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Cochlear Nerve Deficiency and Associated Clinical Features in Patients With Bilateral and Unilateral Hearing Loss

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Objective: To clarify the prevalence and clinical characteristics of cochlear nerve deficiency (CND) in patients with congenital bilateral and unilateral hearing loss.
Study Design: Retrospective case review.
Setting: Tertiary referral center.
Patients: One hundred fourteen children with bilateral and 56 children with congenital unilateral sensoneural hearing loss.
Main Outcome Measures: Review of medical records, audiologic tests, and imaging studies. Imaging studies were evaluated for the presence or absence of abnormalities in the bony cochlear nerve canal (BCNC), internal auditory canal (IAC), and inner ear.
Results: The prevalence of CND, whether unilateral or bilateral, was much higher in the unilateral than in the bilateral hearing loss group: 50% (28/56) versus 5.3% (6/114). Among the 6 children with bilateral hearing loss and CND, 2 had bilateral BCNC stenosis alone, 2 had bilateral BCNC stenosis and unilateral IAC stenosis, 1 had unilateral BCNC stenosis alone, and 1 had unilateral IAC stenosis alone. All 28 children with unilateral hearing loss and CND had BCNC stenosis, whereas 9 (32.1%) also had concurrent IAC stenosis. Three of the 6 children with CND and bilateral hearing loss and 5 of the 28 children with CND and unilateral hearing loss also had other inner ear abnormalities.
Conclusion: Our results suggest differences in the causes and mechanisms of CND in children with bilateral versus unilateral hearing loss. **Key Words:** Bony cochlear nerve canal—Cochlear nerve deficiency—Computed tomography.

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Diagnostic imaging plays a fundamental role both in identifying the causes of hearing problems and in developing appropriate treatment and support plans for individuals with bilateral and unilateral hearing loss. Recent technical advances have significantly improved the accuracy of computed tomography (CT) and magnetic resonance imaging (MRI) in the diagnosis of cochlear nerve deficiency (CND), a malformation often characterized by stenosis of the bony cochlear nerve canal (BCNC) or internal auditory canal (IAC) (1). CND also refers to cases in which T2-weighted MRI shows an absence of the cochlear nerve or a cochlear nerve with a caliber smaller than that of other nerves within the IAC (2). Although MRI is better suited for tracking nerve fibers (3,4), the evaluation time is much longer, which, for children, necessitates deep sedation. Thus, the initial diagnosis of CND remains mostly based on CT findings and is later confirmed using MRI.

According to the findings of recent imaging research, CND is the most common cause of congenital unilateral deafness (2). It occurs less frequently in people with bilateral hearing loss than in those with unilateral hearing loss, but the true prevalence in the former is unknown (2). CND is thought to develop against a background of congenital hypoplasia or postnatal degeneration of the cochlear nerve (2), although the underlying causes and mechanisms remain largely undetermined. However, it has been established that CND involves cochlear nerve damage. Consequently, hearing aids and cochlear implants are thought to be less effective to ameliorate hearing loss in individuals with CND than in those with sensorineural hearing loss without CND (3,5,6). Nonetheless, the benefits of cochlear implants for CND patients with small (but not absent) cochlear nerves have been reported in several studies (5).

In the present work, the CT findings of children with congenital bilateral and unilateral hearing loss were retrospectively reviewed to determine the prevalence of CND and the associated clinical features.

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The authors disclose no conflicts of interest.

MATERIALS AND METHODS

Subjects

This study consisted of 170 children with congenital sensorineural hearing loss who underwent temporal bone CT scanning from January 2009 to March 2011 at the Otorhinolaryngology Department of Chiba Children's Hospital, Chiba, Japan. The study population included children diagnosed with hearing loss either during the study period or those diagnosed with hearing loss before it but undergoing CT imaging for the first time during the study. Hearing loss was either bilateral (114/170) or unilateral (56/170). The age range for the 67 boys and 47 girls with bilateral hearing loss was 0 to 20 years, with a median age of 6 years. In the unilateral hearing loss group, the age range for the 31 boys and 25 girls was 0 to 13 years, with a median age of 4 years.

