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Hearing and Neurodevelopmental Outcomes among Children with Congenital Cytomegalovirus

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Abstract

Objective: Congenital cytomegalovirus (cCMV) infection is the most common congenital infection and the leading non-genetic cause of sensorineural hearing loss. We assessed demographics, clinical characteristics, hearing and neurodevelopmental outcomes by 6 years of age among U.S. children with possible cCMV.

Study Design: Retrospective cohort design.

Setting: The Audiological and Genetic Database (AudGenDB) includes 175,216 pediatric patients who underwent audiology, otology or genetic visits during 2006–2019 in Children's Hospital of Philadelphia, Vanderbilt Children's Hospital, or Boston Children's Hospital.

Methods: Children with possible cCMV were identified by diagnostic codes for cCMV infection and CMV disease up to 6 years of age. We examined clinical signs of cCMV during 0–45 days of birth and neurodevelopmental conditions (including hearing loss) up to 6 years of age. Hearing loss was defined as pure tone average or any frequency threshold ≥ 25 dB.

Results: A total of 180 (0.1%) children with possible cCMV were identified; 70% had diagnosis codes after 45 days of life. The proportions of Black and Hispanic/Latino children comprised a higher proportion in the possible cCMV group compared to the non-cCMV group. Overall, 129 (72%) children with possible cCMV had diagnoses codes for neurodevelopmental conditions,

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including hearing loss (56), communication delays (45) and cerebral palsy (22). Hearing loss was diagnosed at a median age of 2 (1–4) years.

Conclusion: Neurodevelopmental delays were common among children with possible cCMV included in this study. AudGenDB provides access to longitudinal outcomes for a large and diverse cohort that remains helpful in lieu of state-mandated screenings.

Keywords

Congenital Cytomegalovirus Infection; Sensorineural Hearing Loss; Neurodevelopmental Disorders; Pediatric Audiology; Hearing Loss, Bilateral; Hearing Loss, Unilateral; Neurological Sequelae

Introduction

Congenital cytomegalovirus (cCMV) infection is the most common congenital viral infection and the leading non-genetic cause of sensorineural hearing loss in children in the developed world, accounting for an estimated 5–10% of congenital hearing loss in U.S. children [1]. In the United States, the prevalence of cCMV infection was estimated at 4.6 per 1,000 live births during 2018–2022, with wide variation across states [2]. Nine in ten children with cCMV do not present clinical signs at birth, though 7–11% of those will develop hearing loss (in comparison to 34–41% of those who are symptomatic at birth) [3]. Hearing loss in children with cCMV is typically sensorineural and progressive; children with unilateral loss are at risk of developing bilateral loss.

Children presenting with clinical signs of cCMV at birth are reported to develop long-term neurological sequelae at a proportion of 31–67% [3]. Limited data exist on neurodevelopmental outcomes of children with cCMV, asymptomatic at birth or who only have hearing loss, particularly prior to hearing-targeted screening (i.e. CMV testing of infants who refer on the newborn hearing screening, as mandated by law in some states or implemented by hospital systems) [3]. Early diagnosis and intervention for children with hearing loss is essential to support language development, whereas the diagnosis of cCMV requires testing within 21 days of life [4]. Therefore, hearing-targeted and universal newborn screening for cCMV have been implemented in multiple U.S. states since 2013.

In this study, we assessed demographics, clinical characteristics, and neurodevelopmental outcomes by 6 years of age among children with possible cCMV using diagnoses recorded in medical records from a large, diverse pediatric population, prior to the implementation of newborn cCMV screening strategies in the United States.

Methods

Study Population and Definitions

The Audiological and Genetic Database (AudGenDB) is a large, publicly available, multi-institutional database containing data from U.S. pediatric patients who sought care at Children's Hospital of Philadelphia, Vanderbilt Children's Hospital, and Boston Children's Hospital from 2006 to 2019 including patients with audiology, otology, or genetic visits;

data were not available after 2019 [5]. This database draws information from electronic health records, audiologic testing results, radiology reports, and clinical genetics results. The study population consisted of children with a diagnosis code for cCMV infection or CMV disease by age 6 in the AudGenDB database. Screening for cCMV was not legislated in Massachusetts, Tennessee, or Pennsylvania during 2006–2019, but some hospitals have voluntarily started hearing-targeted screening [6, 7]. Children with cCMV diagnosis in this cohort were likely identified because they exhibited clinical signs, not passing the hearing screening or a diagnosis of hearing loss, or due to a maternal diagnosis of CMV, as reported by another center [8].

