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Short title: Infant Hearing Loss and Vestibular Screening

Conflict of Interest Disclosures (includes financial disclosures): The authors have no conflicts of interest relevant to this article to disclose.

Funding/Support: All phases of this work were supported by the Research Foundation - Flanders (FWO TBM project: T000917N).

Role of Funder/Sponsor (if any): The Research Foundation – Flanders did not interfere with the content of this work.

Clinical Trial Registration (if any): This study was registered at ClinicalTrials.gov (registration number: NCT05061069, https://clinicaltrials.gov/ct2/show/NCT05061069).

Data sharing statement: Deidentified individual participant data will not be made available.

Abbreviations: UNHSP: Universal Newborn Hearing Screening Program; ABR: auditory brainstem responses; CI: cochlear implant; VIS: Vestibular Infant Screening; cVEMP: cervical Vestibular Evoked Myogenic Potentials; SCM: sternocleidomastoid muscle; cCMV: congenital cytomegalovirus; *Cx26*: *Connexin 26*; DFNB: autosomal recessive deafness; TORCHES: toxoplasmosis, other infections such as syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus, and herpes; GEE: Generalized Estimating Equations; OR: Odds ratios; 95% CI: 95% confidence intervals.

Article Summary

This pioneer study reports the results of the first large-scale vestibular screening for hearing-impaired infants, including important risk factors for abnormal screening results.

What's Known on This Subject

Hearing-impaired children are at risk for vestibular deficits due to the close anatomical and embryological relationship between the auditory and vestibular systems. Although vestibular deficits can affect the child's development, pediatric vestibular assessment is not routinely implemented in clinical practice.

What This Study Adds

The Vestibular Infants Screening – Flanders project was a pioneer to implement a vestibular screening for all hearing-impaired infants in Flanders (Belgium). This large-scale study reports results after three years of vestibular screening and identifies risk factors for abnormal screening results.

Contributors' Statement Page

Drs. Martens collected data, coordinated data collection, carried out data analyses, drafted the initial manuscript, and revised the manuscript.

Prof. Dhooge conceptualized and designed the study, collected data, critically reviewed and revised the manuscript, and supervised the Vestibular Infants Screening – Flanders project.

Drs. Dhondt collected data, contributed to interpretation of data analyses, and critically reviewed and revised the manuscript.

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Prof. Maes conceptualized and designed the study, collected data, contributed to interpretation of data analyses, critically reviewed and revised the manuscript, and supervised the Vestibular Infants Screening – Flanders project.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Objectives

Although vestibular deficits are more prevalent in hearing-impaired children and can affect their development on many levels, pediatric vestibular assessment is still uncommon in clinical practice. Since early detection may allow for timely intervention, this pioneer project has implemented a basic vestibular screening test for each six-month-old hearing-impaired infant in Flanders (Belgium). This study aims to report the vestibular screening results over a period of three years and to define the most important risk factors for abnormal vestibular screening results.

Methods

Cervical Vestibular Evoked Myogenic Potentials with bone-conduction were used as vestibular screening tool in all reference centers affiliated to the Universal Newborn Hearing Screening Program in Flanders. From June 2018 until June 2021, 254 infants (mean age: 7.4 months, standard deviation: 2.4 months) with sensorineural hearing loss were included.

Results

Overall, abnormal vestibular screening results were found in 13.8% (35/254) of the infants. The most important group at risk for abnormal vestibular screening results were infants with unilateral or bilateral severe to profound sensorineural hearing loss (20.8%, 32/154) ($p < 0.001$, Odds Ratio = 9.16). Moreover, abnormal vestibular screening results were more prevalent in infants with hearing loss caused by meningitis (66.7%, 2/3), syndromes (28.6%, 8/28), congenital cytomegalovirus infection (20.0%, 8/40), and cochleovestibular anomalies (19.2%, 5/26).

Conclusions

The vestibular screening results in infants with sensorineural hearing loss indicate the highest risk for vestibular deficits in severe to profound hearing loss, and certain underlying etiologies of hearing loss such as meningitis, syndromes, congenital cytomegalovirus and cochleovestibular anomalies.

INTRODUCTION

In 1993, the National Institutes of Health published a consensus statement recommending early identification of hearing impairment in infants.[1] Subsequently, the Joint Committee on Infant Hearing initiated a Universal Newborn Hearing Screening Program (UNHSP), which allowed early detection (i.e. within the first two months of life) and intervention (i.e. before the age of three months) of infants with permanent hearing loss in order to maximize their linguistic competences, communicative skills and literacy development.[2,3] In 1998, Flanders was a pioneer to implement this UNHSP by means of automated auditory brainstem responses (AABR), which was organized by the infant welfare agency of the Flemish government 'Child and Family'. This UNHSP has already proven its benefits, since an increasing number of children and adolescents with hearing aids or cochlear implants (CI) are enrolled in mainstream education.[4] Therefore, UNHSP can prevent hearing-impaired children to fall behind their hearing peers in language, cognition, and social-emotional development, which may improve the child's educational level and professional career in adulthood.[5]

The close anatomical and embryological relationship between the auditory and vestibular end organs suggests that the underlying etiology of hearing loss may also affect vestibular function.[6,7] Accordingly, a higher occurrence of vestibular deficits in children with sensorineural hearing loss in comparison with normal-hearing children was found in literature.[8] Similar to hearing loss, vestibular deficits can affect the child's development on many levels. Whereas a severe vestibular deficit can result in a reduced balance control and a delayed acquisition of gross motor milestones (e.g. head control, independent sitting and walking) in young children,[6,9-17] this can also affect fine motor, writing, reading and learning skills, as well as cognitive and socio-emotional development at a later age.[15,18-24] Nevertheless, a universal

vestibular infant screening program does not exist and pediatric vestibular assessment in clinical practice often remains limited to specific groups such as CI-candidates or older children with vestibular complaints. In June 2018, twenty years after the start of the Flemish UNHSP, Flanders was the first region worldwide to implement a vestibular screening for all six-month-old infants with confirmed permanent hearing loss.[25,26] The Vestibular Infant Screening (VIS) - Flanders project selected cervical Vestibular Evoked Myogenic Potentials (cVEMP) as vestibular screening tool, because it is a child-friendly, brief and objective examination.[27,28] Moreover, it is feasible to introduce this test on a large scale since ABR devices generally also contain cVEMP modules. Several studies have also shown that the results of the cVEMP, which mainly assesses saccular function,[29-31] strongly correlate with the child's motor performance.[9,11,13] Similar to UNHSP, early vestibular screening will enable early detection of vestibular deficits, which can lead to prompt referral for motor assessment and therapy if needed. However, it still remains to be proven that early detection of vestibular deficits results in better functional outcomes.

The purpose of this paper is to report the results after three years of vestibular screening in Flanders, and to identify the most important risk factors for abnormal vestibular screening results in infants with sensorineural hearing loss.

METHODS

Participants

The vestibular screening was offered to all Flemish infants with permanent hearing loss around the age of 6 months in one of the 25 reference centers involved in the UNHSP. As the preliminary VIS-Flanders study showed normal screening results in infants with permanent conductive hearing loss, only infants with sensorineural hearing loss were included.[26] This multicenter cross-sectional study was approved by the leading Ethical Committee of the Ghent University Hospital and the ethical committees of all participating centers (Belgian registration number: B670201835971, ClinicalTrials.gov registration number: NCT05061069). In accordance with the ethical standards of the Helsinki Declaration, written informed consents of parents were obtained.

