ETIOLOGICAL EVALUATION OF SENSORINEURAL HEARING LOSS IN CHILDREN

EVELINE VAN BEECK CALKOEN

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Colophon

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ETIOLOGICAL EVALUATION OF SENSORINEURAL HEARING LOSS IN CHILDREN

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Geniet, je kunt het!

Voor Pieter en Cato

GENERAL INTRODUCTION

1. THE EPIDEMIOLOGY OF HEARING LOSS IN CHILDREN

The incidence of sensorineural hearing loss (SNHL) is approximately 1.7 in every 1000 live births, making it one of the most common congenital disorders (1-4). This means that in the Netherlands, approximately 300 children are born with hearing impairment per year, of which in 53-60% both ears are affected. In children of primary school age, the prevalence increases to 2.83 per 1000 children, with a further increase to 3.5 per 1000 in adolescents. This increase over time reflects progressive, acquired and late-onset hearing losses (5-7).

2. THE IMPACT OF UNILATERAL AND BILATERAL SNHL ON CHILDREN

Children with hearing impairment meet many challenges growing up in a society that strongly relies on the ability to hear sounds (8). Hearing loss in the first few years of life can have lifelong consequences. This is mainly due to brain plasticity. This gives young children the capacity to learn languages relatively easy. However, plasticity decreases with age, making the brain less susceptible to auditory input as children grow older (9,10). Besides their speech and language difficulties, hearing impaired children are more often confronted with problems in their social and emotional development. Engaging in peer relationships and friendships can be more challenging than for normal hearing children (11,12). Hearing impairment can therefore have a significant impact on the quality of life (11,12). Whereas the deleterious effects of bilateral hearing loss on children have been recognized for a long time, unilateral sensorineural hearing loss (USNHL) in children has been underdiagnosed and its impact underappreciated until relatively recently. Prior to the establishment of universal newborn hearing screening programs (in the Netherlands between 2002-2006), children with USNHL often remained undetected until they entered primary school and underwent hearing screening, unless they had medical problems that led to earlier evaluation of hearing (13). USNHL was considered to be of little consequence because speech and language was presumed to develop normally as long as one ear retained normal hearing capacity. Today, children with USNHL are properly identified and monitored (20). Several studies have suggested that a significantly increased proportion of children with USNHL may have educational and behavioral problems, compared with their normal-hearing peers (14,15). They have an increased rate of failure at school and grade retention, need for additional educational assistance and perceived behavioral issues in the classroom (16). In addition, it has become more and more evident that children with USNHL experience problems with sound localization, recognition of speech in noise and speech development (13,17-19).

The early identification by newborn hearing screening programs has raised awareness of both bilateral and unilateral SNHL in children and allows for early intervention if needed (for example through hearing aids, cochlear implantation, and/or guidance and support), improving speech and language skills (11, 21-24). The current screening is based on the 1-3-6 timeline: screening completed by 1 month, audiologic diagnosis by 3 months and early intervention by 6 months. A good example of the clinical consequence of this active screening and early identification of SNHL is that children identified with bilateral profound SNHL nowadays preferably receive cochlear implants within their first year of life, increasing their chance of improvement of language skills and educational options (25, 26).

3. NEWBORN HEARING SCREENING

Two important developments have led to the implementation of newborn hearing screening programs worldwide. The first development was the demonstration that early identification and intervention influences the language skills and educational outcome as described in section 2. The second development was the application of an objective non-invasive hearing test that could be performed by non-medical personnel (5). In the Netherlands, the current newborn hearing screening program was introduced from 2002 to 2006 and is provided by the Dutch Child Health and Welfare service (JGZ) (27). It replaced the distraction method screening at the age of 9 months, the Compact Amsterdam Paedo-Audiometric Screener (CAPAS) (see 'Draaiboek Neonatale Gehoorscreening Jeugdgezondheidszorg' for an overview) (28). Nowadays, the hearing screening takes place at home or in the hospital as soon as possible after the first 96 hours of the child's life and at the latest within 168 hours after its birth. In the first two rounds, screening is performed using transient evoked otoacoustic emissions (TEOAE) of both ears, usually with an interval of one week. In children who fail the first and second screening, automated auditory brainstem measurements (AABR) is performed. The test results are immediately available. This screening program aims to detect hearing losses exceeding 35 dB. Children who fail all tests are referred within three weeks to an Audiology Center (AC) for further investigation, mainly for Auditory Brainstem Response (ABR), but also tympanometry and OAE. Children admitted at the Neonatal Intensive Care Unit (NICU) are screened in hospital by AABR. If they fail AABR, they are referred to an AC for further investigation. The hearing screening program has a particularly high specificity: 99.8%. Its sensitivity is difficult to determine exactly. This is because it cannot be reliably determined whether hearing impairment that manifests itself at a later stage developed later in life or was already present at the time of newborn hearing screening but remained undetected.

3.1 Diagnostic techniques used in neonatal hearing screening

Transient evoked otoacoustic emissions (TEOAE): The OAE technology is based on a physiologic phenomenon of the inner ear, that is not yet fully understood. OAE's appear to be preneural in origin but the exact origin is still subject to investigations. One of the theories is that OAE's may be a by-product of active movements of the outer hair cells in the healthy inner ear passage which enhance the vibration caused by a sound stimulus. The resulting vibrational energy partially leaks out of the cochlea through the middle ear and can be recorded in the outer ear canal. OAEs can deliberately be evoked by auditory stimuli, and thus be used to evaluate hearing. Using the proper stimulus, OAE's can be detected in 98 % of normal hearing humans. Different types of stimuli may be used in a clinical setting. The Dutch newborn hearing screening program uses transient evoked otoacoustic emissions (TEOAE) (Figure 1). Absence of TEOAEs indicates that there is a hearing threshold of more than 20-40 dB. Measurement of OAE's is not limited by age, but detection of OAE in premature newborns is rather unsuccessful due to the small external ear canal and unfavorable signal to noise ratio in the NICU environment.

Automated auditory brainstem measurements AABR: The Automated Auditory Brainstem Response hearing screener was developed as a screening device. Using a bipolar EEG recording, it detects an auditory brainstem response following a 35 dB HL click stimulus. The built-in algorithm technology, based on AABR recording of normal hearing newborns, produces an objective and reliable interpretation of the response and results in a "pass" or "refer" indication. The AABR hearing screener has a noise and myogenic artefact rejection system (29).

If indicated, early rehabilitation can be started, in the Netherlands by an AC. Early intervention (counseling, hearing aids, support, cochlear implantation in severe cases) will prevent delays in speech and language development and have long-lasting beneficial effects on social and emotional development and quality of life (30,31). A disadvantage of the current newborn hearing screening program is that children with mild hearing impairment are not detected. Also, children with late-onset hearing loss may be missed. This group comprises children with progressive or acquired hearing impairment. Also, for some types of hearing loss, such as auditory neuropathy, diagnostic findings may be inconclusive in newborns because language skills are still developing and may not be evaluable or abnormal at the time of screening (32). Careful attention is advised for at-risk infants (Table 1) (30). Professionals such as pediatricians, otorhinolaryngologists, audiologist, speech and language therapists and schoolteachers should be aware of this limitation of the screening program and be attentive to symptoms of hearing loss at any pediatric age despite good results of newborn hearing screening. Audiological investigation needs to be performed when indicated at the otorhinolaryngology department or audiological center. Hearing and speech development screening is again performed by the JGZ at all children at the age of five years old.

Figure 1 Newborn hearing screening at home using evoked otoacoustic emissions (OAE) (own illustration).

Table 1 Risk factors for permanent congenital, delayed, or progressive hearing loss in childhood, modified from Year 2007 position statement: Principles and guidelines for early hearing detection and intervention programs, Pediatrics, 2007;120(4):898-921.

Risk factors for permanent congenital, delayed, or progressive hearing loss in childhood
Family history of hearing loss
Craniofacial anomalies, including ear tags (small flaps of skin in front of the ear), ear pits (A tiny opening in the skin usually in front of the ear and above the ear canal, connected to a sinus tract travelling under the skin) and anomalies that involve the outer ear, external auditory canal and temporal bone
Physical findings associated with a syndrome known to cause permanent hearing loss (for example, white forelock, a patch of white hair above the forehead)
Syndromes associated with congenital hearing loss or progressive or late-onset hearing loss
Neurodegenerative disorders or sensorimotor neuropathies
Neonatal intensive care unit stay >5 days or receiving any of the following treatments: extra corporal membrane oxygenation, assisted ventilation, ototoxic drugs (for example, gentamycin and tobramycin), loop diuretics or exchange transfusion for hyperbilirubinemia
In utero infections (toxoplasmosis, rubella, cytomegalovirus, herpes simplex or syphilis)
Confirmed bacterial or viral meningitis (in particular if caused by mump, herpes viruses or virus)
Head trauma, especially of the skull base, or temporal bone fractures, that require hospitalization
Chemotherapy

4. DIAGNOSIS OF HEARING LOSS

The audiometric evaluation is performed by the AC and consists at least of ABR, tympanometry and OAE in children under the age of 6 months, or at an older age if indicated. Visual re-enforcement audiometry can be used to test hearing in children between 6-24 months of age. Play audiometry is used in children of two to four years of age, by means of conditioning them to respond to an auditory stimulus through play activities (33). From the age of four years and onwards, generally pure tone audiometry (PTA) is used (34). Children are diagnosed with bilateral SNHL if the sensorineural hearing threshold at the best hearing ear is 30 dB or more. Asymmetric SNHL is defined as 1 or more frequencies with greater than a 30 dB difference, 2 or more frequencies with greater than a 15 dB difference in threshold or 3 or more frequencies with greater than a 10 dB difference in threshold between the 2 ears. The hearing threshold at the best hearing ear is at least 20 dB. Unilateral SNHL is defined as a hearing threshold at the worst hearing ear of 30 dB or more, and a hearing threshold of 20 dB or less at the contralateral ear. Hearing loss is categorized as a slight impairment (26-40 dB), moderate impairment (41-60 dB), severe impairment (61-80 dB) and profound impairment (81 dB or greater) according to the classification of the World Health Organization (WHO) (Figure 2) (35,36).

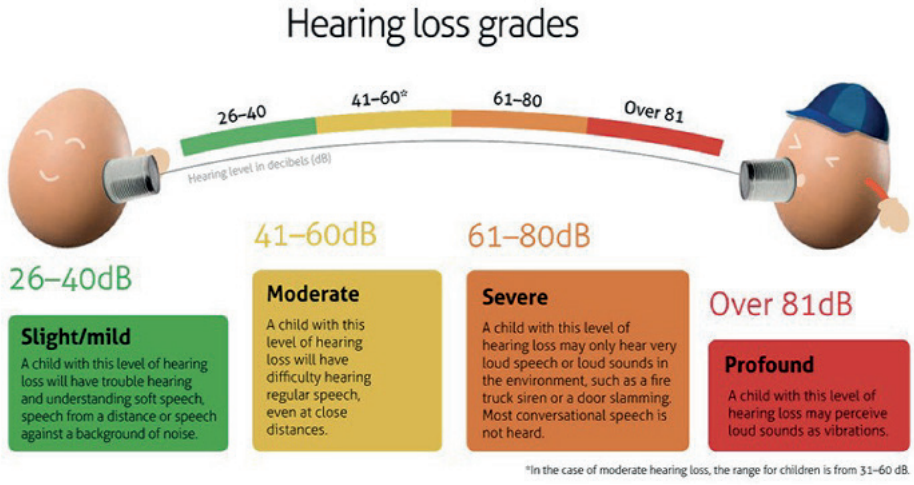

Figure 2 The grades of hearing loss and the range of conversational speech, illustration adapted from the website of the WHO: hearing impairments grades.

5. ETIOLOGY

The diagnosis of hearing loss can be followed by a search for an underlying etiology. Once the underlying cause is established, it might direct therapeutic decision making and guide (secondary) prevention, counseling and if indicated, further investigation (30). It is estimated that a genetic factor is responsible for about 50% of all congenital SNHL cases, of which 70% are estimated to be non-syndromic and 30% syndromic (Figure 3) (2). An acquired factor is found in 25% of the patients with congenital sensorineural hearing loss (SNHL). These include congenital infections (TORCHES: toxoplasmosis, others, rubella, cytomegalovirus, herpes simplex viruses and syphilis) and risk factors such as hypoxia during birth, hyperbilirubinemia, prematurity, and a stay at a neonatal intensive care unit (NICU) longer than 5 days (Table 1). Despite etiological evaluation, the etiology of SNHL currently remains unknown in 25–45% of the cases (5).

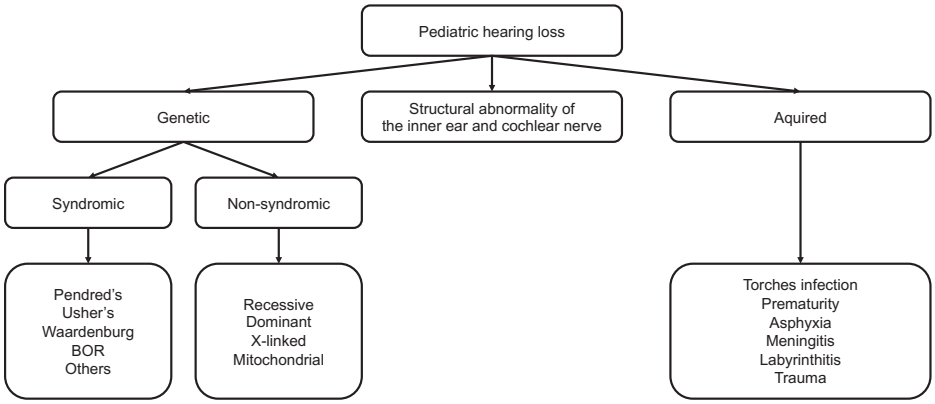

Figure 3 Etiologic categories for pediatric hearing loss, modified from the illustration of Smith RJH, Bale JF, White K, Sensorineural hearing loss in children. Lancet 2005; 5-11;365(9462):879-90.

5.1 Genetic alterations

In more than half of the children with bilateral SNHL, and approximately 30% of the children with unilateral sensorineural hearing loss, a genetic cause can be identified (39). About 70 % of all genetic causes of SNHL are estimated to be non-syndromic. Between 1997 and today, many genes implicated in non-syndromic hereditary forms of SNHL have been localized on the human genome by genetic linkage techniques (n genes = 123). Depending on the pattern of inheritance of the hearing loss, these loci are designated DFNA (autosomal dominant) (n genes = 51), DFNB (autosomal recessive) (n genes = 77) or DFNX (X-linked) (n genes = 5) (40). On the Hereditary Hearing Loss Homepage, all these currently known forms of hereditary hearing loss are summarized (41). The most

frequently found non-syndromic form of SNHL is DFNB1, caused by mutations in the *connexin 26* gene (40). The connexin 26 is a hexamer gap junction protein playing a role in potassium recycling to the endolymph, retaining the high potential crucial for the perception of sound. One mutation occurs very frequently: the 35delG mutation, giving rise to a severely shortened, non-functional protein (42).

About 30 % of all genetic causes of SNHL are estimated syndromic. The term "syndromic" implies the presence of other distinctive clinical features in addition to hearing loss, and to date, more than 300 syndromic forms of hearing loss have been described (43). The most common hereditary syndrome causing SNHL is Pendred syndrome. This syndrome is inherited in an autosomal recessive manner and is caused by mutations in the *SLC26A4* gene, which encodes the multifunctional anion exchanger pendrin (44). Pendred syndrome is characterized by sensorineural or mixed type hearing loss, dilatation of the vestibular aqueduct with or without cochlear hypoplasia (identified on CT or MR imaging) and goiter with euthyroid or mild hypothyroidism. Waardenburg syndrome is autosomal dominant inherited syndromic cause of SNHL. Six genes can be involved: *PAX3*, *MITF*, *EDN3*, *EDNRB*, *SOX10* and *SNAI2* with different frequencies (45). Characteristic features including pigmentation abnormalities such as depigmented patches of the skin and hair and vivid blue eyes or heterochromia irises. Hearing loss is the most common feature of Waardenburg syndrome, occurring in approximately 60% of children with type I and 90% of children with type 2. Temporal bone abnormalities are reported in 50% of the patients, consisting of malformation or absence of the semicircular canals and hypoplasia of the cochlea (46). Branchio-oto-renal (BOR) syndrome is an autosomal dominant syndrome, in which three genes are involved: *EYA1, SIX 5* an *SIX1*. BOR syndrome consists of auricular malformations, branchial arch closure defects (preauricular pits and tags) and renal anomalies. SNHL occurs in 70%–93% of individuals with BOR syndrome, with the age of onset varying from early childhood to young adulthood. A variation of temporal bone abnormalities can be seen, as well as atresia of the external ear canal and ossicular chain abnormalities (47). CHARGE syndrome is autosomal dominant, with mutations in *SEMA3E* and *CHD7* gene. Hearing loss is mostly profound sensorineural, accompanied by the appearance of bowl-shaped and concave ears, knows as 'lop ears'. On imaging, hypoplasia or aplasia of the semicircular canals and abnormalities of the cochlea and vestibule are seen. Usher syndromes are group of autosomal recessive inherited disorders comprising of retinitis pigmentosa, bilateral SNHL and vestibular dysfunction in some cases (48). They are the most prevalent cause of deaf blindness worldwide. Seven genes are identified to be responsible for Usher syndrome: *MYO7A* (USH1b), *USH1C* (USH1c), *CDH23* (USH1d), *PCDH15* (USH1f), *SANS* (USH1g), *USH2A* (USH2a) and *USH3* (USH3) (41). Usher syndromes are divided in three clinical types: Usher syndromes type 1 are characterized by profound congenital SNHL and vestibular areflexia. Usher syndromes

type 2 show mild to moderate SNHL at birth with intact vestibular responses, whereas Usher syndrome type 3 shows progression of SNHL and variable vestibular responses. All patients develop retinitis pigmentosa later in life, starting at the first or second decade.

5.2 Structural abnormalities

Structural abnormalities of the inner ear and cochlear nerve can occur uni- or bilateral. It is suggested that the spectrum of structural abnormalities reflects interruptions to inner ear development occurring at different junctures during embryogenesis (49).

5.2.1 Development of the inner ear

The inner ear is a complex structure that comprises sensory organs that detect angular and linear accelerations (the vestibular system) and sounds (the auditory system). Both organs use hair cell mechanoreceptors to convert either movement or soundwaves into electrical signals. To detect these sensations, both movement and soundwaves are converted into movement of fluid within the inner ear compartments. Movement is transmitted by hair cells of the cristae of the ampullae within the semicircular ducts or by the hair cells of the utricle and saccule within the vestibule. Sound is detected by hair cells located in the organ of Corti within the cochlea (Figure 4).

The inner ear develops from the embryonic ectodermal layer. The first step is a thickening of the ectoderm (otic placode) which gives rise to the bipolar neurons of the cochlear and vestibular ganglions. By week 4, the placode invaginates to become a blind sac, which closes to form the otocyst, surrounded by mesenchymal tissue, the precursor of the membranous labyrinth. The differentiation of the otocyst begins at week 5. At this time, the vestibular pouch grows dorsocranially and becomes the utricle and semicircular canals. The ventrocaudal area develops into the cochlear pouch, which gives rise to the cochlear duct and saccule. By week 6, the semicircular canals and the cochlea can be identified. The cochlear duct contains the organ of Corti and grows spirally, displaying one turn at 7 weeks, 1.5 turns at 8 weeks and the full 2.5 turns at 9-11 weeks (Figure 5).

The vestibulocochlear nerve, or eighth cranial nerve, develops parallel to the membranous labyrinth. It is recognizable by week 7. At around the 9^{th}-10^{th} week numerous nerve fibers reach the basal portion of the hair cells for the first time and afferent synaptic connections occur. Interestingly, just the nerve fibers that reach the target organs and contact the sensory cells survive, other fibers regress. This sensory cell-nerve interaction is called neuronal stabilization (51). In case of disturbance of the interaction, the labyrinth can still develop normally, but the vestibulocochlear nerve cannot. The bony internal auditory canal originates separately out of the labyrinth and is related to the development of the vestibulocochlear nerve. The development of these three structures (labyrinth,

vestibulocochlear nerve and internal auditory canal) are interrelated. Thus, failure of development of one structure can cause developmental disorders of the other structures (52). Congenital inner ear malformations can be variable and are often classified according to the suggested stage of arrest during the development of the labyrinth (49,53,54). Alternatively, some suggest that specific malformations may result from specific, independent paths of aberrant development, instead of being the consequence of a precocious arrest along a single, linear path toward normal labyrinthine development (55). Failure of otic placode formation during the third gestational week results in complete labyrinthine aplasia (Michel anomaly) whereas disturbances occurring later (during the seventh week) would only cause mild abnormalities (such as incomplete partition type II, also known as IP-II or Mondini malformation). In 2002, Sennaroglu and Saatci proposed a classification for cochleovestibular malformations that include, in order of decreasing severity: labyrinthine aplasia, cochlear aplasia, common cavity deformities, cystic cochleovestibular malformations (IP-I), cochleovestibular hypoplasia and IP-II, each of which is thought to result from a disturbance occurring at a progressively later stage of development (Figure 6 and Table 2) (53).

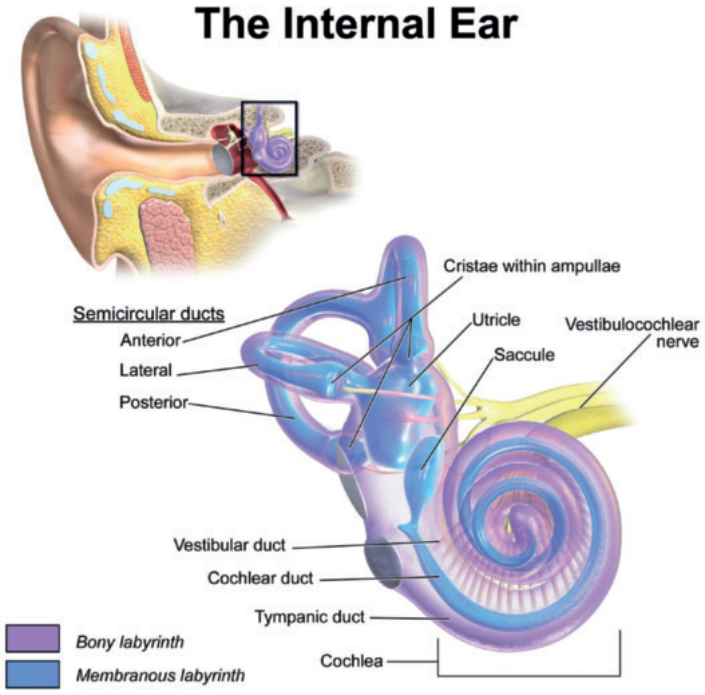

Figure 4 The bony and membranous labyrinth, illustration adapted from the Medical gallery of Blausen Medical 2014, WikiJournal of Medicine.

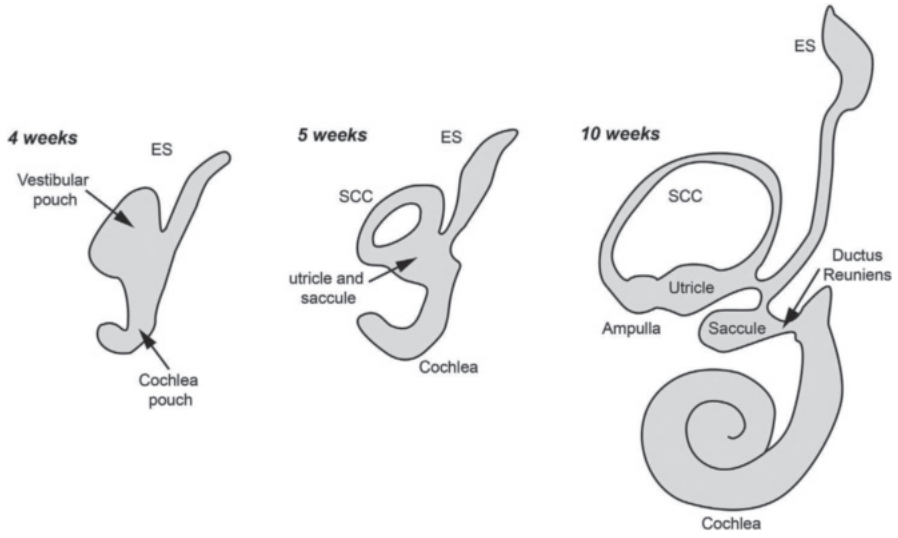

Figure 5 The embryonic development of the inner ear from week 4 to 10, illustration adapted from R. Lim, AM. Brichta, Anatomical and physiological development of the human inner ear Hearing Research 2016;338:9-21 ES endolymphatic sac, SCC semicircular canal.

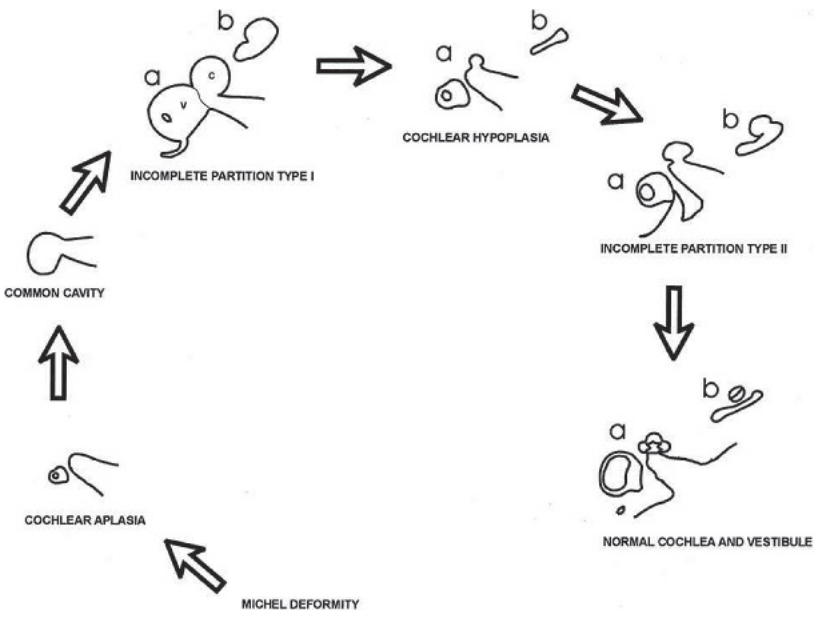

Figure 6 Illustration of the various arrest levels of inner ear development, imaging adapted from Sennaroglu et al, A new classification for cochleovestibular malformation Laryngoscope 2002;112(12):2230-41 (53).

Table 2 Classification of inner ear abnormalities and their definition (table adapted from M Sanna, P Merkus et al, Surgery for cochlear and other auditory implants, 2016).

Structure	Malformation	Definition
Cochlea	Michel deformity	Complete absence of all cochlear and vestibular structures
	Cochlear aplasia	Complete absence of the cochlea
	Common cavity deformity	Cystic cavity representing the cochlea and vestibule without showing any differentiation into cochlea and vestibule
	IP I	Cochlea of normal size but cystic appearance with no internal structures identified
	Cochlear hypoplasia	Small cochlea with either intact or incomplete partition
	IP II	Cochlea of normal diameter and intact basal turn, but shortened to 1.5 turns, combined with an enlarged vestibule and enlarged vestibular aqueduct
Vestibule	Dilated vestibule	Axial width is larger than 4.7 mm and coronal width is larger than 3.8 mm
	Vestibular hypoplasia	Axial width is smaller than 3.6 mm and coronal width is larger than 2.6 mm
SCC	Isolated lateral SCC dysplasia	Bony island width (axial) is smaller than 2.7 mm and bony island width (coronal) is smaller than 2.3 mm or bony island of the LSC is fused to the vestibular wall on coronal section
	Other SCC dysplasia	All SCC abnormalities except for the above two deformities
IAC	Narrow IAC	Simultaneous smaller measurements at the opening: IAC at the posterior cranial fossa (PCF) (axial) < 4.7 mm, coronal opening <3.2 mm and midpoint width coronal <3.2 mm
	Shortened IAC	IAC length shorter than 7.1 mm
Fundus	Opened Fundus	Absence of bony septum between the IAC and cochlea or vestibule (cochlear aperture)
	EVA	The vestibular aqueduct orifice is wider than the diameter if PSC lumen on the axial slice, displaying both structures simultaneously; or the vestibular aqueduct is wider than 1.5 mm at midpoint

Enlargement of the vestibular aqueduct (EVA) is the single most common inner ear abnormality (10-15% of all structural abnormalities) seen in children with SNHL and is frequently seen in association with an incomplete cochlear partition type II. The occurrence and progression of hearing loss in ears affected by EVA is hypothesized to be caused by an increased endolymphatic inner ear fluid pressure or fluctuations in endolymphatic pressure, and results in hair cell damage (56). The most often used definition is the measurement of the vestibular aqueduct at its broadest diameter in the middle of the log axis of the aqueduct, exceeding 1.5 mm (57). The characteristics of hearing loss and radiological findings of patients with EVA are also discussed in chapter 5 and 6. Next to the inner ear, the cochlear nerve and facial nerve are frequently affected (55). Malformations of the vestibulocochlear nerve and inner ear canal is seen in 12-18 % of children with SNHL (58,59). A malformation of the IAC is often seen in combination with a cochlear aplasia, common cavity and IP II. The vestibulocochlear nerve is classified to be hypoplastic when the diameter of the nerve is smaller than the diameter of the facial nerve in the sagittal oblique plane. The nerve is radiologically classified as aplastic when it is not visible on appropriate sagittal MR images (54). A narrow internal auditory canal is associated with hypoplasia or aplasia of the vestibulocochlear nerve. The cochlear nerve canal (cochlear aperture) with a diameter < 1.5 mm is called a cochlear aperture stenosis and is often associated with a cochlear nerve hypoplasia (60). Next to abnormalities of the inner ear and vestibulocochlear nerve, imaging is also used to detect abnormalities of the brain, e.g., in children suspected of a congenital CMV infection. Intracranial calcifications, polymicrogyria, cerebral and cerebellar volume loss, ventriculomegaly, and white matter disease are commonly seen. Identification of these abnormalities is important, amongst other reasons mentioned above, for clinical expectations, surgical planning and weighting risks (perilymph leak, potential electrode misplacement or post implantation meningitis) in cochlear implant candidates. Next to that, in children with USNHL, it provides insight in anatomy of the contralateral ear.

