

## Sensorineural hearing loss in children

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During the past three to four decades, the incidence of acquired sensorineural hearing loss (SNHL) in children living in more developed countries has fallen, as a result of improved neonatal care and the widespread implementation of immunisation programmes. The overall decrease has been accompanied by a relative increase in the proportion of inherited forms of SNHL. The contribution made by one gene in particular, *GJB2*, to the genetic load of SNHL has strongly affected the assessment and care of children with hearing loss. These changes in the incidence of SNHL have not been seen in children living in less developed countries, where the prevalence of consanguinity is high in many areas, and both genetic and acquired forms of SNHL are more common, particularly among children who live in poverty. Focused genetic counselling and health education might lead to a decrease in the prevalence of inherited SNHL in these countries. Establishment of vaccination programmes for several vaccine-preventable infectious diseases would reduce rates of acquired SNHL. Although the primary purpose of such programmes is the prevention of serious and in many cases fatal infections, a secondary benefit would be a reduction in disease-related complications such as SNHL that cause permanent disability in survivors.

Sensorineural hearing loss (SNHL) is a multifaceted condition with profound medical, social, and cultural ramifications. Although various terms are used to refer to people with SNHL, that most commonly used by the lay public is deaf (with a lower case "d"). Deafness (with an uppercase "D") defines a cultural group of people united by distinct traditions and strengths arising from the use of sign language as a communication form. Most people who communicate primarily by sign language have congenital SNHL, and many are the offspring of Deaf parents. People who acquire SNHL in later childhood or adulthood generally continue to use oral communication, and few see themselves as members of the Deaf community.

Doctors, teachers, audiologists, and other professionals often use the term "hearing impaired" to describe people with any degree of SNHL. Although intended to be neutral, this term arouses powerful emotions for many people, especially those in the Deaf community who reject the notion of SNHL as an impairment. Since no term is completely encapsulating, in this Seminar we use SNHL to refer to people who by audiometric testing have any degree of permanent SNHL. We focus on SNHL in children and explore advances in diagnosis, classification, epidemiology, pathogenesis, management, treatment, and prevention.

### Diagnosis

The diagnosis of SNHL depends on the demonstration of reduced hearing acuity by auditory testing. Hearing is measured in decibels (dB) with the threshold of 0 dB for each frequency denoting the value at which normal young adults perceive a tone burst of a given intensity and frequency 50% of the time. A child's hearing acuity is classed as normal if it is within 20 dB of these defined thresholds. Severity of hearing loss is graded as mild (20–40 dB), moderate (41–55 dB), moderately severe (56–70 dB), severe (71–90 dB), or profound (>90 dB), and the frequency of hearing loss is designated as low (<500 Hz), middle (501–2000 Hz), or high (>2000 Hz;

figure 1).<sup>1</sup> Although there is no agreed demarcation, people with severe or profound hearing loss are commonly referred to as deaf and those with mild or moderate hearing loss as hard of hearing.

Hearing acuity can be measured with either objective or subjective testing conditions. Physiological tests objectively assess the functional status of the auditory system and can be done at any age. These tests include auditory brainstem response testing (also known as brainstem auditory evoked response), otoacoustic emissions, auditory steady-state response, and impedance testing (tympanometry). The ability to record normal otoacoustic emissions, auditory brainstem responses, and auditory steady-state responses is dependent on normal middle-ear function.

Auditory brainstem response testing measures the stimulus-evoked electrophysiological response of the VIIIth cranial nerve and brainstem to clicks or tone bursts presented to the external ear. The response is recorded from electrodes on the skin. Wave V detection thresholds correlate best with hearing sensitivity in the range 1.5–4.0 kHz in neurologically normal children. The maximum output value for clinical systems measuring auditory brainstem responses is 130 dB sound pressure level, but after correction for normal

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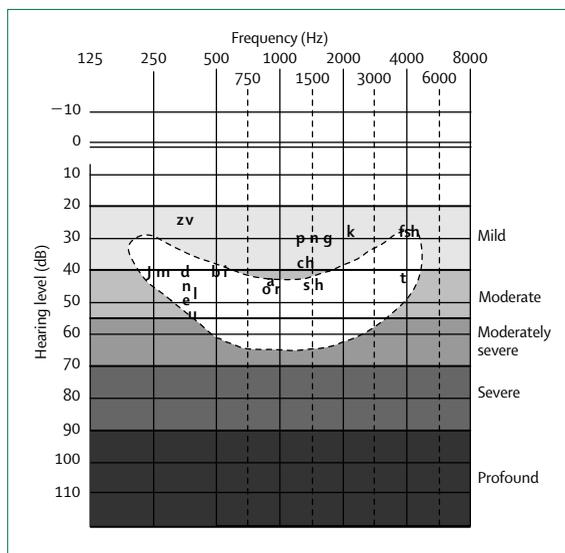
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### Search strategy and selection criteria

We did a computerised and manual search on PubMed to identify studies, with particular focus on original reports published within the past 10 years. Selection criteria included a judgment about the importance of studies and their relevance to the well-informed general practitioner.

Keywords used were "acquired deafness", "genetic deafness", or "sensorineural hearing loss" plus "neonates", "children", or "young adults" plus "[a]etiology", "diagnosis", "classification", "prevention", "management", or "early intervention. There was no restriction on language of publication.



