Congenital hearing loss

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Abstract

Congenital hearing loss (hearing loss present at birth) is one of the most prevalent chronic conditions in children. In the majority of developed countries, neonatal hearing-screening programmes enable early detection; early intervention will prevent delays in speech and language development and have long-lasting beneficial effects on social and emotional development and quality of life. A hearing loss diagnosis is usually followed by a search for an underlying aetiology. Congenital hearing loss might be attributed to environmental and prenatal factors, which prevail in low-income settings; congenital infections, particularly cytomegalovirus, are also a common risk factor for hearing loss. Genetic causes probably account for the majority of cases in developed countries; mutations can affect any component of the hearing pathway, in particular inner ear homeostasis (endolymph production and maintenance) and mechano-electrical transduction (conversion of a mechanical stimulus into electrochemical activity). Once the underlying cause of hearing loss is established, it might direct therapeutic decision-making and guide prevention and (genetic) counseling. Management options include specific antimicrobial therapies, surgical treatment of cranio-facial abnormalities and hearing aids. An improved understanding of the pathophysiology and molecular mechanisms underlying hearing loss and

increased awareness of recent advances in genetic testing will promote the development of new treatment and screening strategies.

Introduction

Congenital hearing loss — hearing loss present at birth—occurs when the ability of the ear to convert the vibratory mechanical energy of sound into the electrical energy of nerve impulses is impaired (Figure 1). Hearing loss is categorized according to the site of the lesion; in conductive hearing loss the outer or middle ear are affected and in sensorineural hearing loss the inner ear, auditory nerve or central auditory pathway are affected. Mixed hearing loss is defined as conductive and sensorineural hearing loss. In conductive hearing loss, sound waves cannot propagate through the ear, either secondary to maldevelopment of the middle ear, the external ear or both, or following transient obstruction of the middle ear caused by effusion (as in the case of otitis media) [1]. Sensorineural hearing loss can be further subdivided in sensory hearing loss (when the hair cells are affected), central hearing loss when the cause is located along the central auditory pathway or Auditory Neuropathy Spectrum Disorder. [2] Auditory Neuropathy Spectrum Disorder includes a wide range of clinical conditions characterized by the presence of oto-acoustic emissions and a cochlear microphonic with abnormal or absent auditory brainstem responses, and results in impaired speech discrimination. Auditory Neuropathy Spectrum Disorder may be caused by a primary lesion located in the inner hair cells, in the auditory nerve of intervening synapse and may also include damage to neuronal populations in the auditory pathway. [3, 4]

In most developed countries, neonatal hearing screening programmes are available for this prevalent condition. These programmes aim to screen all newborns within 1 month of birth. Early diagnosis and subsequent early intervention and treatment promote improved developmental outcome later in childhood. [5] Because hearing loss can progress over time, neonatal hearing screening programmes might miss children with progressive hearing loss. Thus, repeated screening at regular intervals is advised for at-risk infants. Medical and supportive treatment of congenital hearing loss depends on aetiology and type of hearing loss. Hearing loss is most often caused by genetic factors (including both non-syndromic forms, in which hearing loss is the only clinical feature, and syndromes such as Usher or Jervell and Lange–Nielsen syndromes), cranio-facial abnormalities and congenital infections.

In this Primer, we focus on unilateral and bilateral permanent congenital hearing loss, defined as hearing loss   40 dB in the better hearing ear averaged over the frequency range important for speech recognition (500, 1,000, 2,000 and 4,000 Hz), [6] which is typically assessed by hearing screening programmes. [7, 8] The epidemiology, mechanisms, diagnosis and management are discussed.

Epidemiology

Since the end of the last century, neonatal hearing screening programmes have become available in North America, Europe and most developed countries. Universal neonatal hearing screening (that is, screening all newborns rather than only those with risk factors for

hearing loss) is advocated. [7] On the basis of these programmes, the estimated prevalence of permanent bilateral hearing loss is 1.33 per 1,000 live births. [9] In children of primary school age, the prevalence increases to 2.83 per 1,000 children,[10, 11] with a further increase to 3.5 per 1,000 in adolescents. [9] This increase over time presumably reflects the cumulative addition of patients with hearing loss owing to progressive, acquired or late-onset genetic causes. For some types of hearing loss, such as Auditory Neuropathy Spectrum Disorder, diagnostic findings are often not conclusive in newborns because language skills are still developing and not aberrant at that time; accordingly, prevalence estimates vary widely. [12]

In countries without universal neonatal hearing screening programmes, prevalence estimates vary between 19 per 1,000 newborns in sub-Saharan Africa up to 24 per 1,000 in South Asia. [13] The large difference in the prevalence estimates between high-income and low-income countries is only in part accounted for by the use of different diagnostic methods or criteria for hearing loss thresholds. The presence of risk factors is the most important predictor.