Vestibular screening procedure

The vestibular screening protocol and its addition to the existing Flemish neonatal hearing screening protocol are reported by Martens et al. (2019, 2020).[25,26] The cVEMP test was performed with the commercial Neuro-Audio equipment (Neurosoft, version 2010, Ivanovo, Russia). Bone-conducted stimuli (RadioEar B71W, Middelfart, Denmark) (59 dB nHL, 129 dB FL) were presented at the ipsilateral mastoid. More details about the applied stimulus parameters, software algorithm, recording parameters, electrode configuration, and test setup can be consulted in Martens et al. (2020).[26] Electromyographic background activity was automatically quantified by the software (i.e. accepted range of mean rectified voltage: 80 – 250 µV) and displayed on a screen[26]. At least two trials were recorded on each side to check waveform reproducibility. The averaged rectified interpeak amplitude was calculated from the two trials with equivalent sternocleidomastoid muscle (SCM) tension (i.e. averaged

electromyographic differences ≤ 30 μV). Only final screening results were used for further analyses. More specifically, if the child needed a retest (i.e. within 3 months after the first screening, thus before the age of 10 months, prior to possible CI-surgery) in order to confirm the first screening results (e.g. in case of inconclusive results, see Martens et al. (2020)), only the second screening results were included.[26] Results were considered as normal if two reproducible biphasic P1-N1 waveforms were recorded with an averaged rectified interpeak amplitude ≥ 1.3 (i.e. based on normative data of the Ghent University Hospital in 34 control subjects (mean age = 7.6 months; SD = 1.5 months)).[26] Abnormal screening results included inconclusive responses (i.e. insufficient SCM tension) during the retest, absent responses (i.e. no reproducible waveforms), and decreased responses (i.e. reproducible waveforms with an averaged rectified interpeak amplitude < 1.3). Since presence and amplitude of cVEMP responses strongly correlate with the child's motor performance,[9,11] these criteria are clinically relevant to decide if referral for motor assessment is needed.

Possible predisposing factors for abnormal vestibular screening results

All centers collected results of transient evoked or distortion product otoacoustic emissions, high frequency tympanometry (1000 Hz), and click-evoked ABR. These results were used to determine possible predisposing factors for abnormal vestibular screening results (i.e. further described as 'risk factors'). The International Bureau of Audiophonology criteria were taken into account to categorize the degree of hearing loss.[32] Onset of hearing loss was grouped as congenital (i.e. abnormal hearing screening after birth) or early-onset (i.e. normal hearing screening after birth, but permanent hearing loss detected before 10 months of age as a cVEMP retest is advised before this age). Additionally, risk factors related to hearing loss etiology included congenital cytomegalovirus (cCMV)-status, results of *Connexin 26* (*Cx26*

or GJB2, autosomal recessive deafness type 1 (DFNB1)) mutation analysis, and the presence of perinatal factors that are associated with an increased risk for hearing loss. Infants with sensorineural hearing loss were standardly tested for cCMV within three weeks after birth by performing virus isolation or polymerase chain reaction (PCR) in urine or saliva, or after this period with PCR on neonatal dried blot spots (i.e. Guthrie card). cCMV definitions were applied as described in the European Consensus Statement of 2017[33]. Perinatal factors were considered as present in case of prematurity (i.e. gestational age < 36 weeks), low birth weight (i.e. birth weight < 2500g),[34] or hospitalization longer than 5 days at neonatal intensive care unit. Other perinatal factors such as hyperbilirubinemia and ototoxic medications were not included as not provided by all centers. All aforementioned risk factors (including *Cx26*- and cCMV-status) were standardly known at the age of screening, whereas more advanced etiological work-up (such as imaging and genetic testing by means of next generation sequencing technology) was not always allowed by the parents, or available at the moment of screening. Therefore, underlying etiology of hearing loss was reported descriptively to estimate the most important groups at risk for abnormal screening results. Etiological work-up results were classified as genetic non-syndromic, genetic syndromic, TORCHES (i.e. toxoplasmosis, other infections such as syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus, and herpes) infections, meningitis, cochleovestibular anomalies (i.e. cochleovestibular nerve aplasia or inner ear malformations confirmed by magnetic resonance imaging or computed tomography that could not be classified into one of the first four categories), or an unknown etiology.

Statistical analysis

Statistical analysis was completed with SPSS software (IBM, version 27.0, Armonk, NY). On

subject level, abnormal screening results indicated abnormal responses in at least one ear, and the degree of hearing loss was categorized according to the worst ear in case of bilateral hearing loss. The two-tailed Fisher's Exact test was used to evaluate the association between screening results and possible predisposing factors. On ear level, data were analyzed more in-depth by means of Generalized Estimating Equations (GEE), which takes the clustered data structure (i.e. two ears within one child) into account and provides a robust estimator of the covariance matrix. Results of etiological work-up of hearing loss were not included as a predictor in order to avoid multicollinearity, and because the underlying etiology was not known in all infants. Included predictors were on ear level (i.e. degree and onset of hearing loss) or on subject level (i.e. gender, laterality of hearing loss, cCMV-status, *Cx26*-status, and presence of perinatal factors). Odds ratios (OR) with 95% confidence intervals (CI) were reported. The significance level (i.e. two-tailed) was set at $p < 0.01$ to correct for multiple testing.

RESULTS

Subjects

Overall, 301 hearing-impaired infants were screened of which 47 infants were excluded (Fig 1). All twenty-two excluded infants with permanent conductive hearing loss showed normal vestibular screening results. In total, 254 infants (i.e. 125 boys, 129 girls) with sensorineural hearing loss were included (i.e. 508 ears). The mean age during the final screening test was 7.4 months (standard deviation = 2.4 months). Table 1 displays the distribution of hearing loss characteristics and etiology. The majority showed unilateral or bilateral severe to profound hearing loss (60.6%, 154/254). Six infants had normal hearing at birth but developed early-onset hearing loss (2.4%, 6/254), in three children it was due to meningitis, and in three children it was caused by cCMV (symptomatic: n = 1; asymptomatic: n = 2). Genetic (i.e. non-syndromic and syndromic) hearing loss was found in 29.9% (76/254) of the infants, whereas 17.0% (43/254) had acquired hearing loss (i.e. TORCHES and meningitis). The majority of TORCHES infections was caused by cCMV (97.5%, 39/40). DFNB1 (*Cx26*) was the leading cause for genetic non-syndromic hearing loss (66.7%, 32/48), followed by DFNB3 (*MYO15A*) (6.3%, 3/48), DFNB16 (*STRC*) (6.3%, 3/48), and DFNB12 (*CDH23*) (4.1%, 2/48). The most common syndromic causes were Waardenburg syndrome (10.7%, 3/28), CHARGE syndrome (7.1%, 2/28), Usher type 1 syndrome (7.1%, 2/28), Usher type 2 syndrome (7.1%, 2/28), Down syndrome (7.1%, 2/28), and Pendred syndrome (7.1%, 2/28).