5.3 Pre- and perinatal infections

Congenital infections are caused by pathogens transmitted from mother to child during pregnancy or delivery. Some of these infections can cause, among other symptoms, sensorineural hearing loss. Historically, these pre- and perinatal infections related to SHNL are known as the TORCHES infections: Toxoplasmosis, Other, Rubella, Cytomegalovirus (CMV), Herpes simplex virus and Syphilis. Toxoplasmosis is caused by the parasite Toxoplasma gondii and can cause hydrocephalus, intracranial calcifications and SNHL when acquired prenatally. Toxoplasmosis can be acquired by eating undercooked meat or handling cat feces during pregnancy. The incidence of congenital toxoplasmosis is estimated to be 0,01%-0,1% and causes symptoms in 15% of these infants (60). Primary prevention such as hygiene precautions, wearing cloves while handling cat feces and properly cooking meat is important to avoid ingesting oocysts of the parasite. If an infection is detected during

pregnancy, medication to prevent transmission to the fetus is prescribed. Rubella is caused by the Rubivirus. Until the introduction of the vaccine, this was the most common viral cause of SNHL. The most common symptoms were cataract, cardiac defects, developmental delay and SNHL. Currently, this infection is no longer endemic in the Netherlands. Today, a congenital cytomegalovirus (cCMV) infection is the most prevalent acquired cause of SNHL in children (61,62). If the mother has a CMV infection during pregnancy, there is a 40% chance that the infant will get infected. A cCMV is diagnosed in 1:200 newborns in the Netherlands, and around 20 - 35 % of these children will develop permanent sequelae of the infection, such as microcephaly, hepatosplenomegaly, SNHL and general developmental delay (63). Hearing loss associated with cCMV can be uni- or bilateral, fluctuating or progressive, and its onset can be delayed for months, or even years. Extra care to prevent a CMV infection during pregnancy is important, especially for pregnant women who are frequently exposed to toddlers. These women are advised to wash their hands frequently, especially when handling diapers, and to avoid sharing food or drinks. Newborns with a symptomatic CMV infection can be treated with intravenous ganciclovir or oral valganciclovir in the first weeks of life (64). There is evidence that this treatment may stabilize or improve the severity of hearing loss in 84% (compared to 59% in controls) and reduce the number of patients with further hearing deterioration, but serious side effects such as neutropenia and bone marrow suppression have been reported. Herpes simplex virus (HSV) is one of the most prevalent sexually transmitted diseases and exposure is often mentioned as a risk factor for development of SNHL in newborns. Despite the frequency of a maternal infection, a newborn HSV infection is unusual. Unfortunately, in the rare cases of newborn HSV, severe neurological sequelae are described (mental retardation, severe developmental delay) as well as SNHL (65). Congenital syphilis is a preventable and treatable disease entity, when treated with appropriate antibiotics. Hearing of these children can be screened by the newborn hearing screening program. There are no indications for delayed or late onset SNHL caused by syphilis (66).

5.4 Perinatal complications and risk factors

In the Netherlands, around 4000 infants per year are admitted at a Neonatal Intensive Care Unit (NICU) per year, of which approximately 80 are diagnosed with uni- or bilateral SNHL (20% vs 80%) the prevalence of SNHL in NICU infants is much higher than in the general population of newborns (1-3% vs 0,1%) (67). A stay at the NICU is a risk factor for SNHL for a number of reasons: the indication for NICU admittance may be associated with SNHL, such as certain congenital disorders or infections (TORCH, sepsis, bacterial meningitis). But next to that, also a low birth weight (750-1500 g), prematurity (24-31 weeks), an APGAR score <7 and hypoxia, high frequency oxygenation ventilation and admission of >12 days at the NICU are independent risk factors for SNHL (68).

5.5 Postnatal bacterial infections

Some bacterial infections acquired during childhood may also cause SNHL. One of the most prevalent bacterial causes of acquired bilateral SNHL is bacterial meningitis, especially when caused by pneumococci. The hearing loss is caused by bacterial endotoxins and the subsequent immune reaction, affecting not only the meninges and the brain but also the inner ear (69). Severe bilateral SNHL occurs in up to 9% of postmeningitic patients (70). Second, a bacterial labyrinthitis can result in SNHL, usually caused by spread from bacterial middle ear infections (tympanogenic labyrinthitis) to the inner ear via the round or oval window. Patients typically present with unilateral hearing loss and a short period of vomiting and balance disturbance following an ear infection. (71). Rates of pneumococcal meningitis (-20 %) and acute middle ear infection have decreased among children since the heptavalent pneumococcal conjugate vaccine was introduced in 2000 (72,73).

5.6 Metabolic disorders

Metabolic disorders can also be associated with the occurrence of pediatric SNHL, albeit rarely. Mucopolysaccharidoses (MPS) type I (Hurler syndrome) and type II are lysosomal storage disorders caused by a deficiency of one of the enzymes involved in the degradation of glycosaminoglycans. Hearing loss is a common clinical presentation in MPS (in 76-100% of the patients). The sensorineural component develops as the disease progresses, but there is no consensus on the etiology of the sensorineural component (74). Another rare metabolic disorder related to SNHL is Niemann-Pick disease, type C1 (NPC1), a rare autosomal recessive lysosomal lipidosis resulting in a progressive and fatal neurological deterioration (75). As a component of this disease, auditory neuropathy or progressive SNHL is seen.

5.7 Trauma

A head trauma can cause a temporal bone fracture and/or intracranial damage. In children, a head trauma is often caused by bicycle accidents, falls, car accidents or for instance skateboarding. SNHL may be secondary to a fracture of the labyrinth, concussion of the labyrinth, perilymfatic fistula or a brainstem injury (76). In children with a temporal bone fracture, posttraumatic SNHL occurs in up to 17%. The classification of temporal bone fractures can be based on otic capsule involvement. The fracture can be otic capsule violating (OCV) or otic capsule sparing (OCS) (77). OCV fractures have a higher rate of SNHL than OCS fractures.

6. ETIOLOGICAL DIAGNOSIS

In addition to the evaluation of the type and severity of the SNHL (see paragraph 4 'diagnosis of hearing loss'), there is the option of etiological evaluation of the hearing loss. While etiological evaluation may be very useful for reasons discussed below in section 7, SNHL itself is usually irreversible regardless of the cause, and etiological evaluation is therefore not a prerequisite for adequate audiological rehabilitation. Etiological evaluation is an option that can be offered and discussed with the patient and parents and performed upon their consent. Children and their parents are subsequently referred to an otorhinolaryngologist who takes the medical and family history and performs physical examination including otoscopy. In close consultation with the patient and parents, etiological examinations can be performed as described in the following paragraphs. Because of the heterogeneous etiology, a multidisciplinary approach with otologists, audiologists, pediatricians and clinical genetics is recommended. In 2012, the first Dutch medical guideline concerning pediatric SNHL came out, initiated by the clinical genetics' society of the Netherlands (78).

6.1 Genetics

As described above, pediatric SNHL may be caused by pathologic genetic alterations. Since 1977, molecular genetic testing for hereditary SNHL relied on single-gene testing using Sanger sequencing to sequence DNA (79). At that time, the choice of the gene or genes to be tested depended on the clinical evaluation of symptoms, syndromic features, and type and course of the hearing loss. Currently, single-gene testing is still performed if a child is clinically suspected of Pendred syndrome or Usher syndrome type 2 (*SLC26A4, USH2A* respectively) and in children with early onset hearing loss, a single gene test for DFNB1 is performed (*CJB2* followed by *GJB6*). Since 2013, next generation sequencing methods have been deployed in the etiological diagnosis of SNHL, such as whole exome sequencing (WES) which is based on massively parallel sequencing and whole exomes can be simultaneously analyzed. This method has been developed since the field of genetics has seen huge progress in the recent years, not only resulting in an ever-expanding number of genes associated with SNHL, but also in the development of high-throughput methods of analyzing genes and gene alterations. The gene panel is constantly updated according to the latest insights and is currently the best option for a comprehensive genetic analysis (80). This test panel has greatly improved the diagnostic rate of hereditary SNHL.

6.2 Imaging

Structural abnormalities causing SNHL can be identified with imaging of the mastoid and middle ear, the inner ear, the cochlear nerve and more central neurological auditory pathways, i.e., within the cerebellopontine angle and the brain. There have been significant improvements in CT technique over the years with regard to image

quality and resolution, speed of the investigation and radiation dose (for example: hybrid iterative image reconstruction techniques, more dose efficient CT detector materials and larger detector dimensions have contributed to 70-80% radiation dose reduction over 4 years (2014)) (81,82). Since the introduction of the high-resolution computerized tomography (HRCT) of the temporal bone in 1990 and especially with the radiation dose reduction in around 2014 (83), this has been the study of choice in the etiological work up of pediatric SNHL. The current temporal bone CT protocol consists of non-contrast axial 0.6 mm slices, coronal and sagittal reconstructions (0.6 mm thickness) and axial reconstructions following the plane of the lateral semicircular canal. CT is very useful in providing information about bony abnormalities, for instance of the temporal bone, such as fractures, calcifications and structural abnormalities. For detailed soft tissue imaging, MR imaging is better suited and has become increasingly popular in the etiologic diagnosis of SNHL (84). The magnetic resonance imaging technology has come a long way since the technology was first discovered. Advances in MR imaging technology have resulted in a dramatic improvement in clarity, definition and resolution over time. The current MR imaging protocol of the brain and temporal bone (as used in the Amsterdam University Medical Center- location VUmc) includes T1 weighted, transversal T2 weighted, transversal fluid attenuation inversion recovery (FLAIR), sagittal oblique 3D gradient-echo sequences and axial 3D steady state (CISS) images perpendicular to the internal auditory canal. MR imaging is especially useful in providing information about the brain, the brainstem, the cranial nerves in the IAC (including the cochlear nerve) and the fluid filled spaces of the cochlea and labyrinth and its aqueducts. The developments and improvements in both CT and MR imaging have increased the possibility of finding a causative abnormality of SNHL at the pediatric age. More detailed data on the outcome of CT and MR imaging in pediatric (U)SNHL as well as the discussion on the choice of modality can be found in chapters 3 and 4.

6.3 Laboratory tests

In the Netherlands, via the dried-blood-spot (DBS) card, a blood sample is routinely taken from all newborns during the first week of life in order to screen for 25 metabolic, endocrine, genetic and other disorders with severe consequences such as cystic fibrosis and severe combined immunodeficiencies (84). In 2021, mucopolysaccharidosis (MPS) type I is added to this screening. The remaining blood is stored for 5 years as DBS on Guthrie cards by the National Institute for Public Health and Environment (RIVM). In the 5 years that these Guthrie cards are stored, they can be used to diagnose congenital abnormalities in retrospect. In children presenting with late onset SNHL, this feature is of use as these stored DBS can be obtained for CMV DNA detection. This is a practical method for diagnosing cCMV. Unfortunately, the sensitivity is only 32-46%, making DBS not a very effective method to identify children with CMV-related SNHL (85,86). After

the period of 5 years, Guthrie cards are destroyed and possible detection of cCMV is no longer possible. Routinely laboratory screening for infections causing SNHL (such as the TORCHES infections) is currently not recommended (78). Specific blood tests can be performed if indicated, for instance thyroid function in case of an enlarged vestibular aqueduct or incomplete partition type II or IgG CMV, when the Guthrie card is no longer available.

6.4 Additional investigations

As mentioned above, the results of the etiological evaluation are preferably reviewed and discussed in a multidisciplinary team. Consultation of additional medical specialists and performing additional diagnostic tests may be indicated, in close consultation with the patient and parents. Conversely, other specialist such as neurologists or ophthalmologists can refer a child for audiometry and otological investigation if indicated. In some cases, with suspicion of certain diagnosis, specific additional investigations are recommended. For example, a renal ultrasound is recommended in patients suspected for BOR syndrome (87). Electrocardiography is recommended in children with profound SNHL and vestibulopathy and in case of suspicion of Jervell and Lange-Nielsen syndrome. In patients with Alport syndrome, urine investigation is recommended at the age of 10 years old. A visual screening is performed by the JGZ at the age of 3 and 5 years old (88). If indicated, in case of a congenital CMV or toxoplasmosis infection, CHARGE of Usher syndrome, oculo-auriculo-vertebral spectrum, ophthalmologic investigation performed by a pediatric ophthalmologist is recommended. Routinely audiometric investigation in siblings other than the newborn hearing screening and the screening later in life by the JGZ is not recommended and can be performed if indicated.

7. IMPORTANCE OF DIAGNOSTIC EVALUATION OF THE ETIOLOGY OF PEDIATRIC HEARING LOSS

Newborn screening programs have raised awareness of both uni- and bilateral SNHL in children, and as a consequence also increased the interest in the causes of pediatric hearing loss, both in physicians as well as in patients and their parents (89). The expanding etiological test battery and etiological knowledge (and with that, the growing opportunity of finding a cause of pediatric SNHL) also plays a role in this increasing interest. Although SNHL is (still) generally irreversible, an adequate etiological evaluation may be important for a number of reasons: prognostication of the progression of the hearing loss in affected ears, prognosis of an apparently unaffected contralateral ear in unilateral hearing loss, identification of associated physical conditions and associated syndromes, identification of other family members at risk, adequate early intervention if possible, and accurate

counseling and medical guidance of the patients and their parents (90). The option of etiological evaluation can be offered to the parents and patient, and each diagnostic step is performed in close consultation with the parents. The parents and patient have the possibility to opt out at all stages.

SCOPE OF THIS THESIS

The research presented in this thesis has the aim to contribute to the optimal diagnostic work up and counseling of children with (U)SNHL and their parents, with a focus on the etiological diagnosis of imaging of the temporal bone and inner ear. An additional focus is on the diagnosis and prognosis of an enlarged vestibular aqueduct, one of the most prevalent structural abnormalities causing SNHL in children.

Chapter 2 describes the identification of causative genetic, structural and acquired etiologies in a large cohort of patients with uni- or bilateral SNHL, in relation to age at diagnosis and hearing loss severity, using a stepwise etiological diagnostic work-up.

Chapter 3 reports the evaluation of the clinically relevant abnormalities as visualized on CT and MR imaging in children with symmetric and asymmetric SNHL, in relation to age and the severity of hearing loss.

Chapter 4 describes the evaluation of causal abnormalities identified on CT and MR imaging in children with USNHL.

Chapter 5 is a systematic review of the literature on sudden drops in hearing level after minor head trauma in patients with an EVA.

In **chapter 6** the long-term ipsi- and contralateral hearing of patients with a EVA is evaluated.

Chapter 7 consists of a summary and conclusions of this thesis, and a proposal for an etiologic diagnostic flowchart for children with (U)SNHL. Further, the recent developments and future perspectives are addressed.

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THE ETIOLOGICAL EVALUATION OF SENSORINEURAL HEARING LOSS IN CHILDREN

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ABSTRACT

This study aims to evaluate the etiology of pediatric sensorineural hearing loss (SNHL). A total of 423 children with SNHL were evaluated, with the focus on the determination of causative genetic and acquired etiologies of uni- and bilateral SNHL in relation to age at diagnosis and severity of the hearing loss. We found that a stepwise diagnostic approach comprising of imaging, genetic and/or pediatric evaluation identified a cause for SNHL in 67% of the children. The most common causative finding in children with bilateral SNHL were causative gene variants (26%) and in children with unilateral SNHL a structural anomaly of the temporal bone (27%). The probability of finding an etiologic diagnosis is significantly higher in children under the age of 1 year and children with profound SNHL.

Conclusions: With our stepwise diagnostic approach we found a diagnostic yield of 67%. Bilateral SNHL often has a genetic cause, whereas in unilateral SNHL structural abnormalities of the labyrinth are the dominant etiologic factor. The diagnostic yield is associated with the age at detection and severity of hearing loss: the highest proportion of causative abnormalities are found in in children with a young age at detection or a profound hearing loss.

INTRODUCTION

The prevalence of congenital sensorineural hearing loss (SNHL) is one to two per thousand live births, making it one of the most common congenital disorders (23,28). Early diagnosis and intervention is important in the acquisition of hearing, speech and linguistic skills, thereby contributing to the positive development of the child (13). Newborn hearing screening programs have been introduced, facilitating early identification of hearing-impaired children and enabling timely intervention by means of counseling, support, hearing aids, or cochlear implantation in severe cases (20,32). The current newborn hearing screening program in The Netherlands was introduced from 2002 to 2006.

Newborn screening programs have also sparked the interest in the causes of pediatric hearing loss. Although SNHL is generally irreversible, an adequate etiological evaluation may be important for a number of reasons: prognostication of the progression of the hearing loss of the affected ear, and of the unaffected ear in unilateral hearing loss, identification of associated physical conditions, identification of other family members at risk, adequate intervention if possible, and accurate counseling of the patients and their parents (2).

Imaging, DNA tests, screening for congenital infections and metabolic diseases are frequently performed in the etiological evaluation of SNHL. It is estimated that a genetic factor is responsible for about 50% of all congenital SNHL cases, of which 70% are estimated to be non-syndromic and 30% are syndromic (18,23,28). An acquired factor is found in 25% of the congenital SNHL cases (18). These include congenital infections (TORCH: toxoplasmosis, others, rubella, cytomegalovirus, and herpes simplex viruses) and risk factors such as hypoxia during birth, hyperbilirubinemia, prematurity and a stay at a neonatal intensive care unit (NICU) longer than 5 days. Despite etiological evaluation, the etiology of SNHL is reported to remain unknown in 25-45% of the cases (18,23,28).

In this study the outcome of a stepwise diagnostic approach towards an etiological diagnosis in children with unilateral or bilateral SNHL was evaluated, with a focus on the influence of determinants such as degree and laterality of hearing loss and the age of diagnosis on the outcome of etiological diagnostics.

MATERIALS AND METHODS

Upon parental consent, children diagnosed with bilateral or unilateral SNHL between January 2006 until January 2016 were offered etiological diagnostics by a dedicated multidisciplinary team consisting of otologists, audiologists, pediatricians, clinical geneticists, neuroradiologists and, if indicated, neurologists or ophthalmologists at the Free University Medical Center (VUmc) Amsterdam, The Netherlands. Patients were referred by audiology centers, general practitioners and otorhinolaryngologists. The majority of children were referred directly after the diagnosis of the hearing loss, but in some cases the need for etiological evaluation arises later in life, and consequently the referral takes place at an older age.

The protocols for the diagnostic evaluation of the etiology of SNHL in children are based on Dutch guidelines and the experience of the CDS team (27), and include radiology, pediatric and genetic evaluation. The outcome of radiology alone in children with SNHL has been described in more detail elsewhere (24,25). During the 10-year period reviewed in this study, some diagnostic protocols were altered or added to the diagnostic battery due to technological development or the evolving understanding of SNHL in children. Technical improvements have also taken place, for instance single gene testing has been largely replaced by whole exome sequencing (WES), and WES protocols have been improved since their introduction.

Audiometric tests

The audiometric evaluation was performed by the referring Audiology Center or by the VUmc Audiology Center. The audiometric evaluation consisted of pure tone audiometry (PTA) if possible, auditory brainstem response using clicks (ABR), or both.

The degree of hearing loss was determined on the first available audiometric test and summarized by an average threshold at 500, 1000, 2000 and 4000 Hz on PTA or the estimated hearing threshold around 3 kHz on ABR. Children were diagnosed with bilateral SNHL if the sensorineural hearing threshold at the best hearing ear was 30 dB or more. Asymmetric bilateral SNHL was defined as 1 or more frequencies with greater than a 30 dB difference, 2 or more frequencies with greater than a 15 dB difference in threshold or 3 or more frequencies with greater than a 10 dB difference in threshold between the 2 ears (10,22). Unilateral SNHL was defined as a hearing threshold at the worst hearing ear of 30 dB or more, and a hearing threshold of 20 dB or less at the contralateral ear. Hearing loss was categorized as a slight impairment (26-40 dB), moderate impairment (41-60 dB), severe impairment (61-80 dB) and profound impairment (81 dB or greater) according to the classification of the World Health

Organization (WHO). A patients' hearing loss was graded according to the worst hearing side. In case of mixed type hearing loss, the inclusion and consecutive analyses were based on the sensorineural component only. Patients with pure conductive hearing loss were excluded from this study.

Age

The age at detection was defined as the age at which the hearing loss was first diagnosed by the Audiology Center, either by ABR or PTA. Patients were categorized in 4 age groups: 0-1 year old, 1-6 years old, 6-12 years old and 12-18 years old.

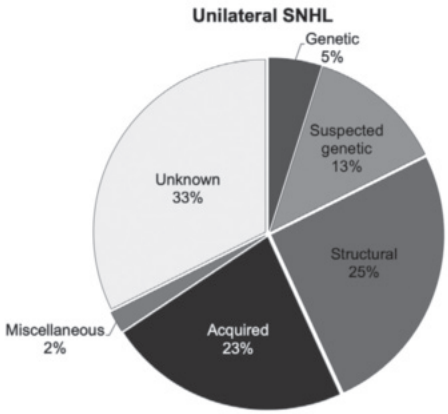
Evaluation etiological work-up

Patient charts were reviewed for demographic data, audiometry and the results of dysmorphologic, pediatric, ophthalmologic and neurologic evaluation. Furthermore, the use and results of imaging, molecular genetic testing and laboratory tests were reviewed. Imaging consisted of Computed Tomography (CT) of the temporal bone and/or MR imaging of the inner ear, cerebellopontine angle and brain. The decision to obtain imaging and the choice of the imaging modality was individualized per patient and made by the multidisciplinary team. Molecular genetic testing consisted at first of Sanger-sequencing of one or several single genes (usually *GJB2*, other genes based on clinical suspicion), 201 children in our population underwent this type genetic testing. Whole-Exome-Sequencing (WES) became available in a diagnostic setting in 2013. WES targeting a panel of hearing loss related genes was performed in 204 children (33). A congenital CMV infection was detected with polymerase chain reaction (PCR) using dried blood spots on Guthrie cards, which are preserved for 5 years after birth in The Netherlands. After this period, Guthrie cards are destroyed and reliable detection of congenital CMV is no longer possible. During the period reviewed in this study, an unrelated nationwide study into the occurrence of congenital CMV infections in children with congenital SNHL in The Netherlands was taking place (12). Some children were already evaluated for the occurrence of congenital CMV by this study before presentation for etiologic diagnosis of SNHL, in these cases the CMV status as determined was used for the analysis in this study, and testing was not repeated at our center. Additional tests were performed when indicated by the multidisciplinary team and included metabolic screening and DNA testing for copy number variations by Single Nucleotide Polymorphism (SNP) array, urine screening for hematuria and proteinuria (in case of childhood onset hearing loss in boys), ECG and evaluation of congenital infections other than CMV.

The etiology of SNHL was divided into different diagnostic categories: genetic, suspected genetic, structural anomalies, acquired, miscellaneous and unknown (Figure 1). A genetic cause was established if it was confirmed with DNA testing. The SNHL was considered to

be of 'suspected genetic' origin if there was a strong suspicion of syndromic SNHL because of a patients' dysmorphic features or comorbidities, a positive family history for SNHL, a gene variant of unknown pathogenicity in a gene known to be associated with hearing loss, or in some cases with a single autosomal recessive pathogenic gene variant and a specific phenotype associated with that gene. A diagnosis was categorized as 'structural anomaly' if a causative abnormality was found on imaging, and no further genetic or syndromic diagnosis could be established. Acquired causes included congenital TORCH infections, meningitis, hyperbilirubinemia requiring exchange transfusion, asphyxia, neonatal intensive care stay longer than 5 days, prematurity, trauma, ototoxic drugs and others. These risk factors were deemed causative of SNHL after exclusion of other possible causes.

A



B

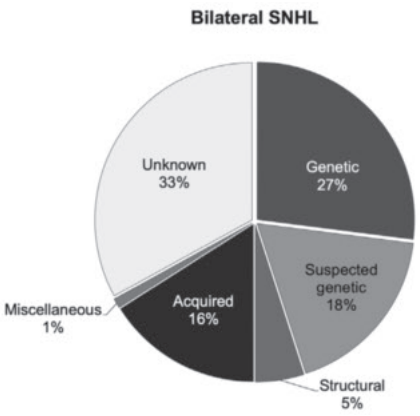


Figure 1. Pie charts illustrating the distribution of etiological causes of (A) unilateral and (B) bilateral sensorineural hearing loss.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0. For inferential statistics, a χ^2-test was used. McNemar test was used for the comparison of detecting abnormalities between imaging and genetic testing. The criterion for statistical significance was set at $p < 0.05$. Descriptive analyses and cross tables were used to outline results of this study.

RESULTS

Clinical characteristics

A total of 498 children with SNHL were retrospectively evaluated. Seventy-five children were excluded from the study because further evaluation was not performed at their parent's request, the hearing loss was not of sensorineural origin, or the sensorineural component did not exceed 30dB. A total of 423 children were reviewed, 239 males and 184 females. Age at detection of hearing loss ranged from 1 week to 16,9 years (median age of 0,9 year). The mean age of children with bilateral SNHL was 0,7 years old and the mean age of children with USNHL was 3,3 years old. One hundred and ninety-seven children were diagnosed with hearing loss before the age of six months (47%). They were referred directly after newborn hearing screening. Two hundred and twenty-six children (53%) were referred at an older age.

Source of referral

Two hundred fifty-one (59%) children were referred by audiology centers, 99 (23%) by otolaryngologists, 24 (6%) by other medical specialists including pediatricians, 18 (4%) children by NICU's, 20 (5%) by child health and care service and 11 (3%) by general practitioners.

Hearing loss

Bilateral SNHL was diagnosed in 300 patients (71%) and unilateral SNHL in 123 children (29%). The hearing loss was most frequently profound in nature, both in uni- and bilateral SNHL (48% and 39% respectively) (Table 1). The hearing loss was detected by Automated Auditory Brainstem Response (AABR) in 242 children (57%), at a mean age of 9 months old. The remaining children underwent pure tone audiometry (PTA).

Table 1. Demographics and clinical characteristics of 423 children who underwent etiological evaluation for uni- or bilateral SNHL.

Characteristics	Total	(n/%)	Unilateral	(n/%)	Bilateral	(n/%)
Number of patients	423	(100%)	123	(29%)	300	(71%)
Sex n (M/F)	M 239 F 184	(57%) (43%)	M 67 F 56	(54%) (46%)	M 172 F 128	(57%) (43%)
Hearing loss category *						
1 Slight (26-40 dB)	64	(15%)	19	(15%)	45	(15%)
2 Moderate (41-60 dB)	114	(27%)	22	(18%)	92	(31%)
3 Severe (61-80 dB)	69	(16%)	23	(19%)	46	(15%)
4 Profound (80 dB or greater)	176	(42%)	59	(48%)	117	(39%)
Age at diagnosis (median/range) years	0,9	(0-1,9)	3,3	(0-15,8)	0,7	(0-16,9)

Age: Age at diagnosis is the age at which the hearing loss was first diagnosed by an Audiology Center.
** Hearing loss categories according to the WHO classification (11).*

Etiological work-up

The etiological evaluation was performed using a stepwise protocol in 67% of the children with USNHL and in 61% of the children with bilateral SNHL (Figure 2). Reasons to deviate from the protocol were medical indications (including meningitis, neurodevelopment disorders and syndromic features), a cochlear implant procedure or parental request.

Etiology

The etiology of the SNHL could be established in 67% of the children. The distribution of etiologic diagnoses is presented in Figure 1. Among the children with an established etiology, the cause was most frequently genetic (n = 87, 31%) or acquired (n = 75, 26%) (Supplementary table 3). The probability of identifying an etiologic diagnosis is significantly higher in the youngest age group (74% vs. 60%, p<0,01). We also found a significantly higher diagnostic yield in the most severe hearing loss category (p=0,01). As suspected, there was a significant association between age and the level of hearing loss (p=0,03), i.e. the most severe hearing loss category is overrepresented in the youngest age group. Using a likelihood ratio test, the level of hearing loss was found to be of significant added value to a logistic regression model that included age only (p=0,01), and vice versa (p=0,04). This suggests that both severity of hearing loss and age are independent prognosticators for finding an etiologic diagnosis.