Methods

Temporal bone scanning was performed using the LightSpeed VCT 64-slice scanner (GE Medical Systems, Milwaukee, WI, USA) with the following settings: detector configuration, 2 × 0.625 mm; slice thickness, 0.625 mm; field of view, 160 × 160 mm; resolution, 150 mA (60 mAs), 120 kVp; reconstruction matrix, 512 × 512. Coronal images were reconstructed with a slice thickness of 1.0 mm. BCNC stenosis, IAC caliber, and morphologic abnormalities of the inner ear were examined using the SDS Viewer software (TechMatrix, Tokyo, Japan). Diagnostic readings of the CT images were independently performed by 2 pediatric otorhinolaryngologists. For the purposes of this study, BCNC stenosis was defined as a BCNC diameter of 1.5 mm or less (7). IAC stenosis was defined as a maximal IAC diameter in the axial plane of 3 mm or less (8). Stenosis of the BCNC, ICA, or both, was classified as CND. Large vestibular aqueduct, a form of inner ear deformity, was defined as a vestibular aqueduct having a diameter of 1.5 mm or greater at the midpoint of the axial plane (7).

To evaluate hearing functions, auditory brainstem responses (ABRs) and distortion-product otoacoustic emission (DPOAE) tests were conducted, in addition to either pure tone audiometry or conditioned orientation reflex audiometry. The ABR recordings were obtained using Neuropack Sigma (Nihon Koden, Tokyo, Japan) while the children were naturally sleeping or under sedation. Stimulation with click sounds (100-μs duration) was used to measure the wave-V amplitude of the responses. The maximum intensity of the click stimuli was set at 105 dB nHL, with the response categorized as negative if no V waves were elicited by the highest intensity stimuli. DPOAE tests were conducted using the GSI-60 system (Grason-Stadler, Eden Prairie, MN, USA) or EroScan (Maico Diagnostics, Eden Prairie, MN, USA), following a standard setup protocol for both tests. Hearing threshold levels were averaged for frequencies of 0.5, 1.0, 2.0, and 4.0 kHz, and hearing impairment was categorized as mild (20–40 dB), moderate (41–70 dB), severe (71–95 dB), or profound (>95 dB).

The χ^2 test, or Fisher's exact test, was used for statistical analysis. $p < 0.05$ was considered as being statistically significant.

RESULTS

Among the 170 children included in the study, 57 (33.5%) had 1 or more abnormal CT findings. Table 1 summarizes the CT outcomes for subjects with bilateral (114/170) and unilateral (56/170) hearing loss. In the bilateral hearing loss group, 92 children (80.7%) had no detectable CT abnormalities, whereas 22 had bilateral anatomic abnormalities. In the unilateral hearing loss group, 21 (31.4%) children had no CT abnormalities in contrast to 35 children with anatomic abnormalities, either unilaterally or bilaterally. Comparison of the unilateral and bilateral hearing loss groups established that the former had a significantly higher prevalence of BCNC stenosis (p <0.001) and IAC stenosis (p <0.001). The prevalence of CND, either unilateral or bilateral, in this group was 50% (28/56) and, thus, much higher than in the bilateral hearing loss group (5.3%, 6/114). Figure 1 shows the distributions of BCNC and IAC stenosis in association with inner ear abnormalities in children with unilateral and bilateral hearing loss. Ears with CND and bilateral hearing loss had a higher rate (6/12, 50%) of inner ear abnormalities other than CND than those with CND and unilateral hearing loss (5/28, 17.9%). Enlarged vestibular aqueduct was found in 3 children with bilateral hearing loss and 4 children with unilateral hearing loss in the present study (Table 1), but none of the children with CND had enlarged vestibular aqueduct.

TABLE 1. *Abnormal computed tomographic findings of all children in the study*

	Bilateral hearing loss group (n = 114)		Unilateral hearing loss group (n = 56)	
Abnormality	No.	%	No.	%
None	92	80.7 [a]	21	37.5
Small or absent bony cochlear nerve canal	5	4.4	28	50.0 [a]
Small internal auditory canal	3	2.6	9	16.1 [a]
Inner ear abnormality	16	14.0	10	17.9
Enlarged vestibular aqueduct	3	2.6	4	7.1

[a]Statistically significant ($p < 0.05$).