Children with possible cCMV were identified by querying the AudGenDB for diagnostic codes up to 6 years of age [Supplemental Table 1]. The diagnosis of cCMV can only be established with laboratory testing of specimens collected within 21 days of life; however, the database lacked laboratory results. We extended the search to children with possible cCMV diagnosis codes up to 6 years of age to assess co-occurrence of diagnoses codes for neurodevelopmental conditions. This age cutoff was based on the 2023 CMV CSTE case definition [9].

We examined clinical signs of cCMV (thrombocytopenia, petechiae, jaundice, hyperbilirubinemia, splenomegaly, hepatomegaly, microcephaly, chorioretinitis, seizure, brain abnormalities) at birth, searching for those diagnosis codes recorded in the first 45 days of birth to allow for delays in coding [Supplemental Table 1]. We also examined prematurity, intrauterine growth restriction, low birth weight, small for gestational age, feeding difficulties, and failure to thrive using diagnostic codes recorded in the first 45 days of birth.

We assessed diagnosis codes for neurologic or neurodevelopmental conditions up to 6 years of age, which included microcephaly, brain imaging abnormalities, seizures, cerebral palsy, chorioretinitis, vision impairment, gross motor abnormalities (including gait and movement abnormality), vestibular dysfunction, communication delays, other development issues, autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD) [Supplemental Table 1].

We used audiologic data from auditory brainstem response (ABR) and behavioral audiograms to assess hearing loss, defined as pure tone average or any frequency threshold ≥ 25 dB HL, excluding those with a type B tympanogram or an air-bone gap ≥ 10 dBn HL at any frequency. The pure tone average was calculated using the average of responses (dB HL) at 500, 1000, 2000, and 4000 Hz. We categorized hearing loss by laterality (unilateral, bilateral) and severity. Hearing levels were categorized as normal when the PTA was ≤ 20 dB HL, and hearing loss severity was categorized as follows: mild (21–45 dB HL), moderate (46–70 dB HL), or severe (≥ 71 dB HL). This categorization was used in the clinical trial of valganciclovir therapy in infants with cCMV disease [10]. The presence of hearing loss without any other cCMV clinical signs at birth was defined as isolated hearing loss. The database also included information on evaluation of speech, cochlear implantation, and hearing amplification. Data on medications, including treatment with ganciclovir or valganciclovir, were not available.

Analyses

We examined demographics (sex, race, and ethnicity) of children with and without possible cCMV. We examined the frequencies of clinical signs (stratified by with cCMV or CMV diagnosis recorded ≤ 45 or >45 days after birth), long-term outcomes (stratified by hearing status), and hearing loss characteristics. We used Pearson χ^2 or Fisher's exact to compare categorical variables and the Kruskal-Wallis test for continuous variables; p-values <0.05 were considered statistically significant. Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The project was reviewed and approved by the CDC Institutional Review Board.

Results

Diagnostic Codes and Demographic Characteristics

Among 175,216 children in the AudGenDB, 180 (0.1%) with possible cCMV were identified, including 75 (42%) children with a diagnosis of cCMV infection, 83 (46%) with CMV disease, and 22 (12%) with both code types. The first code for cCMV infection or CMV disease was recorded within 45 days of life for 54 (30%) children; for 126 (70%) children with first cCMV or CMV diagnosis codes after 45 days of life, the first code was recorded at a median age of 0.6 (IQR: 0.2–2.4) years.

A higher proportion of children were female among those with possible cCMV (48%) as compared to those without (41%) but this difference was not statistically significant ($p=0.0509$) [Table 1]. Among children with possible cCMV, 75 (42%) were White and 55 (31%) were Black; in comparison, among those without possible cCMV, 106,002 (61%) were White, 27,547 (16%) were Black ($p<0.0001$) [Table 1]. When comparing ethnicity, 26 (14%) of children with possible cCMV were Hispanic/Latino, compared to 13,189 (8%) of children without ($p=0.0094$) [Table 1]. Additional characteristics included in Supplemental Tables 2 and 3.