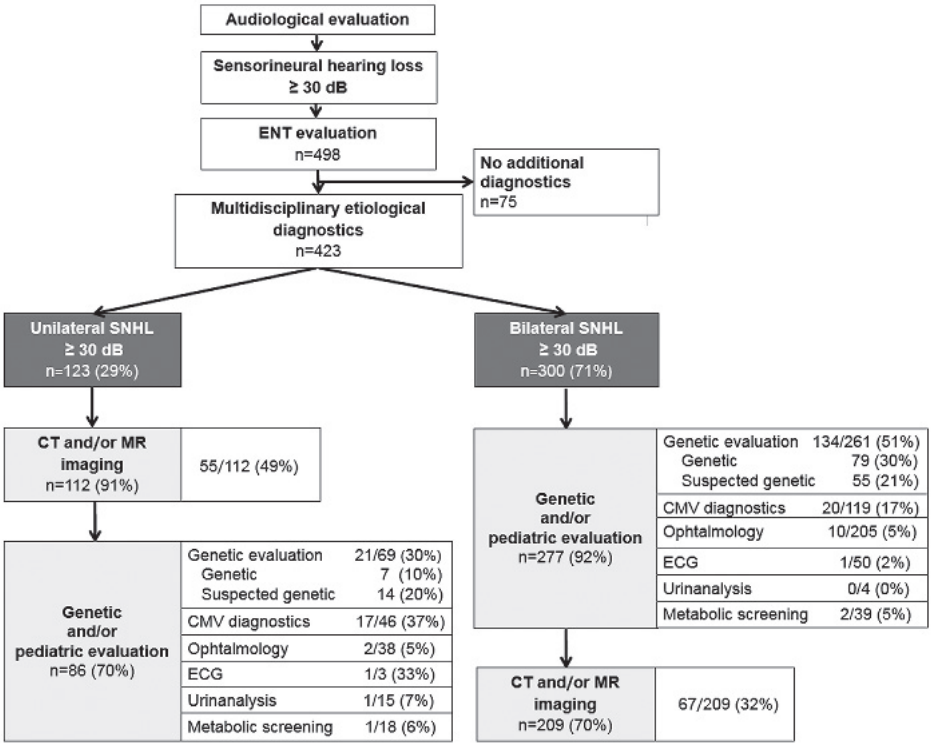


Figure 2. Diagnostic yield (n/n (%)) of the stepwise etiological diagnostic approach of SNHL in children. Not all children underwent all diagnostic modalities or the same diagnostic work-up: if a causative abnormality was identified in the first diagnostic step, additional diagnostics were not always deemed necessary. SNHL = sensorineural hearing loss. CT = computed tomography. MR = magnetic resonance imaging. ECG = electrocardiogram. CMV diagnostics = congenital cytomegalovirus DNA testing by PCR.

The probability of identifying a cause for SNHL did not differ between children with uni- and bilateral hearing loss (67% and 67% respectively, p=0,92). Nevertheless, the distribution of the etiologies was different for these two groups: a genetic etiology was found more frequently in the children with bilateral SNHL (27%), whereas a structural temporal bone abnormality was detected more often in children with USNHL (25%) (Table 2A and B).

Table 2 A+B

A. The etiology of SNHL in children in relation to age.

Etiology		**Unilateral** ***n* = 123**				
Age (years old)	Overall	0-1	1-6	6-12	12-18	Total
Total	423	55 (45%)	38 (31%)	27 (22%)	3 (2%)	123
Genetic	87	6	-	-	1	7
Suspected genetic	70	8	4	2	-	14
Structural	48	9	10	12	2	33
Acquired	85	13	10	3	-	26
Miscellaneous	4	3	-	-	-	3
Unknown	139	16	14	10	-	40

Age: Age at which the hearing loss was first diagnosed by an Audiology Center.

B. Etiology of SNHL in relation to degree of hearing loss.

Etiology		**Unilateral** ***n* 123**			
Degree of SNHL		26-40 dB	41-60 dB	61-80 dB	>81 dB
Total	423	19 (15%)	22 (18%)	23 (19%)	59 (48%)
Genetic	87	1	2	-	4
Suspected genetic	70	3	1	4	6
Structural	48	4	9	2	18
Acquired	85	1	1	6	18
Miscellaneous	4	2	-	-	1
Unknown	139	8	9	11	12

Hearing loss categories according to the WHO classification. SNHL: sensory neural hearing loss.

Genetics

A clinical evaluation by the geneticist was completed in 330/423 children. In 307 of these children a DNA analysis was performed, 57/123 (46%) children with USNHL and 250/300 (83%) with bilateral SNHL. Reasons for genetic testing in children with USNHL included abnormalities found on CT and/or MR imaging, suspicion of syndromic SNHL or strong positive family history of genetic SNHL. A genetic abnormality associated with SNHL was identified in 87/307 children overall (28%). The diagnostic yield of genetic evaluation is higher in children with bilateral SNHL compared to children with USNHL (52% vs. 33% of the tested children). Genetic evaluation also revealed a

		Bilateral *n* = 300		
0-1	1-6	6-12	12-18	Total
159 (53%)	86 (29%)	45 (15%)	10 (3%)	300
50	18	8	4	80
29	14	9	4	56
8	4	3	-	15
32	13	4	-	49
1	-	-	-	1
39	37	21	2	99

		Bilateral *n* = 300			
Total	26-40 dB	41-60 dB	61-80 dB	>81 dB	Total
123	45 (15%)	92 (31%)	46 (15%)	117 (39%)	300
7	9	28	17	26	80
14	10	18	13	15	56
33	1	4	-	10	15
26	5	8	2	34	49
3	-	-	-	1	1
40	20	34	14	31	99

significant higher proportion of genetic causes in the youngest age group (56% vs. 39%, p<0,01). In contrast, the probability of finding a genetic cause was comparable between the different hearing loss categories (p=0,07). Over time, the protocols for genetic evaluation have changed, from single gene testing to WES. Especially since the introduction of WES, the diagnostic yield has increased (in this study from 26% to 36%) and will probably increase even more in the future due to improved protocols.

Of the children with a confirmed genetic cause (n=87) for SNHL, 47% presented with a syndromic etiology and 53% with a non-syndromic etiology (Table 3; Supplementary table 1). The most frequent genetic cause was a mutation in the GJB2 gene (27 patients, 30%), encoding Connexin 26. The most common syndromic cause was Usher syndrome (6 patients, 7%), followed by Stickler syndrome (5 patients, 6%). Ten patients (10%) were identified with Pendred syndrome.

Children with a suspected genetic cause (n=70), presented in 43% with a positive family history for SNHL, 39% presented with a suspected syndrome associated with SNHL and 18% had a gene mutation of unknown pathogenicity, or a single heterozygous variant in a gene (predominantly in the SLC26A4 gene) known to cause SNHL with autosomal recessive inheritance. Fourteen (20%) of these children had USNHL and 56 (80%) bilateral SNHL (Supplementary table 2).

Table 3. Genetic causes confirmed by DNA analysis or metabolic screening tests.

Genetic	Syndrome/disease	Gene	**Total (n)**	**Unilateral (n)**	**Bilateral (n)**
			87	**6**	**81**
Non-syndromic			46	2	44
AR	DFNB1*	GJB2/6	27	2	25
	DFNB7/11	BSND7	1	-	1
	DFNB8	TMPRSS3	1	-	1
	DFNB9	OTOF	1	-	1
	DFNB16	STRC	5	-	5
	DFNB18	USH1C	1	-	1
	DFNB22	OTOA	2	-	2
	DFNB28	TRIOBP	1	-	1
AD	DFNA1	DIAPH1	1	-	1
	DFNA3	GJB2/6	2	-	2
	DFNA4	MYH14	1	-	1
	DFNA10	EYA4	2	-	2
	DFNA22	MYO6	1	-	1
Syndromic			41	4	37
AR	Brown-Vialetto-Van-Laere syndrome	SLC52A2	1	-	1
	Chudley McCullough syndrome	GPSM2	1	-	1
	DFNMYP syndrome**	SLITRK6	1	-	1

Table 3. Continued

Genetic	Syndrome/disease	Gene	**Total (n)**	**Unilateral (n)**	**Bilateral (n)**
			87	**6**	**81**
	Hurler syndrome***	IDUA	1	-	1
	Niemann Pick disease type B	SMPD1	1	1	-
	Pendred syndrome	SLC26A4	10	-	10
	Usher syndrome	MYO7A, USH2A	6	-	6
	Walker warburg syndrome	POMT1	1	-	1
AD	Ayme-Gripp syndrome	MAF	1	-	1
	CHARGE	CHD7	3	1	2
	Primrose syndroom	ZBTB20	1	-	1
	Stickler syndrome	COL9A1	5	-	5
	Waardenburg syndrome	PAX3, SOX10	2	1	1
Chromosomal	Velo-cardio-facial syndrome	-	1	-	1
	Down syndrome	-	3	1	2
X-linked	Alport syndrome	COL4A5	1	-	1
	Hunter syndrome	IDS	1	-	1
	Turner syndrome	X(q21)	1	-	1

*AR = autosomal recessive, AD = Autosomal dominant, CHARGE; coloboma, heart defect, atresia choanae, retarded growth and development, genital, and ear abnormality. *One patient was diagnosed with DFNB1 based on DNA confirmed DFNB1 diagnosis in a sibling with SNHL** Deafness and myopia syndrome. *** Hurler syndrome was established by metabolic screening test.*

Imaging

Radiologic imaging was performed in 321 children (76%), of which 112 children had USNHL and 209 had bilateral SNHL. 90 children (28%) underwent CT as a single modality, 110 children (34%) underwent MR as a single modality, and 122 children (38%) underwent both modalities. The overall prevalence of relevant findings on imaging was 38%. Of all identified abnormalities, 60 % was located within the labyrinth, 15 % in the cochlear nerve and 25 % in the brain. Detailed description of the type of abnormality has been reported elsewhere (24,25).

The diagnostic yield of imaging is higher in children with USNHL than in children with bilateral SNHL (48% vs. 32%). Profound hearing loss is associated with the highest chance of finding a radiological abnormality (p<0,01). In contrast, the probability of finding an abnormality with CT or MR imaging was comparable between the different age groups (42% vs. 34%, p=0,13).

Laboratory and other tests

Congenital CMV was diagnosed in a large proportion of the tested patients (35/165; 21%). Two children had a negative CMV PCR but clear and specific clinical signs and MR findings associated with CMV infections and were therefor diagnosed as patients with congenital CMV by the pediatric neurologist. Twenty children with a congenital CMV infection had bilateral SNHL (20/37; 54%) (Figure 2). We identified a congenital CMV infection in a significantly higher proportion of children with USNHL compared to children with bilateral SNHL (37% vs. 17%, p<0.01). In children with a congenital CMV infection, the severity of the hearing loss is usually profound, milder hearing loss was significantly less frequently observed (p<0.01).

Metabolic screening tests were performed upon indication in 57/423 (13%) children. In 3/423 (1%) patients, had a metabolic disorder was identified (Mucopolysacharidose type I (n=1), Mucopolysacharidose type II (n=1) and Niemann Pick disease (n=1). Urinalysis was performed in 19 (4%) children, one of whom had an abnormality which contributed to the diagnosis of Alport syndrome. An electrocardiogram was performed in 53 (12%) children, in 2 patients an abnormality was identified (in one case related to CHARGE syndrome and the other related to the disease of Niemann Pick. Ophthalmologic examination was performed in 243 children (57%), of which 38 had USNHL and 205 bilateral SNHL. Abnormalities were identified in 84 (35%) children. Twelve children (5%) had eye abnormalities related with syndromic SNHL (i.e. retinitis pigmentosa and coloboma) or congenital CMV infection (chorioretinitis). The remaining children had refractive disorders or strabismus.

DISCUSSION

Using a stepwise diagnostic approach, we could identify an etiological diagnosis in 67% in children with uni- and bilateral SNHL (Figure 3). This diagnostic yield is comparable to previous reports (55%-81%) (3,5,6,14,19,29).

Unilateral vs. bilateral SNHL

The majority of children that were referred for etiological diagnostics suffered from bilateral SNHL (71%). Whereas the chance of identifying an etiological diagnosis is comparable for USNHL and bilateral SNHL (67% vs. 67%), the distribution of etiologies

differs between both groups. The most frequent etiology in children with USNHL was an isolated structural anomaly of the temporal bone, while in children with bilateral SNHL the most common cause was a genetic variant affecting gene function (in short: variant) (21, 29).

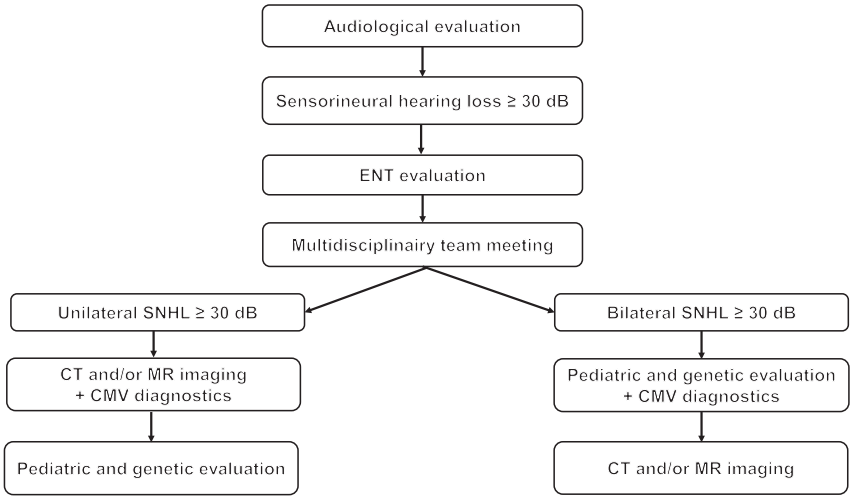


Figure 3. Diagnostic flow chart for children with both unilateral and bilateral sensorineural hearing loss. The results of the first step will direct further examination. Deviations from the protocol may be indicated by the multidisciplinary team (i.e. family history, medical indications or cochlear implant procedure).

Age and degree of hearing loss

The probability of finding an etiologic diagnosis is significantly higher in children with profound SNHL (11,29). In the current study, we also find a higher diagnostic yield in the youngest age group, and both age and severity of hearing loss are independent prognosticators for finding an etiologic diagnosis. However, the diagnostic yield in older pediatric patients, and patients with milder hearing losses is still considerable (Table 2).

Imaging

CT and/or MR imaging was performed in 76% of the patients. Imaging is an essential part of the etiologic analysis of (U)SNHL because of the high prevalence of causative abnormalities that can be identified with radiology (38% in our population). In agreement with previous reports, we find a higher ratio of causative abnormalities in children with USNHL (49%) compared to children with bilateral SNHL (32%), indicating a higher diagnostic yield of imaging in children with USNHL (3,9,30). Because of this, we

recommend performing radiology as the first diagnostic step in patients with USNHL, and genetic evaluation as the first step in bilateral SNHL. We recommend performing CT imaging as the first modality of choice in USNHL, followed by MR imaging if CT results are negative (Supplemental figure 1), and MR imaging in bilateral SNHL (24,25). By performing the modality with the highest diagnostic yield first, additional diagnostics may be avoided, minimizing the impact on the patient and reducing costs.

Genetic evaluation

We found that the diagnostic yield of DNA testing is considerably higher in children with bilateral SNHL than in children with USNHL (27% vs. 5%). In agreement with previous reports, variants of the *GJB2* gene were the most prevalent genetic cause (30%) (1,9,11,14,17,21,29). We found an equal distribution of syndromic and non-syndromic genetic etiologies, in contrast with the reported dominance of non-syndromic diagnoses (1, 19,28). The Pendred spectrum was the most common syndromic diagnosis in our cohort (10%). While this is in accordance with some previous reports, others find that Waardenburg or Usher syndrome are more prevalent (17,28).

Congenital CMV infection

Congenital CMV infection is by far the most prevalent acquired cause of congenital SNHL in this study, an observation that is in line with previous reports. (7,13). In our study population, congenital CMV infection was found in 9% of all included children, and in 21% of children tested for CMV. With the growing recognition of congenital CMV infections as a cause of SNHL, CMV tests are nowadays performed in all children that present with SNHL, but in the first years of this study, this evaluation was not standard protocol. In addition, a neonatal screening program for congenital CMV infections has not yet been introduced in The Netherlands, and the diagnosis relies on CMV PCR using the Guthrie card. As this is available until the age of 5 years in The Netherlands, children that present after the age of 5 cannot be reliably tested for congenital CMV infections. The hearing loss of most of the children with congenital CMV in this cohort was classified as profound, which is in line with prior studies (8,19). We found that the diagnostic yield of the screening for congenital CMV infections is higher in children with USNHL than in children with bilateral SNHL (37% vs. 17%). With the possible advent of newborn screening programs for congenital CMV infections, the diagnosis of congenital CMV may become even more prevalent (8,12).

Limitations

Due to the stepwise approach towards the etiological diagnosis, not all children underwent the same etiological diagnostics. In addition, deviations from the protocol were sometimes indicated by the multidisciplinary team. Reasons to deviate from the protocol were medical indications (e.g. meningitis), a cochlear implant procedure or upon parental request. As a consequence, radiology was performed more often in children with unilateral SNHL, and genetic evaluation was performed more frequently in children with bilateral SNHL. The diagnostic yield of these modalities can therefore not be reliably compared between these two groups of children. If a cause was found by the first diagnostic modality, an additional diagnostic test was not always performed, and an additional cause for SNHL may have been missed in children with multiple etiologies. In our cohort, 2 children were identified with multiple possible causes for SNHL: in one child, a cochlear nerve aplasia was found as well as a GJB2 gene variant, in the other a congenital CMV infection was identified as well as Down syndrome. Performing all etiological tests in all children could possibly increase the detection rate of children suffering from multiple etiologies, however this should be weighed against the additional costs and impact on all children undergoing etiological evaluation for SNHL.

CONCLUSION AND RECOMMENDATIONS

The chance of identifying the cause of SNHL in children is high. Using our stepwise diagnostic approach, we found a diagnostic yield of 67%, both in children with uni- and bilateral SNHL (Figure 3). Bilateral SNHL often has a genetic cause, whereas in unilateral SNHL structural abnormalities of the labyrinth are the dominant etiologic factor. Based on these results we start the etiologic diagnostic work-up with genetic evaluation in children with bilateral SNHL, and with radiology in children with USNHL (Supplementary figure 1). Congenital CMV infections are a cause for both uni- and bilateral SNHL, and we recommend evaluation of congenital CMV infections in all children that present with SNHL. The highest proportion of causative abnormalities are found in children younger than 1 year and in children suffering from profound hearing loss. However, the diagnostic yield in older pediatric patients, and patients with milder hearing losses is still considerable. We therefor offer etiological diagnostics to all pediatric patients with SNHL exceeding 30dB, irrespective of age or degree of hearing loss.

Supplementary table 1 List of gene variants

Gene	Variant 1 nucleotide change
USH2A	C.7950dup; p.(Asn2651fs)
USH2A	c.1256G>T; p.(Cys419Phe)
USH2A	c. 15089C>A;p.(Ser5030X)
MYO6	c.-3_1delinsTT (p.?)
GJB2	c.109G>A; p.(Val37Il)
GJB2	c.109G>A; p.(Val37Il)
GJB2	c.35del; p.(Glyfs)
GJB2/6	c.35del; p.(Gly12fs)
GJB2	c.35del; p.(Gly12fs)
GJB2	c.35del; p.(Gly12fs)
GJB2	c.35del; p.(Gly12fs)
SOX10	c.482G>A; p.(Arg161His)
PAX3	c.808C>T; p.(Arg270Cys)
CHD7	c.8077-2A>C (spl.?)
CHD7	c.2520G>A; p.(Trp840*)
GJB2	c.223C>T; p.(Arg75Trp)
GPSM2	c.742del; p.(Gly249fs)
EYA4	c.1234del; p.(Met412X)
GJB2	c.126G>T; p.(Glu42Asp)
GJB2	c.109G>A; p.(Val37Ile)
SMPD1	c.308T>C; p.(Leu103Pro)
COL4A5	c.2513dupT; p.(Leu838Phefs*17)
USH2A	c.7121-8313_11048-962delins12 (deletion exon 38 - 56)
GJB2	(c.109G>A(p.Val37Ile)
GJB2/6	c.35 delG; p.(Gly12fs)
GJB2	c.250G>A; p.(Val84Met)
MYO7A	c.3109-2A>G (r.spl?)
ZBTB20	c.1794C>G; p.(Phe598Leu)
G JB 2	c.35del; p.(Gly12fs)
DIAPH1	c.3637C>T; p.(Arg1213X)
GJB2/6	c.269T>C; p.(Leu90Pro)
SLC26A4	c.1790T>C; p .(Leu597Ser)

Variant 2 nucleotide change	Zygosity	Segragation with HI
C.10561T>C; p.(Trp3521Arg)	compound het	Yes
c.2299del; p.(Glu767fs)	compound het	Yes
(c.6713A>C;p.Glu2238Ala) + (c. 12294+3A>G;p.?)	compound het	Yes
	het	Yes
c.109G>A; p.(Val37Il)	hom	ND
c.109G>A; p.(Val37Il)	hom	Yes
c.35del; p.(Glyfs)	hom	ND
c.35 del; p.(Gly12fs)	hom	ND
c.35del; p.(Gly12fs)	hom	Yes
c.35del; p.(Gly12fs)	hom	Yes
c.35del; p.(Gly12fs)	hom	ND
	het	De novo
	het	Yes
	het	ND
	het	De novo
	het	Yes
c.742del; p.(Gly249fs)	hom	Yes
	het	ND
	het	Yes
c.109G>A; p.(Val37Ile)	hom	ND
c.308T>C; p.(Leu103Pro)	hom	Yes
	het	ND
c.5813G>A; p.(Gly1938Asp) + c.15017C>T; p.(Thr5006Met)	compound het	Yes
(c.109G>A(p.Val37Ile)	hom	Yes
del 342kb	compound het	Yes
p.109G>A; p.(Val37Ile)	compound het	Yes
c.3476G>T; (p.(Gly1159Val)	compound het	Yes
	het	De novo
c.71G>A; p.(Trp24X)	compound het	Yes
	het	ND
	compound het	Yes
c.1790T>C; p .(Leu597Ser)	hom	Yes

Supplementary table 1 Continued

Gene	Variant 1 nucleotide change
IDS	c,998C>T; p.(Ser33Leu)
COL9A2	c.406C>T; p.(Arg136)
GJB2	c.35del; p(Gly12fs)
SCL26A4	c.412G>T; p.(Val138Phe)
TRIOBP	c.3460_3461; p.(Leu1154fs)
SLC26A4	c.505del; p.(Thr169fs)
CHD7	c,2959C>T; p.(arg987X)
MAF	c.197C>G; p.(Ser66Trp)
GJB2	c.-3170G>A
OTOF	c.505C>T; p.(Arg169Trp)
GJB2	c.-23+1G>A
GJB2	c.358_360 del; p.(Glu120del)
TMPRSS3	c.916G>T; p.(Ala306Thr)
COL11A2	c.3877C>T; p.(Arg1293*)
GJB2	c.35del; p.(Gly12fs)
CATSPER2 and STRC	15q15.3
CATSPER2 and STRC	15q15.3
GJB2	c.35del; p.(Gly12fs)
MYO7A	c.5618G>A; p.(1873Gln)
SLC26A4	c.707T>C; p.(Leu236Pro)
OTOG	c.1009C>T; p.(Gln337*)
SLC52A2	c.167C>T; p.(Ala56Val)
GJB2	c.35del; p.(Giy12fs)
CATSPER2 and STRC	15q15.3
OTOA	c.2207G>A; p.(Gly736Glu)
STRC	exon 19-26
SLITRK6	c.1438del; p.(Ser480fs)
COL9A2	c.406C>T; p. (Arg136*)
SLC26A4	c.85G>C; p.(Glu29Gln)
GJB2	c.235del; p.(Leu79fs)
GJB2	(c.35del p.(Gly12fs)
COL11A1	c.1798C>T; p.(Arg600X)

Variant 2 nucleotide change	Zygosity	Segragation with HI
	hemi	Yes
c.406C>T; p.(Arg136)	hom	ND
c.358_360del; p.(Glu120del)	compound het	Yes
c.707T>C; p.(Leu236Pro)	het	Yes
c.3232dup; p.(ARg1078fs)	compound het	Yes
c. 1334T>G; p.(Leu445Trp)	compound het	Yes
	het	ND
	het	De novo
c.-3170G>A	hom	ND
c.505C>T; p.(Arg169Trp)	hom	Yes
c.71G>A; p.(Trp24X)	compound het	Yes
c.-23+1G>A	compound het	ND
c.413C>A; p.(Ala138Gln)	compound het	Yes
	het	De novo
c.101T>C; p.(Met34Thr)	compound het	Yes
15q15.3	hom	ND
15q15.3	hom	ND
c.109G>A; p.(Val37Ile)	compound het	Yes
c.6028G>A; p.(Asp2010Asn)	compound het	Yes
c.1334T>G; p.(Leu445Trp)	compound het	Yes
c.7454del; p.(Arg2485fs)	compound het	ND
c.593G>A; p.(Trp198*)	compound het	ND
c.35del; p.(Giy12fs)	hom	Yes
15q15.3	hom	ND
exon 1 - 21	compound het	Yes
exon 19-26	hom	Yes
c.1438del; p.(Ser480fs)	hom	Yes
c.406C>T; p. (Arg136*)	hom	Yes
c.1151A>G; p.(Glu384Gly)	compound het	Yes
c.427C>T;p. (Arg143Trp)	compound het	ND
c.427C>T: p.(arg143Trp)	compound het	ND
	het	De novo

Supplementary table 1 Continued

Gene	Variant 1 nucleotide change
GJB2	c.313_326del; p.(Lys105fs)
TMC1	c.247G>T; p.(Glu83X)
OTOA	c.2359G>T; p.(Gly787X)
STRC	exon 19 - 26
GJB2	c.35del; p.(Gly12fs)
GJB2	c.109G>A; p.(Val37Ile)
SLC26A4	c.707T>C (p.Leu236Pro)
GJB2	c.35del; p.(Gly12fs)
SLC26A4	c.1001+1G>A
SLC26A4	c.1784G>A; p.(Gly595Glu)
SLC26A4	c.1001+1G>A (p.?)
SLC26A4	c.84C>A; p.(Ser28Arg)
SLC26A4	c.412G>T; p.(Val138Phe)
SLC26A4	c.1246A>C; p.(Thr416Pro)
SLC26A4	c.707T>C; p.(Leu236Pro)
SLC26A4	c.1198del; p.(Cys400fs)
CHD23	c.5117G>A; p.(Arg1706His)
LOXHD1	c.2696G>C; p.(Arg899Pro)

Abbreviations: Het: heterozygous. Hom: homozygous. Hemi: hemizygous. ND: not determined or not conclusive.

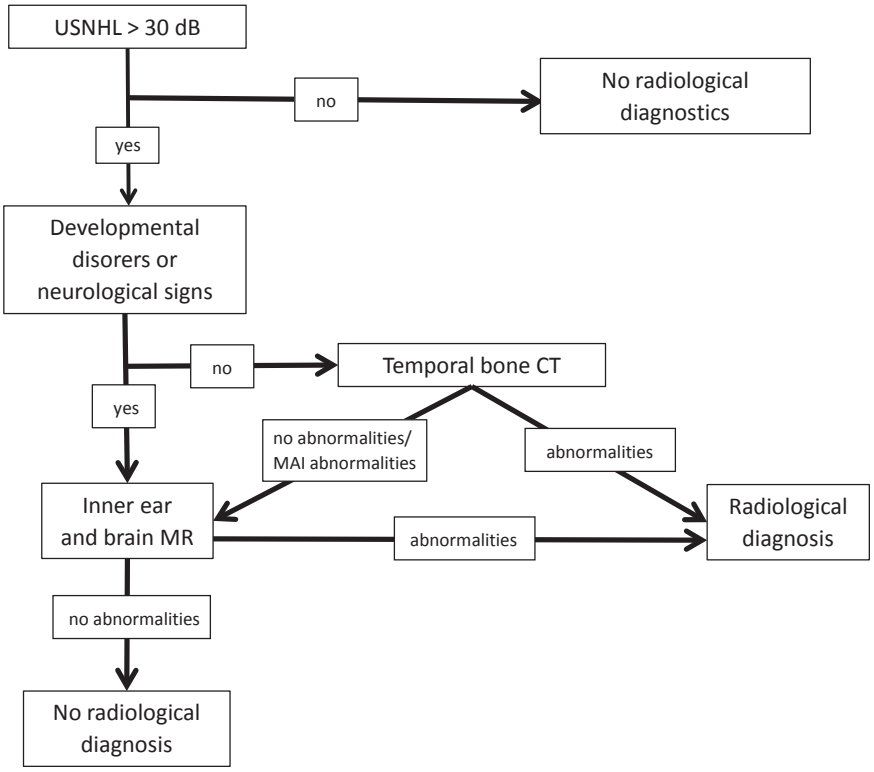
Supplementary table 2 Overview of the suspected genetic causes.

Suspected genetic category	N= 70
Non syndromal	35
Positive family history for SNHL	29
Syndromal	27
Single heterozygote SLC26A4 mutation	8
Unilateral EVA	1
Bilateral EVA	7

Variant 2 nucleotide change	Zygosity	Segragation with HI
c.101T>C; p.(Met34Thr)	compound het	Yes
c.1763+3A>G; (r.spl?)	compound het	Yes
c.2359G>T; p.(Gly787X)	hom	ND
exon 19 - 26	hom	Yes
c.-23+1G>A (r.spl?)	compound het	Yes
c.44A>C; p.(Lys15Thr)	compound het	Yes
c.1342-2A>C	compound het	Yes
c.269T>C; p.(Leu90Pro)	compound het	Yes
no second variant found	het	ND
no second variant found	het	ND
no second variant found	het	ND
no second variant found	het	Yes
no second variant found	het	ND
no second variant found	het	ND
no second variant found	het	Yes
no second variant found	het	ND
c.5945A>G; p.(Asn1982Ser)	compound het	Yes
c.5934C>T; (r.spl?)	compound het	Yes

Supplementary table 3 Overview of the acquired causes and risk factors for SNHL identified in this study, categorized according to the American Academy of Pediatrics.