Table 2 shows the CT findings, audiologic features, and other associated clinical characteristics of the 6 children with bilateral hearing loss who were diagnosed with CND. Bilateral CND was diagnosed in 4 children and unilateral CND in 2. Two children had bilateral BCNC stenosis alone, 2 had bilateral BCNC stenosis and unilateral IAC stenosis, 1 had unilateral BCNC stenosis alone, and 1 had unilateral IAC stenosis alone. Three of these 6 children also had other inner ear bilateral abnormalities. Hearing loss was moderate to severe in CND ears, which also did not respond to ABR. In this group, one of the 7 ears had a positive DPOAE test. None of these 6 children were born prematurely or had a low birth weight. Three (Paients 3, 4, and 5) of the 6 were diagnosed with hearing loss during newborn screening, whereas the clinical histories for the other 3 suggested congenital nonprogressive hearing loss.

Hearing loss was partially compensated by the use of hearing aids in 4 children (Patients 1, 2, 5, and 6). The remaining 2 children were not old enough at the time of this study to be evaluated for the effect of hearing aids. In 2 of the children (Patients 5 and 6) with hearing aids,

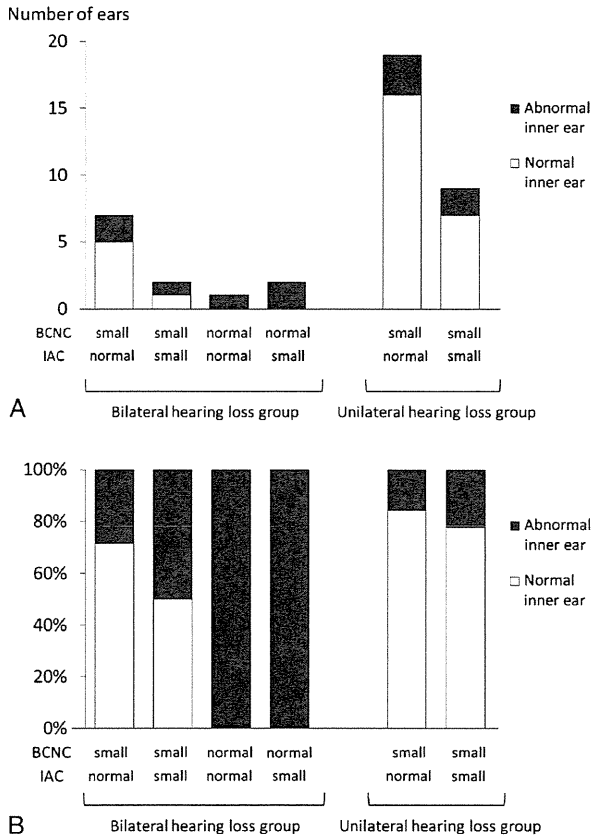

FIG. 1. Cochlear nerve deficiencies (CNDs) and associated inner ear abnormalities other than CND in children with bilateral and unilateral hearing loss group. *A*, The number of ears with normal or abnormal inner ear. *B*, The percentage of ears with normal or abnormal inner ear. CND was defined as a pathologically small BCNC, internal auditory canal (IAC), or both. Ears with (gray) and without (white) associated inner ear abnormalities other than CND are shown. Each ear of the children with bilateral hearing loss was assessed and counted separately because the respective CT findings differed.

effective amplification was achieved using the ear without CND. However, in the other 2 (Patients 1 and 2), the use of hearing aids did not produce the significant results expected from the pure tone test.

Table 3 summarizes the results for the 28 children with unilateral hearing loss who were diagnosed with CND. All of them had BCNC stenosis, including 9 (32.1%) with concurrent IAC stenosis. Five (17.9%) children also had other inner ear anomalies. Hearing loss in those children in whom pure tone audiometry could be performed was moderate to severe, with the ABR threshold ranging from 70 dB nHL to no response at all. DPOAE tests were positive in 1 of 15 ears tested. In the group with unilateral hearing loss, 2 children had an inner ear malformation in the normal-hearing ear, in addition to the ear with hearing loss. One of these children also had BCNC stenosis on the affected side and semicircular canal hypoplasia on the normal-hearing side; the other had bilateral large vestibular aqueducts. Overall, in this group (n = 28), 3 children had an extremely low birth weight (<1,000 g), and 2 children had trisomy 21.

