk of congenital hearing loss, there are few detailed reports on the hearing outcome of patients with HDR syndrome from infancy. In addition, newborn hearing screening (NHS), using the automated auditory brainstem response (AABR), has been reported to be inadequate for detecting sensorineural hearing loss due to HDR syndrome because the results are often normal [7,8].

We reported a case of HDR syndrome with bilateral sensorineural hearing loss suspected by NHS using AABR. This is a valuable case of HDR syndrome diagnosed in infancy

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https://doi.org/10.1016/j.anl.2023.08.007

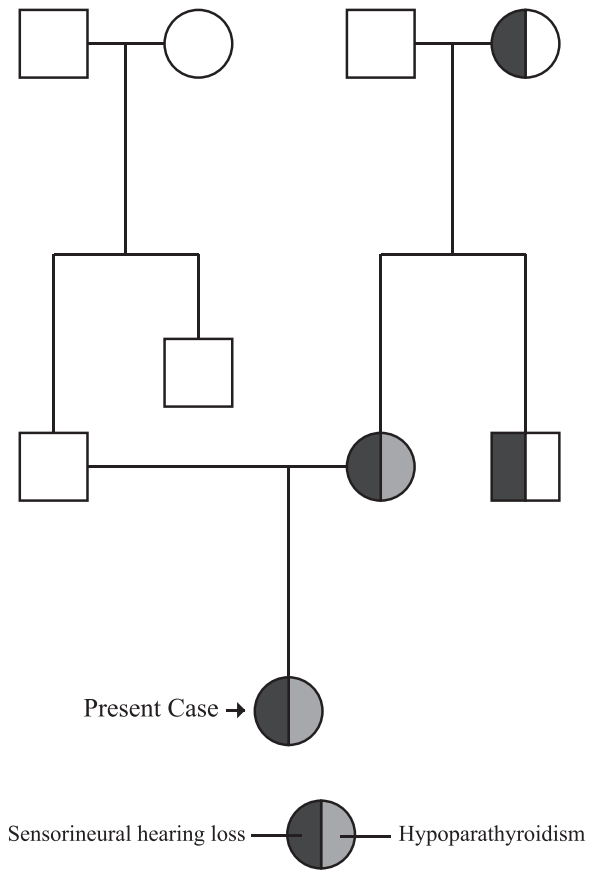

Fig. 1. The family tree for the present case (indicated by the arrow). The three-generation family tree shows family members and ancestors. Females are represented by circles and males by squares. Individuals occurred with sensorineural hearing loss and hypoparathyroidism are indicated.

based on NHS results, hypocalcemia, and family history, and treated early with calcium supplementation and hearing aids. It suggests that there is a reasonable number of HDR syndromes that show abnormalities in the NHS.

2. Case report

A 24-day-old girl consulted by pediatrician for NHS abnormality and hypoparathyroidism. She was born by natural childbirth at 38 weeks gestation, with a birth weight of 3026 g. Her mother had bilateral hearing loss and used hearing aids since adolescence. She had also been treated for idiopathic hypoparathyroidism prior to pregnancy. Her maternal uncle had also been treated for hypoparathyroidism (Fig. 1).

At 3-day-old, NHS was performed using AABR. The results of NHS were REFER in both ears. Based on her family history, at 4-day-old, a blood examination showed hypocalcemia with Ca 6.1 mg/dL and P 8.6 mg/dL (reference values at 0 months were Ca 9.0–11.0 mg/dL and P 5.0–7.7 mg/dL). However, she was asymptomatic, without tetany or convulsive seizures associated with hypocalcemia, and was started on calcium gluconate hydrate and alfacalcidol. At 7-day-old, intact PTH level was as low as 7 pg/ml and idiopathic hypoparathyroidism was diagnosed.

At 24-day-old, she was referred to our hospital for definitive diagnosis. The maternal family history suggested the possibility of HDR syndrome. To determine a definitive diagnosis, ultrasound examination, auditory brainstem response (ABR) and genetic analysis were performed. Genetic analysis was offered to her mother as well, but she did not want it and it was not performed. Ultrasound examination of the urogenital organs revealed no obvious morphological abnormalities. ABR revealed moderate to severe bilateral sensorineural hearing loss, with a wave V threshold of 70 dB HL in the right side ear and 60 dB HL in the left side ear. Next-generation sequencing identified a heterozygous GATA3 mutation, splice donor site mutation (c.1050+1G>A). At 5-month-old, from these results, she was diagnosed with HDR syndrome.

