High prevalence of inner-ear and/or internal auditory canal malformations in children with unilateral sensorineural hearing loss

Sawako Masuda a,*, Satoko Usui a, Tatsuo Matsunaga b

a Department of Otorhinolaryngology, Institute for Clinical Research, National Mie Hospital, Tsu, Mie, Japan
b Department of Otolaryngology, Laboratory of Auditory Disorders, National Institute of Sensory Organs, National Tokyo Medical Center, Tokyo, Japan

ARTICLE INFO

Article history:
Received 14 August 2012
Received in revised form 29 October 2012
Accepted 3 November 2012
Available online 30 November 2012

Keywords:
Unilateral sensorineural hearing loss
Temporal bone computed tomography
Malformation
Inner ear
Cochlear nerve canal
Internal auditory canal

ABSTRACT

Objective: Radiological and genetic examination has recently advanced for diagnosis of congenital hearing loss. The aim of this study was to elucidate the prevalence of inner-ear and/or internal auditory canal malformations in children with unilateral sensorineural hearing loss (USNHL) for better management of hearing loss and genetic and lifestyle counseling.

Methods: We conducted a retrospective study of charts and temporal bone computed tomography (CT) findings of 69 consecutive patients 0–15 years old with USNHL. In two cases, genetic examination was conducted.

Results: Of these patients, 66.7% had inner-ear and/or internal auditory canal malformations. The prevalence of malformations in infants (age <1 year) was 84.6%, which was significantly higher than that in children 1–15 years old (55.8%; p < 0.01). Almost half of the patients (32; 46.4%) had cochlear nerve canal stenosis; 13 of them had cochlear nerve canal stenosis alone, and in 19 it accompanied other malformations. Internal auditory canal malformations were observed in 22 subjects (31.8%), 14 (20.3%) had cochlear malformations, and 5 (7.2%) had vestibular/semicircular canal malformations. These anomalies were seen only in the affected ear, except in two of five patients with vestibular and/or semicircular canal malformations. Two patients (2.9%) had bilateral enlarged vestibular aqueducts. Mutations were found in SLC26A4 in one of the two patients with bilateral large vestibular aqueducts. The prevalence of a narrow internal auditory canal was significantly higher in subjects with cochlear nerve canal stenosis (50.0%) than in subjects with normal cochlear nerve canals (11.1%; p < 0.01). There were no correlations between the type and number of malformations and hearing level.

Conclusions: The prevalence of inner-ear and/or internal auditory canal malformations detected by high-resolution temporal bone CT in children with USNHL was very high. Radiological and genetic examination provided important information to consider the pathogenesis and management of hearing loss. Temporal bone CT should be recommended to children with USNHL early in life. SLC26A4 mutation also should be examined in cases with bilateral enlarged vestibular aqueduct.

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1. Introduction

Abnormalities of the temporal bone have been associated with congenital sensorineural hearing loss (SNHL) since reported by Mondini in 1791 [1]. However, most cases of congenital SNHL were believed to be caused by abnormalities of the membranous labyrinth that could not be detected by conventional imaging techniques [2,3]. Conventional computed tomography (CT) could identify congenital cochlear malformations such as complete labyrinthine aplasia (Michel deformity), a common cavity, cochlear aplasia/hypoplasia, and incomplete partition [2–4]. Because of improvements in high-resolution CT techniques, previously unrecognized bony abnormalities—including a large vestibular aqueduct, wide and stenotic internal auditory canal (IAC), and cochlear nerve canal (CNC) stenosis—have been reported [3,5]. Currently, abnormalities found by imaging techniques not only provide diagnostic information but also aid in genetic and lifestyle counseling [1] and guide clinicians to better management of hearing loss [6].

The aim of this study was to elucidate the prevalence of inner-ear and/or IAC malformations in children with unilateral SNHL (USNHL).
2. Patients and methods

We conducted a retrospective study of charts and temporal bone CT findings of consecutive USNHL patients 0–15 years old who were seen in the Department of Otorhinolaryngology of National Mie Hospital between January 2008 and December 2011. All procedures were approved by the Ethics Review Committee of National Mie Hospital.