**Figure 1: An audiogram showing grades of hearing loss on the right and the range of conversational speech (clear crescent)**

Hearing is measured in dB to accommodate the wide dynamic range of normal human hearing. Consonants are generally spoken more softly and are higher pitched than vowels. As a result, with even mild to moderate hearing loss, understanding of speech can be difficult.

behavioural thresholds of 30–36 dB sound pressure level, the maximum presentation values for click stimuli are 94–100 dB sound pressure level.<sup>2</sup>

Otoacoustic emissions are sounds originating within the cochlea. They are measured in the external auditory canal and primarily reflect the activity of outer hair cells across a broad frequency range. These sounds can be emitted spontaneously, in response to acoustic stimuli of short duration (transient evoked otoacoustic emissions), in response to two stimulus tones of different frequencies (distortion-produced otoacoustic emissions), or in response to a continuous tone (sustained-frequency otoacoustic emissions). When hearing loss is greater than 40–50 dB, transient evoked otoacoustic emissions are typically absent; an important exception, however, is auditory neuropathy, which is characterised by the presence of otoacoustic emissions and the absence of a normal auditory brainstem response.

The auditory steady-state response is an electrophysiological measure of hearing acuity that has been used extensively in Australia, Asia, and Canada and is now being used much more frequently in the USA and Europe. Skin electrodes are used to measure whether the auditory response is phase-locking to changes in a continuous tonal stimulus. Since the stimulus is a continuous signal, a higher average sound pressure level can be delivered than is possible with click stimuli. This difference means that auditory steady-state response testing can provide an estimate of hearing sensitivity in many children who show no response to auditory brainstem response testing.<sup>2,3</sup>

Impedance audiometry does not assess hearing. Instead, it examines the peripheral auditory system by measuring middle-ear pressure, tympanic-membrane movement, Eustachian-tube function, and mobility of the middle-ear ossicles (figure 2).

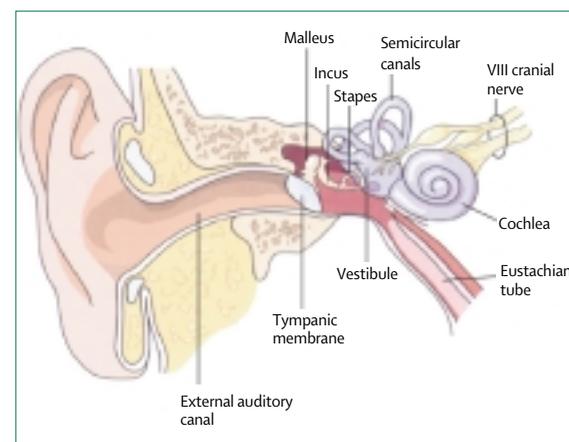
Subjective tests of hearing acuity assess how a child processes auditory information and include behavioural and pure-tone testing. Behavioural observation audiometry is used in infants aged 0–6 months; however, because it is highly tester dependent, it has been supplanted by auditory brainstem response, otoacoustic emissions, and auditory steady-state response testing. Visual reinforcement audiometry is used in children aged 6 months to 2.5 years and can be used to generate a reliable, complete audiogram, although results depend on the child's maturational age and the skill of the tester.

Pure-tone audiometry is used to establish conduction thresholds in air, bone, or both by identifying the lowest intensity at which a child hears a pure tone half of the time. Octave frequencies from 250 Hz (close to middle C) to 8000 Hz are tested by use of earphones or a vibrator. To assess air conduction thresholds, sounds are presented through earphones, and the observed results depend on the condition of the external ear canal, middle ear, and inner ear. To assess bone conduction thresholds, sounds are presented through a vibrator placed on the mastoid cortex or forehead, thereby bypassing the external and middle ears.

Pure-tone audiometry requires the active participation of the child. Because test instructions can be difficult to understand for children younger than 5 years, a modification called conditioned play audiometry is commonly used to obtain a complete frequency-specific audiogram for each ear in children aged 2.5–5.0 years.<sup>1</sup>

### Classification

In addition to the degree and frequency of SNHL for a given child, other features, such as type of loss, time of onset, and causality should be defined wherever



**Figure 2: Cross-section of the outer, middle, and inner ear**

possible. In general, type of loss is categorised as conductive, sensorineural, or mixed and either stable or progressive. Time of onset is established as either congenital or acquired (or late-onset). Causality is broadly divided into genetic (hereditary) or non-genetic (environmental) categories.

Although this approach enables the clinician to formulate a more complete differential diagnosis with treatment options and prognosis, it does belie the complex interaction of genetics and environment that confounds the study of SNHL. For example, noise is an increasingly important cause of SNHL; although noise-induced hearing loss can be viewed as the simple cause-and-effect consequence of acoustic trauma, genetic factors are an important determinant of outcome in a noisy environment.<sup>4</sup>

Our rapidly evolving understanding of the genetics of hearing is refining much of our knowledge about the aetiology, treatment, and prevention of SNHL. Hereditary SNHL is most commonly inherited as a simple mendelian trait and consequently can be classified by mode of inheritance as autosomal dominant, autosomal recessive, or X-linked; matrilineal inheritance associated with mitochondrial mutations occasionally also occurs. Inherited SNHL generally appears as an isolated physical finding (non-syndromic SNHL; table 1), but about 30% of cases are syndromal (ie, associated with other disorders, such as kidney, heart or vision abnormalities; table 2).