At 6-month-old, conditioned orientation response audiometry (COR) was performed. The average binaural hearing level tested by COR was 73.4 dB HL (Fig. 2). Based on the results of the COR and ABR, she started wearing hearing aids. The average COR threshold with hearing aids at 12 months of age was 40 dB HL, and the functional gain was approximately 30 dB (Fig. 3).

At 1-year-old, temporal bone computed tomography (CT) revealed no morphological abnormalities in either ear. Genetic analysis of the congenital hearing loss did not detect any mutations. Oral alfacalcidol was continued for treatment of hypoparathyroidism. At 1 year and 10-months-old, her serum calcium level is stable and within reference range, and there were no developmental abnormalities. Regarding her hearing and speech development, we have evaluated her hearing level and fitted her hearing aids every two months. There is no significant progression of hearing loss and no delay in speech acquisition.

3. Discussion

We presented a case of HDR syndrome whose congenital hearing loss was diagnosed early by newborn hearing screening (NHS) using AABR, and early auditory intervention could be performed. HDR syndrome is a rare autosomal dominant genetic disorder characterized by the triad of hypoparathyroidism, sensorineural hearing loss, and renal dysplasia. This condition is known to be primarily caused by the haploinsufficiency of the GATA 3 gene [2]. Autosomal dominant genetic disorders with haploinsufficiency, such as HDR syndrome, generally present “expression variability” [9]. Therefore, HDR syndrome is phenotypically defined by the triad, the combination of the triad and the severity of symptoms are variable, and plays an important role in the development of the parathyroid gland, inner ear, kidney, thymus gland, and central nervous system during embryonic development [3].

Sensorineural hearing loss is the most common finding in HDR syndrome. It is present in 96% of patients with HDR syndrome. Hypoparathyroidism and renal dysplasia are reported in 93% and 72%, respectively, whereas only 64% of patients with HDR syndrome have the clinical triad [10]. In this case, hearing loss and hypocalcemia were observed. The severity of hypoparathyroidism varies, ranging from asymp-

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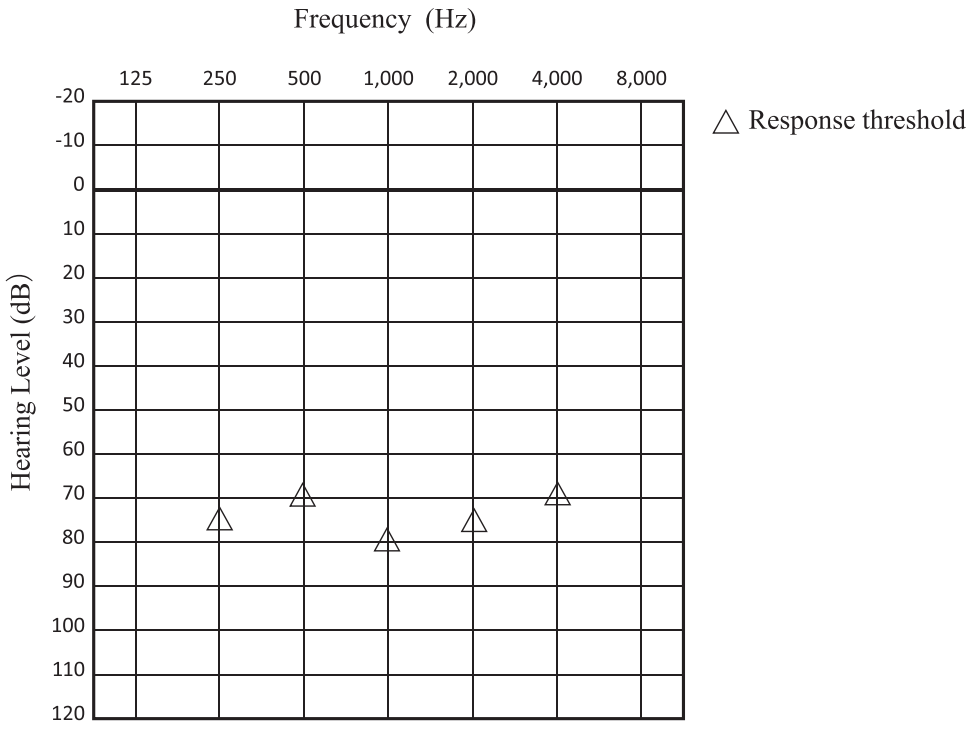

Fig. 2. Conditioned orientation response audiometry in the present case at 6 months of age.