DISCUSSION

In this study, CND was defined as stenosis of the BCNC, IAC, or both, as evaluated on CT scans. Four (3.5%) and 2 (1.8%) of the 114 children with bilateral hearing loss also had bilateral and unilateral CND, respectively. Although Adunka et al. (7) estimated that CND accounted for approximately 1% of newly diagnosed cases of sensorineural hearing loss, our results are consistent with a higher rate.

CND was detected in 50% (28/56) of children with unilateral hearing loss compared with 5.3% (6/114) with bilateral hearing loss. Song et al. (8) reported an IAC stenosis rate of 7% (23/322) in children with unilateral sensorineural hearing loss. MRI studies documented CND in 73% (1) and 60% (9) of children with unilateral hearing loss, indicating that this disorder is the most common type of malformation observed in the setting of congenital unilateral hearing loss. These findings are in agreement with our own observations, in which CND was more prevalent in children in whom congenital hearing loss was unilateral rather than bilateral.

In this study, in accordance with previous reports (8,10), CT abnormalities were significantly more prevalent among children with unilateral hearing loss than among those with bilateral hearing loss (62.5% versus 19.3%, respectively). By contrast, the prevalence of inner ear malformations other than CND did not significantly differ in children with bilateral versus unilateral hearing loss (14.0% and 17.9%, respectively). However, of the children diagnosed with CND, other inner ear malformations were noted in 3 of the 6 with bilateral hearing loss and 5 of the 28 with unilateral hearing loss. Although a statistically significant difference was not determined, because of the small number of participants in this study, additional abnormalities were more often present in those with CND and bilateral rather than unilateral hearing loss. Although the frequent association of CND with inner ear abnormalities other than CND was previously reported (5,10,11), this study is the first to compare the association of CND and other inner ear abnormality against a background of unilateral versus bilateral hearing loss.

Of the 6 children with bilateral hearing loss and CND, two (Patients 4 and 6) underwent brain MRI as part of an evaluation for psychomotor retardation, with subsequent findings of intracranial abnormalities. None of the children with unilateral hearing loss and unilateral CND underwent MRI because of the absence of specific clinical indications. Huang et al. (11) detected intracranial abnormalities in 60.0% and 15.8% of children with bilateral and unilateral CND, respectively. They speculated that bilateral CND is the result of an early developmental insult that affects both the hindbrain and cochlear formation, whereas unilateral CND was attributed to a later, localized insult confined to the cochlear inner hair cells, spiral ganglion,

TABLE 2. *Computed tomographic findings and other clinical features in children with bilateral hearing-impairment and cochlear nerve deficiency*

Subject			Computed tomographic findings			Audiologic findings			
No.	Age	Ear	Bony cochlear nerve canal	Internal auditory canal	Inner ear	Hearing[a]	Auditory brainstem response[b]	Otoacoustic emission	Syndrome/ complication
1	7	Right	**Small**	Normal	Normal	Moderate	NR	Absent	
		Left	**Small**	Normal	Normal	Profound	NR	Present	
2	15	Right	**Small**	Normal	Normal	Moderate	NA	Absent	
		Left	**Small**	Normal	Normal	Severe	NA	Absent	
3	0	Right	**Small**	**Small**	Normal	NA	NR	NA	Trisomy 21
		Left	**Small**	Normal	Normal	NA	NR	NA	
4	0	Right	**Small**	**Small**	**Abnormal**	NA	NR	Absent	Brain abnormality
		Left	**Small**	Normal	**Abnormal**	NA	NR	Absent	
5	4	Right	Normal	Normal	**Abnormal**	Mild	30	Absent	Congenital facial palsy
		Left	**Small**	Normal	**Abnormal**	Moderate	NR	Absent	
6	4	Right	Normal	**Small**	**Abnormal**	Profound	NR	NA	Encephalocele
		Left	Normal	Normal	**Abnormal**	Mild	50	NA	

[a]Hearing, pure-tone audiometry.
[b]Auditory brainstem response thresholds (dBnHL).
NA indicates data not available; NR, no response.

or the cochlear nerve itself. Our results also suggest differences in the causes and mechanisms of CND in children with bilateral and unilateral hearing loss. Future research into the cause and mechanisms of CND will contribute to the development of measures for its treatment and prevention.