2.1. Subjects

The study included 69 patients. USNHL was defined as a hearing threshold greater than 30 dB hearing level for at least one frequency (500–2000 Hz). Of the 69 patients, 32 were male and 37 were female. Their ages of diagnosis ranged from 0 to 15 years (mean ± 1 SD: 4.3 ± 6.7 years, median: 4 years). The distribution of age was shown in Fig. S1. Twenty-six (37.3% of the subjects) were infants less than 1 year old. Twenty-two children had failed newborn hearing screening (NBHL) in unilateral ear and 21 of them identified USNHL in 1 year of age. One boy who had failed NBHL first visited ENT clinic and diagnosed USNHL at the age of 3 years. There was neither subjects who passed NBHL nor ones who suspected progressive hearing loss before their diagnosis. One subject had Down’s syndrome and one had tetralogy of Fallot. Patients with middle ear diseases and abnormalities, conductive and combined hearing loss revealed by pure-tone audiometry, and obvious acquired hearing loss were excluded from the study.

Supplementary material related to this article, found in the online version, at http://dx.doi.org/10.1016/j.ijporl.2012.11.001.

2.2. Audiometric evaluations

Severity of hearing loss was defined from the pure-tone average as follows: hearing level of 21–40 dB, mild; 41–70 dB, moderate; 71–95 dB, severe; and greater than 95 dB, profound [7]. Pure-tone average was defined as the average hearing threshold at 500, 1000, and 2000 Hz. Thirty-four patients in this study were too young to be examined with pure-tone audiometry initially; for these patients, USNHL was determined on the basis of auditory brainstem response (ABR) and auditory steady state response (ASSR) using an Audera® system (Grason-Stadler). Distortion product otoacoustic emissions (DPOAE) and tympanometry were performed for all subjects.

2.3. Evaluation of temporal bone CT findings

All the patients underwent high-resolution CT of temporal bone using a single-slice helical CT (HiSpeed DX/i, GE Healthcare Japan Ltd., Tokyo Hino, Japan). Contiguous 1 mm-thick sections parallel to the infraorbital line were acquired through the temporal bone, with a field of view of 230 mm, matrix size of 512 × 512, in-plane pixel size of 0.45 mm × 0.45 mm, tube voltage of 120 kV, tube current of 150 mAs and a reconstruction kernel for bone.

CT results for each patient were examined by two otologists who did not know which ear had hearing loss. Classification of inner-ear and IAC malformations was based on Sennaroglu’s classification [4] and modified as follows:

1. Cochlear malformations: Michel deformity, cochlear aplasia, common cavity deformity, cochlear hypoplasia, incomplete partition type I (IP-I); incomplete partition type II (IP-II: Mondini deformity).
2. Vestibular/semicircular canal malformations: absent vestibule, hypoplastic vestibule, dilated vestibule/absent semicircular canal, hypoplastic semicircular canal, enlarged semicircular canal.
3. IAC malformations: absent, narrow, enlarged.
4. Vestibular aqueduct finding: large.
5. CNC finding: stenosis.

We defined IAC as narrow when the diameter at the level of the porous of the IAC was less than 3 mm or 2 mm smaller than the normal side and as wide when greater than 10 mm. A large vestibular aqueduct was defined as being greater than 1.5 mm at the midpoint of the vestibular aqueduct on axial images [8]. The width of the CNC was measured at its midportion. The measurements were manually obtained using calipers [5]. CNC stenosis was defined as when the width was less than 1.5 mm [9]. An example of CNC stenosis in the right ear is shown in Fig. 1.

2.4. Genetic examinations

Patients with large vestibular aqueducts participated in genetic examination. Blood samples were obtained from the proband and his/her parents. DNA was extracted from blood samples using the Gentra Puregene DNA isolation kit (Qiagen, Hamburg, Germany), and primers specific for SLC26A4 (GenBank NG_008489) were designed. Primer sequences for SLC26A4 are listed in Table S1, supporting information. Screening for SLC26A4 mutations was performed by bidirectional sequencing of amplicons generated by PCR amplification of each exon (exons 1–21) and splice sites using an Applied Biosystems 3730 DNA Analyzer (Applied Biosystems, Foster City, CA, USA) and analyzed by SeqScape v2.6 (Applied Biosystems). Examinations were conducted only after written informed consent had been obtained from each individual or parents of the patients.
Supplementary material related to this article found, in the online version, at http://dx.doi.org/10.1016/j.ijporl.2012.11.001.