## Epidemiology

SNHL is the most common sensory deficit in more developed societies.<sup>5,6</sup> In the USA, congenital SNHL occurs about three times more frequently than Down's syndrome, six times more frequently than spina bifida, and over 50 times more frequently than phenylketonuria.<sup>7-9</sup> An estimated 4000 infants are born each year with severe to profound bilateral hearing loss,<sup>10,11</sup> and another 8000 are born with unilateral or mild to moderate bilateral SNHL.<sup>12</sup> Thus, at least one

Locus	Gene	Audio phenotype
DFN3	<i>POU3F4</i>	Conductive hearing loss due to stapes fixation mimicking otosclerosis; superimposed progressive SNHL.
DFNA1	<i>DIAPH1</i>	Low-frequency loss beginning in the first decade and progressing to all frequencies to produce a flat audioprofile with profound losses throughout the auditory range.
DFNA2	<i>KCNQ4</i>	Symmetrical high-frequency sensorineural loss beginning in the first decade and progressing over all frequencies.
	<i>GJB3</i>	Symmetrical high-frequency sensorineural loss beginning in the third decade.
DFNA 6/14/38	<i>WFS1</i>	Early-onset low-frequency sensorineural loss; about 75% of families dominantly segregating this audioprofile carry missense mutations in the C-terminal domain of wolframin.
DFNA10	<i>EYA4</i>	Progressive loss beginning in the second decade as a flat to gently sloping audioprofile that becomes steeply sloping with age.
DFNA13	<i>COL11A2</i>	Congenital mid-frequency sensorineural loss that shows age-related progression across the auditory range.
DFNA15	<i>POU4F3</i>	Bilateral progressive sensorineural loss beginning in the second decade.
DFNA20/26	<i>ACTG1</i>	Bilateral progressive sensorineural loss beginning in the second decade; with age, the loss increases with threshold shifts in all frequencies, although a sloping configuration is maintained in most cases.
DFNB1	<i>GJB2</i> , <i>GJB6</i>	Hearing loss varies from mild to profound. The most common genotype, 35delG/35delG, is associated with severe to profound SNHL in about 90% of affected children; severe to profound deafness is observed in only 60% of children who are compound heterozygotes carrying one 35delG allele and any other <i>GJB2</i> SNHL-causing allele variant; in children carrying two <i>GJB2</i> SNHL-causing missense mutations, severe to profound deafness is not observed.
DFNB4	<i>SLC26A4</i>	DFNB4 and Pendred's syndrome (table 2) are allelic. DFNB4 hearing loss is associated with dilatation of the vestibular aqueduct and can be unilateral or bilateral. In the high frequencies, the loss is severe to profound; in the low frequencies, the degree of loss varies widely. Onset can be congenital (prelingual), but progressive postlingual loss is also common.
mtDNA 1555A>G	12S rRNA	Degree of hearing loss varies from mild to profound but is generally symmetrical; high frequencies are preferentially affected; precipitous loss in hearing can occur after aminoglycoside therapy.

DFN, X-linked; DFNA, dominant; DFNB, recessive; integer, locus number.

**Table 1: Common types of hereditary non-syndromic SNHL**

child in 1000 is born with bilateral SNHL of at least 40 dB, including four profoundly per 10000 deaf infants.<sup>13-20</sup> Hearing losses of this degree affect educational attainment, the likelihood of future employment, future earnings, the use of health-care systems, and life expectancy.<sup>10,21</sup>

These data are consistent with findings of universal newborn hearing screening programmes in other more

Gene	Phenotype	
<b>Dominant</b>		
Waardenberg (WS1)	<i>PAX3</i>	Major diagnostic criteria include dystopia canthorum; congenital hearing loss; heterochromic irises; white forelock; and an affected first-degree relative. About 60% of affected children have congenital hearing loss; in 90%, the loss is bilateral.
Waardenberg WS2	<i>MITF</i> , others	Major diagnostic criteria are as for WS1 but without dystopia canthorum. About 80% of affected children have congenital hearing loss; in 90%, the loss is bilateral.
Branchio-otorenal	<i>EYA1</i>	Diagnostic criteria include hearing loss (98%), preauricular pits (85%), and branchial (70%), renal (40%), and external-ear (30%) abnormalities. The hearing loss can be conductive, sensorineural, or mixed, and mild to profound in degree.
<b>Recessive</b>		
Pendred's	<i>SLC26A4</i>	Diagnostic criteria include sensorineural hearing loss that is congenital, non-progressive, and severe to profound in many cases, but can be late-onset and progressive; bilateral dilatation of the vestibular aqueduct with or without cochlear hypoplasia; and an abnormal perchlorate discharge test or goitre.
Usher (USH1)	<i>USH1A</i> , <i>MYO7A</i> , <i>USH1C</i> , <i>CDH23</i> , <i>USH1E</i> , <i>PCDH15</i> , and <i>USH1G</i>	Diagnostic criteria include congenital, bilateral, and profound hearing loss, vestibular areflexia, and retinitis pigmentosa (commonly not diagnosed until tunnel vision becomes severe enough to be noticeable).
Usher (USH2)	<i>USH2A</i> , <i>USH2B</i> , <i>USH2C</i> , others	Diagnostic criteria include mild to severe, congenital, bilateral hearing loss and retinitis pigmentosa; hearing loss may be perceived as progressing over time because speech perception decreases as diminishing vision interferes with subconscious lip reading.
Usher (USH3)	<i>USH3</i>	Diagnostic criteria include postlingual, progressive sensorineural hearing loss, late-onset retinitis pigmentosa, and variable impairment of vestibular function.