Clinical Characteristics

Among children with possible cCMV, 35 (19%) had cCMV-related clinical signs at birth [Figure 1], 23 (43%) among those with a diagnosis code within 45 days and 12 (10%) among those after 45 days [Table 2]. A total of 145 (81%) children with possible cCMV had no clinical signs recorded within 45 days of birth [Table 2]. Most common cCMV-related signs included thrombocytopenia in 22 (12%) children, jaundice in 14 (8%), and microcephaly in 10 (6%).

Neurodevelopmental and Hearing Outcomes

A total of 129 (72%) children with possible cCMV had one or more neurologic or neurodevelopmental conditions recorded by 6 years of age, including 56 (43%) children with hearing loss. Additional conditions included microcephaly (36, 20%), vision impairment (30, 16%), seizures (25, 14%), communication delays (45, 25%), and ASD (8, 4%) [Table 3].

Overall, 107 (59%) children with possible cCMV had one or more ABR or audiogram visits. Among these 107 children, 14 (13%) had unilateral hearing loss, 42 (39%) had bilateral hearing loss, and 51 (49%) had normal hearing bilaterally. Hearing loss was diagnosed at a median age of 2 (1–4) years. Among 56 (31%) children with hearing loss, 40 (71%) had isolated hearing loss (i.e. no cCMV-related clinical signs at birth) but 25 also had other neurodevelopmental conditions [Table 3]. Among 60 children with one or more audiometric testing for both ears, hearing levels in the poorer-hearing ear showed 22 (37%) children with normal hearing, 16 (27%) mild, 3 (5%) moderate, and 19 (31%) severe loss at the last visit.

Overall, 55 children with possible cCMV had at least two ABR or audiograms with enough data to calculate PTA for both ears at first and last visits. Interval between visits was 112 days (IQR: 63–222 days). Thirty-seven (67%) children had hearing loss at the first visit. This number remained unchanged at the last visit. Of those with hearing loss, at first visit, 13 (35%) children had unilateral hearing loss and 24 (65%) had bilateral loss. By the last visit, 2 additional children developed bilateral loss. Among all 55 children with possible cCMV and at least 2 ABR or audiograms, severity in the poorer hearing ear at last visit showed 18 (33%) normal hearing, 14 (25%) mild HL, 2 (4%) moderate HL, and 21 (38%) severe HL. Ten (6%) of all 180 children with possible cCMV had a cochlear implant, with a median age at first implant of 2 years, and 8 (4%) received a hearing aid, with a median age at first device of 1 year.

Speech Outcomes

Among 86 (48%) children with information on their speech testing, only 14 (16%) had information on the percentage of correct words identified, median of 90% for 12 children with hearing loss (9 bilateral and 3 unilateral; 3 mild, 2 moderate, and 7 severe in the poorer-hearing ear) as compared to 92% for 2 children without hearing loss. The speech awareness threshold (SAT), available for 42 children, was a median of 20dB for 22 children with hearing loss (19 bilateral and 3 unilateral; 8 mild, 1 moderate, and 13 severe in the poorer-hearing ear) and 15dB for 20 children without hearing loss ($p=0.0286$). Communication delays were diagnosed in 23 (41%) of 56 children with hearing loss compared to 22 (18%) of 124 children without hearing loss. None of the children with possible cCMV diagnosis of vestibular dysfunction recorded.

Discussion

In this study, we described hearing and neurodevelopmental outcomes by 6 years of age among children with possible cCMV, i.e. cCMV or CMV diagnosis codes up to 6 years of age, using data from the AudGenDB. This cohort is characterized by either delayed or false-positive cCMV or CMV diagnosis (70% after 45 days of life), a substantial proportion of children with isolated hearing loss (22%), and diagnosis codes for other neurodevelopmental conditions (62%). In total, 31% of children with possible cCMV had hearing loss, which was bilateral in most cases, with a substantial proportion having severe loss in the poorer-hearing ear. Among all children with possible cCMV, 10% underwent cochlear implantation or received hearing amplification. Additionally, a diagnosis code for ASD was recorded in

visits for 4% of children with possible cCMV, compared to 2.8% in the general population [11].