Risk factors

The Joint Committee on Infant Hearing from the American Academy of Pediatrics has identified several risk factors for congenital or late-onset childhood hearing loss (Box 1). [7] A positive family history of permanent congenital hearing loss is suggested as a risk factor, but the body of evidence for its relevance is low, as only 1.43% of children with a positive family history have hearing loss.[14] Admission to a neonatal intensive care unit is a relevant risk factor; with the prevalence of hearing loss increasing as gestational age and birth weight decrease (1.2–7.5% in premature babies born at 24–31 weeks and 1.4%–4.8% in babies weighing 750–1500 g).[15] Necessary medical interventions (such as assisted ventilation, venous access and aminoglycoside use) while in the neonatal intensive care unit increase the likelihood of hearing loss. Duration of hospitalization of 12 days and a history of treatment by high-frequency ventilation have also been identified as independent risk factors for hearing loss in this population.[16] In addition, delayed maturation of the auditory system is has been postulated as a concern in infants hospitalized in this setting.[17]

In the majority of hearing-impaired children, hearing loss is due to genetic factors, most often a single gene defect. [18] These defects can have different modes of inheritance and different prevalences. Hearing loss is classified to reflect the presence (syndromic hearing loss, Table 1) or absence (non-syndromic) of co-inherited physical or laboratory findings. Non-syndromic hearing loss is extremely heterogeneous. Autosomal recessive non-syndromic hearing loss, which accounts for 80% of genetic cases, is typically congenital, whereas autosomal dominant non-syndromic hearing loss, which accounts for the remaining 20% of cases, is often progressive with a later age of onset X-linked or maternal mitochondrial DNA-related modes of inheritance are rare. [19]

Although the frequency of causative genes varies across different populations and ethnicities, the most frequent genetic cause of severe-to-profound autosomal recessive non-syndromic hearing loss is mutation in the gap junction protein beta 2 gene (*GJB2*). [20] Mutations in this gene account for 50% of the autosomal recessive non-syndromic hearing loss cases in the white populations of Europe and the United States. [20]

In some patients, clinical examination might point towards a syndromic cause. Physical findings such as pre-auricular pits and tags, branchial cysts or fistulae or dystopia canthorum (the lateral displacement of the inner corners of the eyes, giving the appearance of a widened nasal bridge), heterochromia iridis and pigmentary abnormalities might be associated with syndromes known to cause hearing loss, which must also be considered. [21] Over 400 of these syndromes have been described. The responsible genes for several are known and genetic testing is available for many of these. [22]

Congenital infection is also an important risk factor, with congenital cytomegalovirus (CMV) infection standing out as the most common non-genetic cause of sensorineural hearing loss.[23] Whereas the prevalence of congenital CMV infection is 0.58% in industrialized countries, this figure increases to 1–6% in developing countries with a high rate of maternal seroprevalence. [24] The virus is shed in bodily fluids, such as urine, saliva and blood, and exposure to CMV is most commonly encountered both through sexual contact or contact with bodily fluids of young children with CMV infection. The risk of congenital hearing loss caused by an infection might largely depend upon socio-economic status (congenital CMV infection), availability of prevention strategies such as vaccination (congenital rubella) or hygienic measures (congenital toxoplasmosis). In countries without a rubella vaccination programme, congenital rubella infection is the leading environmental cause of congenital hearing loss. [25]

All the aforementioned risk factors are included in surveys of the aetiology of congenital hearing loss, which divide causality between genetic and environmental factors. However, in most studies, a definitive cause cannot be identified in a considerable proportion of children with hearing loss.[26–28]

Mechanisms/pathophysiology

Congenital hearing loss can be divided into genetic and acquired forms. The mechanisms and pathophysiology of these two forms differ considerably.

Genetic congenital hearing loss

The study of hearing loss of genetic origin has greatly increased our understanding of normal auditory function and the pathophysiological processes that can disrupt it. Genetic mutations can affect any component of the hearing pathway. Most genes implicated in syndromic hearing loss are associated with an eponymous syndrome, whereas the loci linked to non-syndromic hearing loss are conventionally named using a prefix followed by a suffix integer: DFNA for autosomal dominant loci, DFNB for autosomal recessive loci and DFNX for X-linked loci. A regularly updated overview of all hearing loss-associated genes can be found online (http://hereditaryhearingloss.org). In this Primer, we have concentrated on genes that affect inner ear homeostasis, (particularly endolymph production and maintenance) and mechano-electrical transduction (especially stereociliary bundle formation and function), as these genes are the most extensively studied.