Etiology: acquired causes and risk factors	Number
Congenital TORCH infection	38
CMV	36
Meningitis	13
Hyperbilirubinemia requiring exchange transfusion	2
Asphyxia	8
Pre- and dysmaturity, NICU stay longer than 5 days	14
Trauma	2
Total	75



Supplementary figure 1. Flowchart of imaging in children with USNHL. USNHL = unilateral sensorineural hearing loss. CT = computed tomography. MR = magnetic resonance imaging. IAC = internal auditory canal.

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EVALUATION OF THE OUTCOME OF CT AND MR IMAGING IN PEDIATRIC PATIENTS WITH BILATERAL SENSORINEURAL HEARING LOSS

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ABSTRACT

Objective: To evaluate the clinically relevant abnormalities as visualized on CT and MR imaging in children with symmetric and asymmetric bilateral sensorineural hearing loss (SNHL), in relation to age and the severity of hearing loss.

Study design: Retrospective cohort study.

Setting: Tertiary referral otology and audiology center.

Patients and diagnostic interventions: From January 2006 until January 2016, a total of 207 children diagnosed with symmetric and asymmetric bilateral SNHL were included. They underwent CT and/or MR imaging for the evaluation of the etiology of their hearing loss.

Main outcome measures: Radiologic abnormalities associated with SNHL.

Results: 302 scans were performed in 207 children (median age of 0.8 years old) with bilateral SNHL. The most frequently identified cause of bilateral SNHL was a malformation of the labyrinth. The combined diagnostic yield of CT and MR imaging was 32%. The diagnostic yield of MR (34%) was considerably higher than that of CT (20%). We found a higher rate of abnormalities in children with profound hearing loss (41%) compared to milder hearing loss (8–29%), and in asymmetric SNHL (52%) compared to symmetric SNHL (30%).

Conclusion: Imaging is essential in the etiologic evaluation of children with bilateral SNHL. The highest diagnostic yield is found in children with bilateral asymmetric SNHL or profound SNHL. Based on our findings, MR is the primary imaging modality of choice in the etiological evaluation of children with bilateral SNHL because of its high diagnostic yield.

INTRODUCTION

Sensorineural hearing loss (SNHL) in pediatric patients may be present at birth or become apparent later during infancy. In both cases, the cause of the hearing loss may be hereditary or acquired. Congenital hearing impairment is the most common birth defect, with an incidence of 1,9 in 1000 newborns in the Netherlands and 1 to 3 per 1000 births worldwide (1,2). In the Netherlands, congenital hearing loss is detected at a very early age by the current newborn hearing screening program provided by the Dutch Child Health and Welfare service (JGZ) which was implemented from 2002 to 2006 (3). Currently, 96,5% of the newborn in The Netherlands are screened for hearing impairment (1). Screening for hearing loss during the newborn period has led to early detection and diagnosis of SNHL, facilitating timely intervention (4,5). Congenital hearing loss is nowadays generally detected within the first weeks of life in The Netherlands, however hearing loss may also be diagnosed later during infancy, because of a late onset (due to acquired pathologies such as infection or trauma) or a progressive nature of hereditary etiologies. Whereas adequate and timely revalidation has been the primary goal of newborn hearing screening, it has also sparked the interest in the causes of pediatric SNHL. In addition to genetic and laboratory testing, imaging by computed tomography (CT) and/or magnetic re- sonance (MR) imaging has become an essential part of the evaluation of pediatric SNHL (6–8). CT and MR imaging are regarded as complementary modalities. CT is considered a better modality for the identification of bony abnormalities, while MR imaging provides superior information about the cochlear nerve, the intracranial structures, and early stages of fibrosis in cases of meningitis [9]. Previous studies of children with SNHL show temporal bone abnormalities in 18–37% when CT is performed, or 24–33% when MR imaging is performed as a single modality (6,7). Combined, the overall reported diagnostic yield is 25–38% (10,11).

Children with SNHL form a heterogeneous group of patients, with a varying age at detection and varying degrees of hearing loss. These different patient groups may represent different SNHL etiologies, resulting in a different radiologic outcome and yield. Here, we evaluate the prevalence and spectrum of causative radiological abnormalities in children with bilateral SNHL and their associations with the severity of the hearing loss, the symmetry of the hearing loss and the age at diagnosis.

MATERIALS AND METHODS

Patients

Patients between 0 and 18 years of age diagnosed with bilateral SNHL were referred for etiological evaluation to the VU University Medical Center (VUmc) in Amsterdam, The Netherlands. The majority of these children was referred directly after detection of their hearing loss by the Dutch newborn hearing screening, and subsequent bilateral SNHL was confirmed by the audiological center of the VUmc or other regional audiology centers. In some cases, the detection of SNHL or need for etiological evaluation arose later in life and referral took place at an older age, either by audiology centers, general practitioners, the Dutch child health and welfare service, or otorhinolaryngologists. At the VUmc, the etiological evaluation was performed by a dedicated multidisciplinary team (The Center for Diagnostics of Sensorineural hearing loss (CDS)). It consists of otologists, audiologists, pediatricians, clinical geneticists, neuroradiologists and, if indicated, neurologists or ophthalmologists.

Age

The age at detection was defined as the age at which the hearing loss was first diagnosed by the Audiology Center, either by ABR of PTA. Patients were categorized in 4 age groups: 0–1 year old, 1–6 years old, 6–12 years old and 12–18 years old.

Audiometric evaluations

The first test of the Dutch newborn screening protocol is performed at home and consists of transient evoked otoacoustic emissions (TEOAE). Children who fail the first test are retested using TEOAE, and subsequently using automated auditory brainstem measurements (AABR). Children admitted at a Neonatal Intensive Care Unit (NICU) are screened in the hospital by AABR. Children who fail all tests are referred within three weeks to an audiology center for further investigation for Automated Auditory Brainstem Response (AABR) in newborn children, or age-appropriate assessment like Visual Reinforcement Audiometry (VRA), Behavioral Observation Audiometry (BOA) or pure tone audiometry (PTA) in older children. To determine the ABR thresholds (dB nHL) we used a clear appearance of wave V upon clicks. For the estimated behavioral hearing thresholds around 3 kHz (dB eHL) we use a correction of 10 dB. When PTA is performed, an average threshold at 500, 1000, 2000 and 4000 Hz is used for the analysis.

Children were diagnosed with SNHL if the sensorineural hearing threshold at the best hearing ear 30 dB was or more. Asymmetric bi- lateral SNHL was defined as 1 or more frequencies with a greater than 30 dB difference, 2 or more frequencies with a greater

than 15 dB difference or 3 or more frequencies with a greater than 10 dB difference in threshold between the left and right ear. The hearing loss category was based on the hearing level of the most severely affected ear.

Hearing loss was categorized as a slight impairment (26–40 dB), moderate impairment (41–60 dB), severe impairment (61–80 dB) and profound impairment (81 dB or greater) according to the commonly used classification of the World Health Organization (WHO). In case of mixed type hearing loss, the inclusion and consecutive analyses were based on the sensorineural component only. Patients with pure conductive hearing loss were excluded from this study.

Evaluation of imaging

The decision to obtain imaging and the choice of imaging modality was individualized per patient and made by the CDS multidisciplinary team in close consultation with the parents.

The majority of the imaging was performed at the VUmc, Amsterdam, The Netherlands, following a standard temporal bone CT protocol, consisting of non-contrast axial 0.6 mm slices. Coronal and sagittal reconstructions (0.6 mm thickness) were performed, as well as axial reconstructions following the plane of the lateral semicircular canal. The MR imaging protocols of the brain and temporal bone include transversal T2 weighted, transversal FLAIR, sagittal 3D gradient- echo sequences and axial 3D constructive interference steady state (CISS) or FIESTA-C images centered at the level of the internal auditory canal. In some cases, imaging was performed in the referring center using a local CT and/or MR imaging protocol. These scans were re- evaluated by a radiologist and the otologist of the CDS multidisciplinary team.

The imaging was evaluated with a focus on abnormalities associated with sensorineural hearing loss at the level of the middle ear, the inner ear, the inner auditory canal (IAC), the cochlear nerve and the brain. The inner ear abnormalities included acquired pathologies and congenital malformations, which were classified as cochlear aplasia, cochlear hypoplasia, common cavity, incomplete partition type I and II, isolated enlarged vestibular aqueduct (EVA) (defined as a vestibular aqueduct diameter exceeding 1,5 mm, measured halfway between the common crus and the medial aspect of the opening of the operculum on the posterior wall of the temporal bone), isolated lateral semicircular canal dysplasia, vestibular hypoplasia, and malformations of the cochlear nerve [12]. With regard to abnormalities at the level of the labyrinth and IAC each side was evaluated separately. The brain abnormalities were categorized in diagnostic findings (i.e., signs of CMV), associated findings (i.e. signs of asphyxia, vasculopathy, hydrocephalus,

encephalitis) or non-associated findings (i.e. aspecific white matter abnormalities). The evaluation of the CT and/or MR imaging of the temporal bone and brain was performed by an experienced neuroradiologist and an otologist. In case of disagreement, joined evaluation by the neuroradiologist and otologist was performed in order reach consensus.

Statistical analysis

Statistical analyses were performed using SPSS 22.0. The criterion for statistical significance was set at $p < 0,05$. Descriptive analyses and cross tables were used to outline results of this study. In order to evaluate the correlation between age and hearing loss, logistic regression was used.

RESULTS

Clinical characteristics

From January 2006 until January 2016, a total of 425 children with SNHL were evaluated by the CDS multidisciplinary team, 303 of which had symmetric or asymmetric bilateral SNHL (> 30 dB). Of these 303 children, 96 were excluded because no imaging was performed, either because the cause of the hearing loss was already identified by the pediatric and/or genetic evaluation or by parental request and imaging was deemed of no additional diagnostic value. The main objective of the imaging in the majority of remaining 207 children was the identification of the etiology of the hearing loss, but in some cases with profound hearing loss, it was also performed as part of the work-up for cochlear implantation. The age of diagnosis of the hearing loss ranged from one month to 17 years (an overall median of 0,8 years) (Table 1). One hundred and five children were diagnosed before the age of 1 year (51%) and referred to the CDS multidisciplinary team directly after the newborn hearing screening. One hundred and two children were referred to the CDS at an older age.

Imaging results

A total of 302 radiological investigations were performed in 207 children. 39 children underwent a CT scan only, 73 children underwent MR imaging only, and 95 underwent both. Overall, a causative abnormality was found in 66 children (32%). The inner ear was the most frequently affected site (61% of abnormal scans), and an isolated EVA was the most commonly found abnormality (24%). Different abnormalities in the left and right ear was found in 3 patients with bilateral SNHL (5%). In 1 patient an EVA was diagnosed only on the left side, in 1 patient an isolated deformity of the right LSCC was identified, and in1 patient a narrow internal auditory canal and associated cochlear nerve hypoplasia was found only on the right side. CT was performed as a single modality in 39 children,

identifying a causative abnormality in 10/39 patients (26%). MR imaging was per- formed as a single modality in 73 children, identifying abnormalities in 26/73 patients (36%). When both imaging modalities were performed (in 95 children), an abnormality was found in 32% of the patients (Table 1). The majority of abnormalities identified by CT consisted of abnormalities of the inner ear (81%). The abnormalities detected on MR imaging also mainly consisted of abnormalities of the inner ear (52%) but also comprised anomalies of the brain (38%) (Table 2A and 2B).

Degree of hearing loss and age

The hearing loss was detected by ABR in 125 children and by PTA in 82 children. Twenty-five children were diagnosed with slight SNHL, 48 with moderate SNHL, 28 with severe SNHL and 106 with profound SNHL (Table 3A). Of the 207 children, 21 had asymmetrical SNHL and 186 had symmetric bilateral SNHL. A significant difference in the prevalence of causative abnormalities on imaging in was found between these two groups: in 11/21 (52%) of children with asymmetric SNHL, vs. in 55/ 186 (30%) of children with symmetric SNHL ($p = 0{,}03$) (Table 3A). We found a significant higher prevalence of radiologic abnormalities in the youngest age group ($p = 0.01$) as well as in patients with the most severe hearing loss ($p = 0.01$). However, we also found a significant association between age and degree of hearing loss, i.e. the most severe hearing loss category is overrepresented in the youngest age group ($p < 0.01$). Using a likelihood ratio test we found that hearing loss is of significant added value to age ($p = 0.01$) but that age is of no additional value to severity of hearing loss ($p = 0.05$). This suggests that the severity of hearing loss, and not age, is the dominant factor.

Dual imaging

In the 95 children that underwent both modalities, the number and type of relevant findings detected by CT were compared to the number and type of relevant findings detected by MR imaging (Table 4). Using both modalities, a cause for SNHL was identified in 32%. Concordant (positive or negative) CT and MR imaging findings were found in 82/95 patients (86%). When a causative abnormality was found, CT and MR imaging yielded concordant diagnoses. In fourteen children, abnormalities of the inner ear, cochlear nerve and brain were detected by MR imaging only (14%) (Tables 1, 2 and 4) (see Figure. 1). We therefore found a significantly higher diagnostic yield of MR compared to CT ($P < 0.01$) in this group of 95 children.

Table 1 Demographics and clinical characteristics of 207 children with SNHL who underwent CT and/or MR imaging in the etiological work-up.

Characteristics	Patient n	(%)	CT total n
Number of patients**	207		134
Sex n (M/F)	M 113	(55%)	M 77
	V 94	(45%)	V 57
Hearing loss***n			
Slight (26- 40 dB)	25	(12%)	12
Moderate (41–60 dB)	48	(23%)	21
Severe (61–80 dB)	28	(14%)	18
Profound (> 80 dB)	106	(51%)	83
Symmetric	186	(90%)	117
Asymmetric	21	(10%)	17
Age at diagnosis (median/range)	0,8	(0–17)	0,8
Abnormalities found (n/n %)	66/207	(32%)	27/134

*Age at diagnosis: median age and range in years at which the hearing loss was first diagnosed by an Audiology Center. * These 95 patients are copied from the columns CT and MR imaging, which means that they are mentioned twice in this table. **

Table 2A Type of abnormalities associated with SNHL as identified on CT and MR imaging.

Type of pathology	CT	(%)	MR	(%)	Total	(%)
Number of scans	134	(44%)	168	(56%)	302	
Labyrinth (total)	22 (+2)	(16%)	29 (+2)	(17%)	51 (+4)	(17%)
Obliteration/ ossification	0		8		8	
IP I	2 (+1)		3 (+1)		5 (+2)	
IP II	8 (+1)		5 (+1)		13 (+2)	
EVA	10		10		20	
Isolated lateral SCC dysplasia	2		3		5	
Narrow internal auditory canal/ Cochlear nerve hypo/aplasia	4	(3%)	6	(4%)	10	(3%)
Brain abnormalities (total)	1	(1%)	21 (+1)	(12%)	22 (+1)	(7%)
Diagnostic abnormality	0		8 (+1)		8 (+1)	
Associated abnormality	1		13		14	
Non-associated abnormality	0		6		6	
No abnormalities	107	(80%)	112	(67%)	219	(72%)

(%)	MRI total n	(%)	Both (CT + MRI)*	(%)
	168		95	
(58%)	M 95	(56%)	59	(62%)
(42%)	V 73	(43%)	36	(38%)
(9%)	18	(11%)	5	(5%)
(16%)	35	(21%)	8	(8%)
(13%)	23	(14%)	13	(14%)
(62%)	92	(55%)	69	(73%)
(87%)	152	(91%)	83	(87%)
(17%)	16	(9%)	12	(13%)
(0–16)	0,6	(0–16)	0,3	(0–17)
(20%)	57/168	(34%)	30/95	(32%)

** 302 scans were performed in 207 children. *** Hearing loss categories according to the WHO classification [14].*
CT = temporal bone computed tomography. MR = magnetic resonance imaging.

Table 2B Type of abnormalities associated with asymmetric and symmetric bilateral SNHL.

Type of pathology	Asymmetric SNHL	(%)	Symmetric SNHL	(%)	Total	(%)
Number of scans	33	(11%)	269	(89%)	302	
Labyrinth (total)	12	(36%)	39 (+4)	(14%)	51 (+4)	(17%)
Obliteration/ossification	1		7		8	
IP I	0		5 (+1)		5 (+2)	
IP II	5		7 (+2)		13 (+2)	
EVA	4		16		20	
Isolated lateral SCC dysplasia	2		3		5	
Narrow internal auditory canal/ Cochlear nerve hypo/aplasia	0	(0%)	10	(4%)	10	(3%)
Brain abnormalities (total)	3	(9%)	19 (+1)	(7%)	22 (+1)	(7%)
Diagnostic abnormality	1		7 (+1)		8 (+1)	
Associated abnormality	2		12		14	
Non-associated abnormality	1		5		6	
No abnormalities	18	(55%)	201	(74%)	219	(72%)

Table 3A Number of abnormalities found on CT and MR imaging, in relation to the type and the degree of hearing loss.

Hearing loss (dB)	Number of patients	%	Patients with abnormalities identified on CT and/or MR	%
Asymmetric	21	(10%)	11	(52%)
Symmetric	186	(90%)	55	(30%)
Slight (26–40 dB)	25	(12%)	2	(8%)
Moderate (41–60 dB)	48	(23%)	14	(29%)
Severe (61- 80 dB	28	(14%)	7	(25%)
Profound (80 dB or greater)	106	(51%)	43	(41%)

Table 3B Number of abnormalities found on CT and MR imaging, related to the age categories.

Age category (years)	Number of patients	%	Abnormalities identified on CT and/or MR	%
0–1	105	(51%)	42	(40%)
1–6	63	(30%)	17	(27%)
6–12	32	(15%)	7	(18%)
12–18	7	(3%)	0	(0%)
Total	207	(100%)	66	(32%)

Age at diagnosis: the age at which the hearing loss was first diagnosed by an Audiology Center. In patients with asymmetric hearing loss the percentage of causative abnormalities identified by CT and/or MR imaging is higher than in patients with symmetric hearing loss (p =0,03). Likewise, the highest diagnostic yield of CT and/or MR imaging is found in the most severe hearing loss category (hearing loss categories according to the WHO classification).

Table 4 Comparison between CT and MR imaging for positive and negative findings.

Imaging	Number of patients (total n = 95)	(%)	Type of abnormality
CT +/MR -	0	(0%)	–
CT -/MR +	13	(14%)	3 obliteration of the labyrinth, 2 cochlear nerve a- or hypoplasia, 4 CMV associated brain abnormality, 4 associated brain abnormalities.
CT +/MR +	17	(18%)	12 labyrinth abnormalities, 4 malformation of the internal auditory canal, 1 associated brain abnormality.
CT -/MR -	65	(68%)	–

+ = causative findings on the imaging. - = no causal findings on the imaging. CT = temporal bone computed tomography. MR = magnetic resonance imaging. SCC = semicircular canal total, 95 children underwent both imaging modalities. MR was able to detect 13 relevant abnormalities that were not seen on CT, whereas CT detected no relevant abnormalities that were not seen on MR. This was a significant difference (P < 0.01). Concordant (positive and negative) results were found in 82 cases (86%).

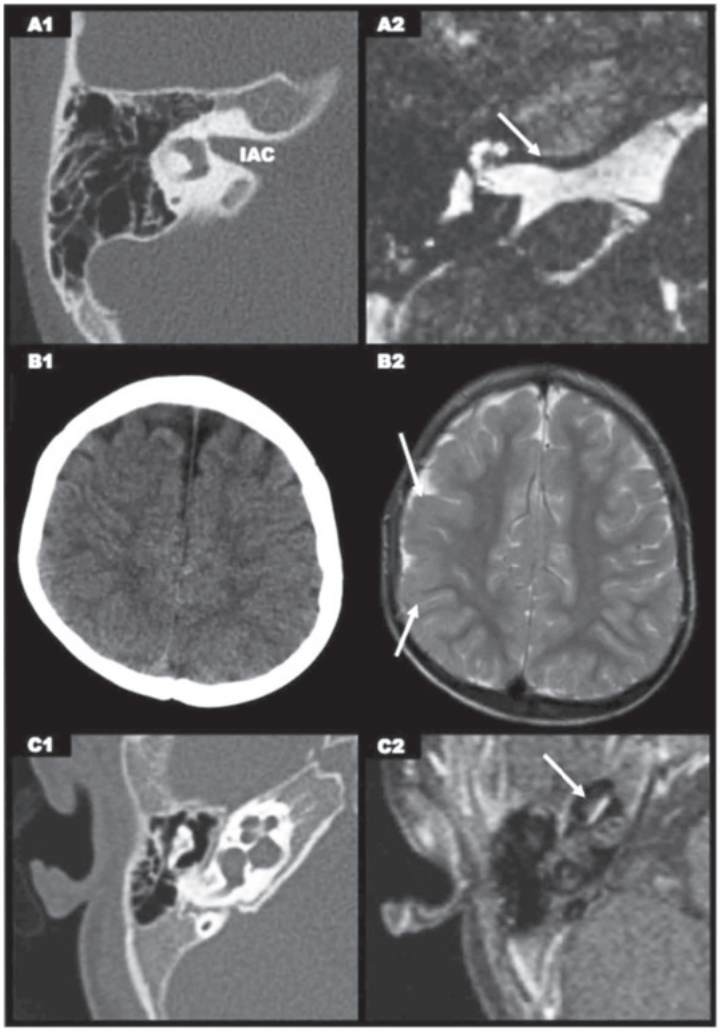

Fig. 1. Differences in CT and MR findings in children with bilateral sensorineural hearing loss. (A1 + A2) imaging of a patient with asymmetric bilateral sensorineural hearing loss (SNHL), (A1) Axial CT image showing a normal internal auditory canal (IAC), the cochlea was normal in this patient (not shown), (A2) Axial T2 weighted MR image of the same patient illustrating the absence of the cochlear nerve (white arrow). (B1 + B2) imaging of a patient suffering from congenital CMV infection. (B1) Axial CT image showing no intracranial abnormalities. (B2) Axial T2 weighted MR image illustrating signs of a CMV infection: anomaly of the cortical development, with marked thickening of the cortex, most probably polymicrogyria (white arrow). (C1 + C2) imaging the of a patient suffering from postmeningitic SNHL. (C1) Axial CT image showing no abnormalities of the right cochlea. (C2) contrast enhanced T1 weighted MR imaging showing enhancement of the basal turn of the right cochlea indicative of cochlear inflammation.

DISCUSSION

In this study we evaluate the outcome of CT and MR imaging in a large cohort of children with symmetric and asymmetric bilateral SNHL. There are several reasons to perform imaging in children with SNHL, even though it is usually not possible to reverse the SNHL regardless of the outcome of radiology. The prevalence of causative radiological findings in children with bilateral SNHL is considerable: 32% in the current study, similar to previous reports (25–38%) (10,11). A radiologic diagnosis may alert the physician to a syndromic cause or direct the choice of additional etiological diagnostics. Identifying the etiology of SNHL may assist in an adequate prognosis and help parents deal with the questions that are raised by a diagnosis of (congenital) SNHL in their child. In selected cases, the radiologic diagnosis may assist in management decisions, such as offering lifestyle advise (in case of EVA) or antiviral therapy (in case of a congenital CMV infection). In children with profound bilateral SNHL and an indication for cochlear implantation (CI), radiology is mandatory not only to clarify the etiology but also for the assessment of the feasibility of CI. These advantages of performing radiology must be weighed against the dis- advantages, including radiation exposure (in case of CT), the need for sedation (especially in case of MRI), and the additional costs.

The definition of a causative finding is an issue when considering the diagnostic yield and significance of radiology. Some radiologic findings, especially brain anomalies, are associated with SNHL but not a definite cause in itself. Examples of these are hypoxic-ischemic encephalopathy associated with asphyxia, a specific white matter abnormalities of the brain, ventricular dilatation, or hydrocephalus. In these cases, the radiology should be interpreted in the context of the clinical presentation and history, and the decision whether or not such an abnormality should be seen as causative of SNHL may depend on additional factors.

In the current study, we have evaluated the occurrence of causative radiologic abnormalities in relation to the type, the degree and the age at detection of bilateral SNHL. We found a significantly higher per- centage of causative radiologic findings in children with asymmetric bilateral SNHL compared to children with symmetric SNHL (52% vs. 30%). This higher prevalence seems more in line with the prevalence of causative abnormalities reported in unilateral SNHL (37–62%) (9–11,13). Differences between asymmetric and symmetric bilateral SNHL are also found for the prevalence of certain types of abnormalities. In asymmetric bilateral SNHL, abnormalities of the labyrinth are the dominant radiologic finding (80% of abnormal scans), with an isolated EVA as the most frequently encountered anomaly (27% of abnormal scans). In symmetric SNHL, the majority of causative findings is also found in the labyrinth (in 57% of abnormal scans), however other sites are more frequently affected (the brain in 28% and the cochlear nerve in 15%) (Table 2B).

Children with bilateral (symmetric and asymmetric) SNHL were diagnosed at a relatively early age (mean age 0,8 years old), probably due to the newborn hearing screening program and the obvious problems in communication and language and speech development induced by bilateral SNHL. The age at detection of the hearing loss is considerably younger than in children with unilateral SNHL (3,7–5,9 years old) (9,13).

We found the highest number of radiologic abnormalities in the youngest age group (40%) and in patients suffering from profound hearing loss (the most severe hearing loss category) (41%) (Table 3A and B). As patients suffering from profound hearing loss are over- represented in the youngest age group, we performed a likelihood ratio test in order to identify which factor determines the radiologic yield and found that the degree of hearing loss is the dominant factor. However, as the diagnostic yield is still considerable in milder hearing loss categories (8–29%), we feel that imaging is also relevant in the evaluation of the etiology of mild to moderate bilateral SNHL in children.

The ideal algorithm for the radiologic evaluation of children with SNHL is still subject of debate (8,14). Historically, CT has been the imaging modality of choice in children with SNHL (11). CT is considered the better modality for the identification of bony abnormalities. It has low costs and a quick procedure time, but there is the downside of exposure to ionizing radiation. MR imaging on the other hand is usually characterized by higher costs, a longer procedure time, and a need of sedation especially in young children. MR is however considered to be superior in the evaluation of cochlear patency and detecting soft tissue abnormalities of the cochlear nerve and brain. An equal diagnostic yield of CT and MRI for the identification of causative abnormalities in bilateral SNHL has been reported previously (10). In the current study, we find a significantly higher diagnostic yield of MR (34%) compared to CT (20%) in the group of children who underwent both imaging modalities ($P < 0.01$). An important factor in the greater yield of MR is probably its superior ability to identify abnormalities of the brain and cochlear nerve, and signs of cochlear inflammation or obliteration. In this study, no abnormalities were found on CT that were not detected on MR imaging. Based on these findings, MR would be the modality of choice in bilateral SNHL when the etiological diagnosis is the sole purpose of performing imaging. The decision to perform MRI, CT or both depends not only on the expected diagnostic yield with regard to the etiology of SNHL, but also on local availability, costs and reimbursements, additional motives for performing radiology (i.e. in the context of cochlear implantation) and the careful consideration of the advantages and disadvantages of each modality as outlined above. We therefor take these decisions in a multidisciplinary setting, in close consultation with the parents and if possible, with the patients themselves.

CONCLUSION

Imaging is an essential part of the etiologic evaluation of children with bilateral SNHL. The highest diagnostic yield is found in children suffering from asymmetric bilateral SNHL and in children suffering from profound SNHL. Based on our findings, MR is the primary imaging modality of choice in the etiological evaluation of children with bilateral SNHL because of its high diagnostic yield.

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HIGH PREVALENCE OF ABNORMALITIES ON CT AND MR IMAGING IN CHILDREN WITH UNILATERAL SENSORINEURAL HEARING LOSS IRRESPECTIVE OF AGE OR DEGREE OF HEARING LOSS

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ABSTRACT

Objective: Evaluation of causal abnormalities identified on CT and MR imaging in children with unilateral sensorineural hearing loss (USNHL), and the association with age and severity of hearing loss.

Study design: Retrospective cohort study.

Setting: Tertiary referral otology/audiology center.

Patients and diagnostic interventions: 102 children diagnosed with USNHL between 2006 and 2016 were included. They underwent CT and/or MR imaging for the evaluation of the etiology of their hearing loss. Main outcome measures: Radiologic abnormalities of the inner ear and brain associated with USNHL. Results: Using CT and/or MR imaging, causal abnormalities were identified in 49%, which is higher than previously reported (25-40%). The most frequently affected site was the labyrinth (29%), followed by the cochlear nerve (9%) and brain (7%). No significant difference in the number or type of abnormalities was found for the degree of hearing loss or age categories.

Conclusions: Imaging is essential in the etiologic analysis of USNHL because of the high prevalence of causative abnormalities that can be identified with radiology, irrespective of the patients' age or degree of hearing loss. CT and MR imaging are complementary imaging options. The ideal imaging algorithm is controversial. Based on our findings, we conclude that there is limited additional diagnostic value of simultaneous dual modality imaging over sequential diagnostics. We therefore perform a stepwise radiological workup in order to maximize the diagnostic yield while minimizing impact and costs. If the primary imaging modality does not identify a cause for USNHL, performing the alternative imaging modality should be considered.