Vestibular screening results

On subject level, abnormal results were found in 13.8% of the infants (35/254) (Appendix 1). Unilateral abnormal results were found in 8.3% (21/254), whereas bilateral abnormal results were seen in 5.5% (14/254). The latter group contained six infants with bilateral inconclusive

results, in which a bilateral vestibular deficit was confirmed in five infants during vestibular follow-up at a later age (Table 2). Abnormal results were found significantly more often in infants with unilateral or bilateral severe to profound hearing loss (20.8%, 32/154) compared to unilateral or bilateral mild-moderate hearing loss (3.0%, 3/100) ($p < 0.001$) (Fig 2). Moreover, abnormal results were more frequently noticed in early-onset hearing loss (i.e. only caused by meningitis and cCMV) (50.0%, 3/6) compared to congenital hearing loss (12.9%, 32/248) ($p = 0.036$) (Fig 2). cCMV-positive infants more often showed abnormal results (20.5%, 8/39) compared to infants without cCMV (12.6%, 27/215) ($p = 0.207$) (Fig 3). No major differences in screening results were noticed between infants with and without perinatal factors ($p = 0.840$) (Fig 3). In *Cx26*-infants, abnormal results were less common (3.1%, 1/32) compared to infants without *Cx26* (15.3%, 34/222) ($p = 0.095$) (Fig 3). cCMV detection was negative on the Guthrie card of the only *Cx26*-infant with abnormal results. In respect to advanced etiological work-up, most abnormal results were found if the hearing loss was caused by meningitis (66.7%, 2/3), followed by syndromic hearing loss (i.e. especially Usher type 1 and CHARGE syndrome) (28.6%, 8/28), hearing loss caused by TORCHES infections (i.e. only in cases with cCMV) (20.0%, 8/40), and cochleovestibular anomalies (19.2%, 5/26) (Fig 4).

Multivariable model predicting abnormal screening results

On ear level, abnormal vestibular screening results were found in 9.6% (49/508) of the ears (Table 3). More in-depth analysis on ear level by means of GEE-modeling demonstrated that the odds ratios of an abnormal result were only significant for the degree of hearing loss (Table 4). More specifically, the odds of an abnormal result were about 9 times higher ($p < 0.001$, OR = 9.16, 95% CI = [2.75 – 30.58]) for ears with severe to profound hearing loss

compared to the ears with normal hearing, for equal values on the other risk factors. No significantly increased risk ($p = 0.76$, OR = 0.83, 95% CI = [0.25 – 2.80]) was found between ears with mild-moderate hearing loss and normal hearing. In one of the three normal hearing ears with abnormal results, the vestibular screening was normal for the contralateral hearing-impaired ear (i.e. cCMV-positive). Moreover, the odds ratio of an abnormal result was almost 13 times higher but on the border of statistical significance ($p = 0.01$, 95% CI = [1.80 – 89.92]) for the confined group of ears with early-onset hearing loss (i.e. solely caused by cCMV and meningitis) in comparison with congenital hearing loss, for equal values on the other risk factors.

DISCUSSION

This pioneer study aimed to map the occurrence of and to identify the most important risk factors for abnormal vestibular screening results in a large group of infants with congenital or early-onset sensorineural hearing loss. The cVEMP was selected as vestibular screening tool as saccular function is essential for the development of head control and gross motor milestones in young children.[9] Abnormal cVEMP results were found in 14% of all included infants, and in 21% of infants with severe to profound hearing loss, whereas higher percentages of abnormal cVEMP results (i.e. between 17% and 91%) were reported in literature.[6,10,16,35-45] However, various test protocols and cut-off criteria have been used to evaluate cVEMP abnormality in literature, resulting in a wide range of cVEMP abnormalities.[8,25] Additionally, previous studies mainly focused on older children with severe to profound sensorineural hearing loss, and were mostly conducted in specialized CI centers, therefore dealing with a population of children more at risk for vestibular deficits. Since hearing losses with various degrees and etiologies were included in the present study, the results are more representative for the whole group of infants who fail the neonatal hearing screening. As only the cVEMP was used to screen the vestibular function, which only assesses one part of the vestibular system, ongoing longitudinal vestibular research at the Ghent University Hospital will map the sensitivity of the vestibular screening to evaluate the overall vestibular function in hearing-impaired infants.

The current study showed that infants with severe to profound sensorineural hearing loss are the most important group at risk for abnormal cVEMP results, thereby confirming the preliminary VIS-Flanders results.[26] Consistent with these findings, Maes et al. (2014) reported significantly higher cVEMP abnormality rates in children with profound hearing loss

compared to those with non-profound hearing loss.[43] Also the systematic review of Verbecque et al. (2017) concluded that pediatric vestibular loss was reported more frequently with increasing degrees of hearing loss as the auditory and vestibular end organs are closely related.[8] Screening results did not differ significantly according to the laterality of hearing loss, which is supported by previous studies that described vestibular deficits in unilaterally hearing-impaired children.[44,46] In early-onset hearing loss, screening results seemed to be more abnormal compared to congenital hearing loss. However, only six infants with early-onset hearing loss could be included in the current study since infants were screened at an early age. In all infants with early-onset hearing loss, the underlying etiology was meningitis or cCMV, which are two etiologies repeatedly associated with a high risk for vestibular deficits in literature.[42,47-52] Besides cCMV and meningitis, abnormal screening results were noticed more often in infants with syndromic hearing loss, such as Usher type 1 and CHARGE syndrome, and cochleovestibular anomalies, which is in agreement with findings of previous studies and the recent review of Hazen et al. (2020).[42,53-57] No significant odds ratio for abnormal screening results was found in the group of cCMV-positive infants, because the group without cCMV also consisted of infants at risk for vestibular deficits, such as infants with meningitis, syndromic hearing loss and cochleovestibular anomalies. Furthermore, infants with genetic non-syndromic hearing loss were only at risk for abnormal vestibular screening results if the hearing loss was severe to profound (Appendix 1). Similar to the current findings, only a few pediatric cases with genetic non-syndromic hearing loss and concurrent severe vestibular deficits have been described in literature.[10,38,42] However, a major limitation of the current study was that advanced etiological work-up was not performed in all included infants, resulting in a large group of infants with an unknown underlying etiology of hearing loss. Nevertheless, only a minority of the latter group showed

abnormal screening results, which were mostly found in infants with severe to profound hearing loss (Appendix 1). Finally, abnormal screening results occurred approximately equally in hearing-impaired infants with and without perinatal factors. In line with the results of Zagólski et al. (2006), abnormal cVEMP results of hearing-impaired infants with perinatal factors were mainly found in case of severe to profound hearing loss (Appendix 1).[58] Thus, it seems that perinatal factors measured in this study are only relevant in the light of predisposing the infant to hearing loss, as it is the degree of hearing loss that determines the risk for vestibular deficits.

CONCLUSION

This is the first study to report results after three years of vestibular screening in a group of infants with congenital or early-onset sensorineural hearing loss. Based on the current results, the authors highly recommend early vestibular screening for all infants with unilateral or bilateral severe to profound sensorineural hearing loss, and additionally for hearing-impaired infants with meningitis, syndromes, cCMV, and cochleovestibular anomalies. Hereby, vestibular deficits can be detected at a young age, which enables early referral for motor assessment and rehabilitation if needed. Future research should map the sensitivity of the cVEMP as vestibular screening tool in order to fine-tune this vestibular screening protocol.