TABLE 3. *Computed tmographic findings and other clinical features in children with unilateral hearing-impairment and cochlear nerve deficiency*

Subject			Computed tomographic findings			Audiologic findings			
No.	Age	Ear	Bony cochlear nerve canal	Internal auditory canal	Inner ear	Hearing[a]	Auditory brainstem response[b]	Otoacoustic emission	Syndrome/ complication
1	0	Right	Small	Normal	Normal	NA	90	Absent	
2	0	Left	Small	Normal	Normal	NA	NR	NA	
3	0	Right	Small	Normal	Normal	NA	80	NA	
4	0	Right	Small	Normal	Normal	NA	105	NA	
5	0	Right	Small	Normal	Normal	NA	90	NA	
6	1	Left	Small	Normal	Normal	NA	105	Absent	Trisomy 21
7	1	Left	Small	Normal	Normal	NA	60	Absent	
8	1	Right	Small	Normal	Normal	NA	90	Absent	
9	2	Left	Small	Normal	Normal	NA	105	Absent	Premature birth (963 g)
10	4	Right	Small	Normal	Normal	NA	60	Absent	Trisomy 21
11	5	Left	Small	Normal	Normal	profound	NA	NA	
12	5	Right	Small	Normal	Normal	severe	NA	Absent	
13	6	Left	Small	Normal	Normal	profound	105	NA	
14	6	Left	Small	Normal	Normal	profound	105	Present	
15	10	Left	Small	Normal	Normal	moderate	70	Absent	
16	7	Right	Small	Normal	Normal	moderate	NA	Absent	
17	2	Right	Small	Normal	**Abnormal**	NA	90	NA	
18	2	Right	Small	Normal	**Abnormal**	NA	70	NA	dectylosymphysis
19	6	Left	Small	Normal	**Abnormal**	severe	90	Absent	
20	0	Right	Small	**Small**	Normal	NA	NR	Absent	
21	0	Right	Small	**Small**	Normal	NA	NR	Absent	Premature birth (615 g)
22	0	Right	Small	**Small**	Normal	NA	105	NA	
23	1	Right	Small	**Small**	Normal	NA	70	NA	Premature birth (626 g)
24	3	Right	Small	**Small**	Normal	NA	70	NA	
25	7	Right	Small	**Small**	Normal	profound	NA	NA	
26	8	Right	Small	**Small**	Normal	profound	NA	Absent	
27	0	Right	Small	**Small**	**Abnormal**	NA	105	NA	
28	5	Right	Small	**Small**	**Abnormal**	Profound	70	Absent	

[a]Hearing, pure-tone audiometry.
[b]Auditory brainstem response thresholds (dB nHL).

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

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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.

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).

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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 infraorbitomeatal 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.

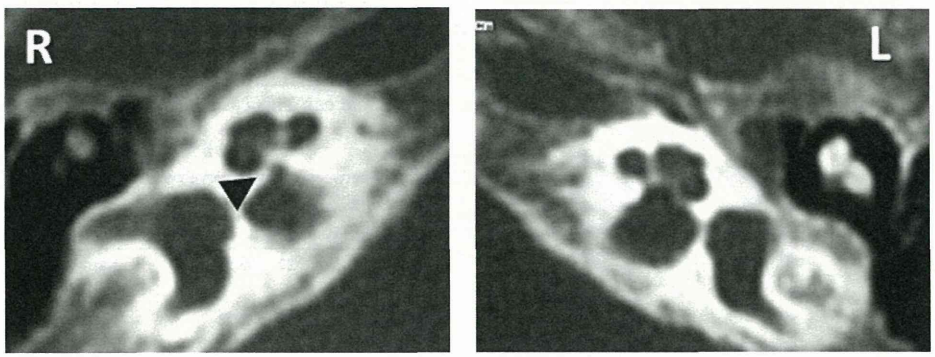

Fig. 1. Cochlear nerve canal stenosis demonstrated by transverse, thin-section CT scan of the temporal bone in three-month old boy. The left panel shows the hearing-impaired right ear (R), and the right panel shows the normal left ear (L). The arrowhead indicates the stenotic cochlear nerve canal in the right ear.