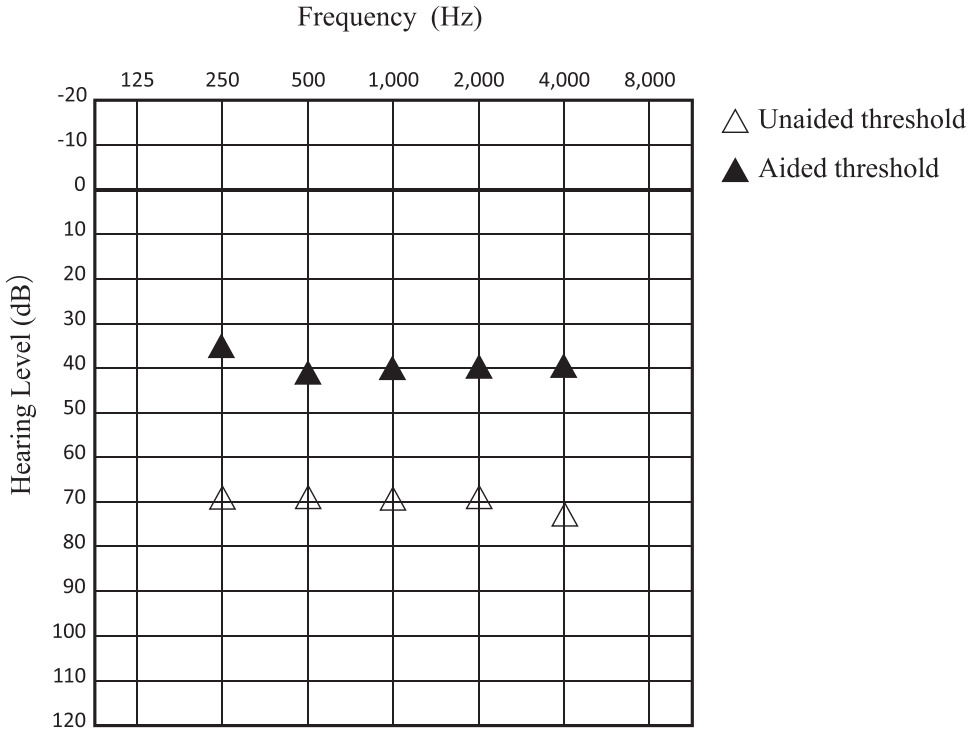

Fig. 3. Conditioned orientation response audiometry in the present case at 12 months of age. outlined; unaided threshold, solid; aided threshold.

tomatic, as in the present case, to with tetany and with convulsive seizures [11]. Renal and urinary tract abnormalities have been reported including hypoplasia, aplasia, cystic kidneys, and vesicoureteral reflux, etc. [12]. In addition, sensorineural hearing loss is relatively often reported to be bilateral [4], and the onset and progression of hearing loss is also expected to be variable.

Several basic studies of hearing loss in HDR syndrome have been reported. Van der Wees et al. investigated the deafness phenotype in heterozygous Gata3 mice [13]. They reported that the cochleae of heterozygous Gata3 mice show significant progressive morphologic degeneration starting with the outer hair cells (OHCs) and eventually affecting all hair cells and supporting cells in the entire cochlea, and that

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Table 1. Summary of phenotypic characteristics, NHS results, and hearing intervention of the present case and previously reported cases with HDL syndrome.