Acknowledgments

Special thanks go to all participating otorhinolaryngology departments, all members of the project's advisory committee, the infant welfare agency of the Flemish government 'Child and Family', the parent organization 'VLOK-CI', the Federation of Centers for Ambulatory Rehabilitation, and all participating rehabilitation centers and private physiotherapists across Flanders. The Unit of Biostatistics at the Faculty of Medicine and Health Sciences of the Ghent University, especially Dr. Ineke van Gremberghe, is thanked for the professional support during statistical analyses. The authors also would like to thank all infants and their parents who participated in this study.

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Figure 1. Number of screened infants, excluded infants and included study population.

Figure 2. Vestibular screening results according to characteristics of hearing loss (n = 254 infants).

Figure 3. Vestibular screening results according to etiology of hearing loss as standardly known at the age of screening (n = 254 infants).
Abbreviations: cCMV = congenital cytomegalovirus; DFNB = autosomal recessive deafness; *Cx26* = *Connexin 26*.

Figure 4. Vestibular screening results according to advanced etiological work-up of hearing loss (n = 254 infants).
Abbreviations: TORCHES = Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, and Herpes infections.

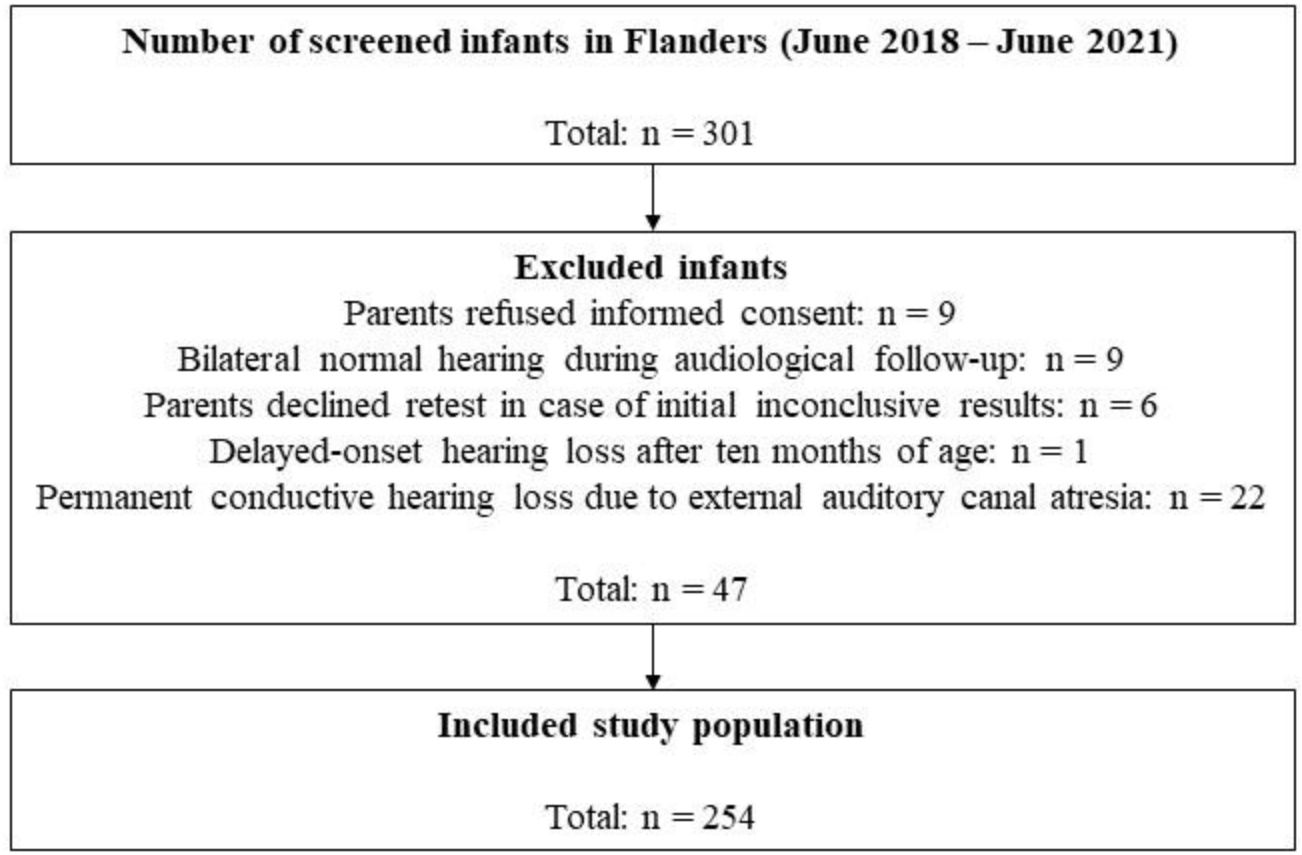
Table 1. Characteristics and etiology of hearing loss (n = 254 infants).

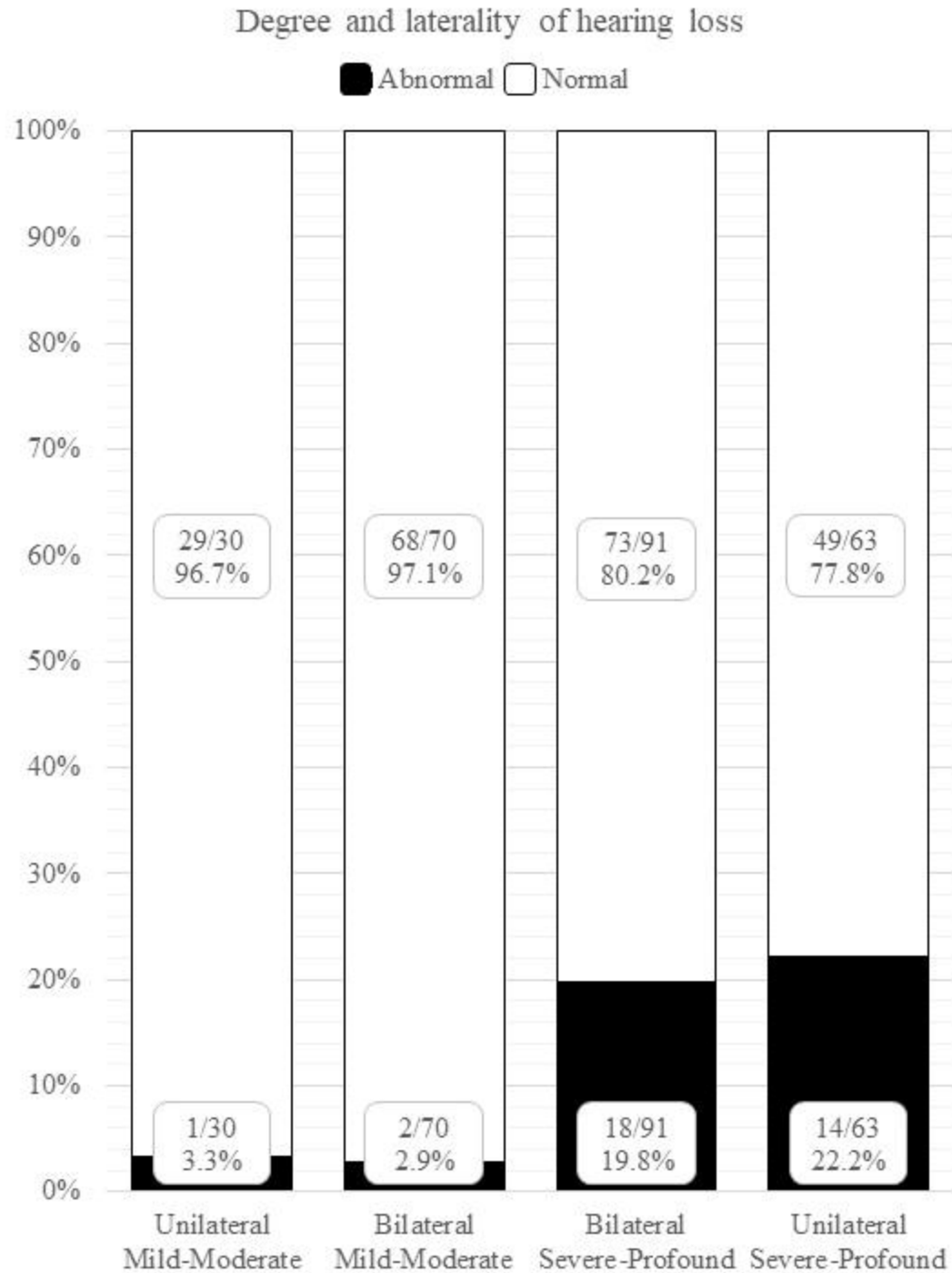
Table 2. Characteristics of infants with inconclusive results during the first and second vestibular screening test (n = 6 infants).