Inner ear homeostasis: stria vascularis and endolymph—At the cornerstone of inner ear homeostasis is the stria vascularis, situated on the lateral wall of the cochlear duct

(Figure 2). This highly specialized tissue produces a unique fluid — the endolymph — that bathes the sensory hair cells of the inner ear and is crucial for auditory transduction. The unique ionic composition of the endolymph, high in potassium ions (K$^+$, 150 mM), low in sodium ions (Na$^+$, 1 mM) and with a high positive endocochlear potential (+80–100 mV), reflects the function of a number of channels, pumps and gap junctions. The stria vascularis consists of marginal, intermediate and basal cell layers. The marginal cells face the endolymph, and the intermediate and basal cells below communicate via gap junctions with each other and with the fibrocytes of the underlying spiral ligament (the thick periosteum that forms the outer wall of the cochlear duct) of the lateral wall. This network of gap junctions, whose proteins are encoded by the gap junction protein beta 2 and 6 genes, *GJB2* and *GJB6*, among others, facilitates ion transport between cells and couples the cells electrically.[29] Mutations in *GJB2* are the commonest cause of severe-to-profound autosomal recessive congenital hearing loss in many populations.

The intrastrial space (the intermediate cell layer and capillaries), is separated from the marginal cell layer and the basal cell layer by two tight junction barriers, which limit the passive movement of ions. Components of tight junctions include claudins, such as Claudin-14, encoded by *CLDN14*, and MARVEL domain-containing protein 2 (also known as tricellulin), encoded by *MARVELD2*, and mutations in either gene give rise to autosomal recessive non-syndromic hearing loss in humans. [30, 31] Mutations in a number of other genes expressed in the stria vascularis that are important for ionic homeostasis in the endolymph result in a variety of syndromic forms of hearing loss (Table 1, and also EAST syndrome – causing epilepsy, ataxia, sensorineural hearing loss and renal tubulopathy – and Bartter syndrome – causing renal tubulopathy and hearing loss) and non-syndromic forms (for example, DFNB73).

Maintenance of the correct pH of the endolymph is also crucial for inner ear homeostasis. Mutations in genes coding for ion transporters and pumps that control the pH and ionic composition of the endolymph can cause Pendred syndrome (resulting in hearing loss and goiter), distal renal tubular acidosis with deafness or non–syndromic early-onset severe-to-profound hearing loss, which is associated with enlarged vestibular aqueducts. Enlarged vestibular aqueducts, whether syndromic (eg. Pendred syndrome) or non-syndromic, cause a fluctuating hearing loss in about one-third of patients. [32] These fluctuations might be associated with endolymphatic hydrops (an excessive accumulation of endolymph in the cochlea and the vestibular system), but the exact mechanism causing hearing impairment and sudden drops in hearing is not well known. [33]

Mechano-electrical transduction: stereocilia—Several other forms of inherited hearing loss affect the morphology or function of the inner and the stereociliary bundle of inner and outer hair cells, the cells that converts mechanical stimuli into electrical activity (Figure 2). Stereocilia are actin-rich projections on the apical surface of the hair cells that are arranged in a staircase-like fashion and are tethered together by protein links. The tips of the tallest stereocilia of the outer hair cells are embedded in the overlying tectorial membrane, an acellular gel composed of radial collagen fibres embedded in non-collagenous glycoproteins such as alpha-tectorin, beta-tectorin, otogelin, otogelin-like protein, otolin-1 and carcinoembryonic antigen-related cell adhesion molecule 16. Thus, when the basilar

membrane moves in response to sound, the stereocilia anchored in the hair cells move against the tectorial membrane causing a shearing motion.

This deflection of the stereocilia physically opens mechano-electrical transduction channels on the apical surface of the stereocilia (Figure 2) and K^+ flows into the sensory hair cells under the electrochemical gradient. This K^+ influx depolarizes the hair cells leading to a cascade of events that triggers activity in the fibres of the auditory nerve. K^+ in the hair cells is subsequently released from the basolateral surface via channels encoded by the potassium voltage-gated channel subfamily Q member 4 gene (*KCNQ4*). Mutations in *KCNQ4* cause a relatively common form of autosomal dominant non-syndromic progressive hearing loss.