Children in our cohort had a hearing loss diagnosis first recorded at median age 2 years. Access to longitudinal, albeit incomplete follow-up data, allowed us to assess other neurodevelopmental outcomes (microcephaly, brain abnormality, seizures, cerebral palsy, chorioretinitis, vision impairment, hearing loss) included as clinical evidence for classification of cCMV disease as per surveillance case definitions [9]. These were present in 59% of children with possible cCMV and the median age of first recorded diagnosis was 0.8 years. Our findings highlight potential challenges for surveillance. Case classification may not be straightforward, requiring longitudinal data collection for up to 6 years of age (in addition to laboratory testing information).

The relatively high prevalence of communication delays (25%) and other neurodevelopmental conditions (32%) in our cohort is consistent with previous literature that highlights the broad spectrum of neurodevelopmental challenges faced by children with cCMV, including motor, cognitive, and speech delays [3, 12, 13]. Other studies that looked at long-term outcomes found communication delays in ~30–50% and neurodevelopmental delays in ~30–40% of children with cCMV [14, 15]. Communication delays were diagnosed in 18% of children without hearing loss, highlighting a potential link between cCMV and speech even in the absence of hearing loss. Other studies have previously reported a higher rate of speech-language impairment in children with cCMV and no hearing loss, when compared to controls or the general population [12, 15]. In this study, 6% of children received a cochlear implant and 4% received at least one hearing aid. Early intervention for children with hearing loss leads to better speech and communication outcomes [13]. Since hearing loss in this population can develop after birth, the American Academy of Audiology recommends monitoring children with cCMV for the development and progression of hearing loss [16].

This study has several limitations. The retrospective nature of the data, possibility of missing data in the newborn period including newborn hearing screening, and reliance on diagnostic codes, without laboratory records, for identifying possible cCMV cases may have led to underreporting or misclassification. In the absence of universal screening, we likely missed children with asymptomatic. The estimated prevalence of cCMV in the US is 4.6 per 1000 [2] and among the study population, we only identified 1 per 1,000 children with cCMV. We could not validate the use of cCMV infection or CMV disease diagnostic codes for identifying children with cCMV, particularly when recorded after 45 days of life. Prior studies have shown that only 1 in 10 children with CMV-positive laboratory results within 21 days of life receive a diagnostic code for cCMV within 90 days of life [17, 18]. It is unknown if these children could have received a cCMV diagnosis code later if diagnosed with neurodevelopmental conditions.

Additionally, the AudGenDB database, while extensive, may not capture all relevant clinical and audiological details, potentially limiting the generalizability of our findings. Clinical care may have also differed by center, though extensive work was done to validate and standardize information entered into the database. Our study revealed

significant demographic differences between children with possible cCMV and those without, particularly in terms of race and ethnicity (e.g. children with possible cCMV were more likely to be Black and Hispanic/Latino, consistent with previous U.S. studies) [19]. AudGenDB is a convenience sample, limited to children from three tertiary care medical centers in three states, and is therefore not representative of the entire U.S. population. Finally, AudGenDB captured data from children who underwent audiology, otology, or genetic evaluation. Therefore, selection of children with or at risk for hearing loss is likely. However, results of the newborn hearing screening were not included, and some children with hearing loss or who did not pass the newborn hearing screening may not be in the database [20]. Information on the type of tympanometry used, and data on any vestibular tests performed were not available.

Conclusion

This study describes long-term outcomes for a large and diverse U.S. cohort of children with possible cCMV identified prior to more recent state-mandated screenings. AudGenDB demonstrates the potential of using electronic health records data to gather comprehensive and longitudinal data and may be useful to inform ongoing efforts in cCMV surveillance. Information on CMV laboratory testing, including specimen type, timing of specimen collection, and laboratory methods is crucial for accurate classification of cCMV cases according to the surveillance case definitions [9].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