**Table 2: Common types of syndromic SNHL**

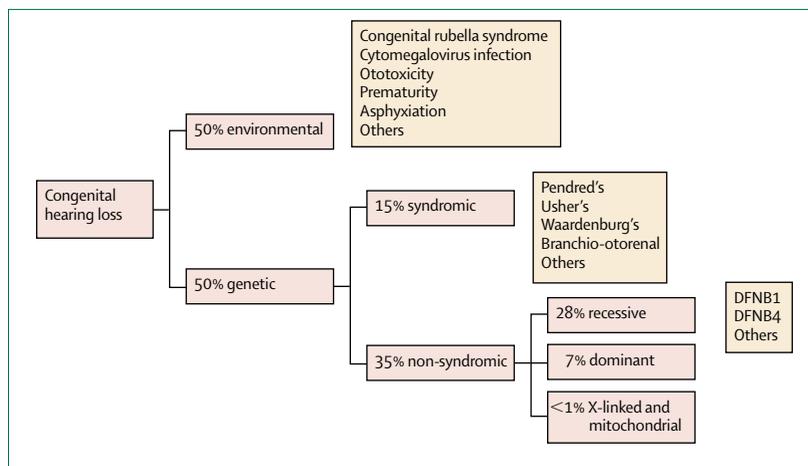


Figure 3: Environmental and genetic contributions to total congenital SNHL

developed countries, which report identification of two to four children per 1000 with SNHL despite the difficulty in obtaining diagnostic results for 10–40% of the infants who do not pass the screening test.<sup>22–30</sup> Although data from less developed countries are limited, those available suggest that the incidence of congenital SNHL is much higher in these countries.<sup>31–33</sup>

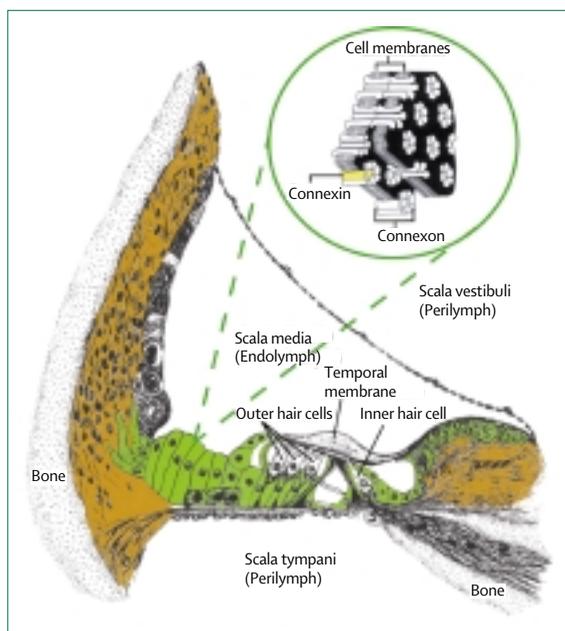


Figure 4: A cross-section of the cochlea showing two important cell groups that express connexin 26

The non-sensory epithelial cells are shown in green; this group includes interdental cells of the spiral limbus, inner and outer sulcus cells, sensory supporting cells, and cells within the root process of the spiral ligament. The connective-tissue cell system is shown in brown; this group includes fibrocytes within the spiral ligament and spiral limbus, basal and intermediate cells of the stria vascularis, and mesenchymal cells, which line the scala vestibuli and interconnect the two populations of cell types. The inset shows how connexons allow cells to become a functional syncytium. Each connexin 26 molecule is known as a connexin, one of which is highlighted. Six connexins oligomerise to form a connexon. Two connexons join to form a gap junction.

### Genetic SNHL in neonates

By aetiology, more than half of neonates with SNHL have inherited hearing loss (figure 3). In most cases, both parents have normal hearing and, as a result of simple mendelian recessive inheritance, have a child with non-syndromic SNHL (75–80% of cases). Autosomal dominant (about 20%), X-linked (2–5%), and mitochondrial (about 1%) contributions to the burden of inherited congenital SNHL also occur.

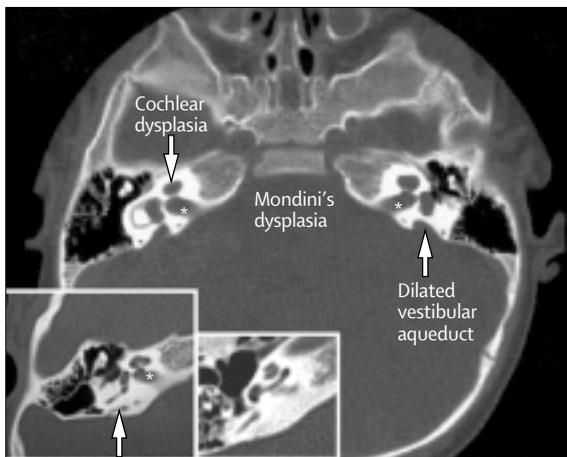
Because autosomal recessive SNHL is heterogeneous, the finding that mutations in a gene called *GJB2* account for roughly half of hereditary cases of SNHL in the USA, many European countries, Israel, and Australia was quite unexpected. *GJB2*-related SNHL also has been repeatedly described in several Asian, Latin American, and African countries, but it is less common in these regions.<sup>34–42</sup>

SNHL-causing allele variants of *GJB2* alter function of the encoded protein, connexin 26, in the inner ear. Connexin 26 aggregates in groups of six around a central 2.3 nm pore to form a doughnut-shaped structure called a connexon. The connexons from contiguous cells covalently bond to form intercellular channels. Aggregations of connexons are called plaques and are the constituents of gap junctions.<sup>43–45</sup> The gap-junction system might be involved in potassium circulation, allowing ions that enter hair cells during mechanosensory transduction to be recycled to the stria vascularis (figure 4).<sup>46,47</sup>