INTRODUCTION

Historically, unilateral sensorineural hearing loss (USNHL) in children has been underdiagnosed and underappreciated (1). It was considered to have a few, if any, adverse functional consequences on children. Since the early 1980s it has become more and more evident that children with permanent unilateral hearing loss experience problems with sound localization, recognition of speech in noise and speech development (2-5). They have an increased rate of school grade failures, need for additional educational assistance and perceived behavioral issues in the classroom (6). Since the introduction of newborn hearing screening programs, USNHL can be detected at a very young age, enabling early intervention such as preferential classroom seating and adequate hearing rehabilitation of these children (1). In the Netherlands, the current newborn hearing screening program was introduced from 2002 to 2006 and is provided by the Dutch Child Health and Welfare service (JGZ) (7). It replaced the distraction method screening at the age of 9 months, the Compact Amsterdam Paedo- Audiometric Screener (CAPAS) (see Hof et al. for an overview) (8). Nowadays, the hearing test takes place at home or in the hospital within 4-10 days after birth. The first screening is performed using transient evoked otoacoustic emissions (TEOAE). Children who fail the first screening are screened a second time using TEOAE, and a third time using automated auditory brainstem measurements (AABR). Children who fail all tests are referred within three weeks to an Audiology Center for further investigation, mainly for Auditory Brainstem Response (ABR), but also tympanometry and OAE. Children admitted at the Neonatal Intensive Care Unit (NICU) are screened in hospital by AABR. If they fail this screening, they are referred to the Audiology Center for further investigation. If needed, early rehabilitation can then be started by the Audiology Center.

With the advent of early detection, the interest in the etiology of unilateral sensorineural hearing loss has grown. Imaging could be a part of the diagnostic work up. Recent studies of children with USNHL show temporal bone abnormalities in 29%-40% when temporal bone computed tomography (CT) is performed, or 10-25% when magnetic resonance (MR) imaging is performed as a single modality (4,9-12). In general, CT is the better modality for the identification of bony abnormalities, while MR imaging provides superior information about the cochlear nerve and the brain (11). Historically, CT has been the study of choice, but MR imaging has become increasingly popular (13). The aim of this study is to review the prevalence and spectrum of causative radiological abnormalities as identified by CT and/or MR imaging with respect to age category and degree of hearing loss.

MATERIALS AND METHODS

The Center for Diagnostics of Sensorineural hearing loss (CDS) at the VU University Medical Center (VUmc) in Amsterdam, The Netherlands, is a multidisciplinary team consisting of otologists, audiologists, pediatricians, clinical geneticists, neuroradiologists and, if indicated, neurologists or ophthalmologists dedicated to the evaluation of children with sensorineural hearing loss. Upon parental request, the CDS offers etiological diagnostics to children diagnosed with USNHL as defined below. Patients are referred for etiological evaluation by the audiological center of the VUmc and by regional audiology centers, general practitioners and otorhinolaryngologists. The majority of the children is referred directly after the diagnosis of the hearing loss, but in some cases, the detection or need for etiological evaluation arises later in life, and referral takes place at an older age. In this retrospective cohort study, we evaluate the experience of the CDS regarding the outcome of radiology in USNHL patients.

Audiometric evaluation

The audiometric evaluation was performed by the referring Audiology Center or by the VUmc Audiology Center, using (developmental) age-appropriate tests including pure tone audiometry (PTA) (an average threshold at 500, 1000, 2000 and 4000 Hz is taken for the analysis) or auditory brainstem response (ABR). To determine the ABR thresholds (dB nHL) we used a clear appearance of wave V upon clicks. For the estimated behavioral hearing thresholds around 3 kHz (dB HL) we use a correction of 10 dB. Children were diagnosed with USNHL if the sensorineural hearing threshold at the worst hearing ear was 30 dB HL or more, and the hearing threshold of the best hearing ear did not exceed 20 dB. Hearing loss was categorized as a slight impairment (26-40 dB), moderate impairment (41-60 dB), severe impairment (61-80 dB) and profound impairment (81 dB or greater) according to the commonly used classification of the World Health Organization (WHO) (14). In case of mixed type hearing loss, the inclusion and consecutive analyses were based on the sensorineural component only. Patients with pure conductive hearing loss were excluded from this study.

Age at diagnosis of UNSHL

Age at detection was defined as the age at which the hearing loss was first diagnosed by an Audiology Center, either by ABR of PTA. We categorized the patients in 4 age groups: 0-1 year old, 1-6 years old, 6-12 years old and 12-18 years old.

Imaging

The decision to obtain imaging and the choice of the imaging modality was individualized per patient and made by the CDS multidisciplinary team in close consultation with the parents. Therefore, not all children underwent an equal pathway of investigations during

the study period. The choice of imaging modality was guided by the type of hearing loss, additional clinical indications and accessibility. As a rule, patients with USNHL underwent CT imaging of the temporal bone as a first choice modality because of no or less need for sedation, lower costs and easier scheduling. MR imaging was preferred as first choice modality in cases of fluctuating hearing loss or suspicion and auditory neuropathy, in children with neurological symptoms, developmental impairments, or known or suspected congenital CMV infection. In some cases both modalities were performed. The majority of the patients was scanned in our clinic following a standard temporal bone CT protocol, consisting of non-contrast axial 0.6 mm slices. Coronal and sagittal reconstructions (0.6 mm thickness) were performed, as well as axial reconstructions following the plane of the lateral semicircular canal. The MR imaging protocol of the brain and temporal bone includes T1 weighted, transversal T2 weighted, transversal fluid attenuation inversion recovery (FLAIR), sagittal 3D gradient-echo sequences and axial 3D steady state (CISS) images centered at the level of the internal auditory canal. In some cases, imaging was performed in the referring center using their own protocols. These scans were revised in our clinic. The imaging was evaluated with a focus on abnormalities associated with sensorineural hearing loss at the level of the middle ear, the inner ear, the cochlear nerve and the brain. The inner ear abnormalities included acquired pathologies and congenital mal- formations, which were classified as cochlear aplasia, cochlear hypoplasia, common cavity, incomplete partition type I and II, isolated enlarged vestibular aqueduct (EVA) (defined as a vestibular aqueduct with a diameter exceeding 1,5 mm, measured halfway between the common crus and the medial aspect of the opening of the operculum on the posterior wall of the temporal bone), semi- circular canal (SSC) dysplasia, isolated lateral semi-circular canal dysplasia, vestibular hypoplasia, and malformations of the cochlear nerve (15). The evaluation of the CT and/or MR imaging of the temporal bone and brain was performed by an experienced neuroradiologist and an otologist. In case of disagreement by the neuroradiologist and otologist, joined evaluation was performed in order achieve consensus.

Statistical analysis

Statistical analyses were performed using SPSS 22.0. The criterion for statistical significance was set at $p < 0.05$. Descriptive analyses and cross tables were used to outline results of this study.

RESULTS

Clinical characteristics

From January 2006 until January 2016, a total of 121 children with USNHL were evaluated by the CDS multidisciplinary team. Seven children were excluded from the study because imaging was not performed at the parent's request. In 12 children, imaging was not performed because the hearing loss was a component of an already diagnosed disorder and imaging had no additional diagnostic value. One hundred and two children were suitable for analysis, of which 54 were male and 48 of which were female. Right ears were involved in 43 cases (42%), and left ears were involved in 59 cases (58%). The age at diagnosis of the hearing loss ranged from one month to 15 years (median 1⁄4 3,7 years) (Table 1). Forty-one children were diagnosed before the age of six months (40%). They were referred to the CDS directly after the newborn hearing screening. Sixty-one children (60%) were referred to the CDS at an older age.

Hearing loss

Of the 102 children, nine had slight hearing loss (9%), 16 had moderate hearing loss (16%), 14 had severe hearing loss (14%) and 63 (62%) had profound USNHL. The unilateral hearing loss was detected by ABR in 56 children (55%), at a median age of 1,7 years and by PTA in 46 children (45%) at a median age of 5,9 years. There was no significant difference in severity of the hearing loss between the age categories (P value = 0.08).

Imaging modality

A total of 122 radiological investigations were performed in 102 children. Fifty children underwent a CT scan only (49%), 32 children underwent MR imaging only (31%), and 20 (20%) underwent both (Table 1). The number of patients who underwent CT compared to the number of patients who underwent MR imaging was equally distributed over the age categories, hearing loss categories and over the years of research.

Imaging results

The overall prevalence of radiological findings associated with USNHL was 49%. The prevalence of relevant findings detected by temporal bone CT was 36%. The prevalence of relevant findings detected by MR imaging was 58% (Table 1). The number and type of radiological abnormalities are listed in Table 2.

The abnormalities identified on CT mainly consisted of abnormalities of the labyrinth (33%) including malformations and signs of obliteration or ossification. The abnormalities detected on MR imaging mainly consisted of abnormalities of the cochlear nerve (17%) and the brain (17%). The brain abnormalities consisted of signs indicative of a CMV infection, such as ventriculomegaly, cortical gyral abnormalities, or white matter abnormalities (Figure 1). The differences in the type of abnormalities identified by MR vs. CT imaging not only reflect the different properties of these imaging modalities but are also the result of the active selection of a specific modality by our CDS multidisciplinary team. We found no significant differences in the number or type of abnormalities, nor for the different grades of hearing loss (P 0.3), nor for the different age categories (P 0.3) (Tables 3A and 3B). In the 20 children who underwent both modalities, the number and type of relevant findings detected by CT were compared to the number and type of relevant findings detected by MR imaging (Table 4). In the latter cases a cause for USNHL was identified in 50%. Concordant (positive or negative) CT and MR imaging findings were found in 15/20 cases (75%). One malformation of the oval window was identified only on CT (5%). Four abnormalities of the cochlear nerve and brain were detected only by MR imaging (20%). In this series, if CT identified a causative abnormality, no additional lesions were identified by MR imaging and vice versa.

Table 1 Demographics and clinical characteristics of 102 children with USNHL who underwent CT and/or MR imaging in the etiological work-up.

Characteristics	Patient n	(%)	CT total n
Number of patients[b]	102		70
Sex n (M/F)	M 54	(53%)	M 35
	F 48	(47%)	F 35
Hearing loss[c]			
Slight (26-40 dB)	9	(9%)	6
Moderate (41-60 dB)	16	(15%)	12
Severe (61-80 dB)	14	(14%)	11
Profound (80 dB or greater)	63	(62%)	41
Age at diagnosis (mean/range) years	3,7 (0-15)		3,6 (0-15)
Abnormalities found (n/n %)	50/102	(49%)	25/70

Age: Age at diagnosis is the age at which the hearing loss was first diagnosed by an Audiology Center. a These 20 patients are extracted from the columns CT and MR imaging, which means that they are mentioned twice in this table.

Table 2 Clinically relevant abnormalities identified on CT and MR imaging.

Type of pathology	Total	(%)	CT	(%)	MR	(%)
Number of scans	122		70		52	
Labyrinth	35+2	(29%)	23+1[a]	(33%)	12+1[a]	(23%)
Ossification oval window	1		1		0	
Cochlear hematoma	1		0		1	
Obliteration/ossification	4		4		0	
Common cavity	1		1		0	
Incomplete partition type I	1		1		0	
Incomplete partition type II	7		6		1	
Cochlear aplasia	1		1		0	
Cochlear hypoplasia	4		2		2	
Isolated EVA	10		4		6	
Isolated lateral SCC dysplasia	2+1[a]		1+1[a]		1	
Vestibular hypoplasia	3+1[a]		2		1+1[a]	
Narrow internal auditory canal/ Cochlear nerve dys/aplasia	11	(9%)	2	(3%)	9	(17%)
Brain abnormalities	9	(7%)	0	(0%)	9	(17%)
No abnormalities	67	(55%)	45	(64%)	22	(42%)

[a] *In combination with an abnormality of internal auditory canal/cochlear nerve. CT = temporal bone computed tomography. MR = magnetic resonance imaging. EVA = enlarged vestibular aqueduct. SCC = semicircular canal.*

(%)	MRI total n	(%)	Both (CT+MRI)[a]	(%)
(69%)	52	(51%)	20	(20%)
	M 30		M 11	
	F 22		F 9	
	4		1	
	8		4	
	6		3	
	34		12	
	4,2 (0-12)		5,3 (0-15)	
(36%)	30/52	(58%)	10/20	(50%)

b 122 scans were performed in 102 children.
c Hearing loss categories according to the WHO classification [14]. USNHL=unilateral sensorineural hearing loss. CT=temporal bone computed tomography. MR=magnetic resonance imaging.

Table 3A Abnormalities found on CT and MR imaging, related to the degree of hearing loss.

Hearing loss category	Number of patients	(%)	Abnormalities identified on CT and MR (n abnormalities)/n patients)	(%)
Slight (26-40 dB)	9	(9%)	2/9	(22%)
Moderate (41-60 dB)	16	(13%)	9/16	(56%)
Severe (61-80 dB)	14	(14%)	6/14	(43%)
Profound (80 dB or greater)	63	(64%)	33/63	(52%)

Hearing loss categories according to the WHO classification. Overall, there is no significant difference between the number of abnormalities found on CT and MR between the hearing loss categories (P=0.3).

Table 3B Abnormalities found on CT and MR imaging, related to the age categories.

Age category (years	Patients (n/%)		Abnormalities identified on CT and/or MR (n/%)	
0-1	42	(41%)	19	(45%)
1-6	34	(33%)	17	(50%
6-12	23	(23%)	11	(48%)
12-18	3	(3%)	3	(100%)

Age: Age at diagnosis is the age at which the hearing loss was first diagnosed by an Audiology Center. Overall, no significant difference between the number of abnormalities was found on CT and MR (P=0.3) regarding the age categories.

Table 4 Comparison between CT and MR imaging for positive and negative findings in 20 children who underwent both imaging modalities. MR was able to detect 4 relevant abnormalities that were not seen on CT, whereas CT detected 1 relevant abnormality that was not seen on MR. Concordant (positive and negative) results were found in 15 cases (75%).

Imaging modality	Number of patients (total n=20)	(%)	Type of abnormality
CT+/MR-	1	(5%)	Aplasia of the oval window
CT-/MR+	4	(20%)	1 cochlear hematoma, 2 cochlear nerve a- or hypoplasia, 1 CMV associated brain abnormality
CT+/MR+	5	(25%)	1 cochlear hypoplasia, 1 isolated lateral SCC dysplasia, 1 vestibular hypoplasia, 1 malformation of the internal auditory canal, 1 EVA
CT-/MR-	10	(50%)	

+ = causal findings on the imaging. - = no causal findings on the imaging. CT = temporal bone computed tomography. MR = magnetic resonance imaging. SCC = semicircular canal. EVA = enlarged vestibular aqueduct.

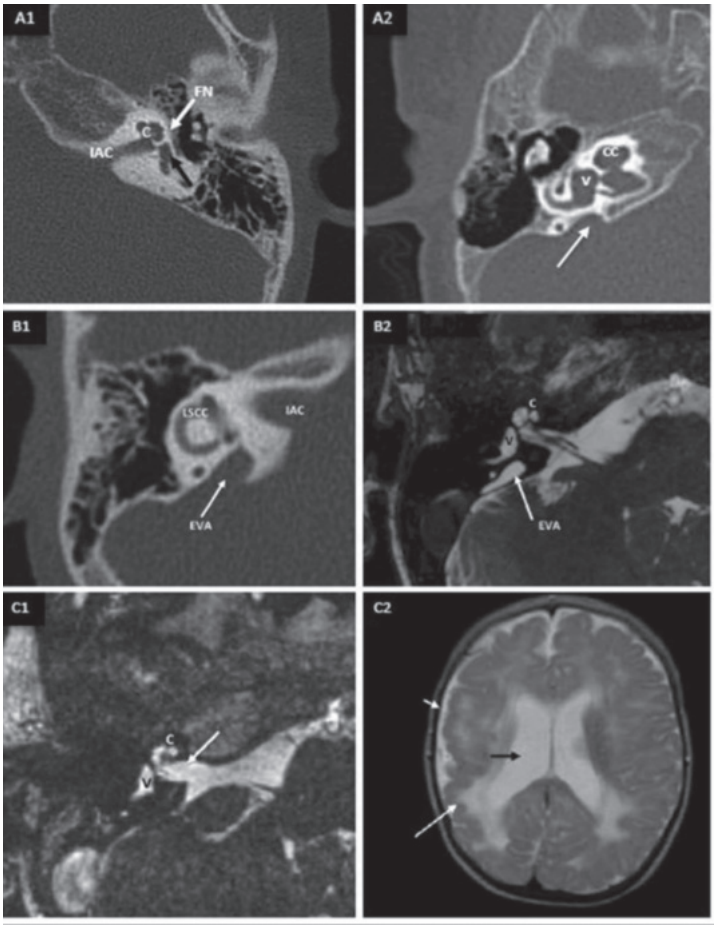

Figure. 1. CT and MR imaging of children with unilateral sensorineural hearing loss. (A1) Axial CT image showing oval window atresia (black arrow) with aberrant location of the tympanic segment of the facial nerve (white arrow). C=cochlea. IAC=inner auditory canal. FN=facial nerve. (A2) Axial CT image showing an incomplete partition type II malformation of the labyrinth. CC=cystic cochlea. V=vestibule. EVA=enlarged vestibular aqueduct (white arrow). (B1) Axial CT image showing a right EVA (white arrow). (B2) Axial T2 weighted MR image illustrating a right EVA (white arrow). LSCC= lateral semicircular canal. (C1) Axial T2 weighted MR image showing the absence of the cochlear nerve in the inner auditory canal (white arrow). (C2) Axial T2 weighted MR image illustrating signs of a CMV infection: ventriculomegaly (black arrow), cortical gyral abnormalities (short white arrow) and white matter atrophia (long white arrow).

DISCUSSION

In this study we evaluate the outcome of CT and MR imaging in a large cohort of children with USNHL, in relation to age and degree of hearing loss. The overall prevalence of causal radiological findings in our study is 49%, which is higher than previously reported (25-40%) [9,11,12,16]. In our study population, the most frequent site of the causal abnormality was the labyrinth (29%), followed by the cochlear nerve (9%) and the brain (7%). The most prevalent abnormality of the labyrinth in this study is an isolated EVA (18% of abnormal scans). This is comparable with the previous reports on USNHL, in which EVA is reported as the most common cause of USNHL (17-25%), followed by other abnormalities of the inner ear (10-21%), the cochlear nerve (1-10%) and brain (6%) (1,11,16).

The majority of the children included in this study have profound USNHL (64%), compared to 52% in previous reports (1). A higher diagnostic yield of imaging with increasing severity of hearing loss has been reported previously [9]. In the current study, we find no significant difference in the prevalence of abnormalities found on imaging in patients with moderate, severe or profound hearing loss ($p = 0.3$). Mild hearing loss seems to be associated with a lower prevalence of radiologic abnormalities (22%), although this observation is based on a small number of patients. This indicates that performing imaging is not only relevant in the etiological diagnosis of severe or profound hearing loss, but also of slight and moderate hearing loss. The median age at detection in this study is 3,7 years old, and 42 children were diagnosed before the age of 6 months (40%). This makes the study well comparable with the previous studies, in which the mean age is 2,6-7 years old and 42% of the children is detected before 6 months after implementation of the Universal Newborn Hearing Screening (1,11,16). To our knowledge, this is the first study to evaluate the type and number of the abnormalities found on CT and/or MR imaging in USNHL patients per age category. We found no significant difference between the different age categories for the prevalence of radiological abnormalities or the type of abnormalities found (Table 3B). Therefore, we recommend per- forming imaging for USNHL in all age groups.

As previous studies have shown, CT and MR are complementary imaging modalities (11,16). Generally, CT is considered the better modality for the identification of bony abnormalities, while MR imaging provides superior information about the cochlear nerve and the brain (11). The ideal algorithm for their use in USNHL patients is however still controversial. In our center, the choice for an imaging modality (CT or MR) was individualized per patient by the multidisciplinary team of the CDS. The choice for a specific modality was based on the type of hearing loss and additional clinical characteristics such as neurological signs, developmental impairment or a known or suspected congenital CMV infection. In addition, the inherent disadvantages of both modalities have to be taken into account.

CT imaging of the temporal bone requires exposure to radiation, albeit in a low dose. When CT imaging is indicated, the delivered dose should be optimized to use the lowest possible dose level while still answering the clinical question, in accordance with the ALARA principle (As Low As Reasonably Achievable) (17). Other relevant considerations are accessibly, need for sedation (more often in MR imaging), overall impact on the pediatric patient, parental preference and costs effectiveness. The consequence of this active selection is that not all children underwent the same diagnostic protocol, which would bias the direct comparison of the performance of CT and MR in diagnosing the cause of USNHL. However, with this active selection, we found a higher diagnostic yield (49%) than reported in the previous literature (25-40%) (9,11,12,16,18). This suggests that there is limited additional value of performing dual imaging modality over a sequential approach.

Based on our experience, we now perform imaging of USNHL patients according to the presented flowchart (Figure 2). We perform CT as the initial imaging modality because of its effectiveness in detecting the most prevalent types of abnormality (of the labyrinth) in this patient group, but also because of practical considerations such as better accessibility, lower cost and less need for general anesthesia. In case no abnormality is found on CT, or if CT identifies an abnormality that requires further evaluation (i.e. internal auditory canal malformations), sequential MR imaging can be performed to rule out anomalies of the cochlear nerve or brain. MR imaging is the preferred first modality in selected cases of suspected cochlear nerve or brain abnormalities, fluctuating hearing loss, a known congenital CMV infection, neurological signs or developmental impairment. If MR shows no abnormalities in these cases, performing CT imaging could be considered.

CONCLUSION

Imaging is essential in the etiologic analysis of USNHL because of the high prevalence of causative abnormalities that can be identified with radiology, irrespective of the patients' age or degree of hearing loss. CT and MR imaging are complementary imaging options, but simultaneous dual modality imaging has no additional diagnostic value over sequential diagnostics. If the primary imaging modality does not identify a cause for USNHL, performing the alternative imaging modality should be considered.

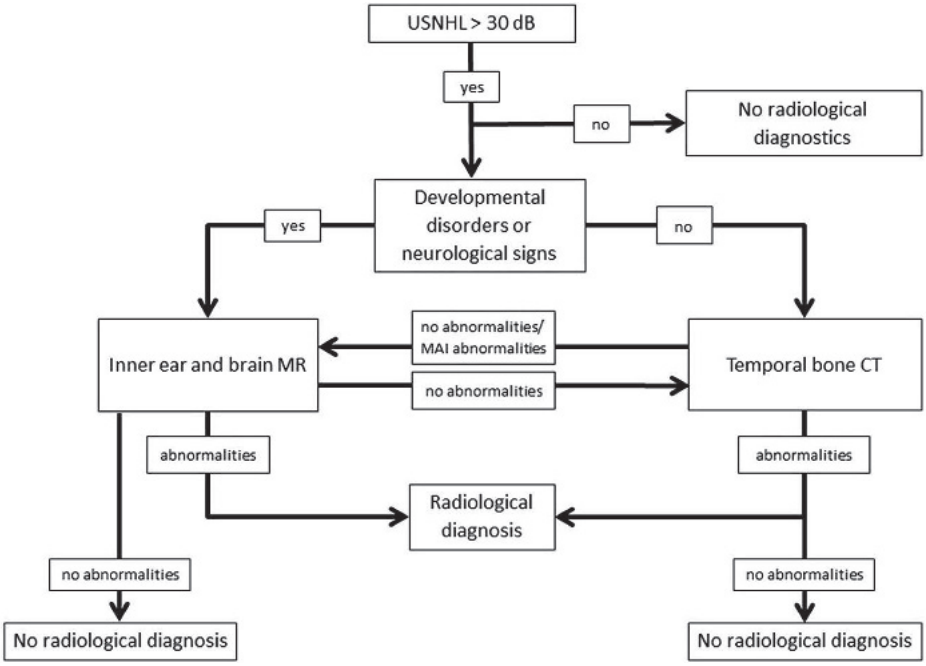

Figure 2. Flowchart of imaging in children with USNHL. USNHL = unilateral sensorineural hearing loss. CT = computed tomography. MR = magnetic resonance imaging. IAC = internal auditory canal.

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PROGNOSTIC FACTORS FOR SUDDEN DROPS IN HEARING LEVEL AFTER MINOR HEAD INJURY IN PATIENTS WITH AN ENLARGED VESTIBULAR AQUEDUCT: A META-ANALYSIS

BJ Noordman, EA van Beeck Calkoen, B Witte, T Goverts, EF Hensen, P Merkus

ABSTRACT

Objective: To identify factors associated with sudden drops in hearing level after minor head trauma in patients with an enlarged vestibular aqueduct (EVA).

Methods: A systematic review of the literature on sudden drops in hearing level after minor head trauma in patients with an EVA was conducted. The studies were retrieved from Embase, PubMed, CINAHL, and Cochrane and critically appraised using predefined criteria. Data on all described parameters were collected, and their relationship with sudden drops after minor head trauma was statistically analyzed.

Results: Pooled data of 31 articles included 179 patients with 351 EVAs. Drops in hearing level after minor head trauma were experienced by 34% of the patients. We found a significant association between sudden deterioration of hearing after minor head trauma and preexisting fluctuating hearing loss (HL) (odds ratio, 8.6; $p<0.001$; 95% confidence interval, 3.9-19.3). The diameter of the VA, type of preexisting HL, severity of HL, preexisting progressive HL, and the diagnosis Pendred syndrome were not significantly associated with sudden drops in hearing levels after head trauma.

Conclusion: Only one-third of the patients with a proven EVA experienced sudden drops in hearing level because of head trauma. There is a significant association between preexisting fluctuating HL and the chance of sudden drops in hearing level caused by trauma. Stringent lifestyle advices, like avoiding activities with a risk of minor head trauma such as contact sports, might be restricted to patients with a fluctuating HL and those with a history of sudden drops on minor head trauma.

INTRODUCTION

The vestibular aqueduct (VA) is a bony channel in the temporal bone that courses from the posterior cranial fossa to the medial wall of the vestibule. It contains the endolymphatic duct, which connects the endolymphatic sac with the vestibule. The normal width of the VA has been described to be less than 0.9 mm at its midpoint or less than 1.9 mm at the operculum (1). The operculum is a variable projection of bone on the posterior face of the petrous bone that outlines the opening of the VA (2).

An enlarged VA (EVA) is a common finding in children with congenital hearing loss (HL) (3,4). About 10% of all children with significant permanent HL have an EVA, making this the most frequent morphogenetic abnormality in these children (5-7). Different criteria for the diagnosis EVA are found in the literature. Originally, the VA was considered enlarged if it was greater than 1.5 mm at the midpoint (8). Other investigators define EVA as a diameter greater than 2 mm at the midpoint or a diameter greater than 4 mm at the operculum (9-12). In the majority of EVA patients, computed tomography or magnetic resonance imaging scans reveal additional inner ear anomalies, mostly a Type 2 incomplete partition of the cochlea (IP2), previously known as Mondini malformation (13-15). The IP2 or classical Mondini malformation consists of at riad: an EVA, a dilated vestibule, and a dysplastic cochlea, with 1.5 turns caused by a cystic cochlear apex with a normal basal turn. Combinations of EVA with other isolated malformations are also possible, such as an abnormally large vestibule, enlargement of semicircular canals, or a hypoplastic cochlea (8,16-18). Furthermore, EVA is associated with defects in thyroid iodine organification caused by mutations in the SLC26A4 (PDS) gene, resulting in hypothyroidism and goiter (19,20). The combination of EVA and thyroid dysfunction is called Pendred syndrome, which is an autosomal recessive disorder (21). Other associated syndromes are distal renal tubular acidosis (5,6), branchio-oto-renal syndrome (22), and Waardenburg's syndrome (7).

HL in EVA patients is predominantly sensorineural. A conductive component, explained by a third window effect, may be observed at the lower frequencies, and fluctuations in hearing level and progression of HL are frequent (9,23,24).

A sudden drop in hearing level triggered by minor head injuries, barotrauma, or noise trauma is a well-known feature of EVA patients. The reported risk of sudden drops on minor head trauma, noise trauma, or barotrauma in patients with EVA is highly variable (3%-80%) (10,25). Because of the risk of deterioration of hearing on these events, some clinicians recommend all EVA patients to avoid activities such as contact sports and scuba diving or to wear helmets (26-28). This policy can be quite restricting, especially in young children. Because only a minority of EVA patients experience HL on head trauma

or barotrauma, we conducted the present meta-analysis to define prognostic factors for sudden HL and identify subgroups of EVA patients that would benefit from these recommendations and, more importantly, subgroups that would not.

MATERIALS AND METHODS

Search Strategy and Study Selection

A systematic literature search was performed on EVA in PubMed, Embase, CINAHL, and the Cochrane Library databases from the inception of the databases to July 2, 2013, using the search term enlarged vestibular aqueduct and its synonyms in the title and abstract fields. A complete overview of the search terms is shown in Table 1. To increase the yield of relevant studies, the reference lists of all identified articles were screened, and related publications were searched in Web of Science. Two reviewers (P. M., B. N.) independently screened titles and abstracts of the retrieved publications. Discrepancies between the reviewers in the assessment of the articles were resolved by consensus discussion. All articles on Pendred syndrome, Mondini/IP2-type malformation, EVA, and/or large VA syndrome in which hearing was reported were selected. The full text of these eligible studies was screened for a more detailed selection. Studies had to meet all of the following criteria to be included in this meta-analysis: the described patients have a radiographically proven EVA in at least one ear and sudden drops in hearing after head trauma, barotrauma, or noise trauma is reported. Furthermore, at least one of the following was described: the existence of Pendred syndrome, fluctuating HL or progressive HL, the degree of HL in dB or classification, the type of HL, the mid-diameter or size of the operculum of the VA in millimeters, and/or the occurrence of vestibular symptoms. Parameters had to be described separately per patient and/or per ear. The criteria for the diagnosis of an EVA were used as defined by the authors of the included studies.