2.5. Statistical analysis

The significance of the prevalence of the inner-ear and/or IAC malformations between infants younger than 1 year of age and children from 1 to 15 years of age, and the association between the existence of malformations and hearing level was determined by the χ² test.

3. Results

The prevalence of inner-ear and/or IAC malformations is shown in Fig. 2. Of the 69 subjects, 66.7% had malformations. The prevalence of malformations in infants younger than 1 year of age (84.6%) was significantly higher than that in children 1–15 years of age (55.8%; p < 0.01).

Table 1 shows the prevalence of each malformation. The most common anomaly was CNC stenosis of the affected ear, seen in 46.4% of the subjects. Next in frequency were IAC malformations, followed by cochlear malformations and vestibular and/or semicircular canal malformations. These anomalies were seen in the affected ear alone, except for two of five patients with vestibular and/or semicircular canal malformations. Two patients had bilateral enlarged vestibular aqueducts.

The combination of malformations we observed is summarized in Table 2. Of the 69 patients, 13 (18.8%) had CNC stenosis alone, 19 (27.5%) had CNC stenosis accompanied with other malformations, and 4 (5.8%) had narrow IAC alone. Two patients with bilateral enlarged vestibular aqueducts had cochlear or cochlear and vestibular/semicircular canal malformations. In both cases, unilateral hearing loss was found by newborn hearing screening. In one case, a 4-month-old boy, genetic examination identified a compound heterozygous mutation [p.T410M (c.1229C>T)/p.L743X (c.2228T>A)] in SLC26A4 (Fig. S2). p.T410M was previously reported as a missense mutation [10] and p.L743X was previously reported as a nonsense mutation [11]. This nonsense substitution truncates the protein at codon 743, which is 38 amino acids from the end of the protein. This case was confirmed as Pendred syndrome. The hearing loss in his normal hearing ear developed at 1 year of age. In another case, a 2-month-old girl, pathological mutations were not found in SLC26A4. Her hearing level has been stable for 3 years.

Supplementary material related to this article found, in the online version, at http://dx.doi.org/10.1016/j.ijporl.2012.11.001.

Table 2 shows the relationship between CNC malformations and IAC malformations. Of 32 cases of CNC stenosis, 16 (50.0%) were comorbid with narrow IAC. In 36 subjects with normal CNC, 4 (11.1%) had narrow IAC. The prevalence of narrow IAC was significantly higher in subjects with CNC stenosis than in subjects with normal CNC (p < 0.01).

Table 3 shows the combination of malformations and hearing level. There were 6 cases of mild hearing loss, 13 cases of moderate hearing loss, 7 cases of severe hearing loss, and 43 cases of profound hearing loss. DPOAE was absent in the affected ear in all subjects, except for two patients with unilateral profound hearing loss with CNC stenosis and narrow IAC without cochlear/vestibular/semicircular canal malformations. These two patients demonstrated normal responses in DPOAE in both ears. In one of these cases, ABR was performed. The threshold of wave V was 95 dBnHL (normal Hearing Level) in the affected ear and 20 dBnHL in the normal ear. This case was confirmed as unilateral auditory

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Prevalence of each malformation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malformation</td>
<td>Number (prevalence)</td>
</tr>
<tr>
<td>Cochlea</td>
<td>14 (20.3%)</td>
</tr>
<tr>
<td>Cochlear aplasia</td>
<td>0</td>
</tr>
<tr>
<td>Common cavity deformity</td>
<td>2 (2.9%)</td>
</tr>
<tr>
<td>Cochlear hypoplasia</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Incomplete partition (IP-I, IP-II)</td>
<td>11 (15.9%)</td>
</tr>
<tr>
<td>Vestibular/semicircular canal</td>
<td>5* (7.2%)</td>
</tr>
<tr>
<td>Internal auditory canal</td>
<td>22 (31.8%)</td>
</tr>
<tr>
<td>Narrow</td>
<td>20 (29.0%)</td>
</tr>
<tr>
<td>Enlarged</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Absent</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Vestibular aqueduct: enlarged (bilateral)</td>
<td>2 (2.9%)</td>
</tr>
<tr>
<td>Cochlear nerve canal: stenosis</td>
<td>32 (46.4%)</td>
</tr>
</tbody>
</table>