The most common form of syndromic hereditary SNHL is Pendred's syndrome. It is characterised by sensorineural hearing impairment that is congenital in most cases and commonly severe to profound, although mild to moderate progressive hearing loss also occurs; bilateral dilatation of the vestibular aqueduct with or without cochlear hypoplasia (the presence of both dilatation of the vestibular aqueduct and cochlear hypoplasia is known as Mondini's malformation or dysplasia); and either an abnormal perchlorate discharge test or goitre (figure 5). Pendred's syndrome is rarely recognised in the neonatal period because the thyroid abnormality does not present at birth and temporal-bone CT is seldom included as part of the neonatal screening battery. The majority of affected children have mutations in a gene called *SLC26A4* on chromosome 7q31.<sup>48</sup>

### Acquired SNHL in neonates

Although many women are exposed to infectious pathogens during pregnancy, only a few of these infections damage the placenta and fetus. Those that cause such damage remain important causes not only of acquired SNHL but also of visual loss and behavioural and neurological dysfunction. They are traditionally grouped as TORCH infections (toxoplasmosis, others, rubella, cytomegalovirus, and herpes simplex viruses); a more complete list is shown in the



**Figure 5: Mondini's dysplasia shown by CT of the temporal bone in a child with Pendred's syndrome**

Both dilatation of the vestibular aqueduct and cochlear dysplasia are present in this section. In the larger of the two inset images of a normal temporal bone, the vestibular aqueduct is visible but much smaller (arrow). The cochlea appears normal, and in the smaller inset image of a more inferior axial section, the expected number of cochlear turns can be clearly counted (\* in internal auditory canal).

panel.<sup>49</sup> The incidence of congenital rubella has been greatly decreased in more developed countries by the introduction of the rubella vaccine in the late 1960s. However, the world-wide burden of SNHL secondary to congenital rubella syndrome remains high, and in countries without a rubella vaccination programme, congenital rubella syndrome continues to rank as the most important cause of acquired congenital SNHL.<sup>50</sup>

In more developed countries, congenital cytomegalovirus infection is generally recognised as the most frequent cause of acquired hearing loss in neonates. In the USA, for example, 0.4–2.5% of infants shed cytomegalovirus at birth, corresponding to about 40 000 cytomegalovirus-infected infants each year. At least 1000 of these infants have hearing loss detectable at birth, and a further 3000–4000 have hearing loss in infancy or childhood.<sup>51–53</sup> Similar rates of cytomegalovirus infection have been observed in France and Brazil, whereas the rate of congenital cytomegalovirus infection in the UK seems to be slightly lower at 0.3–0.4%. The incidence of congenital cytomegalovirus in many less developed regions is unknown.<sup>54</sup>

Most congenitally infected neonates have no apparent signs of cytomegalovirus infection at birth, but about 10% have systemic disease manifested by jaundice, hepatosplenomegaly, a petechial or purpuric rash, intrauterine growth retardation, or respiratory distress.<sup>55,56</sup> Half of these infants with clinical signs have SNHL, and many experience progressive postnatal deterioration in their hearing.<sup>57</sup> Neonates with silent cytomegalovirus infections generally escape neurodevelopmental sequelae, but 8–10% later develop some degree of SNHL. Indicators for the development of SNHL in this group of neonates have not been defined.<sup>58</sup>

### Genetic SNHL in infants and young children

The relative contribution of genetics to the total number of infants and young children with SNHL is unknown. Inherited hearing loss diagnosed among children of these age-groups is congenital hearing loss that was present but missed during the neonatal period, negligible or mild congenital hearing loss that was undetectable by available screening methods but has become more serious and thus detectable, or late-onset SNHL. In children with late-onset and progressive hearing loss, dilatation of the vestibular aqueduct must be considered; CT imaging of the temporal bones is warranted to exclude this possibility (figure 5). Dilatation of the vestibular aqueduct is found with both Pendred's syndrome and DFNB4, allelic conditions caused by mutations in *SLC26A4*. Although the DFNB4 phenotype lacks the thyroid disease associated with Pendred's syndrome, distinction between these types of SNHL can be difficult if the thyroid disease is occult, and the distinction may be somewhat artificial because the diseases lie on a continuum.<sup>48</sup>

### Acquired SNHL in infants and young children

The most common cause of intermittent mild to moderate hearing loss in infants and young children is the conductive hearing loss caused by acute otitis media or otitis media with effusion.<sup>59</sup> Acquired SNHL in infants and children is most commonly caused by bacterial meningitis. Altogether, bacterial meningitis accounts for about 6% of all cases of SNHL in children.<sup>60</sup> The prevalence is about seven per 100 000 with a heavy age bias for younger children.<sup>61</sup> 75% of affected children are younger than 2 years, 15% are aged 2–5 years, and 10% are older than 5 years.<sup>62</sup> Postmeningitic SNHL can

#### Panel: Infectious pathogens implicated in SNHL in children

##### Congenital infections

Cytomegalovirus  
Lymphocytic choriomeningitis virus  
Rubella virus  
*Toxoplasma gondii*  
*Treponema pallidum*

##### Acquired infections

*Borrelia burgdorferi*  
Epstein-Barr virus  
*Haemophilus influenzae*  
Lassa virus  
Measles virus  
Mumps virus  
*Neisseria meningitidis*  
Non-polio enteroviruses  
*Plasmodium falciparum*  
*Streptococcus pneumoniae*  
Varicella zoster virus

be unilateral or bilateral, but bilateral loss is slightly more common.<sup>62</sup> The use of vaccines against *Haemophilus influenzae* type B and several serotypes of *Streptococcus pneumoniae* (seven-valent pneumococcal conjugate vaccine; 23-valent pneumococcal polysaccharide vaccine) have decreased the incidence of these infections, and the use of steroid therapy early in the disease course has lowered the associated morbidity and mortality.<sup>63,64</sup> More seriously ill children now survive with several sensory and neural impairments, which include SNHL in many cases.