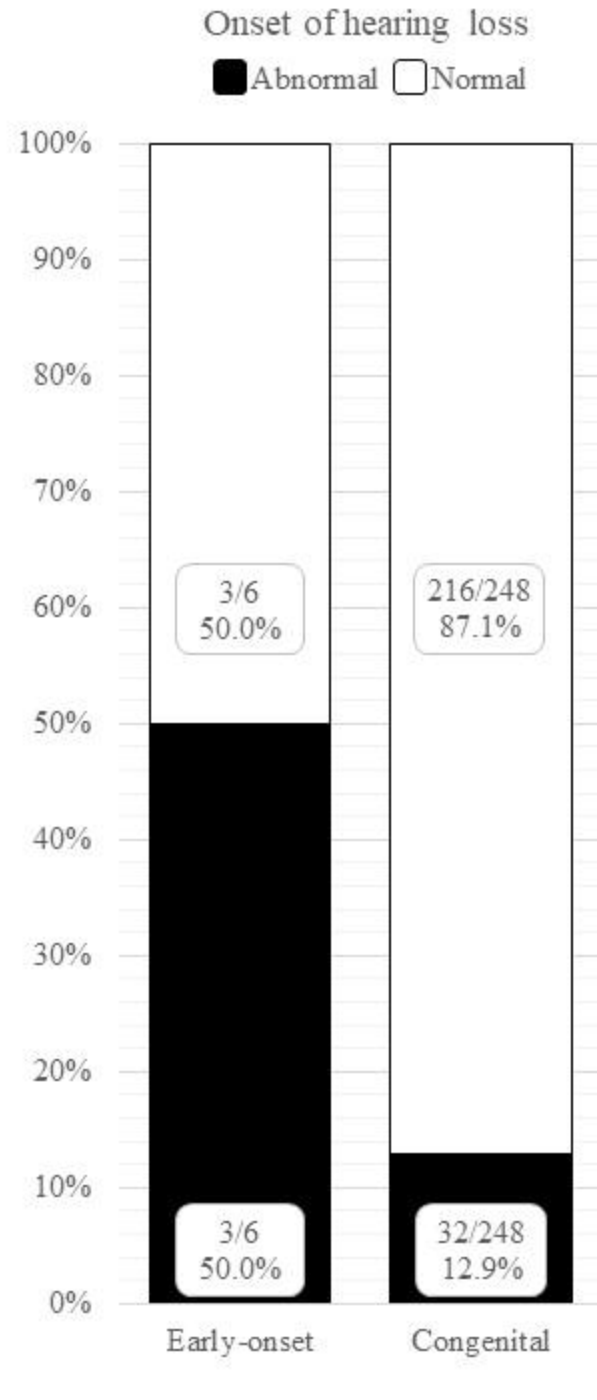
Table 3. Vestibular screening results according to gender, characteristics and etiology of hearing loss (n = 508 ears).

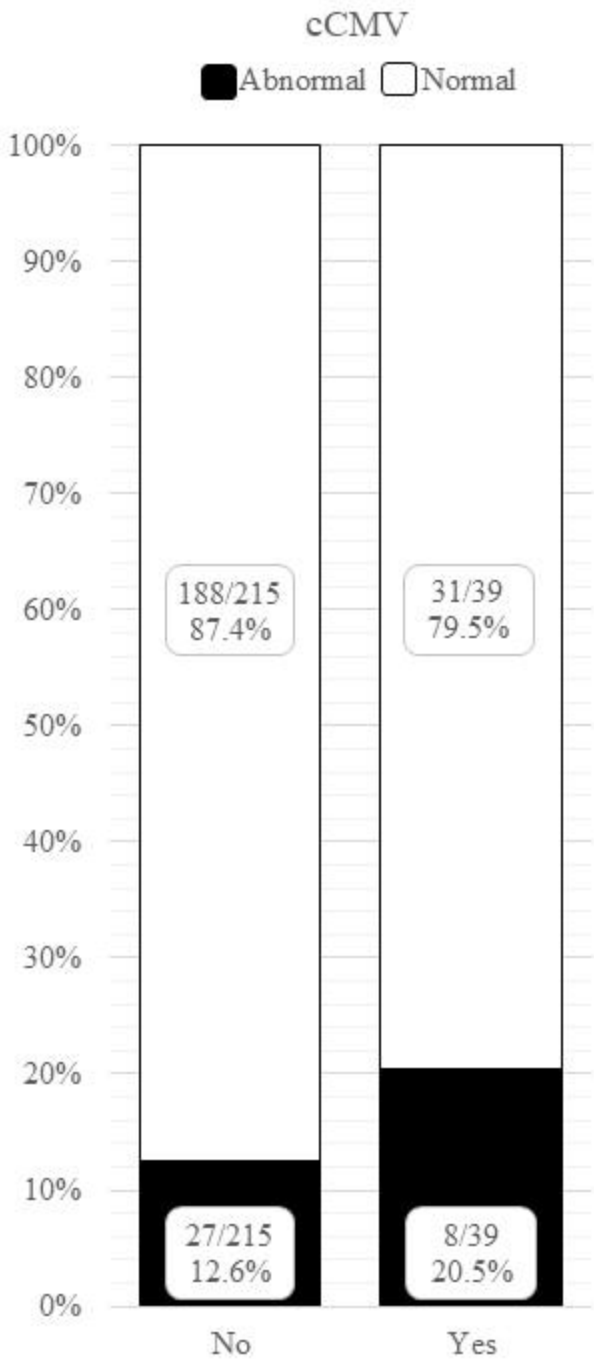
Table 4. Multivariable model predicting abnormal screening results (n = 508 ears).