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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 χ^2 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.

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Table 3 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 ($p < 0.01$).

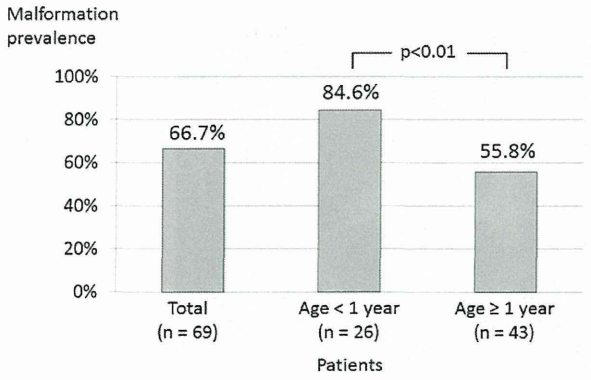

Fig. 2. Prevalence of inner-ear and/or internal auditory canal malformations found by temporal bone computed tomography.

Table 1
Prevalence of each malformation.

Malformation	Number (prevalence)
Cochlea	14 (20.3%)
Cochlear aplasia	0
Common cavity deformity	2 (2.9%)
Cochlear hypoplasia	1 (1.4%)
Incomplete partition (IP-I, IP-II)	11 (15.9%)
Vestibular/semicircular canal	5[a] (7.2%)
Internal auditory canal	22 (31.8%)
Narrow	20 (29.0%)
Enlarged	1 (1.4%)
Absent	1 (1.4%)
Vestibular aqueduct: enlarged (bilateral)	2 (2.9%)
Cochlear nerve canal: stenosis	32 (46.4%)

[a] Two cases had malformation in both ears.

Table 2
Combination of malformations.

Combination of malformations	Number (percentage)
CNC stenosis	13 (18.8)
CNC stenosis + narrow IAC	10 (14.5)
CNC stenosis + narrow IAC + C malformations	5 (7.2)
CNC stenosis + narrow IAC + V/SC malformations	1[a] (1.4)
CNC stenosis + C malformations	3 (4.3)
Narrow IAC	4 (5.8)
Large IAC	1 (1.4)
C malformations	2 (2.9)
C/V/SC malformations	2 (2.9)
V/SC malformations	2[b] (2.9)
Large VA + C malformations	1 (1.4)
Large VA + C malformations + V/SC malformations	1 (1.4)
CC with absent IAC	1 (1.4)
Normal	23 (33.3)
Total	69 (100.0)

CNC stenosis, cochlear nerve canal stenosis; IAC, internal auditory canal; C, Cochlear; V/SC, vestibular/semicircular canal; VA, vestibular aqueduct; CC: common cavity.
[a] This patient had bilateral V/SC malformations.
[b] One patient had bilateral V/SC malformations.

Table 4 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 3
Relationship between cochlear nerve canal malformations and internal auditory canal malformations.

Cochlear nerve canal		Internal auditory canal	
Stenosis	32 (46.4%)	Narrow	16 (50.0%)
		Normal	16 (50.0%)
Normal	36 (52.2%)	Narrow	4 (11.1%)
		Normal	31 (86.1%)
		Large	1 (2.8%)
Absent	1 (1.4%)	Absent	1 (100.0%)

Table 4
Combination of malformations and hearing level.

Cochlear nerve canal stenosis		+				–				Total
Narrow internal auditory canal		+		–		+		–		
Cochlear/vestibular/semicircular canal malformations		+	–	+	–	+	–	+	–	
Hearing level	Mild (21–40 dB)			1			1		4	6
	Moderate (41–70 dB)	1			3		1	4	4	13
	Severe (71–95 dB)	2			1			1	3	7
	Profound (>95 dB)	4[a]	10[b]	2	9		2	4	12	43
Total		7	10	3	13		4	9	23	69

[a] One patient had common cavity with IAC deficiency.
[b] Two patients demonstrated normal distortion product otoacoustic emissions.

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 84.6% 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 with 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 hypoplastic 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 real 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 thyroid impairment. Thy 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.

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