#### School-aged children

Hearing loss that is presumed to be late onset and at least moderate in severity is diagnosed in 1.2–3.3 per 10 000 school-aged children.<sup>14</sup> Some of this hearing loss is probably mild congenital progressive hearing loss that does not become severe enough to be detected until early childhood. Mild hearing loss that remains stable, by contrast, can escape detection especially if only a few frequencies are affected. As a result, much less is known about this degree of hearing loss. Increasingly, however, attention is being focused on milder hearing losses (including unilateral losses) that affect 10–15% of school students and have substantial adverse effects on school performance and social interactions.<sup>65</sup>

#### Genetic SNHL in school-aged children

Autosomal dominant non-syndromic SNHL is commonly first detected in school-aged children during routine audiological screening (table 1).<sup>66</sup> Some types of syndromic SNHL are also first recognised at this time, reflecting the diagnosis of associated comorbidity that was not previously noted on physical examination. Common examples included Pendred's and Usher's syndromes, both inherited as autosomal recessive diseases so a family history is unhelpful as an indicator of risk (table 2).<sup>48,67,68</sup>

#### Acquired SNHL in school-aged children

There are no prevalence estimates of acquired SNHL in school-aged children. New-onset SNHL can reflect silent congenital cytomegalovirus infection;<sup>54</sup> however, if threshold shifts are restricted to the range 3–6 kHz, noise trauma should be considered. In the USA, about 12.5% of children aged 6–19 years (7 million children) have mild hearing loss at about 6 kHz, including about 6% of 7-year-olds.<sup>69,70</sup> Data from Germany and Finland are similar, with a loss of 20 dB or more in at least one frequency affecting 7% of German and 8% of Finnish schoolchildren aged 6–7 years.<sup>71,72</sup> More boys than girls are affected.

#### Risk factors and pathogenesis

##### Neonates

Although mutations in many different genes are predictive of SNHL, the gene that accounts for most

cases by far is *GJB2*. Allele variants of this gene cause roughly half of cases of congenital autosomal recessive non-syndromic SNHL in the white population. In children of northern European ancestry, the most common SNHL-causing allele variant of *GJB2* is the c35delG mutation (hereafter called 35delG), which has a carrier frequency of about 2.5% in the general population.<sup>73</sup> The prevalence of this mutation decreases from south to north across Europe and from northwest to southeast across Iran, which is consistent with a purported founder effect in southern Europe about 8000 years ago.<sup>74–76</sup> Also consistent with a founder effect is the observation that in some populations the 35delG mutation is rare. For example, the c167delT and c235delC mutations are the most common *GJB2* SNHL-causing allele variants among Ashkenazi Jews and Japanese people, respectively. The former has an ethnic-specific carrier rate of 4.03% predicting a prevalence of *GJB2*-related SNHL of 1 in 1765 among Ashkenazi Jews; the Japanese-specific carrier rate of c235delC is about 1%.<sup>77,78</sup>

The high carrier frequency for the 35delG mutation in children of northern European ancestry means that roughly two-thirds of children with *GJB2*-related SNHL are 35delG homozygotes.<sup>73</sup> Of the remaining children with *GJB2*-related SNHL, most are 35delG heterozygotes and carry a second, non-complementary mutation. Studies of several of these genotypes have shown that the degree of hearing loss is related to the type of mutation present. In general, children segregating a nonsense and a missense mutation or two missense mutations have better hearing than those homozygous for the 35delG mutation.<sup>79,80</sup> The delineation of this genotype–phenotype correlation, together with data obtained by large multicentre follow-up studies, will provide valuable information within the framework of universal newborn hearing screening. Since the purpose of this screening is the early detection and habilitation of children with congenital hearing loss, complementing physiological testing of hearing with *GJB2* genotype–phenotype data could provide prognostic information that might aid in the selection of appropriate habilitation options for children with *GJB2*-related SNHL.

Non-genetic risk factors for hearing loss during the neonatal period include treatment in a neonatal intensive-care unit, craniofacial anomalies, and meningitis.<sup>81,82</sup> Treatment in a neonatal intensive-care unit alone, in the absence of an identifiable syndrome or a family history of SNHL in childhood, increases the likelihood of significant bilateral sensorineural or mixed hearing loss in a neonate by at least ten times.<sup>83</sup> Much of the increase in risk is secondary to the morbidity related to disorders necessitating or associated with treatment in a neonatal intensive-care unit, such as hyperbilirubinaemia, prematurity, aminoglycoside use, and mechanical ventilation; 40% of children who survive

treatment in neonatal intensive-care units with SNHL have other medical problems.<sup>14</sup> The role of genetic factors in this outcome has not yet been explored in detail but is undoubtedly very complex.<sup>54,85</sup>

### Infants and young children

The risk factor most frequently associated with late-onset SNHL is meningitis. As a result of vaccination programmes, *H influenzae* type B meningitis has virtually disappeared from most more developed countries.<sup>86,87</sup> *S pneumoniae* is now the dominant causative organism of both bacterial meningitis and meningitis-related SNHL.<sup>61</sup> Vaccination programmes against *S pneumoniae* are reducing morbidity and mortality, but the effect of this preventive measure on SNHL among children is not yet known.<sup>62</sup> The onset of SNHL after meningitis can be highly variable. Although most children who lose their hearing do so within 48 h of hospital admission,<sup>88,89</sup> follow-up testing is important since progression and fluctuation of hearing loss occur.<sup>88</sup>