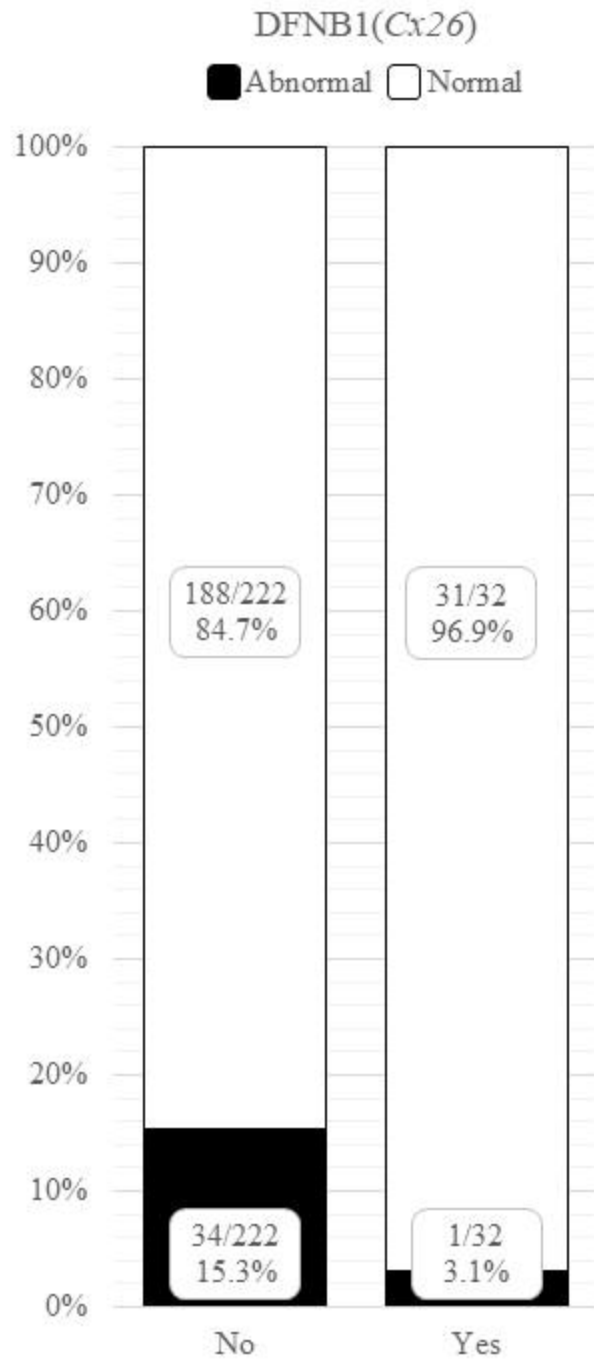
Appendix 1. Overview of all infants with abnormal screening results (n = 35 infants).

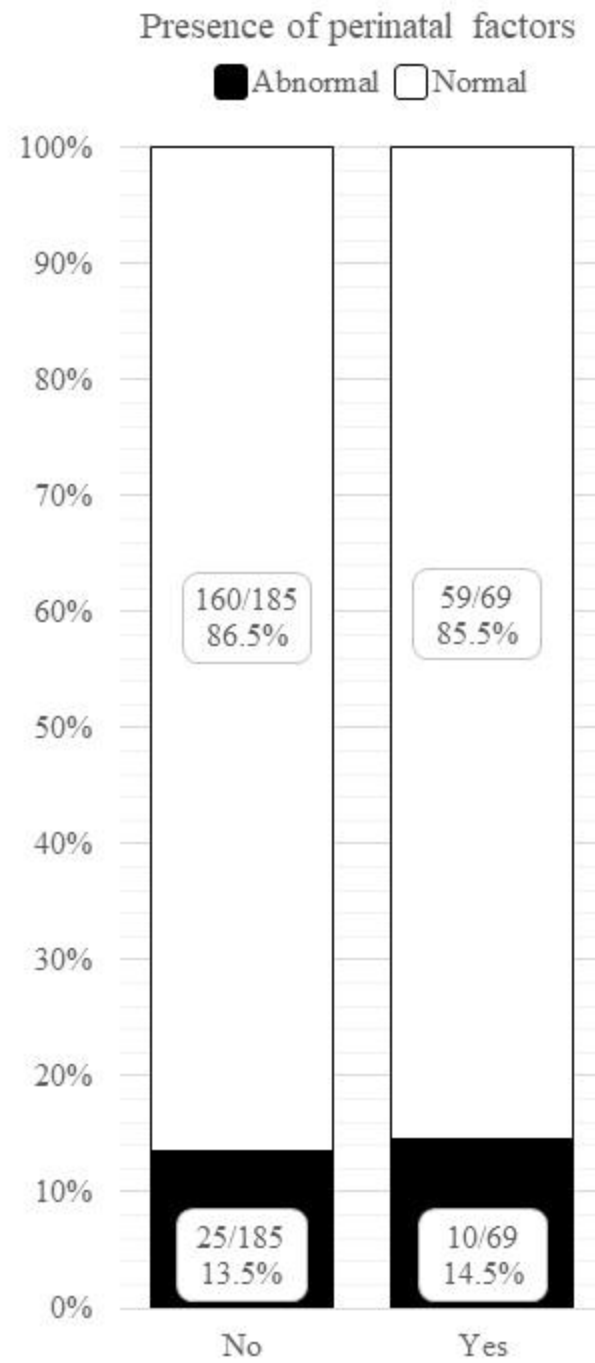

Number of screened infants in Flanders (June 2018 – June 2021)
Total: n = 301
Excluded infants
Parents refused informed consent: n = 9
Bilateral normal hearing during audiological follow-up: n = 9
Parents declined retest in case of initial inconclusive results: n = 6
Delayed-onset hearing loss after ten months of age: n = 1
Permanent conductive hearing loss due to external auditory canal atresia: n = 22
Total: n = 47
Included study population
Total: n = 254