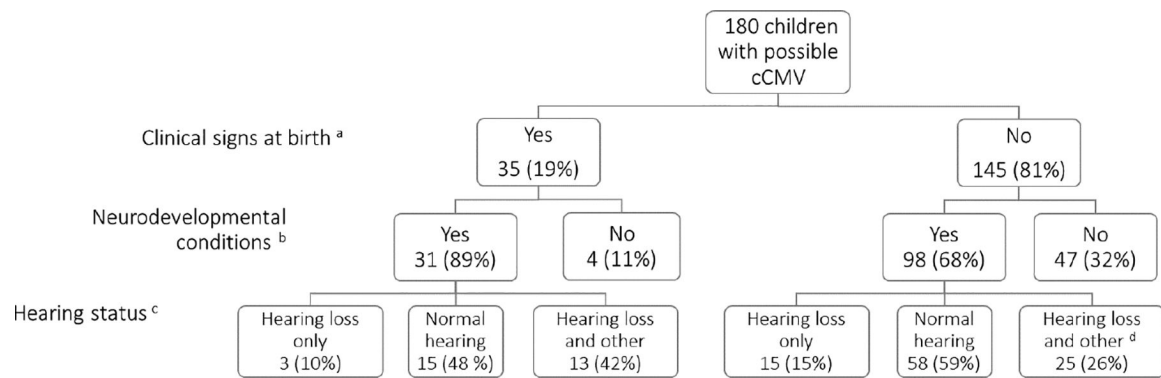
ABR	auditory brainstem response
ADHD	attention deficit hyperactivity disorder
ASD	autism spectrum disorder
AudGenDB	Audiological and Genetic Database
cCMV	congenital cytomegalovirus
CMV	cytomegalovirus
dB	decibel

dBHL	decibel hearing level
IQR	interquartile range
SAT	speech awareness threshold

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**Figure 1.**

Classification Scheme of Possible cCMV Cases, AudGenDB, United States, 2006–2019

Abbreviations: cCMV, congenital CMV

^a Clinical signs of cCMV at birth: thrombocytopenia, petechiae, jaundice, hyperbilirubinemia, splenomegaly, hepatomegaly, microcephaly, chorioretinitis, seizure, brain abnormalities, recorded up to 45 days after birth to allow for delays in coding.

^b Neurologic or neurodevelopmental conditions up to 6 years of age: microcephaly, brain imaging abnormalities, hearing loss, seizures, cerebral palsy, chorioretinitis, vision impairment, gait abnormality, movement abnormality, communication delays, other development conditions, autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD).

^c Hearing loss: pure tone average (PTA) or any frequency threshold ≥ 25 dB, excluding those with a type B tympanogram or an air-bone gap ≥ 10 dB at any frequency based on data from auditory brainstem response (ABR) and behavioral audiograms.

^d Among 40 children with hearing loss and no clinical signs at birth, 15 had neurodevelopmental conditions recorded before, and 10 after hearing loss was recorded.

Table 1.
Demographic Characteristics of Children with and without Possible cCMV in AudGenDB (N= 175,216)

Variables	cCMV case status				p-Value
	Possible cCMV N=180		No cCMV N=175,036		
Sex					0.0509
Female	87	48%	72,039	41%	
Male	93	52%	102,945	59%	
Unknown	0	0%	52	0%	
Race					<0.0001
White	75	42%	106,002	61%	
Black	55	31%	27,547	16%	
Asian	7	4%	5,629	3%	
Native Hawaiian/Other Pacific Islander	1	1%	96	0%	
American Indian/Alaskan Native	0	0%	224	0%	
Other	25	14%	20,075	11%	
Multiple	11	6%	2,274	1%	
Unknown	6	3%	13,189	8%	
Ethnicity					0.0094
Hispanic/Latino	26	14%	13,898	8%	
Not Hispanic/Latino	137	76%	126,774	72%	
Other	0	0%	37	0%	
Unknown	17	9%	34,327	20%	

Table 2.
Clinical Signs within 0–45 Days of Age among Children with Possible cCMV in AudGenDB