### School-aged children

An increasingly important risk factor for late-onset hearing loss among school-aged children is noise-induced hearing loss from toys and personal listening devices. An investigation of 25 toy cell phones and walkie-talkies, for example, found that 17 produced sound in amounts that would cause noise-induced hearing loss ( $\geq 150$  dBA; a sound reading in decibels made on the A-weighted scale of the sound meter).<sup>90</sup> Much attention has been focused on loud music. Personal listening devices can produce sound in excess of 100 dBA. In the USA, current safety standards mandated by the Occupational Safety and Health Administration allow for 8 h of unprotected ear exposure to sounds up to 90 dBA; therefore, an output of 100 dBA has raised concern.<sup>91</sup> However, work-place standards are not necessarily applicable to leisure music standards, since amplified music emphasises low frequencies rather than the flat spectra of industrial noise, and exposure to music is more likely to be intermittent than continuous.<sup>92,93</sup> Conflicting data have been reported on whether leisure-noise-induced changes in high-frequency thresholds occur in older teenagers,<sup>94,95</sup> but all investigators agree that chronic exposure to hazardous noise can result in hearing loss and that noise-induced hearing loss is insidious and incremental.

### Management and treatment of SNHL

Unlike many clinical conditions, the management and treatment of SNHL largely involves the social welfare and educational systems rather than the medical care system. For a child with congenital severe to profound SNHL, the total lifetime cost of hearing loss exceeds US\$1 000 000. Special education costs amount to over half of this total, and medical expenses and the purchase of assistive devices add another US\$100 000.<sup>96</sup>



**Figure 6:** All cochlear implants share key components, including a microphone, speech processor, and transmitter coil, shown in a behind-the-ear position in this diagram

The microphone/speech processor picks up environmental sounds and digitises them into coded signals. The signals are sent to the transmitter coil and relayed through the skin to the internal device imbedded in the skull. The internal device converts the code to electronic signals, which are transmitted to the electrode array wrapping around the cochlea. The inset shows the radiographic appearance of the stimulating electrode array. Reproduced with permission from MED-EL Corporation, Innsbruck, Austria.

### Neonates

On the basis of the premise that early identification improves speech and language and decreases the expected lifetime cost of SNHL, universal newborn hearing screening programmes have been established in many countries; screening is incorporated into early hearing detection and intervention programmes in many places.<sup>12,29,97</sup> As a result of these programmes, the average age of detection of children with SNHL has fallen from 12–18 months to 6 months or younger.<sup>28,98–107</sup> Although the efficacy of universal newborn hearing screening to improve long-term language outcomes remains uncertain,<sup>10</sup> results suggest that these programmes facilitate normal language achievement for more children with SNHL,<sup>108–110</sup> thus offering cost savings in the long term compared with either no screening and selective screening.<sup>107</sup>

Whether false-positive screening results create undue parental anxiety or have other adverse effects on family dynamics has been explored. Investigations on false-positive data for disorders such as cystic fibrosis and phenylketonuria show that identification of a child as abnormal in the neonatal period can engender lasting

parental anxiety and have long-term adverse effects on the relationship between parent and child and later psychological development.<sup>108–111</sup> Some investigators have suggested that there may be similar effects for false-positive results in universal newborn hearing screening programmes.<sup>112,113</sup> However, studies conducted with parents of infants screened in these programmes have failed to find evidence of undue parental anxiety or long-term adverse effects on the parent–child relationship.<sup>114–118</sup>

For virtually all children with bilateral SNHL, a trial with hearing aids or a frequency-modulation device is appropriate, although for those with severe to profound SNHL, the habilitation approach is likely to become more complex. For these children, the earliest parental decision may be focused on the choice of communication. The options are generally categorised as: auditory-oral, which includes auditory verbal training, oral training, lip reading, and cued speech; visual/gestural/manual training, which includes various recognised sign languages such as the American and British forms; and a combination of speech and sign, referred to as total communication.<sup>119</sup>

Another consideration is cochlear implantation (figure 6). For infants with SNHL, this technique has become standard treatment in many areas when there is lack of progress with well-fitted hearing aids and intensive auditory training.<sup>120</sup> In the early days of paediatric implantation, candidates had to have a pure-tone average (average of 1 kHz, 2 kHz, and 4 kHz) of at least 100 dB and aided thresholds of 60 dB or more in the absence of open-set speech discrimination (the ability to understand spoken words),<sup>121</sup> but current criteria are less stringent.

Several implant programmes have shown that children given implants between the ages of 12 months and 36 months outperform those treated at ages 37–60 months.<sup>122</sup> When tested after a fixed postimplantation interval, children who undergo the procedure when younger have better scores on speech perception measures than those treated when older.<sup>123</sup> On the basis of these findings, implant criteria in the USA have been adjusted to include children aged 12 months or older with pure-tone averages of at least 90 dB and discrimination scores of 30% or less in the best condition, and now the most lenient current criteria include children with severe losses (pure-tone averages of 70 dB or more). The principle behind these relaxed criteria is that children typically perform better after implantation. However, implantation in children with residual hearing is a cause for concern because outcomes are not always predictable.<sup>121</sup>

Speech recognition performance increases as age at implantation decreases and as length of use increases.<sup>122</sup> Preliminary studies of the cause of SNHL as an indicator of successful implant use have also shown that a child's *GJB2* mutation status independently affects reading and

cognitive performance outcomes. Children with *GJB2*-related SNHL score significantly higher on a non-verbal cognitive measure of intelligence (block design) and on a measure of reading comprehension than do children with SNHL caused by other factors.<sup>124</sup>

### Infants and young children

According to recommendations by the American Academy of Pediatrics, children aged 2 months and older with bacterial meningitis should be treated with dexamethasone at a daily dose of 0.6 mg/kg divided into four doses for the first 4 days of therapy.<sup>125</sup> This treatment protocol is supported by a meta-analysis of randomised controlled trials from 1988 to 1996, which showed a significant reduction in the frequency of SNHL with *H influenzae* type B meningitis and a trend toward benefit with *S pneumoniae* meningitis.<sup>125</sup> Of concern is the possibility that the use of dexamethasone can decrease the penetration of certain antibiotics, such as vancomycin, into the cerebrospinal fluid. Consequently, many infectious-disease experts recommend repeat examinations after 24–48 h to confirm sterilisation of cerebrospinal fluid in dexamethasone-treated infants and young children with *S pneumoniae* meningitis.