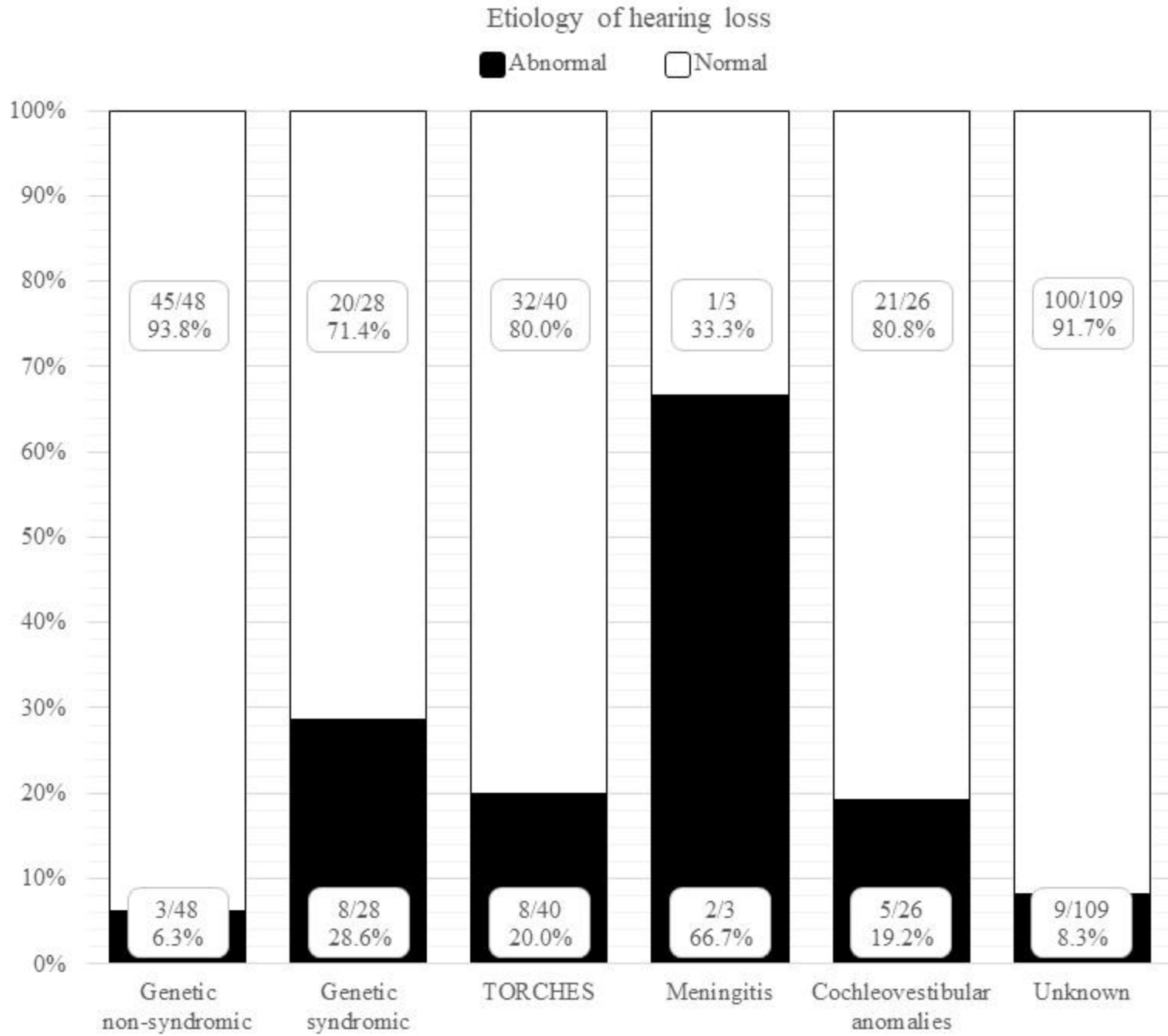

Degree and laterality of hearing loss
Abnormal
Normal
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
29/30
96.7%
68/70
97.1%
73/91
80.2%
49/63
77.8%
1/30
3.3%
2/70
2.9%
18/91
19.8%
14/63
22.2%
Unilateral Mild-Moderate
Bilateral Mild-Moderate
Bilateral Severe-Profound
Unilateral Severe-Profound


Onset of hearing loss
Abnormal
Normal
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
3/6
50.0%
216/248
87.1%
3/6
50.0%
32/248
12.9%
Early-onset
Congenital


cCMV
Abnormal
Normal
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
188/215
87.4%
31/39
79.5%
27/215
12.6%
8/39
20.5%
No
Yes


DFNB1(Cx26)
Abnormal
Normal
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
188/222
84.7%
31/32
96.9%
34/222
15.3%
1/32
3.1%
No
Yes


Presence of perinatal factors
Abnormal
Normal
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
160/185
86.5%
59/69
85.5%
25/185
13.5%
10/69
14.5%
No
Yes


Etiology of hearing loss
Abnormal
Normal
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
45/48
93.8%
20/28
71.4%
32/40
80.0%
1/3
33.3%
21/26
80.8%
100/109
91.7%
3/48
6.3%
8/28
28.6%
8/40
20.0%
2/3
66.7%
5/26
19.2%
9/109
8.3%
Genetic non-syndromic
Genetic syndromic
TORCHES
Meningitis
Cochleovestibular anomalies
Unknown

TABLES

TABLE 1 Characteristics and etiology of hearing loss (n = 254 infants)

Characteristics of hearing loss			
Degree and laterality	Unilateral Mild-Moderate	11.8%	(30/254)
	Bilateral Mild-Moderate	27.6%	(70/254)
	Unilateral Severe-Profound	24.8%	(63/254)
	Bilateral Severe-Profound	35.8%	(91/254)
Onset	Congenital	97.6%	(248/254)
	Early-onset	2.4%	(6/254)
Etiology of hearing loss			
cCMV[1]	No	84.6%	(215/254)
	Yes	15.4%	(39/254)
DFNB1(*Cx26*)[1]	No	87.4%	(222/254)
	Yes	12.6%	(32/254)
Presence of perinatal factors[1]	No	72.8%	(185/254)
	Yes	27.2%	(69/254)
Advanced etiological work-up results	Genetic non-syndromic	18.9%	(48/254)
	Genetic syndromic	11.0%	(28/254)
	TORCHES	15.8%	(40/254)
	Meningitis	1.2%	(3/254)
	Cochleovestibular anomalies	10.2%	(26/254)
	Unknown (cCMV- and *Cx26*-negative)	42.9%	(109/254)

[1]Standardly known at the age of screening.

Abbreviations: cCMV = congenital cytomegalovirus; DFNB = autosomal recessive deafness; *Cx26* = *Connexin 26*; TORCHES = Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, and Herpes infections.

TABLE 2 Characteristics of infants with inconclusive results during the first and second vestibular screening test (n = 6 infants)

	Hearing loss characteristics	Underlying etiology of hearing loss	Vestibular deficit confirmed at later age
1.	Bilateral severe-profound congenital sensorineural	Genetic syndromic (CHARGE syndrome)	Yes
2.	Bilateral severe-profound congenital sensorineural	Genetic non-syndromic (DFNB35)	Yes
3.	Bilateral severe-profound congenital sensorineural	Genetic syndromic (Usher syndrome type 1)	Yes
4.	Bilateral severe-profound congenital sensorineural	TORCHES (cCMV)	Yes
5.	Bilateral severe-profound congenital sensorineural	TORCHES (cCMV)	Yes
6.	Bilateral severe-profound congenital sensorineural	Unknown	No[1]

[1]Parents declined vestibular follow-up as the child had epileptic attacks and motor therapy was already initiated due to severe motor retardation.

Abbreviations: DFNB = autosomal recessive deafness; TORCHES = Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, and Herpes infections; cCMV = congenital cytomegalovirus.