	Present case	Kondo et al. (2019) [5]	Kita et al. (2019) [7]	
			Patient 1	Patient 2
Gender	Female	Female	Female	Male
Age at diagnosis	5 months	11 years	6 years	1year
Hypoparathyroidism	Yes	Yes	Yes	Yes
Renal dysplasia	No	No	Yes	No
Sensorineural hearing loss	Yes	Yes	Yes	No
NHS type	AABR	AABR	AABR	AABR
NHS result	refer/refer	refer/refer	normal	normal
Hearing aids use	Bilateral	Bilateral	unknown	unknown
Age at hearing aids fitting	6 months	2 years	unknown	unknown

AABR; auto auditory brainstem response,NHS; newborn hearing screening.

the deficits in both DPOAE and ABR begin to appear in the first few months of life. Van Looij et al. examined auditory response and hair cell morphology in heterozygous Gata3 knockout mice and wild-type mice [14]. They reported that heterozygous Gata3 knockout mice had an early elevated ABR response threshold, significantly lower DPOAEs, and morphologically, like Van der Wees et al. [13], more rapid degeneration of OHCs in the apex and base of the cochlea compared to wild-type mice.

According to these reports, the sensorineural hearing loss in HDR syndrome may be related to the degeneration of cochlear hair cells. This suggests that hearing loss may not be detected early by ABR and that OAE is more sensitive than ABR. In addition, cochlear hair cell degeneration occurs progressively over time, which may explain why sensorineural hearing loss in HDR syndrome is not only congenital but also includes postnatal progressive hearing loss.

Bilous et al. [1] and Hernandez et al. [6] reported that hearing loss in HDR syndrome is not progressive with age. On the other hand, Van Looij et al. [4] and Kondo et al. [5] reported that hearing loss in HDR syndrome is progressive. Kondo et al. evaluated hearing from age 4 to 12 years of age and reported that hearing loss progressed more rapidly after the age 10 years of age [5]. In the present case, there is no progressive hearing loss at the age of 17 months, but because of the possibility of progressive hearing loss in the future, regular audiometry will be performed.

The efficacy of NHS in detection of HDR syndrome is also controversial. In this case and in the case of Kondo et al. [5], AABR was performed as NHS, and in both cases, it did not pass bilaterally (Table 1). In both case, subsequent testing revealed a moderate hearing loss bilaterally. On the other hand, Kita et al. [6] reported that the auditory brainstem response for newborn hearing screening in two patients with HDR syndrome was normal and concluded that the auditory brainstem response for newborn hearing screening is probably insufficient for the detection of HDR syndrome. However, most previous reports were published before HNS became common and considering the frequency of hearing loss complications in HDR syndrome, it is not uncommon for hearing loss to be detected by HNS in the neonatal period in the future, considering that HDR phenotypes are highly variable.

Even if NHS is normal, continued follow-up may be necessary. In addition, even if HDR is not diagnosed, we believe that ongoing audiologic testing is necessary in cases of hypoparathyroidism and in cases with a family history of HDR. Ongoing follow-up could lead to early hearing detection and intervention for late onset sensorineural hearing loss.

4. Conclusion

In the present case, the sensorineural hearing loss caused by HDR syndrome could be identified by the newborn hearing screening test (AABR), and appropriate auditory intervention could be provided thereafter. However, because HDR syndrome has a variety of phenotypes due to its genetic pathogenesis, continuous hearing evaluation is considered necessary in children with a family history or congenital hypoparathyroidism, even in cases with a normal newborn hearing screening test.

Declaration of Competing Interest

The authors declare no financial relationships or conflict of interest.

Compliance with ethical standards

The authors declare no financial relationships or conflict of interest.

Funding

This work was partially supported by endowed course and funded by endowed grant (J220002008).

Informed consent

Written informed consent was obtained from the patient for publication of this Case report. This study was approved by the Tohoku University Hospital Institutional Review Board (IRB protocol number: 25202) with the requirements of the ethical committee. All the studies were performed in accordance with the guidelines of the Helsinki Declaration (1991).

Acknowledgement

We would like to thank Dai Suzuki, Department of Pediatrics, Tohoku University Graduate School of Medicine for providing significant clinical support.

Authors' contributions

Contributor S.T. and M.A. were responsible for the organization and coordination of this manuscript. All authors took part in writing the manuscript, reviewing it, and editing it. All authors have read and approved the final aspects of this manuscript.

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