Pendred syndrome was classified as an EVA with at least one of the following concurrent findings: a positive perchlorate test, a positive genetic analysis (two mutant SLC26A4 [PDS] alleles), or hypothyroidism in combination with goiter. Hearing loss was classified as no HL (<20 dB), mild HL (20-40 dB), moderate HL (41-70 dB), severe HL (71-95 dB), and profound HL (>95 dB), as described earlier by Martini and Mazzoli (29). Hearing level was evaluated with a pure-tone average of 500, 1,000, and 2,000 Hz. When audiologic data were not shown, the classification of HL as used by the authors was used. Progressive hearing loss was, pragmatically, defined as a deterioration of more than 10 dB at two or more frequencies or a deterioration of 15 dB at one or more frequencies in 1 year. Fluctuating hearing loss was defined as a 10-dB improvement in hearing in two or more

frequencies or a 15-dB improvement at one frequency. When audiologic data were not shown, the definitions for progressive and fluctuating hearing loss as used by the authors were used. In the absence of information on whether the fluctuations/progression in HL or the presented level of HL preceded the sudden drops in hearing level or vice versa, fluctuating HL, progressive HL, and level of HL were classified as preexisting. The complete selection process is presented in Figure 1.

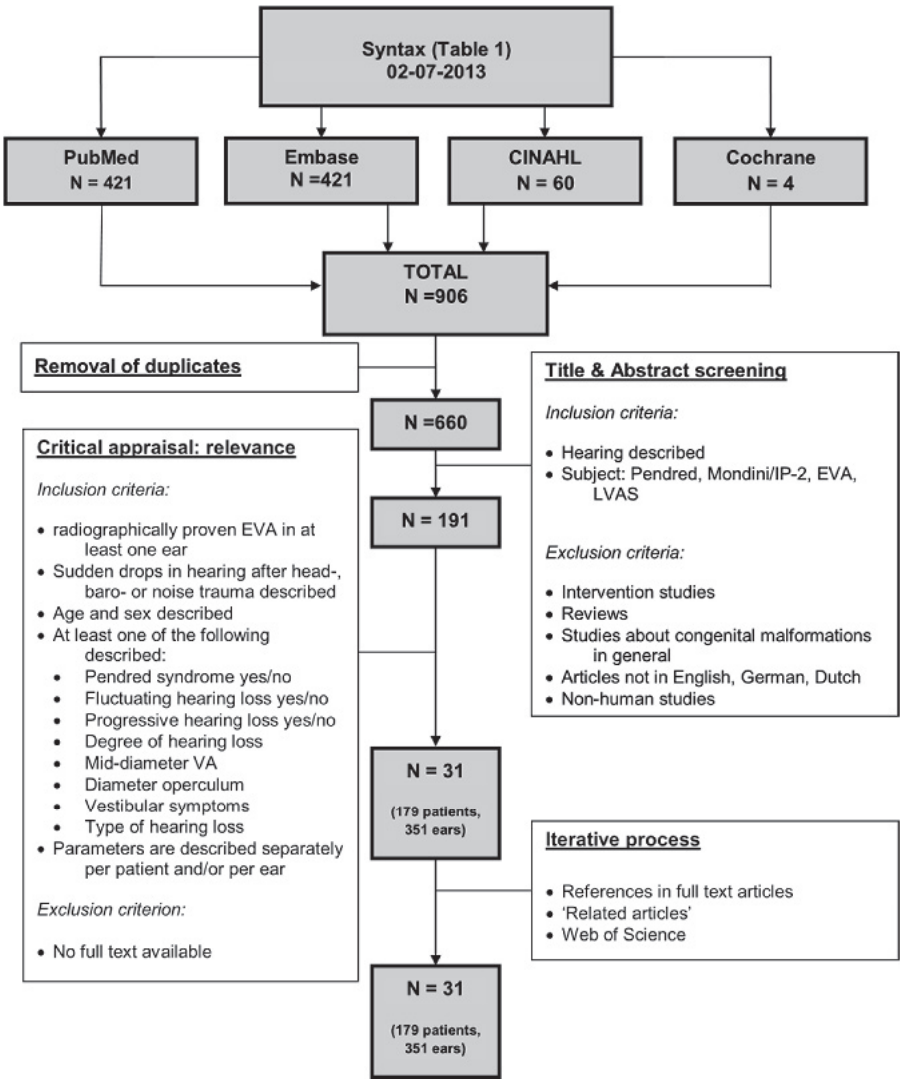

Figure 1. Flowchart for the selection process of studies on sudden drops in hearing level in EVA patients. LVAS indicates large vestibular aqueduct syndrome; IP-2, type 2 incomplete partition

Table 1. Systematic search for studies on enlarged vestibular aqueduct (date of search: July 2, 2013)

Database	Search	Hits
PubMed	(Large[Title/Abstract] AND vestibular[Title/Abstract] AND aqueduct[Title/Abstract]) OR (Large[Title/Abstract] AND vestibular[Title/Abstract] AND aqueducts[Title/Abstract]) OR (Enlarged[Title/Abstract] AND vestibular[Title/Abstract] AND aqueduct[Title/Abstract]) OR (Enlarged[Title/Abstract] AND vestibular[Title/Abstract] AND aqueducts[Title/Abstract]) OR (Wide[Title/Abstract] AND vestibular[Title/Abstract] AND aqueduct[Title/Abstract]) OR (Wide[Title/Abstract] AND vestibular[Title/Abstract] AND aqueducts[Title/Abstract]) OR (Enlargement[Title/Abstract] AND vestibular[Title/Abstract] AND aqueduct[Title/Abstract]) OR (Enlargement[Title/Abstract] AND vestibular[Title/Abstract] AND aqueducts[Title/Abstract]) OR (Widened[Title/Abstract] vestibular[Title/Abstract] aqueduct[Title/Abstract]) OR (Widened[Title/Abstract] vestibular[Title/Abstract] aqueducts[Title/Abstract])	421
Embase	(Large:ab,ti AND vestibular:ab,ti AND aqueduct:ab,ti) OR (Large:ab,ti AND vestibular:ab,ti AND aqueducts:ab,ti) OR (Enlarged:ab,ti AND vestibular:ab,ti AND aqueduct:ab,ti) OR (Enlarged:ab,ti AND vestibular:ab,ti AND aqueducts:ab,ti) OR (Wide:ab,ti AND vestibular:ab,ti AND aqueduct:ab,ti) OR (Wide:ab,ti AND vestibular:ab,ti AND aqueducts:ab,ti) OR (Enlargement:ab,ti AND vestibular:ab,ti AND aqueduct:ab,ti) OR (Enlargement:ab,ti AND vestibular:ab,ti AND aqueducts:ab,ti) OR (Widened:ab,ti vestibular:ab,ti aqueduct:ab,ti) OR (Widened:ab,ti vestibular:ab,ti aqueducts:ab,ti)	421
CINAHL	TI (large AND vestibular AND (aqueduct OR aqueducts)) OR TI (enlarged AND vestibular AND (aqueduct OR aqueducts)) OR TI (wide AND vestibular AND (aqueduct OR aqueducts)) OR TI (enlargement AND vestibular AND (aqueduct OR aquedecuts)) OR TI (Widened AND vestibular AND (aqueduct OR aqueducts)) OR AB (large AND vestibular AND (aqueduct OR aqueducts)) OR AB (enlarged AND vestibular AND (aqueduct OR aqueducts)) OR AB (wide AND vestibular AND (aqueduct OR aqueducts)) OR AB (enlargement AND vestibular AND (aqueduct OR aqueducts)) OR AB (widened AND vestibular AND (aqueduct OR aqueducts))	60
Cochrane	No. 1 [in ''record title''] (large AND vestibular AND (aqueduct OR aqueducts)) OR (enlarged AND vestibular AND (aqueduct OR aqueducts)) OR (wide AND vestibular AND (aqueduct OR aqueducts)) OR (enlargement AND vestibular AND (aqueduct OR aqueducts)) OR (Widened AND vestibular AND (aqueduct OR aqueducts)) No. 2 [in ''abstract''] (large AND vestibular AND (aqueduct OR aqueducts)) OR (enlarged AND vestibular AND (aqueduct OR aqueducts)) OR (wide AND vestibular AND (aqueduct OR aqueducts)) OR (enlargement AND vestibular AND (aqueduct OR aqueducts)) OR (Widened AND vestibular AND (aqueduct OR aqueducts)) No. 1 OR No. 2	4

Data collection

The data from all patients included in the selected studies were pooled. A standardized data collection form was developed, pilot tested, and refined. Information on the following themes was extracted for each patient (and when possible, for each ear) that was evaluated in the included studies: Pendred syndrome, preexistent fluctuations in HL, preexistent progression of HL, degree of HL, mid-diameter of the VA, size of the operculum, preexistent vestibular symptoms, and type of HL (Table 2). Only studies with data on sudden deterioration of the hearing of individual patients were selected. If information on sudden drops of hearing was absent for one of the patients, whereas the presence of drops of hearing was reported for other patients within the same study, the patient was classified as having no drops in hearing. The parameters Pendred syndrome and vestibular symptoms or abnormalities were analyzed per patient. The anatomic aspects or aspects of hearing were analyzed per ear. In case of a radiologically proven bilateral EVA and missing information on lateralization of one of these parameters, the concerning parameter was classified as bilateral. Two authors independently extracted data from the included studies (P. M., B. N.). Any discrepancies were resolved by consensus discussion.

Statistical Analysis

The results were calculated using logistic regression analysis and are expressed as odds ratio (OR), p value, and 95% confidence interval (CI). All results were corrected for age and sex using logistic regression analysis. Therefore, only patients with available data on age and sex were included in the statistical analyses. All statistical analyses were performed using the

Statistical Package for the Social Sciences software version 20.0 (IBM Corp., Armonk, NY, USA). A value of $p < 0.05$ was considered statistically significant.

Table 2. Logistic regression analysis of precipitating factors related with sudden hearing drops

Variable		n/N	OR	p value	95% CI
Pendred syndrome	No	6/11 patients	1.0	0.197	
	Yes	13/40 patients	0.40		0.10-1.6
Fluctuating hearing loss	No	6/85 ears	1.0	<0.001	
	Yes	44/86 ears	8.6		3.9-19.3
Progressive hearing loss	No	20/75 ears	1.0	0.606	
	Yes	44/148 ears	1.2		0.63-2.2
Degree of hearing loss	No	3/12 ears	1.0	0.497	
	Mild	3/10 ears	1.3		0.20-8.8
	Moderate	16/41 ears	2.3		0.53-10.1
	Severe	21/70 ears	1.4		0.34-5.7
	Profound	46/118 ears	2.2		0.56-8.9
Mid diameter VA	≤2.0 mm	5/31 ears	1.0	0.446	
	2.01-2.50 mm	6/18 ears	2.5		0.57-10.5
	2.51-3.00 mm	7/19 ears	3.4		0.73-16.0
	93.0 mm	4/18 ears	2.0		0.42-9.6
Size operculum	≤7.00 mm	2/21 ears	1.0	0.134	
	7.00 mm	4/13 ears	4.6		0.63-33.5
Vestibular symptoms	No	7/22 patients	1.0	0.612	
	Yes	27/70 patients	1.3		0.45-3.9
Type of hearing loss	SNHL	7/24 ears	1.0	0.259	
	Mixed	29/79 ears	1.8		0.64-5.3

n indicates the number of patients or ears with sudden hearing drops; N, the number of patients or ears that were subtracted from the literature that fulfilled the criteria to be analyzed on this specific variable; OR, odds ratio; 95% CI, 95% confidence interval; VA, vestibular aqueduct.

RESULTS

Search Results

Figure 1 shows the flowchart of our search. We identified 906 records from the database search (search date, July 2, 2013). After removing the duplicates, 660 unique articles remained. A total of 191 articles concerning hearing in EVA patients were identified. Full text screening using the inclusion and exclusion criteria as previously described resulted in the selection of 31 articles, describing 179 patients with 351 ears with EVA (6,24,30-58).

Definition of EVA

Definitions for EVA used by the included studies are shown in Table 3. Fifteen of the included studies (48%) use the definition as presented by Valvassori and Clemis (8) in 1978; a diameter greater than 1.5 mm halfway between the common crus and the medial aspect of the opening of the operculum on the posterior wall of the temporal bone. How to measure the EVA is explained in Figure 2. In 10 (32%) of the studies, no clear definition is presented. Other definitions found in this study were those described by Levenson et al., Willbrand et al., and Okumura et al. (Table 3) (11,12,59).

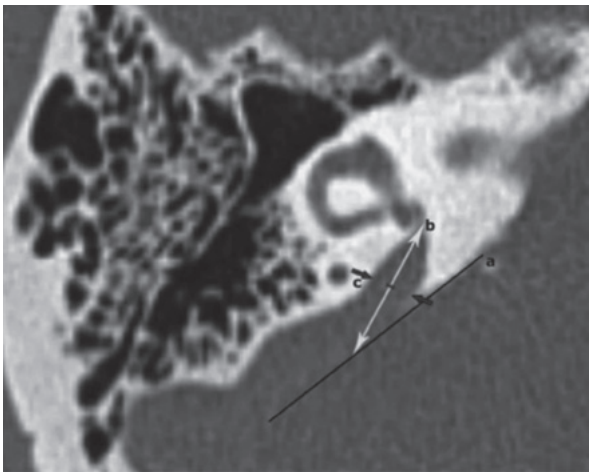

Figure 2. Vestibular aqueduct: mid duct diameter measurement. Example to explain how to measure an enlarged vestibular aqueduct at the mid duct diameter. a, create a virtual line (black line) of the posterior cranial fossa dura; the duct cannot be measured beyond this point. b, create in the middle of the duct a line between the most anteromedial point and the posterolateral point. c, in the middle of this line (cross mark) is the best position to measure the diameter of the vestibular aqueduct in millimeters. In this case, between the two arrows.

Table 3. Definition of EVA

Definition	Studies
>1.5 mm measured halfway between the common crus and the medial aspect of the opening of the operculum on the posterior wall of the temporal bone (8).	n = 14 (6,24,31,32,34,35, 38,39,46,48-51,55,57)
Explanation of the mid duct measurement is given in Figure 2. Definition not mentioned	n = 10 (30,33,36,37, 42,43,45,47,52,56)
>2.0 mm, by measurement of a line extending between the two lips of the external aperture (11).	n = 2 (40,41)
Diameter >2 mm, based on the work of Wilbrand et al. (59) who described the diameter of the VA on normal temporal bones as 0.4-1.0 mm.	n = 1 (53)
Aperture larger than 4 mm and a distance between the vestibule and the traceable outline of the VA of less than 1 mm on high-resolution CT scans (12).	n = 1 (44)
>1.5 mm at the midpoint between the common crus and the external operculum or 2.0 mm at the operculum itself	n = 1 (48)
Multiple definitions mentioned. "Cases fulfill all definitions."	n = 1 (54)

The definition is mentioned in the left column, and the studies using this definition are listed in the right column.

Statistical Analysis

To find factors associated with sudden drops in hearing level after minor head trauma, noise trauma, or barotrauma, we analyzed the presence of sudden drops and its association with Pendred syndrome, preexisting fluctuating HL, preexisting progressive HL, the preexisting severity of HL, the mid-diameter VA, the diameter of the operculum, vestibular symptoms, and the type of HL. All parameters will be discussed separately below and are shown in Table 2.

Sudden Drops in Hearing

In 61 (34%) of 179 patients, sudden drops in hearing after minor head trauma, barotrauma, or noise trauma in at least one ear were reported. Of all 351 ears with EVA, 108 (30%) were described to suffer from sudden drops. For most patients, minor head trauma was reported as a trigger for sudden HL; other reported triggers are barotrauma, noise trauma, and upper respiratory tract infection.

Pendred Syndrome

Data on Pendred syndrome, as diagnosed by the perchlorate test, genetic analysis, and/or the presence of hypothyroidism in combination with goiter, was available in 51 (28%) of all included patients. Of these 51 patients, 40 (78%) were classified to suffer from Pendred syndrome. No significant relationship between Pendred syndrome and the presence or absence of sudden drops was found (OR, 0.40; p = 0.197; 95% CI, 0.10-1.6).

Fluctuating HL

Information on preexistent fluctuating HL was available in 171 (49%) of all included ears. Fluctuating HL was found in 86 of these ears (50%). Detailed audiometric data (including tympanometry and bone conduction measures) were not provided in 8 (38%) of 23 studies. Therefore, fluctuating, and progressive HL as reported in these studies may be caused by fluctuating sensorineural thresholds or fluctuating middle ear function, for example, based on otitis media with effusion. Otitis media with effusion might even obscure fluctuations in sensorineural thresholds in some cases. Our analysis showed a significant association between preexistent fluctuating HL and sudden drops (OR, 8.6; p< 0.001; 95% CI, 3.9-19.3). This OR represents the ratio of the odds that a patient with fluctuating HL will experience sudden drops in hearing compared with the odds of a patient with no history of fluctuating HL. Thus, the odds for experiencing a sudden drop in hearing is 8.6 times higher in patients with preexistent fluctuating HL compared with patients without preexistent fluctuating HL.

Progressive HL

Data on progression of HL were available in 223 (64%) of all included ears. Of those ears, 148 (67%) were found to have progressive HL before the head trauma. No significant relationship between preexistent progressive HL and sudden drops in hearing level after minor head trauma was found (OR, 1.2; p = 0.606; 95% CI, 0.63-2.2).

Degree of HL

The preexistent degree of HL was described in 251 (72%) of all included ears. In the majority (20/26, 77%) of studies with data on the degree of HL, hearing level was evaluated using a pure-tone average of 500, 1,000, and 2,000 Hz. The other studies used the mean hearing level of all frequencies (250, 500, 1,000, 2,000, 4,000, and 8,000 Hz) or speech reception threshold. HL was classified as no HL (n = 12; 5%), mild HL (n = 10; 4%), moderate HL (n = 41; 16%), severe HL (n = 70; 28%), and profound HL (n = 118; 47%) (29). The odds for developing sudden HL were calculated for each subgroup and, for the OR, no HL was set as the reference group. No significant relation was found between the degree of HL and the incidence of sudden drops in hearing level after minor head trauma (mild HL: OR, 1.3; 95% CI, 0.20-8.8; moderate HL: OR, 2.3; 95% CI, 0.53-10.1; severe HL: OR,1.4;95%CI,0.34-5.7; profound HL:OR,2.2;95%CI, 0.56-8.9; overall p = 0.497).

Mid-diameter VA

The diameter of the midpoint of the VA was presented in 86 (25%) of all included ears. In the absence of a linear relationship between the mid-diameter of the VA and sudden drops in hearing level (data not shown), VA midpoint diameter was classified in four categories (<2.00 mm, 2.01-2.50 mm, 2.51-3.00 mm, and 93.00 mm). Evaluation of the relationship between the midpoint diameter of the VA and the presence or absence of sudden drops did not show a significant association (overall p = 0.446; ORs were calculated compared with the <2.0-mm group); 2.01 to 2.50 mm: OR, 2.5 (95% CI, 0.57-10.5); 2.51 to 3.00 mm: OR, 3.4 (95% CI, 0.73-16.0); and greater than 3.0 mm: OR, 2.0 (95% CI, 0.42-9.6).

Size of the Operculum

The size of the operculum of the VA was described in 34 of all included ears (9%). No linear relationship between the size of the operculum and sudden drops was found (data not shown). Therefore, operculum diameter was classified in two categories (<7.00 mm and >7.00 mm) No significant association was found between sudden drops and the size of the operculum (OR, 4.6; p = 0.134; 95% CI, 0.63-33.5).

Vestibular Symptoms or Abnormalities

In 92 (51%) of all included patients, the occurrence of vestibular symptoms or abnormalities was described. Vestibular symptoms were found in 70 (76%) of these patients. Further analysis did no not show a significant relationship between preexisting vestibular symptoms or abnormalities and the occurrence of sudden drops in hearing level on minor head trauma (OR, 1.3; p = 0.612; 95% CI, 0.45-3.9).

Type of HL

Data on the type of HL were available for 108 ears (31%). The predominant type was mixed HL (n = 79, 73%). Sensorineural HL was found in 24 ears (22%), no HL in 5 ears (5%), and none of the included ears showed a pure conductive HL. Our analysis did not reveal a significant association between type of HL and sudden drops of hearing (OR, 1.8; p = 0.259; 95% CI, 0.64-5.3).

DISCUSSION

The objective of this article is to provide EVA patients with evidence-based lifestyle advice and to identify cases in which there is a need for restricting activities to avoid hearing deterioration. Previous studies show a wide variability in the percentage of EVA patients that develop sudden drops in hearing levels on minor head trauma, noise trauma, or barotrauma (3%-80%) (10,25). In this meta-analysis, we found that approximately one-third

of all EVA patients experience deteriorations of hearing after head trauma and, therefore, the majority of EVA patients do not. Similar percentages on sudden drops in hearing level were found in a previous study on long-term follow-up of HL in 27 patients with EVA (33%) (27). Unfortunately, because of missing data on individual patients, this study could not be included in our analysis.

In this meta-analysis, we found that the occurrence of sudden drops in hearing level after minor head trauma, barotrauma, or noise trauma in EVA patients is significantly associated with preexisting fluctuating HL. The other studied parameters (Pendred syndrome, the severity of HL, the diameter of the VA, vestibular symptoms or abnormalities, and type of HL) did not show a significant relationship with deterioration of hearing after head trauma. In contrast to the report of Colvin et al. (27), we also found no association between preexistent progressive HL and sudden drops in hearing after head trauma. Possible explanations for this discrepancy are the difference in definition of EVA and the relatively small number of included EVA patients (n = 27) in the study by Colvin et al. (27).

The findings of this review may have important implications for the counselling of EVA patients and their parents. It seems unnecessary to recommend all EVA patients to restrain from activities such as contact sports and scubadiving or recommend young children to wear helmets (26-28). Especially for children, these restrictions may have far-reaching social consequences. This study provides a rationale for the limitation of these lifestyle advices to the following subgroups of EVA patients: first, the group who presents themselves with a history of sudden drops in hearing level after minor head trauma, barotrauma, or noise trauma. The second group consists of EVA patients who are characterized by spontaneous preexistent fluctuations in hearing level. These fluctuations can only be recognized when audiometric assessment is appropriate, and follow-up has been long enough to have several documented episodes of fluctuations in HL (without trauma). We therefore recommend accurate age-appropriate and frequent audiologic assessment of children with EVA, distinguishing sensorineural and conductive components.

To our knowledge, this is the first study to review the occurrence of sudden drops of hearing level in EVA patients on head trauma in a systematic way. The obvious benefit of this approach is the large number of EVA patients included in the analysis. Our study has also a number of limitations. First, because of the number of parameters included in this review and the fact that not all parameters were studied in each of the individual studies, there is a substantial amount of missing data. This explains the different patient numbers included in the analyses of the different parameters. Second, most included studies only describe the presence of sudden drops in hearing level, whereas the absence of

sudden drops is not described in most patients. To overcome this, we have included only studies reporting on patients with sudden drops on minor head trauma, noise trauma, or barotrauma. Within these studies, we have classified patients who were not reported to have experienced sudden deterioration of hearing as patients with stable hearing after head trauma. Third, because of the retrospective study design, it was not always possible to determine if the fluctuations in HL preceded the sudden drop or vice versa. A sudden loss of hearing on head trauma may be permanent or reversible. In case of a reversible event, one might argue that it is an expression of fluctuating HL, thereby explaining the association with preexisting fluctuating HL. However, the deterioration in hearing level is often permanent or not completely reversible after head trauma. In these cases, an association with preexisting progressive HL might be expected, but we did not find such an association. Finally, our analyses may be affected by the use of different definitions for EVA by the included studies. We expect this effect to be negligible because the differences between the various definitions are marginal (Table 3). This holds also for the definitions of the variables included, especially fluctuations in hearing loss and progression of hearing loss. To improve the comparability between patients and studies in the future, a uniform definition is necessary. We prefer the initial definition for EVA, the size criterion as put forth by Valvassori and Clemis (8) in 1978 (91.5 mm measured halfway between the common crus and the medial aspect of the opening of the operculum on the posterior wall of the temporal bone). It is a frequently used straightforward definition that is easily applicable in all axial high-resolution computed tomography scans of the temporal bone with a slice thickness of 1 mm or less. If the length of the VA to the posterior fossa is short, it can be hard to measure the mid duct diameter. In these cases, the operculum measurement can be of help as an alternative criterion.

Even with these limitations, our results suggest a strong association between preexistent fluctuating HL and sudden deterioration of hearing on head trauma in this systemic review. It is a prognostic factor that should be further explored in future prospective research on EVA patients.

CONCLUSION

The majority of patients with a proven EVA do not experience sudden drops in hearing level caused by (minor) head trauma. This meta-analysis shows that only approximately one-third of the reported EVA patients are affected. Patients who experience fluctuations in their hearing level before the minor head trauma, noise trauma, or barotrauma have a significantly increased risk of hearing deterioration on this event. We found no other significant prognostic factors. Therefore, recommendations such as the use of helmets by young EVA patients and restricting activities such as contact sports might be reserved for EVA patients with preexistent fluctuating HL or patients with a history of sudden perception loss after head trauma. It is therefore essential to closely follow the progression of HL and the way in which the progression of HL takes place in all EVA patients.

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CONTRALATERAL HEARING LOSS IN CHILDREN WITH A UNILATERAL ENLARGED VESTIBULAR AQUEDUCT

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ABSTRACT

Objective. To evaluate the long-term ipsi- and contralateral hearing of patients with a unilateral enlarged vestibular aqueduct (EVA).

Study design: Multicenter retrospective cohort study.

Setting: Three tertiary otology and audiology referral centers.

Patients and diagnostic interventions: A total of 34 children with a unilateral enlarged vestibular aqueduct as identified on CT and/or MR imaging were evaluated with pure tone and speech perception audiometry.

Mean outcome measures: Radiologic measurements of the vestibular aqueduct, ipsi- and contralateral hearing loss, ipsi- and contralateral hearing loss progression over time and DNA test results.

Results: All patients in this cohort with unilateral EVA presented with hearing loss. Hearing loss was progressive in 38% of the ipsilateral ears. In 29% of the children, hearing loss was also found in the contralateral ear without EVA. In 90%, the contralateral hearing was stable, with a mean follow up of 4.2 years. We found a significant correlation between the severity of the hearing loss and the size of the EVA. A genetic diagnosis associated with EVA and/or SNHL was found in only 7%.

Conclusion: About a third of the children with unilateral EVA are at risk of developing hearing loss in the contralateral ear. This indicates that at least in some patients with a unilateral EVA, a bilateral pathogenic process underlies the hearing loss, in contrary to what the imaging results suggest. These findings are important for counseling of EVA patients and their parents and have implications for follow up.

INTRODUCTION

The prevalence of congenital sensorineural hearing loss (SNHL) in one to two per thousand live births makes this one of the most common congenital disorders (1,2). A recent study of children referred for sensorineural hearing loss in The Netherlands showed that in 29%, the hearing loss was unilateral (3). The cause of unilateral hearing loss is frequently a structural abnormality of the labyrinth, as identified by radiology (49%) (3). In children with unilateral sensorineural or mixed type hearing loss, 9-15% is reported to be caused by an enlarged vestibular aqueduct (EVA) (4-6). An EVA may be identified as a separate radiologic entity or in association with other inner ear anomalies (incomplete partition type 2, IP2) (7).

The occurrence and progression of hearing loss in ears affected by EVA is hypothesized to be caused by an increased endolymphatic inner ear fluid pressure or fluctuations in endolymphatic pressure, and results in hair cell damage (8). Although EVA is a congenital disorder, hearing loss may not be present or apparent at birth (9). When present, hearing loss may be fluctuating, slowly progressive or present with sudden exacerbations. In 12% of EVA patients, there is a clear relation between hearing loss and (minor) head injury, barotrauma or noise trauma (10). Identification of an EVA as a cause for progressive or fluctuating hearing loss is important for counseling and hearing rehabilitation of these patients. In children with profound (bilateral) hearing loss, cochlear implantation has been proven to be a successful treatment option in children with EVA (11).

Radiology (CT and MR imaging) has become essential in the etiologic analysis of both uni- and (asymmetric) bilateral SNHL because of the high prevalence of causative abnormalities that can be identified. The diagnosis can be made based on visualization of an enlargement of the vestibular aqueduct on CT or enlarged endolymphatic duct and sac on MR imaging. Different methods for measuring the vestibular aqueduct width and different definitions of an enlarged vestibular aqueduct have been described (12,13). Historically, CT imaging is used to measure the vestibular aqueduct, but MR imaging is more and more used in the etiological diagnosis of SNHL. To date, there is no consensus on the optimal methodology of measuring the VA, nor which definition for EVA best corresponds with the occurrence or severity of hearing loss.

In patients with unilateral EVA, the risk to the affected ear for conductive-, sensorineural- or mixed type hearing loss is well-documented. The development of hearing loss in the contralateral, apparently unaffected ear is somewhat more puzzling. In this study, we focus on the imaging and measurement of the ipsilateral and contralateral VA and correlate this to the observed hearing loss (progression) in both ears.

MATERIALS AND METHODS

Patients

Children diagnosed with unilateral EVA or IP-2 malformation between 2010 and 2019 were selected from the databases of the center of diagnostics of sensorineural hearing loss (CDS) of the VU medical center, the Radboud University Medical Center and the Leiden University Medical Center (LUMC), all tertiary referral centers for the evaluation and management of pediatric hearing loss. The databases consisted of children with uni- or bilateral hearing loss of at least 30 dB, referred for etiological analyses, counseling and rehabilitation. Children included in this study were required to meet the following criteria: adequate otological examination, audiometry, CT of the temporal bone and/or MR imaging of the inner ear. DNA analysis was also evaluated when available.

Age

The age at detection was defined as the age at which the hearing loss was first diagnosed by the Audiology Center, either by auditory brainstem response (ABR) or pure tone audiometry (PTA).