The frequency of SNHL in infants and children who survive bacterial meningitis other than that caused by *H influenzae* type B is 7%; in roughly 25% of these children the hearing loss is detected late.<sup>60,62,126,127</sup> Late detection adversely affects habilitation options, since ossification of the cochlea can occur as soon as 2 months after meningitis.<sup>128</sup> This complication makes cochlear implantation with complete electrode insertion extremely difficult if not impossible, so early identification of SNHL caused by meningitis is extremely important.

A multivariate analysis by Koomen and colleagues<sup>62</sup> showed that five variables are important predictors for bacterial-meningitis-associated hearing loss: duration of symptoms longer than 2 days, absence of petechiae, glucose concentrations in cerebrospinal fluid of 0.6 mmol/L or lower, *S pneumoniae* as the cause, and ataxia. By use of the presence of any one of these risk factors to identify children for hearing screening, 60% of all postmeningitic children will require screening but no child with hearing loss will go undetected.<sup>62</sup> A simpler strategy, based on the premise that bacterial meningitis of any cause can lead to hearing loss of any degree in a child of any age, is to screen all children diagnosed with bacterial meningitis.<sup>60</sup>

### School-aged children

Most children with moderate to profound SNHL are recognised and treated before they reach school age, but those with mild or unilateral SNHL can remain undiagnosed for years. The first indication of a mild loss is commonly difficulty in understanding speech in adverse conditions, although in addition to the severity of SNHL, various factors including age at onset, the

presence of other disabilities, and the attitudes and beliefs of the family can compound the effect of any degree of hearing loss.

Mild SNHL can have effects in the areas of academic, social, and emotional development that should be recognised and treated. For example, in the early school years, a child with mild SNHL is more likely to experience difficulties in academic activities, attention, and communication that are greater than might be predicted from the degree of hearing loss alone.<sup>65</sup> Early differences in academic test scores disappear in many older school students, but many of these children continue to have difficulty with emotional and social interactions.

### Prevention

No satisfactory therapy is yet available to correct SNHL by the replacement of inner and outer hair cells, although the ability to generate new hair cells in the mature organ of Corti in mammals does pave the way for research focused on optimising repair of inner-ear damage at a structural and functional level.<sup>129–131</sup> Current measures to prevent SNHL in children should be focused on decreasing the incidence of genetic SNHL through educational programmes and prevention of acquired SNHL through the use of vaccination programmes.

### Prevention of genetic SNHL

In most human populations, marriages are not random. Religion, economy, cultural traditions, geography, and family pressures are decisive factors that influence selection of spouses. These factors also increase consanguinity and lead to endogamy. The resultant genetic homogeneity increases the incidence of rare autosomal recessive diseases, a relation first described by Garrod over 100 years ago and used today to localise many of the genes implicated in autosomal recessive non-syndromic SNHL.<sup>132</sup>

The prevalence of consanguinity varies by culture and is highest in Arab countries, followed by India, Japan, Brazil, and Israel.<sup>133</sup> The most common union is a marriage between first cousins.<sup>134–137</sup> These couples tend to come from lower educational and socioeconomic groups, the traditionally religious, and the early married.<sup>137</sup> Offspring of such marriages inherit identical complementary strands of DNA through a parentally shared common ancestor at 6.25% of all loci, a reflection of the high coefficient of inbreeding. Focused genetic counselling and health-education efforts might help to decrease the incidence of autosomal recessive non-syndromic SNHL in these populations.

### Prevention of acquired SNHL

In less developed countries without a rubella vaccination programme, congenital rubella syndrome remains the most important cause of acquired congenital SNHL.<sup>50</sup> The burden of mortality and morbidity falls most heavily

on people living in poverty and in crowded urban centres, and a well-run vaccination programme would be a simple way to improve their life expectancy. Disease burden is a central issue in the implementation of any vaccination programme, and data on disease burden are necessary for patients' advocacy, development of public-health policy, and vaccine development. The WHO Global Program for Vaccines and Immunization has provided recommendations for the prevention of congenital rubella syndrome, and preliminary studies also support the inclusion of vaccines against *H influenzae* and *S pneumoniae*.<sup>138,139</sup> In more developed countries, where congenital cytomegalovirus has supplanted congenital rubella syndrome as the commonest cause of acquired congenital SNHL in children, the development of an effective vaccine remains a high priority.<sup>140</sup>

### Conclusion

The prevalence of SNHL is decreasing as a result of improvements in health care and the expansion of immunisation programmes around the world. At the same time, advances and discoveries in human genetics have improved our ability to diagnose genetic SNHL. Current habilitation options centre on hearing aids and cochlear implants, the latter being the foremost treatment for children with severe to profound SNHL. In the coming decades, novel habilitation options will become available for specific types of SNHL. Most probably these therapies will involve medical treatments to reduce the risk of noise-induced hearing loss and gene-targeting therapies to prevent the progression of inherited SNHL.

### Conflict of interest statement

We declare that we have no conflict of interest.

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