TABLE 3 Vestibular screening results according to gender, characteristics and etiology of hearing loss (n = 508 ears)

		Vestibular screening results			
		Abnormal		Normal	
Gender	Female	10.1%	(26/258)	89.9%	(232/258)
	Male	9.2%	(23/250)	90.8%	(227/250)
Degree of hearing loss	Normal	3.2%	(3/93)	96.8%	(90/93)
	Mild-Moderate	2.1%	(4/191)	97.9%	(187/191)
	Severe-Profound	18.8%	(42/224)	81.2%	(182/224)
Onset of hearing loss	Congenital	9.1%	(45/496)	90.9%	(451/496)
	Early-onset	33.3%	(4/12)	66.7%	(8/12)
Laterality of hearing loss	Unilateral	9.1%	(17/186)	90.9%	(169/186)
	Bilateral	9.9%	(32/322)	90.1%	(290/322)
cCMV[1]	No	8.8%	(38/430)	91.2%	(392/430)
	Yes	14.1%	(11/78)	85.9%	(67/78)
DFNB1(*Cx26*)[1]	No	10.6%	(47/444)	89.4%	(397/444)
	Yes	3.1%	(2/64)	96.9%	(62/64)
Presence of perinatal factors[1]	No	9.2%	(34/370)	90.8%	(336/370)
	Yes	10.9%	(15/138)	89.1%	(123/138)

[1]Standardly known at the age of screening.
Abbreviations: cCMV = congenital cytomegalovirus; DFNB = autosomal recessive deafness; *Cx26 = Connexin 26*.

TABLE 4 Multivariable model predicting abnormal screening results (n = 508 ears)

		OR	95% CI	*p-value*
Gender	Female*			
	Male	0.80	[0.36 - 1.74]	*0.56*
Degree of hearing loss	Normal*			
	Mild-Moderate	0.83	[0.25 - 2.80]	*0.76*
	Severe-Profound	**9.16**	**[2.75 - 30.58]**	***< 0.001***
Onset of hearing loss	Congenital*			
	Early-onset	12.70	[1.80 - 89.92]	*0.01*
Laterality of hearing loss	Unilateral*			
	Bilateral	1.180	[0.51 - 2.69]	*0.70*
cCMV	No*			
	Yes	0.78	[0.27 - 2.27]	*0.65*
DFNB1(*Cx26*)	No*			
	Yes	0.17	[0.02 - 1.42]	*0.10*
Presence of perinatal factors	No*			
	Yes	1.18	[0.51 - 2.70]	*0.70*

*Reference group.
Abbreviations: OR = Odds Ratio; 95% CI = 95% Confidence Interval for OR; cCMV = congenital cytomegalovirus; DFNB = autosomal recessive deafness; *Cx26* = *Connexin 26*.

Appendix 1a Overview of all infants with abnormal screening results (n = 35 infants)

Final screening result	Degree and laterality of hearing loss	Onset of hearing loss	Underlying etiology of hearing loss	Presence of perinatal factors
Bilateral absent	Bilateral severe-profound	Congenital	Genetic syndromic (CHARGE syndrome)	No
Bilateral absent	Bilateral severe-profound	Congenital	Genetic syndromic (Johanson-Blizzard syndrome)	Yes
Bilateral absent	Bilateral severe-profound	Congenital	Genetic syndromic (Usher syndrome type 1)	Yes
Bilateral absent	Bilateral severe-profound	Congenital	Genetic non-syndromic (DFNB1(*Cx26*))	No
Bilateral absent (left) decreased (right)	Unilateral severe-profound (right)	Congenital	TORCHES (cCMV)	No
Bilateral absent (left) decreased (right)	Unilateral mild-moderate (left)	Early-onset	Meningitis	Yes
Bilateral decreased	Bilateral severe-profound	Congenital	Genetic non-syndromic (DFNB3)	No
Bilateral decreased	Bilateral severe-profound	Congenital	Unknown	No
Bilateral inconclusive	Bilateral severe-profound	Congenital	Genetic syndromic (CHARGE syndrome)	No
Bilateral inconclusive	Bilateral severe-profound	Congenital	Genetic non-syndromic (DFNB35)	No
Bilateral inconclusive	Bilateral severe-profound	Congenital	Genetic syndromic (Usher syndrome type 1)	No
Bilateral inconclusive	Bilateral severe-profound	Congenital	TORCHES (cCMV)	No

Abbreviations: DFNB = autosomal recessive deafness; *Cx26* = *Connexin 26*; TORCHES = Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, and Herpes infections; cCMV = congenital cytomegalovirus.

Appendix 1b Overview of all infants with abnormal screening results (n = 35 infants)

Final screening result	Degree and laterality of hearing loss	Onset of hearing loss	Underlying etiology of hearing loss	Presence of perinatal factors
Bilateral inconclusive	Bilateral severe-profound	Congenital	TORCHES (cCMV)	Yes
Bilateral inconclusive	Bilateral severe-profound	Congenital	Unknown	Yes
Unilateral absent (right)	Unilateral severe-profound (right)	Congenital	Genetic syndromic (Duane retraction syndrome)	No
Unilateral absent (left)	Unilateral severe-profound (left)	Early-onset	TORCHES (cCMV)	No
Unilateral absent (right)	Bilateral severe-profound	Congenital	TORCHES (cCMV)	No
Unilateral absent (right)	Unilateral severe-profound (right)	Congenital	TORCHES (cCMV)	No
Unilateral absent (left)	Unilateral severe-profound (left)	Congenital	Cochleovestibular anomalies (left)	Yes
Unilateral absent (left)	Bilateral severe-profound (left) mild-moderate (right)	Congenital	Bilateral cochleovestibular anomalies	Yes
Unilateral absent (right)	Unilateral severe-profound (right)	Congenital	Cochleovestibular anomalies (right)	No
Unilateral absent (left)	Unilateral severe-profound (left)	Congenital	Unknown	No
Unilateral absent (right)	Unilateral severe-profound (right)	Congenital	Unknown	Yes
Unilateral absent (right)	Unilateral severe-profound (right)	Congenital	Unknown	No

Abbreviations: DFNB = autosomal recessive deafness; *Cx26* = *Connexin 26*; TORCHES = Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, and Herpes infections; cCMV = congenital cytomegalovirus.

Appendix 1c Overview of all infants with abnormal screening results (n = 35 infants)

Final screening result	Degree and laterality of hearing loss	Onset of hearing loss	Underlying etiology of hearing loss	Presence of perinatal factors
Unilateral decreased (right)	Bilateral severe-profound (right) mild-moderate (left)	Congenital	Genetic syndromic (Feingold syndrome type 2)	Yes
Unilateral decreased (right)	Bilateral severe-profound (right) mild-moderate (left)	Congenital	Genetic syndromic (Down syndrome)	No
Unilateral decreased (left)	Unilateral severe-profound (left)	Congenital	TORCHES (cCMV)	No
Unilateral decreased (left)	Unilateral severe-profound (right)	Congenital	TORCHES (cCMV)	No
Unilateral decreased (right)	Bilateral severe-profound (left) mild-moderate (right)	Early-onset	Meningitis	No
Unilateral decreased (right)	Bilateral severe-profound	Congenital	Bilateral cochleovestibular anomalies	No
Unilateral decreased (right)	Unilateral severe-profound (right)	Congenital	Cochleovestibular anomalies (right)	No
Unilateral decreased (right)	Unilateral severe-profound (right)	Congenital	Unknown	No
Unilateral decreased (left)	Unilateral severe-profound (left)	Congenital	Unknown	Yes
Unilateral decreased (right)	Bilateral mild-moderate	Congenital	Unknown	No
Unilateral decreased (left)	Bilateral mild-moderate	Congenital	Unknown	No

Abbreviations: DFNB = autosomal recessive deafness; *Cx26* = *Connexin 26*; TORCHES = Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, and Herpes infections; cCMV = congenital cytomegalovirus.