Audiometric evaluations

When PTA was performed, an average threshold at 500, 1000, 2000 and 4000 Hz was used for the analysis. Children were diagnosed with SNHL if the sensorineural hearing threshold was 30 dB HL or more. Asymmetric bilateral SNHL was defined as one or more frequencies with a greater than 30 dB HL difference, two or more frequencies with a greater than 15 dB difference or three or more frequencies with a greater than 10 dB difference in threshold between the left and right ear. Progression of hearing loss was defined as a decrease in hearing of more than or equal to 30 dB affecting at least three consecutive frequencies (14).

Evaluation of imaging

Imaging studies consisted of unenhanced temporal bone CT imaging, high resolution T2 weighted MR imaging of the inner ear, or both. Both ears were assessed for EVA. The available imaging was revised in all patients, both of the affected side and the 'normal' contralateral side, using the following criteria: The vestibular aqueduct was defined as enlarged if at least one of two measurements reached the criteria for EVA: 1. Operculum measurement: A line is drawn from the medial border of the operculum perpendicular to the anterolateral wall of the vestibular aqueduct (VA). A VA was defined as EVA if this diameter exceeded 2 mm (Figure 1A+B). 2. Midpoint measurement: A line is drawn along the operculum, parallel to the posterior fossa dura. Another line is drawn through the center of the EVA along its longitudinal axis. Halfway between the most anterior extension

of the EVA and the operculum line is defined as the midpoint of the EVA. The EVA width at the midpoint is measured by drawing a line perpendicular to this longitudinal line at its midpoint, from the medial to the lateral surface of the EVA. A VA was defined as EVA if this diameter exceeded 1.5 mm (Figure 1C+D). We also performed a third measurement of the VA in the sagittal plane (on CT only) by defining the midpoint of the VA and measuring the diameter at this point of the VA This measurement was not part of the inclusion criteria (Figure 1E). A VA was defined as EVA if this diameter exceeded 1.5 mm (4). A VA was defined as 'normal' if the diameter was 1.5 mm or less in the midpoint measurements and 2 mm or less in the operculum measurement. An incomplete partition type 2 (IP-2) was diagnosed if the enlarged vestibular aqueduct was accompanied by two additional components: a cystic cochlear apex with a normal basal turn and a dilated vestibule.

DNA analysis

Molecular genetic testing, as described previously, was performed and reviewed when available (15).

Statistical analysis

Statistical analyses were performed using SPSS 22.0. The criterion for statistical significance was set at $p < 0.05$. Descriptive analyses, cross tables and Pearson correlation tests were used to outline results of this study.

This study was approved by the medical ethics review committee of the VU University Medical center Amsterdam (number 2018.402).

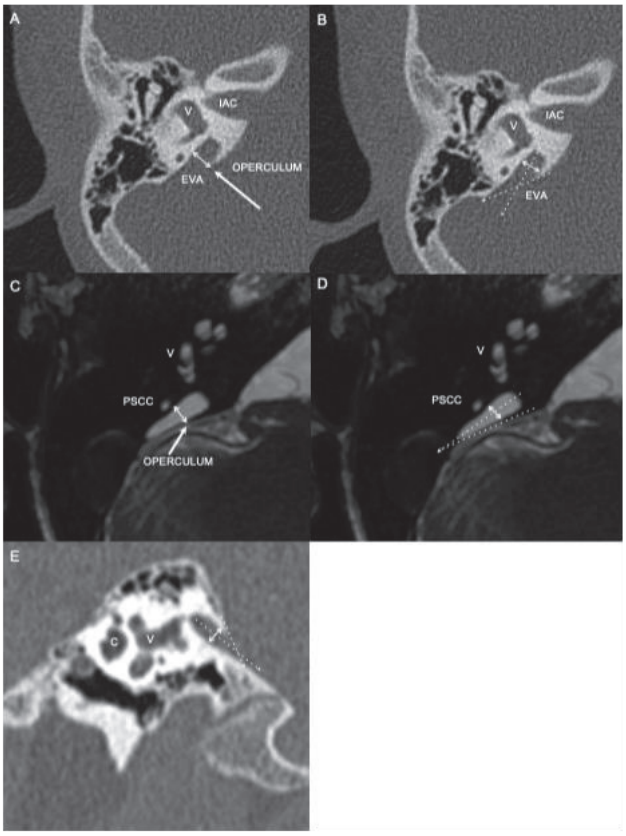

Figure 1. A, B: axial CT image of the right temporal bone: Operculum measurement is shown by arrow in A, midpoint measurement by arrow in B. C, D: axial MR T2 image of the right inner ear revealing an enlarged endolymphatic duct and sac: Operculum measurement is shown by arrow in C; Midpoint measurement s shown by arrow in D. E sagittal CT image of the right temporal bone. Midpoint measurement is shown by arrow. C = cochlea, V= vestibulum, IAC = internal auditory canal, EVA= enlarged vestibular aqueduct. PSCC= posterior semicircular canal.

RESULTS

Clinical characteristics

A total of 34 children with a unilateral EVA and/or incomplete partition type II were extracted from the databases of the three tertiary referral centers as mentioned above. The mean age at diagnosis of the hearing loss ranged from one month to 20 years old (an overall median of 7.2 years). The M/F ratio was 50/50. Thirteen right ears and 21 left ears were affected by EVA (n=27) or incomplete partition type II (n=7) (Table 1 and Figure 2).

Table 1 Demographic and clinical characteristics of the children with a unilateral EVA on CT and/or MR imaging.

Characteristics	N
Number of patients	34
Sex n (M/F)	
M	17
F	17
Age at detection of the hearing loss (mean/range) years	7.2 (0-20)
Hearing loss at detection affected ear (mean/range) dB	60 (33-120)
Follow up time (mean/range) years	4.2 (1-11)
Number of patients with contralateral hearing loss	10
Number of ears with progressive hearing loss	
Ipsilateral	13
Contralateral	1
Imaging studies	39
CT	23
MR	16
DNA test performed	27
Comorbidities	
Juvenile idiopathic arthritis	1
Minimal facial asymmetry at the side of the hearing loss	1
Branchial arch cleft	1
Vestibular symptoms	10
Episodic vertigo	3
Imbalance	3
Developmental delay in motor skills	4

Hearing loss

The mean age at diagnosis of the hearing loss ranged from one month to 20 years (an overall median of 7.2 years). In 27 of the 34 children, longitudinal measurements of hearing were available. The mean follow-up was 4.2 years (1 – 11 years).

The mean hearing loss of all 34 children at the ipsilateral side was 60 dB HL (33-120 dB) at the initial measurement. Ipsilateral hearing loss was progressive in 13 children (38%). In this group of patients with progressive hearing loss, the mean hearing loss at the first audiogram was 39 dB HL (33-87 dB) and 60 dB (47-120 dB) at the last follow up audiogram (equating to a mean hearing loss of 20 dB), with a mean follow-up of 4.8 years. In addition, 2/34 (6%) had fluctuating hearing loss, and hearing loss was already profound at detection in 5/34 (15%) children.

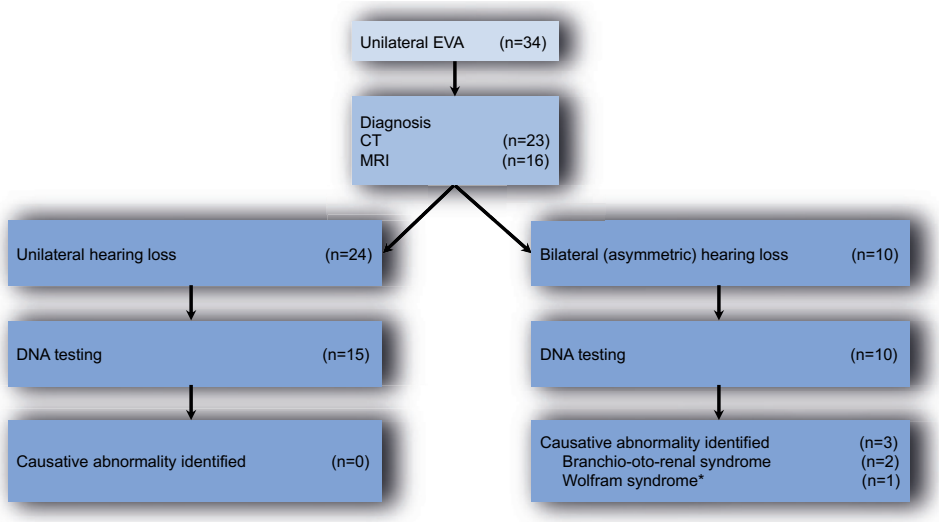

Figure 2 Overview of the etiological work up.

**One patient was found to have two diagnoses, a unilateral EVA and the Wolfram syndrome. As of yet, there is no known relation between these two diagnoses.*

Contralateral hearing loss was found in 10/34 (29%) children. The mean hearing loss of the contralateral ear was 30 dB HL. Audiometric follow-up was available in 6 of these patients, with a mean follow-up of 4.2 years. In all patients with contralateral hearing loss, this hearing loss was already present at presentation. In only one patient, hearing loss was progressive (from 47 to 60 dB between the first and last audiogram, with a follow up of 6 years). When present, the contralateral hearing loss was characterized by a mild sensorineural hearing loss in the lower frequencies in 8/10 children, in one patient the hearing loss was profound on both sides, and one patient suffered from bilateral high frequency hearing loss (Figure 3). None of the normal hearing contralateral ears developed hearing loss during the follow-up period (mean follow up 4.2 years). Two children with contralateral SNHL were found to have BOR syndrome (see also 'genetics'), no genetic cause was found in 8/10 children with contralateral SNHL. We found no additional predisposing factors for contralateral hearing loss, such as age at diagnosis, morphological characteristics, or severity of hearing loss at the side affected by EVA.

Imaging

A total of 39 radiological investigations were performed in 34 children (23 CT and 16 MR scans). All patients had a unilateral EVA as diagnosed on imaging using the criteria mentioned above. Twenty-seven children were diagnosed with an isolated EVA and 7 with IP-II. Two of the patients initially diagnosed with unilateral EVA were found to have

bilateral abnormalities to the labyrinth, namely an incomplete partition of the cochlea without an EVA (both with only ipsilateral hearing loss). The mean operculum diameter of the VA of the ipsilateral ear was 2.7 mm, the mean midline diameter in this group was 2.6 mm. The mean operculum diameter of the VA of the contralateral ear was 0.6 mm and the mean midline diameter of the non-EVA side was 0.5 mm in this ear (Table 2). In the 10 patients with (asymmetric) bilateral hearing loss, the mean operculum diameter of the VA of the contralateral (non-EVA) ear was 0.7 mm, the mean midline diameter in this group was 0.5 mm.

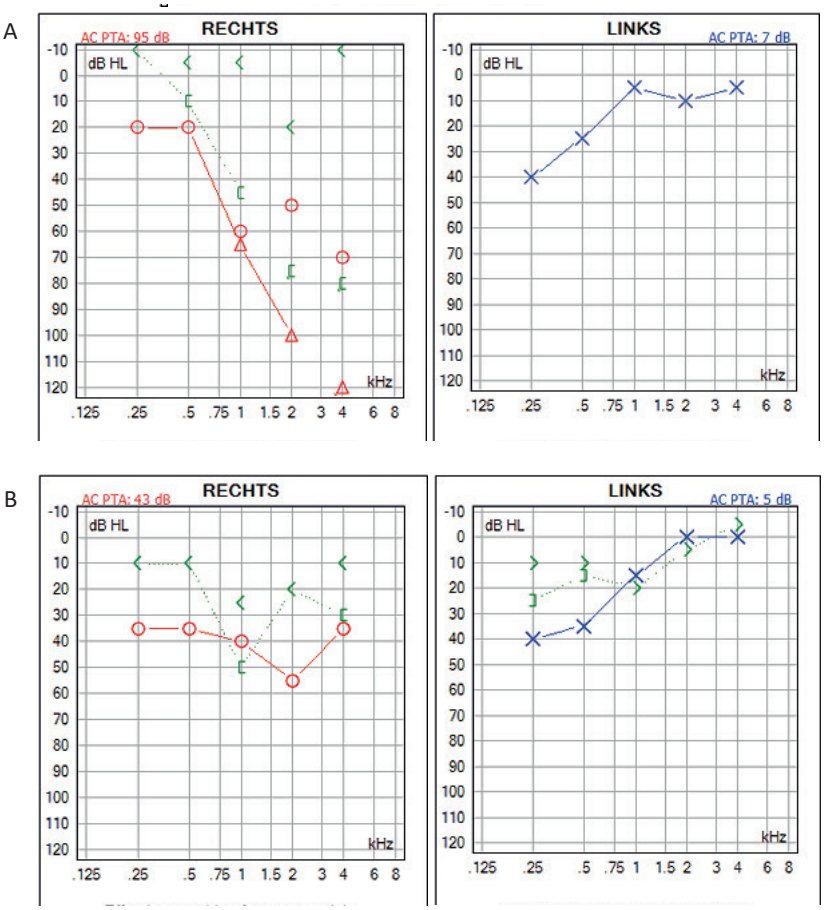

Figure 3 Two examples of children with a unilateral EVA and bilateral asymmetric hearing loss. A: audiogram of a patient diagnosed with brachio-oto-renal (BOR) syndrome and an EVA at the right side. The ipsilateral hearing loss was progressive; the contralateral hearing loss was present at detection and remained stable. B Patient diagnosed with EVA at the right side. The hearing loss remained stable on both ears. DNA testing showed no abnormalities.

Table 2 Hearing loss and mean and range of EVA measurements (mm).

	VA midpoint ipsilateral (mm)	VA midpoint contralateral (mm)
EVA patients with normal contralateral hearing (n=24)	2.6 (1.5-3.7)	0.5 (0-1.4)
EVA patients with contralateral hearing loss (n=10)	2.6 (1.7-5.3)	0.5 (0-1.3)

Midpoint measurement: A VA was defined as EVA if the diameter exceeded 1.5 mm. Operculum measurement: a VA was defined as EVA if this diameter exceeded 2 mm (4).

Imaging vs. hearing loss

We analyzed all ears with hearing loss (both ipsi- and contralateral, n = 44), and found a significant correlation between the severity of the hearing loss at detection and the operculum diameter of the VA (p=0.05) and between the severity of the hearing loss and the midline diameter of the VA (p=0.02). When only evaluating the hearing loss of ears affected by EVA, no correlation between severity of hearing loss and operculum or midline diameters was found (p=0.6 and p=0.6, respectively). We found no significant correlation between progression of hearing loss and the operculum diameter (p=0.9) or the midline diameter (p=0.6). No correlation was found between the diameter of the EVA and the contralateral hearing loss (operculum diameter p=0.5 and midline diameter p=0.3).

Genetics

DNA analysis was performed in 27/34 children, consisting of primarily targeted sequencing of SLC26A4 at first, followed by whole exome sequencing when the initial test was negative. A genetic cause for the hearing loss was found in only three cases. Two patients were diagnosed with branchio-oto-renal (BOR) syndrome. One child was diagnosed with Wolfram syndrome. As of yet, there is no reported relationship between an EVA and the Wolfram syndrome, we therefore assume these to be two unrelated pathologies. All of these patients had bilateral asymmetric hearing loss, with mild SNHL of the lower frequencies at the contralateral ear. In one child who had only ipsilateral hearing loss only, a heterozygous pathogenic variant in *SLC26A4* was found. Single-allele *SLC26A4* mutations have been associated with hearing loss and EVA. In these cases, with apparently heterozygous pathogenic *SLC26A4* alterations, the assumption is that the wild type allele is affected by an as of yet unidentified pathogenic alteration. The spectrum of pathogenic SLC26A4 mutations is still expanding (16).

VA operculum ipsilateral (mm)	VA operculum contralateral (mm)	VA sagittal ipsilateral (mm)	VA sagittal contralateral (mm)
2.7(1.5-3.6)	0.6 (0-1.8)	2.2 (1.1-2.9)	0.6 (0-1.1)
2.7 (1.6-5.3)	0.4 (0-1.4)	2.2 (1.8-3)	0.9 (0-1.5)

VA = vestibular aqueduct. Ipsilateral = side of the enlarged vestibular aqueduct (EVA). Contralateral: side of the normal VA.

DISCUSSION

In this study we evaluated radiological findings and the presence or development over time of ipsi- and contralateral hearing loss in children with a unilateral EVA. Hearing loss at the side of an EVA is well described and known to be very variable (17). The hearing loss of the contralateral side is often overlooked in unilateral EVA patients. This study shows that SNHL also occurs in about a third of the patients in the contralateral ear. As bilateral hearing loss has a more pronounced impact on auditive functioning, development of linguistic skills and scholastic performance than unilateral hearing loss, these findings have important implications for counseling, follow-up, and rehabilitation of unilateral EVA patients. While it has been common practice to be less stringent in the follow up of apparently unilaterally affected patients, based on these findings we now advise long term audiological follow up of both ears and feel that adequate counseling of patients and parents should include the risk of bilateral hearing loss, also in unilateral EVA patients.

Hearing loss

The onset of hearing loss in patients with an EVA may occur at birth until adolescence, with the highest frequency in childhood (18). In this study, the mean age at detection of the hearing loss was 7.2 years. This is somewhat older than the mean age at detection (3.7 years old) of the hearing loss in a large cohort of children with unilateral sensorineural hearing loss (USNHL) evaluated previously (19). The age difference could be explained by the fact that hearing loss may not be present at birth in EVA patients, as opposed to many other pathologies causative of USNHL.

Hearing loss at the side of the EVA was progressive in 38% of the children. This is in line with previous studies, describing progression of hearing loss in 12 – 65% of the patients (5,20,21). Remarkably, we found an incidence of SNHL at the contralateral side in children with a unilateral EVA of 29%. To date, the literature has been sparse regarding the prevalence of contralateral hearing loss in patients was a unilateral EVA. Three studies reported patients with contralateral SNHL, with a prevalence of 5 - 55%, and a follow-up of

0 - 3.1 years (20,22,23). The wide range in the literature may be explained by differences in the study populations, inclusion criteria, imaging modalities and diagnostic criteria. In the current study, the contralateral hearing loss was already present at first detection of the ipsilateral EVA. In children with normal contralateral hearing at first detection, hearing loss did not develop later on, with a relatively long audiological follow up (4.2 years). In most children, the contralateral hearing loss was characterized by a mild sensorineural hearing loss in the lower frequencies. In the majority of the patients, this hearing loss was stable. In only one child, the contralateral hearing loss was progressive. In addition, children with USNHL that is not associated with EVA can develop contralateral hearing loss as well, for instance SNHL caused by a cCMV infection or children with progressive asymmetric hearing loss caused by temporal bone anomalies. A study focusing on USNHL without EVA found contralateral hearing loss in 11 % of the patients. Some of these patients had bilateral temporal bone anomalies other than EVA (24).

CT and MR Imaging

As previous studies have shown, CT and MR imaging are complementary imaging modalities in the diagnosis of hearing loss (25, 26). Generally, CT is considered the better modality for the identification of bony abnormalities, while MR imaging provides superior information about fluid compartments and soft tissue structures such as the intralabyrinthine anatomy, the cochlear nerve and brain. In choosing a radiologic modality, especially in the pediatric population, radiation exposure of CT, logistics, and the need for anesthesia in MR imaging of young children may also play a role. (13,19). In the present retrospective study, the choice for an imaging modality was individualized per patient, based on the type of hearing loss and additional clinical characteristics such as age, neurological signs, developmental impairment, and the clinical setting. An EVA is detectable on both CT and MR imaging. In our study, we found a good correspondence between the CT and MR imaging in the patients in which both modalities have been performed and this is in line with previous literature (13). Based on our experience, we perform CT as an initial imaging modality in this group of patients. MR imaging is the preferred first modality when cochlear nerve or brain abnormalities are suspected, in case of additional neurological signs or fluctuating hearing loss. There are no standardized diagnostic criteria for EVA, which makes it difficult to compare the measurement outcomes of these two modalities (12,13). The most commonly used cut-off values for EVA are a VA diameter at the midpoint exceeding 1.5 mm and exceeding 2.0 mm at the operculum on axial images (4). On CT, a midpoint and an operculum measurement can be performed. When the axial CT images are not conclusive, we find a measurement of the VA in a sagittal reconstruction a good alternative to diagnose EVA. On axial T2 weighted MR, both operculum and midpoint measurements can be performed as well. However, we found the midpoint measurement the most reliable measurement to define an EVA

on MR imaging, as the tip of the bony operculum is more difficult to identify. The correct measurement and definition of EVA is particularly relevant in the evaluation of bilateral hearing in unilateral EVA patients. In this study, most contralateral ears were well within the range of normal midpoint and operculum VA diameters. In only one patient had a borderline normal VA, with a midpoint and operculum diameters of 1.4 mm. This patient had normal hearing in this ear.

Imaging vs. hearing loss

Previous studies do not agree on the relation between hearing loss (severity) and the size of the VA (5,21,27). In the current cohort, a significant correlation was found between the severity of the hearing loss and the diameter of the VA in ears with hearing loss, in agreement with a previous study by Madden et al. (5). However, when evaluating ears affected by EVA only, no association between VA diameter and hearing loss severity was found, indicating that the association of hearing loss severity and VA diameter is mainly determined by the presence or absence of an EVA. In other words, on average non-EVA ears with hearing loss have a mild hearing loss, ears affected by EVA have a more severe hearing loss. Two previous studies using the same measurement criteria also did not report a correlation between EVA and hearing loss severity (21,27).

Genetics

Bilateral EVA is strongly associated with DFNB4/Pendred syndrome but is also regularly reported in patients with other syndromes such as Waardenburg or BOR syndromes (27-31). Although in patients with a unilateral EVA the relation with a genetic diagnosis is less common, it has also been reported for patients with DFNB4/Pendred, Waardenburg and BOR syndrome (30-32,33). In this study, two children with BOR syndrome and one child with Wolfram syndrome had a unilateral EVA and bilateral asymmetric hearing loss. As of yet, no relation between the EVA and Wolfram syndrome has been reported in the literature, and we therefore assume that these are two unrelated identities. The audiological phenotype of these three children was not different from the children with asymmetric bilateral hearing loss without a clear molecular genetic diagnosis.

Currently, the cause for contralateral hearing loss in patients with a unilateral EVA is unclear. It has been suggested that the observation of bilateral hearing loss in subjects with a unilateral EVA is caused by an asymmetric phenotypic expression of a yet unknown disease mechanism (20). Most likely this is not caused by a monogenetic disorder but a complex disease mechanism, for example a variable expression of key genes in the embryonic development of (both) cochleae.

CONCLUSION

A radiologically 'normal' anatomy of the contralateral temporal bone in unilateral EVA patients does not preclude bilateral SNHL. In fact, SNHL at the contralateral side seems to occur rather frequently (in 29%). This information should be shared with the patients and their parents. Regardless of the etiology, bilateral stringent audiological follow-up of unilateral EVA patients is mandatory. As the consequences of bilateral SNHL are more critical than unilateral SNHL, timely intervention and hearing rehabilitation is crucial for the optimal development of hearing, speech, and communication skills.

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SUMMARY

CONCLUSIONS AND CLINICAL IMPLICATIONS

RECENT DEVELOPMENTS AND FUTURE PERSPECTIVE

SUMMARY

Chapter 1 provides an overview of the principles and current practice of the newborn hearing screening in the Netherlands and the etiology of pediatric sensorineural hearing loss (SNHL). The history and currently available etiological diagnostic instruments are described.

In **Chapter 2**, the etiology of pediatric sensorineural hearing loss (SNHL) in a large cohort (n= 423) of children with both uni- and bilateral SNHL is evaluated, focusing on the determination of causative genetic, structural and acquired etiologies. This study shows that, using a stepwise diagnostic approach comprising of imaging, genetic, and/or pediatric evaluations, a cause for SNHL is identified in 67% of the affected children. The most common causative finding in children with bilateral SNHL is a pathologic gene variant (26%), and in children with unilateral SNHL, a structural abnormality of the inner ear (27%). We found that the diagnostic yield is associated with severity and the age at detection of the hearing loss: the highest proportion of causative abnormalities is found in children with profound hearing loss and/or a young age at detection.

Chapter 3 presents a study with the focus on the specific value of CT and MR imaging of the inner ear and brain in the etiological diagnostic work-up of children with bilateral SNHL. The prevalence of causative radiological findings in children with bilateral SNHL is considerable: 32%. The highest diagnostic yield is found in children with asymmetric and/or profound SNHL. The inner ear was the most frequently affected site (61% of abnormal scans), and an enlarged vestibular aqueduct (EVA) was the most commonly found abnormality (24%). In the group of children who underwent both imaging modalities, a significantly higher diagnostic yield of MR (34%) compared to CT (20%) was found. We conclude that imaging is essential in the etiologic evaluation of children with bilateral SNHL. Based on our findings, MR imaging of the inner ear and brain is the primary imaging modality of choice in the etiological evaluation of children with bilateral SNHL because of its high diagnostic yield.

In **Chapter 4**, the imaging results of children with unilateral sensorineural hearing loss (UNSHL) are presented. Using CT and/or MR imaging, a causal abnormality was identified in 49% of the children with USNHL. The most frequently affected site was the labyrinth (29%), followed by the cochlear nerve (9%) and the brain (7%). We conclude that imaging is essential in the etiologic analysis of USNHL because of the high prevalence of causative abnormalities that can be identified with radiology. CT and MR imaging are complementary imaging options. As the most prevalent causative abnormalities of

USNHL can be readily identified on CT, we propose to use this as the first modality, and perform sequential MRI if CT results are negative. However, one can opt to deviate from this protocol for various medical and practical reasons.

Chapter 5 presents a systematic review with the focus on the identification of factors associated with sudden drops in hearing level after minor head trauma in patients with an EVA. The data of 31 articles were pooled with a total of 179 patients with 351 EVAs. Only one-third of the patients with a proven EVA experienced sudden drops in hearing level because of a head trauma. We found a significant association between preexisting fluctuating hearing loss and the chance of sudden drops in hearing level caused by trauma. Based on these results, we suggest that stringent lifestyle advice, like avoiding activities with a risk of minor head trauma such as contact sports, might be restricted to patients with a (pre-existent) fluctuating hearing loss and those with a history of sudden hearing loss following minor head trauma.

Chapter 6 comprises a study evaluating the ipsi- and contralateral hearing loss of 34 children with a unilateral EVA as identified on CT and/or MR imaging. The risk of hearing loss in the ear affected by EVA is well-known, the occurrence of hearing loss in the contralateral, apparently unaffected ear is somewhat more puzzling. In this study, multiple methods of measuring the vestibular aqueduct on CT and MR imaging are described. We focused on the imaging and measurement of the ipsilateral and contralateral vestibular aqueduct width and correlated this to the observed hearing loss (progression) in both ears. We found that children with a unilateral EVA are at risk of hearing loss in the contralateral ear (in 29%) too. This finding indicates that at least in some patients with a unilateral EVA, a bilateral pathogenic process underlies the hearing loss, in contrary to what the imaging results suggest. These findings are important for counseling of EVA patients and their parents and have implications for follow up.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Sensorineural hearing loss is one of the most prevalent chronic conditions in children. Introduction of the newborn hearing screening followed by definitive audiological diagnostics resulted in early detection and rehabilitation and with that, better developmental outcomes in childhood. Next to that, it sparked the interest in the underlying etiology, both in physicians as well as in patients and their parents. An adequate etiological evaluation may be important for several reasons: prognostication of the progression of the hearing loss in affected ears, prognosis of apparently unaffected ears in unilateral hearing loss, identification of associated physical conditions and associated syndromes, identification of other family members at risk, adequate early intervention if possible, and accurate counseling and medical guidance of the patients and their parents (1). Good progress has been made in the etiological knowledge by improvement of clinical phenotyping, genetic diagnostics and imaging quality. These improvements have increased the opportunity of finding a cause of the SNHL: previous studies (describing different diagnostic approaches between 2000-2011) show a diagnostic yield of about 50% (2-4). In the current manuscript an etiological diagnosis was identified in 67% of children using a stepwise, multidisciplinary approach. In children younger than 1 year, an etiological diagnosis was identified in 74 %. The choice and order of etiological diagnostics is subject of debate. For the cohorts described in this thesis, decisions on the diagnostic strategy were made by a multidisciplinary team, in close consultation with the parents. The advent of the newborn hearing screening program in the Netherlands allowed the collection of the data of children with SNHL on a substantial scale. This made it possible to analyze the results of the stepwise approach and made it possible to create a diagnostic flowchart (Figure 1). This stepwise approach allows for a more personalized use of diagnostics and limits the cost and burden of noncontributing investigations as opposed to using a 'complete test battery' in all patients. In this flowchart, we propose genetic evaluation as the first step in bilateral SNHL and radiology as the first diagnostic step in children with USNHL. The results of the first test will direct further examination. CMV diagnostics is recommended in all children with SNHL. This flowchart might serve as a practical approach to the etiological diagnosis of SNHL and may contribute to relevant guidelines, such as the Dutch *'richtlijn voor etiologisch onderzoek naar slechthorendheid op de kinderleeftijd'* (5).