Clinical signs within 0–45 days of age	All N=180		First cCMV or CMV diagnosis			
			≤45 days N=54		>45 days N=126	
cCMV-related clinical signs						
Thrombocytopenia	22	12%	16	30%	6	5%
Petechiae	4	2%	3	6%	1	1%
Jaundice	14	8%	8	15%	6	5%
Hyperbilirubinemia	3	2%	1	2%	2	2%
Splenomegaly	2	1%	1	2%	1	1%
Hepatomegaly	1	1%	0	0%	1	1%
Microcephaly	10	6%	8	15%	2	2%
Chorioretinitis	2	1%	2	4%	0	0%
Seizure	0	0%	0	0%	0	0%
Brain abnormalities	6	3%	5	9%	1	1%
Any of above ^a	35	19%	23	43%	12	10%
None reported	145	81%	31	57%	114	90%
Other clinical signs						
Prematurity	13	7%	10	19%	3	2%
Intrauterine growth restriction	11	6%	9	17%	2	2%
Low birth weight	2	1%	2	4%	0	0%
Small for gestational age	6	3%	6	11%	0	0%
Feeding difficulties	6	3%	6	11%	0	0%
Failure to thrive	2	1%	1	2%	1	1%

^a Among 35 possible cCMV cases with cCMV-related signs at birth, 19 (54%) had 1 sign, 7 (20%) had 2 signs, and 9 (26%) had 3 or more signs.

Table 3.
Neurodevelopmental Outcomes within 6 Years of Age among Children with Possible cCMV in AudGenDB

Neurodevelopmental outcomes within 6 years of age	Children with Possible cCMV						
	All N=180			Without Hearing Loss N=124		With Hearing Loss N=56	
	n	%	Age at first diagnosis, years ^a	n	%	n	%
Microcephaly	36	20%	2 (0–3)	27	22%	9	16%
Brain imaging abnormalities	24	13%	2 (0–7)	16	13%	8	14%
Seizures	25	14%	4 (2–8)	17	14%	8	14%
Cerebral Palsy	22	12%	3 (2–6)	13	10%	9	16%
Chorioretinitis	8	4%	0 (0–6)	5	4%	3	5%
Vision impairment	30	16%	2 (0–3)	20	16%	10	18%
Gait abnormality	6	3%	5 (4–8)	1	1%	5	9%
Movement abnormality	9	5%	3 (0–9)	7	6%	2	4%
Communication delays	45	25%	3 (2–4)	22	18%	23	41%
Other developmental issues	57	32%	2 (1–3)	31	25%	26	46%
ASD	8	4%	5 (3–6)	5	4%	3	5%
ADHD	3	2%	7 (5–7)	2	2%	1	2%
Any of the above conditions	111	62%	1 (0–3)	73	59%	38	68%
None of the above conditions	69	38%	NA	51	41%	18	32%

^aMedian (q1-q3)

None with recorded diagnoses of hypotonia or vestibular dysfunction.

A total of 107 (59%) of children had at least one of the permanent conditions included as clinical evidence for classification of cCMV disease (microcephaly, brain abnormality, seizures, cerebral palsy, chorioretinitis, vision impairment, hearing loss) as per surveillance definitions. Median age of first recorded diagnosis was 0.8 years.

Among 56 (31%) children with hearing loss, 40 (71%) had isolated hearing loss (i.e. no cCMV-related clinical signs listed in Table 2 within 0–45 days of birth), but 25 of these children also had other neurodevelopmental outcomes that developed within 6 years of age, 15 recorded before and 10 after the hearing loss diagnosis.

Table 4.

Characteristics of Hearing Loss among Children with Possible cCMV in AudGenDB (Based on ABR or Audiogram)

	≥2 PTAs for both ears N=55 ^b			
	First		Last	
	#	%	#	%
Hearing loss ^a	37	67%	37	67%
Laterality				
Unilateral	13	24%	11	20%
Bilateral	24	44%	26	47%
Severity				
Hearing Level ^c , Poorer Ear				
Normal	18	33%	18	33%
Mild	9	16%	14	25%
Moderate	7	13%	2	4%
Severe	21	38%	21	38%

^aHearing loss defined as pure tone average or a frequency threshold ≥ 25 at any frequency, excluding those with tympanogram type B or an air-bone gap difference of ≥10 at any frequency at the visit, based on ABR or audiogram.

The median (q1, q3) number of audiologic visits was 3 (1–7); 27 (25%) had only 1 visit and 80 (75%) had ≥2 visits.

^bSix children were not included in the hearing loss severity for better/poorer ear because the right and left PTA values were equal.

^cHearing level categorized as normal (0–20 dB), mild (21–45 dB), moderate (46–70 dB), and severe (≥71 dB).