* Two cases had malformation in both ears.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Combination of malformations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination of malformations</td>
<td>Number (percentage)</td>
</tr>
<tr>
<td>CNC stenosis</td>
<td>13 (18.8%)</td>
</tr>
<tr>
<td>CNC stenosis + narrow IAC</td>
<td>10 (14.5%)</td>
</tr>
<tr>
<td>CNC stenosis + narrow IAC + C malformations</td>
<td>5 (7.2%)</td>
</tr>
<tr>
<td>CNC stenosis + narrow IAC + V/SC malformations</td>
<td>1* (1.4%)</td>
</tr>
<tr>
<td>CNC stenosis + C malformations</td>
<td>3 (4.3%)</td>
</tr>
<tr>
<td>Narrow IAC</td>
<td>4 (5.8%)</td>
</tr>
<tr>
<td>Large IAC</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>C malformations</td>
<td>2 (2.9%)</td>
</tr>
<tr>
<td>V/SC malformations</td>
<td>2 (2.9%)</td>
</tr>
<tr>
<td>V/SC malformations</td>
<td>2* (2.9%)</td>
</tr>
<tr>
<td>Large VA + C malformations</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Large VA + C malformations + V/SC malformations</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>CC with absent IAC</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Normal</td>
<td>23 (33.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>69 (100.0)</td>
</tr>
</tbody>
</table>

CNC stenosis, cochlear nerve canal stenosis; IAC, internal auditory canal; C, Cochlear; V/SC, vestibular/semicircular canal; VA, vestibular aqueduct; CC: common cavity.

* This patient had bilateral V/SC malformations.

** One patient had bilateral V/SC malformations.

Fig. 2. Prevalence of inner-ear and/or internal auditory canal malformations found by temporal bone computed tomography.
neuropathy spectrum disorder. There were no correlations between the hearing level and the existence of CNC stenosis, narrow IAC, or other malformations in subjects with absence of DPOAE.

4. Discussion

The data in the present study showed a high prevalence of inner-ear and/or IAC malformations in pediatric USNHL. The prevalence was 84.8% in infants younger than 1 year of age. Most USNHL in these infants was considered as congenital, implying that more than 80% of the congenital USNHL was caused by morphological abnormality accompanied by bony anomalies.

The frequency of reported abnormal temporal bone findings in patients with USNHL varies from 7% to 44% [7]. Song et al. [8] studied CT of 322 children with USNHL and reported that 28.9% had malformations. Simons et al. [7] reported that the prevalence of CT abnormalities was 35% (29 of 83 cases), and the prevalence of magnetic resonance imaging (MRI) abnormalities was 25% (10 of 40 cases) in children with USNHL. However, they did not refer to the CNC.

The size of the CNC was first reported by Fatterpekar et al. in 2000 [5]. They demonstrated that the length and width of the CNC were significantly smaller (p < 0.05) in patients with congenital SNHL who had “normal” findings at thin-section temporal bone CT than in the control group. In 2008, Kono [3] investigated 118 patients without inner-ear malformations among 160 patients with USNHL, and 60% showed a significant difference in the CNC diameters between the affected and unaffected sides. Kono suggested that a diameter of less than 1.7 mm on transverse images or less than 1.8 mm on coronal images was hypoplasia. Stjernholm et al. [12] suggested that if the CNC diameter was less than 1.4 mm, then the possibility of cochlear nerve abnormality should be considered. Recent studies [9,13] demonstrated that CNC stenosis with a diameter of 1.5 mm or less as assessed with CT suggested cochlear nerve deficiency or hypoplasia as assessed with MRI. Wilkins et al. [14] showed a significant correlation between the degree of CNC stenosis and the degree of hearing loss. In the present study with the definition that the diameter was less than 1.5 mm, 46.4% of the subjects had CNC stenosis.