As described in the introduction, in previous etiological classifications of SNHL (reported between 2000-2011) 50% of all pediatric SNHL was estimated to be caused by a genetic factor and 50% by acquired factors. At the time, no distinction between the etiology of uni- and bilateral SNHL was made. The current thesis shows a more differentiated distribution (including structural abnormalities and the distinction between uni- and

bilateral SNHL) with different proportions of the causes of SNHL in children. A genetic or suspected genetic cause is identified in 45%, a structural abnormality in 5%, and an acquired factor in 16% of children with bilateral SNHL. In children with unilateral SNHL, a genetic or suspected genetic cause is found in 18%, a structural abnormality in 25%, and an acquired factor in 23% in the children in which a cause was identified. CT and MR imaging of the inner ear and brain have contributed considerably to these findings: a structural abnormality was identified in 32% of the children with bilateral SNHL and in 49% of the children with USNHL. CT and MR imaging can be viewed as complementary radiological modalities in the etiological diagnosis of pediatric SNHL. By performing the modality with the highest diagnostic yield first, additional diagnostics may be avoided. Based on the results reported in chapter 4, we recommend performing CT imaging as the first modality of choice in USNHL, followed by MR imaging if CT results are negative, and MR imaging in bilateral SNHL. One can deviate from these recommendations based on medical, practical and logistic considerations. When choosing between the two radiologic modalities, the advantages of both techniques must be weighed against their inherent disadvantages. Relevant considerations are: the need for sedation (more often in MR imaging), overall impact on the pediatric patient, parental preference, costs, accessibility and logistics. Additionally, one of the most apparent disadvantages of CT imaging of the temporal bone is that it requires exposure to radiation, albeit in a low dose. When CT imaging is indicated, the delivered dose should be optimized to use the lowest possible dose while maintaining adequate image quality and resolution to answer the clinical question, in accordance with the ALARA principle (As Low As Reasonably Achievable) (6). In recent years, increasingly efficient CT scanners have been developed that decrease the radiation dose needed (7,8).

Understanding the etiology of pediatric SNHL provides important information for prognosis, prevention, rehabilitation and possibly treatment in some cases. The studies in this thesis assess the diagnostic yield of the instruments used in a personalized stepwise etiological work-up of children with SNHL and provide insight in the relative prevalence of the causative etiologies.

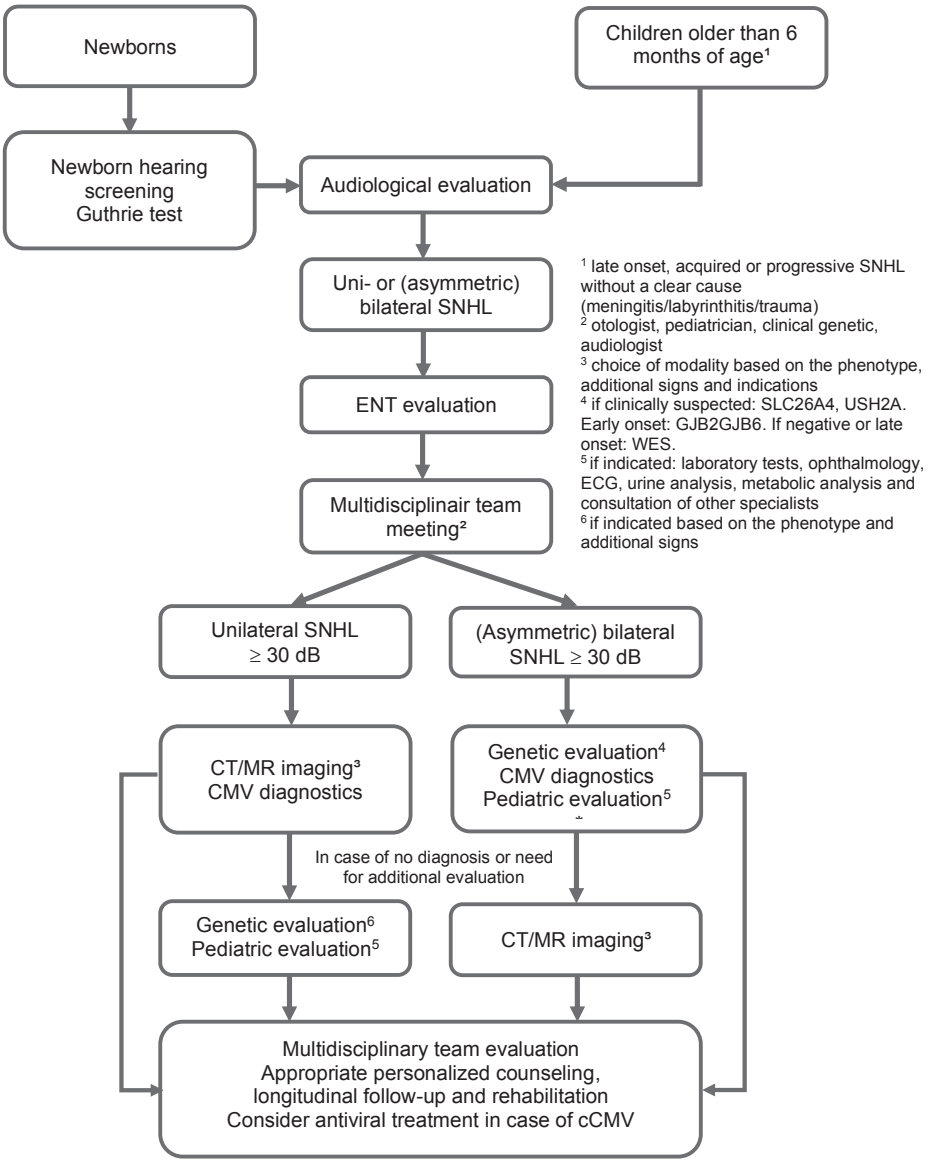

Figure 1. Diagnostic flow chart for children with both unilateral and (asymmetric) bilateral SNHL. The results of the first step will direct further examination. Deviations from the protocol may be indicated by the multidisciplinary team (i.e., family history, medical indications, or cochlear implant procedure).

RECENT DEVELOPMENTS AND FUTURE PERSPECTIVE

CMV

CMV is the most common congenital viral infection and is known to cause numerous abnormalities such as developmental delay, microcephaly and hepatosplenomegaly. cCMV is the most prevalent cause of acquired SNHL and is responsible for 21% of uni- and bilateral SNHL (37% vs 17%) in the children of the cohort described in this thesis. The SNHL can be progressive, and its onset can be delayed for months, even years. As of today, there is no vaccine to prevent cCMV, despite 40 years of research (9). The development of a CMV vaccine has been marked as a top priority by the National Academy of Medicine, and research efforts are on-going. The diagnosis of a cCMV infection is made by viral culture or PRC, obtained within the first 2-3 weeks of life (10). Early testing of CMV is essential, because postnatal exposure can occur, and the test itself cannot differentiate between a congenital and postnatal infection. This is challenging because children can be asymptomatic at the time of birth. Next to that, the sensitivity of CMV in the dried blood spots of the Guthrie chard is only 32-46%, indicating that this is not a very effective method for the identification of children with CMV-related SNHL later in life (11-12). After the period of 5 years, Guthrie cards are destroyed and possible detection of cCMV is no longer possible. With the currently available PCR test, there is a potential for newborn CMV screening (13). However, as of yet there is no cCMV screening program in the Netherlands, because of the limited preventive and therapeutic options (14). Antiviral medication to treat symptomatic CMV infections in neonates (intravenous ganciclovir for 6 weeks or oral valganciclovir for 6 months) is currently available and has been shown to stabilize or improve hearing in 84% of the children with cCMV. Unfortunately, serious side-effects are described, consisting of neutropenia and hepatotoxity. At the moment, careful patient selection is mandatory when considering anti-CMV therapy. Hopefully, in the future less toxic therapies will be developed. When this is achieved, the position on newborn CMV screening should be reconsidered.

Imaging diagnostics

CT and MR imaging are well capable of detecting macroscopic defects in the inner ear and audiovestibular pathways, such as an EVA, inner ear malformations, fibrosis or aplasia of the vestibulocochlear nerve. Currently, CT an MR imaging does not provide sufficient resolution to detect the specific cause of SNHL on a cellular or molecular level. For instance, children with SNHL caused by DFNB1 *(connexin 26),* the morphology of the inner ear is apparently normal. New imaging techniques are promising, such as the use of contrast agents by intratympanic injection or absorbable gelatin sponges placed on the round window niche. Improvements in imaging technology and development of targeted contrast agents may lead to more insight into microscopic structural changes

or even molecular abnormalities in an affected inner ear (15). Further pre-clinical research is needed to determine the ideal targeted contrast agents for CT and MR imaging, their ability to pass through the round window and their (oto)toxicity. In addition, the potential of automated learning and artificial intelligence is increasingly applied in the field of medical imaging. An interesting breakthrough is the use of Generative Adversarial Networks (GAN). This is a type of neural network model, in which two networks (a generator and a discriminator) are trained simultaneously. This network is then used for novel applications such as image-to-image translation and image reconstruction. Based on this, software is designed to generate CT-like reconstructions from MR images to complement the MR sequences for soft tissue visualization. This application of MR imaging is currently performed in spine imaging, and research into the applicability for the inner ear imaging is initiated (16,17).

Genetic diagnostics

The field of genetics and DNA analysis is evolving constantly and at a rapid pace. Single gene evaluations based on clinical characteristics were the mainstay of genetic analysis at the time when evaluations of the cohorts described in this thesis started, before 2013. Nowadays, whole exome sequencing (WES) has become the cornerstone of DNA analysis. This test panel has greatly improved the diagnostic rate, especially in bilateral SNHL. This gene panel is constantly updated, and if no cause of the hearing loss is found using today's WES, a future version of the panel may still reveal a genetic cause of SNHL. Because of these developments, a second evaluation by WES may be offered 5 years after a previous evaluation. Whole genome sequencing (WGS) is likely to replace WES and become the standard diagnostic tool in the future (18). However, the large number of variants identified with WGS presents challenges in interpretation of variants of unknown significance (VUS), storage of data, privacy issues and managing of incidental findings. Even so, this technique will likely reveal new genes and alterations associated with pediatric SNHL.

Because of the relatively high prevalence of EVA in our series, we have a special interest in the spectrum of pathogenic *SLC26A4* mutations, which is still expanding (19). In some children with (U)SNHL, we found a heterozygous pathogenic variant in *SLC26A4*. Single-allele *SLC26A4* mutations have been associated with hearing loss and EVA. In these cases, with apparently heterozygous pathogenic *SLC26A4* alterations, the assumption is that the wild type allele is affected by an as of yet unidentified pathogenic alteration. This may also account for those patients with bilateral SNHL associated with a unilateral EVA, as described in chapter 6.

Inner ear gene therapies

Clinical options for the cure of SNHL are currently very limited, and management is mostly consisting of rehabilitation using devices such as hearing aids, cochlear implants or brainstem implants. The coming decades promise exciting new opportunities for curative treatment of SNHL in selected populations with hereditary SNHL. Therapeutic options targeting the inner ear are based on an evolving knowledge of the inner ear function and the underlying mechanisms of vestibular and auditory defects (20). This improvement in the understanding of the genetic etiology of SNHL is important in the development of treatments of inner ear disorders. Today, 123 non-syndromic genes are known to cause SNHL, and many more remain to be discovered. These genes encode a variety of proteins with different functions in the inner ear (gene regulation, synaptic transmission, ion homeostasis and roles in hair cell bundle morphology and development) (21,22). The diversity of SNHL-associated genes and target cells require gene-specific approaches. A growing number of these approaches have been investigated in animal models, including gene replacement (in case of loss-of-function dominant and biallelic recessive mutations), gene suppression (RNA-based therapies in case of dominant negative SNHL) and gene editing (CRISPR/Cas9 based genome editing for dominant forms of genetic SNHL). One upside of the inner is that the architecture is well suited for local approaches, because it is filled with fluids and application of treatment is possible through the round window membrane, which is easily accessible from the middle ear. Next to that, the inner ear is a relatively closed compartment, minimizing the risk of diffusion of the medication into the surrounding tissues. To transfer the gene therapy into the target cells a gene delivery system is required, called a vector. Viral and non-viral vectors are used, and the choice of a vector depends on the therapeutic goal, specific gene and target cell. For example, non-pathogenic adeno-associated viruses are used to enable gene replacement approaches via application into the inner ear in case of late onset SNHL caused by mutations in the *OTOF* gene (DFNB9) (Figure 2).

In case of dominant SNHL caused by mutations in the *TMC1* gene, gene correction is required, using a non-viral vector. Mutations can be corrected by CRISPR-Cas9 or CRISPRa (with an inactive form of Cas9) (23). The first phase clinical trial is planned testing Cas9 mediated repair in a form of inherited pediatric blindness (24). The success of this trial will determine the use of CRISPR-Cas9 in vivo in the future. While these first steps of these gene therapies are promising, there are still major challenges in terms of time, costs, efficacy, safety and ethical considerations to overcome (25,26). Furthermore, in order to prevent or remedy congenital forms of SNHL, in utero application of the therapy will likely present technical challenges.

The road to the exciting prospects for the near and distant future regarding diagnosis and therapy of pediatric SNHL as described in this chapter begins with the (early) detection of SNHL, facilitated by the advent of the newborn hearing screening programs, and the identification of the etiology of pediatric SNHL by a systematic diagnostic approach such as described in this thesis. The outcome of the studies presented here will hopefully contribute to the existing knowledge in this field, optimization of diagnostic strategies and eventually help to enable the next steps towards preventative and curative approaches to pediatric SNHL.

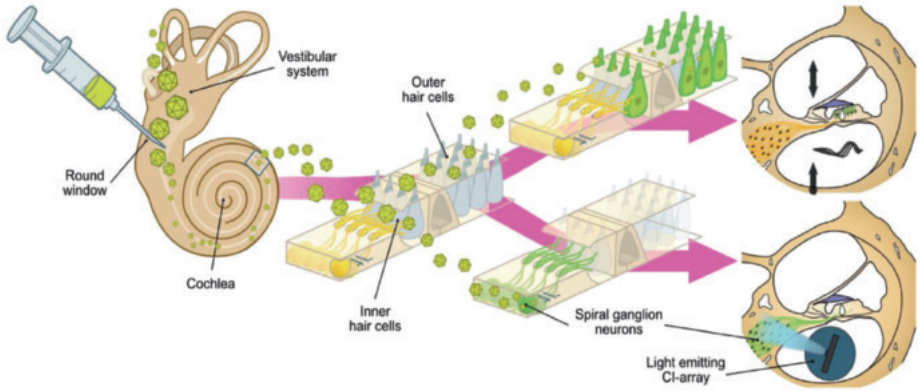

Figure 2 Future gene therapy of the ear. Cartoon illustrates the application of virus suspensions into the inner ear to target for gene therapeutic restoration e.g., of hair cell function (upper right) or optogenetic manipulation of SGNs for optical stimulation (lower right, axial section of a cochlear turn). Wrobel C, Zafeiriou M, Moser T, Understanding and treating paediatric hearing impairment. EBioMedicine 2021;63:103171.

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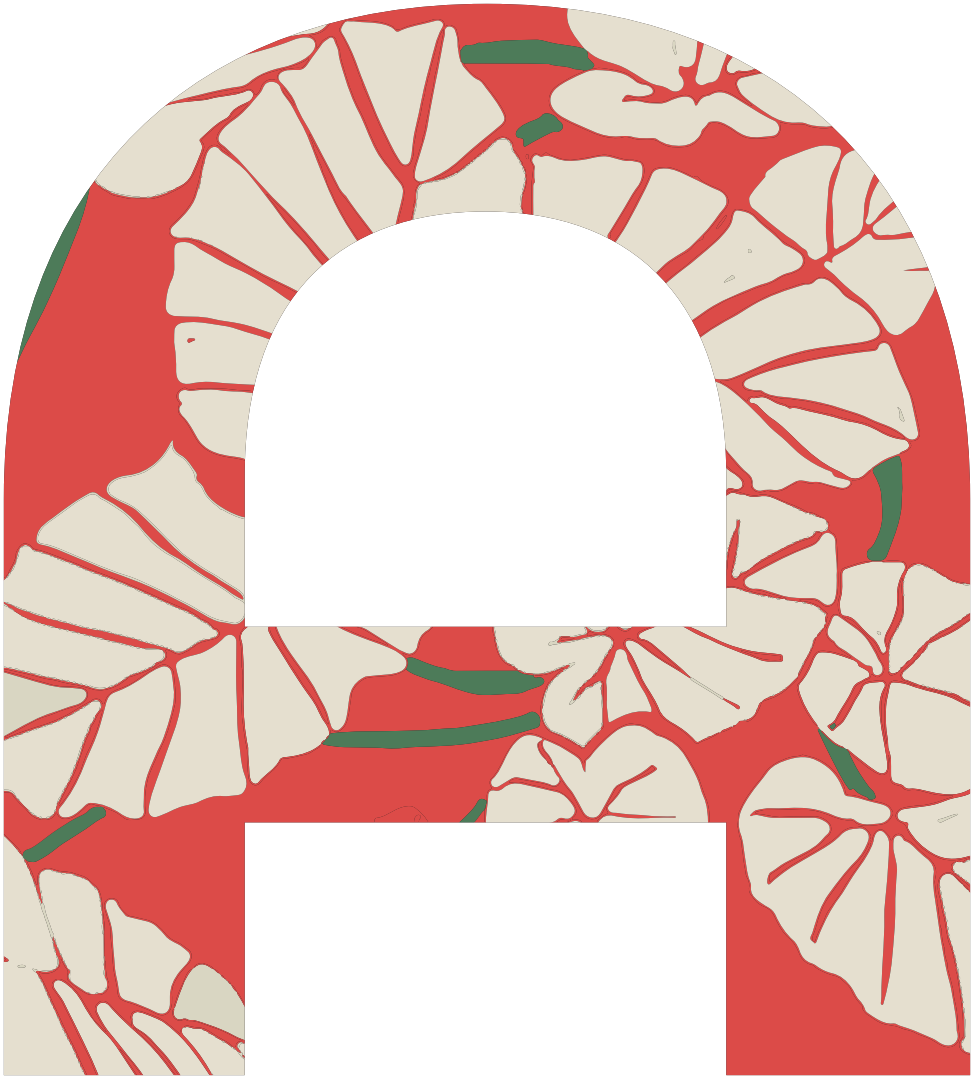

APPENDIX

LIST OF ABBREVIATIONS
NEDERLANDSE SAMENVATTING
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DANKWOORD
CURRICULUM VITAE

LIST OF ABBREVIATIONS

AABR:	Automated Auditory Brainstem Response
AC:	Audiology Center
AD:	Autosomal dominant
AR:	Autosomal recessive
BOA:	Behavioral Observation Audiometry
C:	Cochlea
CAPAS:	Compact Amsterdam Paedo-Audiometric Screener CDS Center of Diagnostics of sensorineural hearing loss
CDS:	Center of Diagnostics of SNHL
CHARGE:	Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital and Ear abnormality
CMV:	Cytomegalovirus
cCMV:	congenital Cytomegalovirus
CT:	Computed tomography
DBS:	Dried blood spots
EVA:	Enlarged vestibular aqueduct
FN:	Facial nerve
IAC:	Internal auditory canal
IP-II:	Incomplete partition type 2
JGZ:	Jeugdgezondheidszorg, Child Health and Welfare service
MPS:	Mucopolysaccharidoses
MR:	Magnetic resonance imaging
NGS:	Next generation sequencing
OAE:	Otoacoustic emission
OCS:	Otic capsule sparing
OCV:	Otic capsule violating
PCR:	Polymerase chain reaction
PSCC:	Posterior semicircular canal
PTA:	Pure tone audiometry
SNHL:	Sensory neural hearing loss
SSC:	Semicircular canal
SVN:	Superior vestibular nerve
TEOAE:	Transient evoked otoacoustic emissions
TORCH:	Toxoplasmosis, Other, Rubella, Cytomegalovirus (CMV), and Herpes infections
USNHL:	Unilateral sensory neural hearing loss
V:	Vestibule

VUmc:	VU University medical center
WES:	Whole exome sequencing
WHO:	World health organization
WGS:	Whole genome sequencing

NEDERLANDS SAMENVATTING

In **Hoofdstuk 1** is een overzicht van de huidige werkwijze van de neonatele gehoorscreening in Nederland en de etiologie van perceptief gehoorverlies op de kinderleeftijd. De huidige etiologische diagnostische testen worden beschreven.

In **hoofdstuk 2** wordt de etiologie van het perceptieve gehoorverlies van een groot cohort (n= 423) kinderen met zowel uni- als bilateraal gehoorverlies geevalueerd. Deze studie toont aan dat met behulp van een stapsgewijze diagnostische benadering bestaande uit beeldvorming, genetische en/of pediatrische evaluatie, een oorzaak wordt geïdentificeerd bij 67% van de kinderen. De meest voorkomende oorzaak bij kinderen met bilateraal perceptief gehoorverlies is een pathologische genvariant (26%). De meest voorkomende oorzaak bij kinderen met unilateraal perceptief gehoorverlies is een structurele afwijking het binnenoor (27%). De diagnostische opbrengst is geassocieerd met de ernst en de leeftijd van detectie van het gehoorverlies: het hoogste percentage oorzakelijke afwijkingen wordt gevonden bij kinderen met ernstig gehoorverlies en/of bij kinderen waarbij het gehoorverlies op jonge leeftijd ontdekt wordt.

Hoofdstuk 3 presenteert een studie met de nadruk op de specifieke waarde van beeldvorming bestaand uit CT en MRI van het binnenoor en brein bij de etiologische diagnostische work-up van kinderen met bilateraal perceptief gehoorverlies. De prevalentie van oorzakelijke radiologische bevindingen bij kinderen met bilateraal perceptief gehoorverlies is aanzienlijk: 32%. De hoogste diagnostische opbrengst wordt gevonden bij kinderen met asymmetrisch en/of ernstig perceptief gehoorverlies. De meeste afwijkingen werden gevonden in het binnenoor (61% van de abnormale scans), waarbij een verwijd vestibulair aquaduct (EVA) de meest voorkomende afwijking was (24%). In de groep kinderen die beide scans hebben ondergaan, werd een significant hoger diagnostisch rendement van MRI (34%) vergeleken met CT (20%) gevonden. We concluderen dat beeldvorming essentieel is bij de etiologische evaluatie van kinderen met bilateraal perceptief gehoorverlies. Op basis van onze bevindingen is MRI van het binnenoor en brein de beeldvorming van keuze in de etiologische evaluatie van kinderen met bilateraal perceptief gehoorverlies, vanwege de hoge diagnostische opbrengst.

In **hoofdstuk 4** wordt opbrengst van beeldvorming bij kinderen met unilateraal perceptief gehoorverlies gepresenteerd. Met behulp van CT en/of MRI werd bij 49% van de kinderen met unilateraal perceptief gehoorverlies een oorzakelijke afwijking vastgesteld. De meeste afwijkingen werden gevonden in het labyrint (29%), gevolgd door de nervus cochleairis (9%) en het brein (7%). We concluderen dat beeldvorming essentieel is in de etologische analyse van unilateraal perceptief gehoorverlies vanwege de hoge prevalentie van

oorzakelijke afwijkingen die kunnen worden geïdentificeerd middels beeldvorming. CT en MRI zijn complementair aan elkaar. Aangezien de meest voorkomende oorzakelijke afwijkingen van unilateraal perceptief gehoorverlies kunnen worden geïdentificeerd op CT, stellen we voor om dit als de eerste modaliteit te gebruiken en sequentiële MRI uit te voeren als de CT geen afwijkingen laat zien. Door verschillende medische en praktische overwegingen kan afgeweken van dit protocol.

Hoofdstuk 5 presenteert een systematische review met de focus op de identificatie van factoren die verband houden met plotseling gehoorverlies na een klein hoofdtrauma bij patiënten met een EVA. De gegevens van 31 artikelen werden samengevoegd met in totaal 179 patiënten met 351 EVA's. Eenderde van de patiënten met een bewezen EVA had een plotseling gehoorverlies als gevolg van een hoofdtrauma. We vonden een significant verband tussen reeds bestaand fluctuerend gehoorverlies en de kans op plotseling gehoorverlies veroorzaakt door een hoofdtrauma. Op basis van deze resultaten stellen we voor dat voorzorgsmaatregelen, zoals het vermijden van activiteiten met een risico op klein hoofdtrauma zoals contactsporten, beperkt kan blijven tot patiënten met een (reeds bestaand) fluctuerend gehoorverlies en patiënten met een voorgeschiedenis van plotseling gehoorverlies na een klein hoofdtrauma.

Hoofdstuk 6 omvat een onderzoek naar het ipsi- en contralaterale gehoorverlies bij 34 kinderen met een unilaterale EVA vastgesteld op CT en/of MRI. Het risico op gehoorverlies in het oor waar het vestibulaire aqueduct verwijd is, is bekend. Het optreden van gehoorverlies in het contralaterale, schijnbaar onaangetaste oor is iets raadselachtiger. In deze studie worden meerdere methoden beschreven om het vestibulaire aquaduct op CT en MRI te meten. We hebben ons gericht op de meting van de diameter van het ipsitalale en contralaterale vestibulaire aquaduct. Vervolgens is gekeken naar de correlatie tussen het (progressieve) gehoorverlies in beide oren en de diameter van de EVA. We ontdekten dat kinderen met een eenzijdige EVA ook het risico lopen op gehoorverlies in het contralaterale oor (29%). Deze bevinding geeft aan dat ten minste bij sommige patiënten met een unilaterale EVA een bilateraal pathogeen proces ten grondslag ligt aan het gehoorverlies, in tegenstelling tot wat de resultaten van de beeldvorming suggereren. Deze bevindingen zijn belangrijk voor de begeleiding van EVA-patiënten en hun ouders en hebben gevolgen voor de follow-up.

LIST OF PUBLICATIONS

1. *The etiological evaluation of sensorineural hearing loss in children.* Van Beeck Calkoen EA, Engel MSD, van de Kamp JM, Yntema HG, Goverts ST, Mulder MF, Merkus P, Hensen EF. Eur J Pediatr. 2019 Aug;178:1195-1205

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Beste otologen van het RadboudUMC, met Ronald (Pennings) in het bijzonder. Dank jullie wel voor het prachtige fellowship otologie dat ik bij jullie mocht doorlopen. Met oog voor persoonlijke ontwikkeling en ambities was dit een heel leerzaam en inspirerend jaar. Ivette (Gooskens), wat een ongelofelijke mazzel heb ik dat door jou dit fellowschip nog steeds loopt! Jouw aanstekelijke lach en grappen op OK maken dit tot een feest.

Lieve vakgroep KNO van het Amstelland ziekenhuis (Judith, Maaike, Charlotte en Anne Marijn). De eerste vrouwelijke vakgroep KNO van Nederland: wat ben ik trots op jullie! De teamspirit, oog voor elkaar en onze ambities maakt dat ik dagelijks met veel plezier naar mijn werk ga. Op nog vele jaren!

Lieve Anne Marijn, we kwamen elkaar tegen op de introductiedag van het VUmc en hebben daarna nooit langer dan een jaar op een andere plek gewerkt. Voor mij een voorrecht dat jij mij altijd een stap voor was, ik kon altijd afkijken en doe dat nog steeds graag. Uitspraken als: '*vakantie? Je kinderen blijven liever thuis', 'ik gun het ieder kind om het tweede kind te zijn'* en *'even uit de situatie halen'* worden bij ons thuis regelmatig aangehaald. Je bent ongelofelijk slim, kan bergen werk verzetten en je bent een prachtig mens.

Lieve Hester, Sjoerd, Corine, Jaap, Nina, Taco, Fiona, mama, Lot en papa in het bijzonder. Dank voor jullie onvoorwaardelijke support, luisterend oor en gezelligheid. Papa, nu hebben we allebei een boek geschreven ;). Van jouw energie, pretogen, verwondering en flexibiliteit om je te blijven ontwikkelen geniet ik enorm, met jouw speech op 4 september 2021 als hoogtepunt. Ik ben ongelofelijk trots op je.

Lieve Roon, liefde van mijn leven en tot mijn grote geluk mijn kersverse echtgenoot. We wisten achteraf allebei niet goed waar ik 'ja' tegen zei toen ik naast mijn opleiding startte met deze promotie. Met jou rotsvaste houding '*het kan wel'* en '*het komt wel goed'* heb je mijn enorm gesteund en geholpen. Je bent een levensgenieter en helpt mij eraan herinneren wat echt belangrijk is in het leven: genieten! Blijf dat vooral doen. Ik kan niet wachten om te ontdekken wat de toekomst ons samen zal brengen.

Tot slot, alle vrienden en familie, dank voor alle afleiding en gezelligheid, waarvan nog veel zal volgen.

Het is af!
Eveline

CURRICULUM VITAE

Eveline van Beeck Calkoen werd op 25 juli 1983 geboren in Zwolle, waar zij opgroeide en in 2002 haar eindexamen B Grieks haalde aan het Gymnasium Celeanum. Na een jaar vrijwilligerswerk in Peru gedaan te hebben verhuisde zij naar Utrecht om Geneeskunde te studeren aan de Universiteit van Utrecht. Tijdens deze opleiding volgde ze meerdere stages bij de Koninklijke Marine en de kustwacht met als doel militair arts te worden. Toch besloot ze een andere keuze te maken, omdat ze de voorkeur gaf aan werken in het ziekenhuis. In 2009 begon zij daarom als ANIOS chirurgie in het Antonius Ziekenhuis in Nieuwegein. De combinatie van denken en doen bracht haar in de richting van de KNO. In 2010 begon ze als onderwijsassistent op de afdeling KNO van het VUmc en in 2011 startte zij de opleiding KNO bij prof dr Leemans. Vanaf 2016 maakte zij deel uit van het Centrum voor Diagnostiek voor Slechthorendheid, een multidisciplinair team wat zich bezighoudt met de diagnostiek en etiologie van slechthorendheid op de kinderleeftijd. Dit is de start en basis geweest van haar promotietraject. In 2018 volgde zij een fellowship otologie in het RadboudUMC in Nijmegen. Sinds 2019 werkt zij met veel plezier als algemeen KNO-arts met aandachtsgebied otologie in het Amstelland ziekenhuis in Amstelveen. De liefde voor skiën, racefietsen en zeilen is groot, maar de liefde voor haar gezin nog groter: in Laren woont zij samen met Ronald Bausch, Pieter (6 jaar) en Cato (5 jaar).