The exact cause of narrow CNC is unclear. Proper development of the IAC requires the presence of a normal cochlear nerve as a stimulus for attaining normal adult dimensions [5]. There is a possibility that the normal development of the CNC similarly needs the nerve for stimulus [5,15]. Fatterpekar et al. [5] speculated that, in patients with abnormality involving the membranous labyrinth, inhibition of the normal trophic effects of nerve growth factors owing to a diminutive cochlear nerve results in a small CNC. That is to say, hypoplasia of the CNC might be secondary to a hypoplasic cochlear nerve associated with some abnormality of a membranous labyrinth that could not be detected by current imaging techniques [3]. Very few of our subjects demonstrated a positive response in DPOAE, suggesting that at least the outer hair cells were affected or may not exist in most patients with USNHL.

The abnormalities found by imaging techniques provide information for diagnosis, management of hearing loss, and genetic and lifestyle counseling [1,6]. Congenital malformed inner ears may be associated with cerebrospinal fluid leakage, and thus development of meningitis is a very rare possibility. Parents of children with inner-ear anomalies should be informed of the early symptoms and signs of meningitis. Consideration also should be given to immunization against common organisms implicated in meningitis [16]. Genetic examination should be recommended for patients with enlarged vestibular aqueducts. Pourova et al. [17] recommend performing SLC26A4 mutation analysis, following GJB2 analysis, in all hearing loss patients with bilateral enlarged vestibular aqueduct and/or associated hearing deficiency. They also mentioned that it is not reasonable to test the SLC26A4 gene in children with sporadic deafness without knowledge of their temporal bone CT/MRI images or even with its normal result. Mutations in the SLC26A4 are responsible for Pendred syndrome [18] as well as DFNB4 (non-syndromic hearing loss with inner ear abnormalities—enlarged vestibular aqueduct and/or Mondini deformity) [19]. Pendred syndrome and bilateral enlarged vestibular aqueduct correlates with the presence of two mutant alleles of SLC26A4 [17,20,21]. Hearing loss in most patients with SLC26A4 mutations fluctuates and is progressive [22]. Mutations in SLC26A4 indicate the necessity for careful management of hearing and comorbidities, such as goiter.

The lack of MRI examination is one of the limitations in the present study. The results suggest the importance of temporal bone CT. Nevertheless, the risks of sedation/anesthesia for imaging in infants and young children, or indeed the radiation risk should be considered. The ideal imaging algorithm in children with unilateral or asymmetric SNHL is controversial [7]. MRI can detect soft-tissue abnormalities such as cochlear nerve deficiency with normal CNC and IAC. Simons et al. [7] suggested that virtually all children with SNHL should have an imaging study as part of their workup. They prefer high-resolution temporal bone CT as the initial study because of a high prevalence of positive findings and less cumbersome logistical issues. They also recommended that a negative CT scan should be followed by MRI to rule out SNHL caused by the central nervous system.

There are some other limitations regarding the current study. The first limitation is the diagnosis of SNHL. USNHL was determined on the basis of ABR and ASSR in 34 young patients. Middle-ear diseases and abnormalities were ruled out by CT and tympanometry; however, there is a possibility that some patients had conductive or combined hearing loss. Another limitation concerns the number of subjects. We examined 69 children, however, the evaluations should be need in the larger group.
In conclusion, a high prevalence of inner-ear and/or IAC malformations was detected by high-resolution temporal bone CT in children with USNHL. Radiological and genetic examination provided important information concerning the pathogenesis and management of hearing loss. The results of this study supported the recommendation of temporal bone CT to children with USNHL early in life. Genetic examination of SLC26A4 also should be performed in all cases with bilateral enlarged vestibular aqueduct. The study in the larger group will likely refine the clinical protocol.

Acknowledgment

This research was supported by a Grant-in-Aid for Clinical Research from the National Hospital Organization, Tokyo, Japan.

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