Within the stereocilia, there are longitudinal actin fibres cross-linked for strength and rigidity by several proteins, one of which is espin, encoded by the *ESPN* gene. Mutations in *ESPN* cause either autosomal recessive non-syndromic hearing loss, with or without balance problems (absence of reflexes) [34], or autosomal dominant hearing loss, which is progressive and associated with normal balance. [35] At the base of the stereocilia, the actin filaments are tightly packed to form rootlets, which extend into the cell body. Mutations in *TRIOBP*, the gene encoding the cytoskeleton-associated TRIO and F-actin binding protein, prevent actin filaments from organizing into dense bundles and cause a non-syndromic recessive hearing loss (DFNB28). [36] At the other end of the stereocilium, tip links run from the apical surface of the shorter stereocilium to the lateral surface of its adjacent taller neighbouring cell, where there is an electron-dense anchor composed of several interacting proteins important for hearing (Figure 2). [37] At the bottom of inner hair cells lies the ribbon synapse, which is a specialized type of neuronal synapse with thousands of vesicles that contain the neurotransmitter glutamate (released by calcium-dependent exocytosis of the vesicles). This structure allows rapid and sustained release of thousands of vesicles to accurately encode sound intensity and temporal acuity necessary for speech perception. In this exocytosis process, otoferlin (encoded by *OTOF*) plays an important part, and *Otof* knockout mice have hearing loss because of the absence of exocytosis from inner hair cells. [38] Mutations of *OTOF* in humans may give rise to Auditory Neuropathy Spectrum Disorder (see above).

Acquired congenital hearing loss

Several infectious causes of acquired congenital hearing loss have been identified (Table 2). The emergence of congenital Zika virus infection as a major cause of fetal injury and newborn disability has revealed that this virus can also produce congenital hearing loss. An analysis of 70 infants of 0–10 months of age with microcephaly and laboratory evidence of Zika virus infection in Brazil demonstrated that 7% had sensorineural hearing loss. [39]

Cytomegalovirus—CMV, a member of the Herpesviridae family, is the most common potentially disabling perinatal infectious agent. [9, 23] Once an individual is infected, viral DNA is detectable in bodily fluids for months (CMV shedding), especially in the saliva and urine of young children, and represents a potential exposure risk for pregnant women.[40] The risk of congenital CMV infection is highest following primary infection during pregnancy, with a risk of vertical transmission in this setting of 32%.[41] In seropositive mothers, however, the risk of vertical transmission during reactivation or reinfection is only ~1.4 %.

Given that seropositivity for CMV in women of childbearing age in developed countries is ~50%, the incidence of congenital CMV infection is roughly 1 in every 100–200 live births.[41]

The pathophysiologic basis of sensorineural hearing loss following congenital CMV infection is unclear. Studies in the temporal bone have demonstrated inflammation and oedema of the cochlea and spiral ganglion, and viral antigens have been found in the spiral ganglion, organ of Corti, scala media and Reissner's membrane.[42] Evidence from murine models suggests infection and direct cytolysis of components of the labyrinth, including hair cells.[43, 44] In another murine model of CMV infection, hearing loss was associated with a loss in spiral ganglion neurons following experimental challenge.[45] In addition to the direct cytolytic effect of viral infection, there is also evidence for immune injury, mediated by both the host immune response as well as the expression of viral genes encoding pro-inflammatory chemokines. [46] The virulence of the virus and the immune responses of the mother, fetus and placenta have a crucial role in the outcome.[47] Approximately 10% of CMV-infected newborns are symptomatic at birth and the risk of symptoms in the neonate is highest when maternal infection occurs around conception or within the first trimester of pregnancy.[48]

Rubella—Infants with congenital rubella virus infection are usually born at term, but often have a lower birth weight than non-infected newborns of the same gestational age. The most common complication of congenital rubella infection is hearing loss.[49] Other common findings are heart defects, cataracts, hepato-splenomegaly and microcephaly. Hearing loss, cataracts and congenital heart disease represent the classic triad of manifestations of congenital rubella syndrome, [50] although clinical signs can vary depending on the timing of fetal infection. In a prospective study of pregnant women with confirmed rubella infection, a range of rubella-associated complications (including congenital heart disease and hearing loss) were observed in nine infants who were infected by the 11th gestational week. 35% (9 out of 26) of infants infected between 13–16 gestational weeks had only one complication — hearing loss.[49] Hearing loss associated with congenital rubella syndrome may not occur until after birth.[51] The mechanism of rubella infection-induced hearing loss has not been fully explained, although the virus can cause direct cochlear damage, cell death in the organ of Corti and stria vascularis and alterations in the composition of the endolymph following strial damage. [52, 53, 42]

Diagnosis, screening and prevention

In the past century, targeted screening was performed exclusively in babies considered at high risk of hearing loss (that is, infants admitted to the neonatal intensive care unit and those with a family history of hearing loss or craniofacial anomalies). However, given the growing evidence that early detection of hearing loss is beneficial to child development, universal neonatal hearing screening programmes have been introduced. In many developed countries, universal neonatal hearing screening is now well established and typically uses a two-phase screening paradigm (that is, two electrophysiological measurements performed sequentially).

Assessment of hearing status

Screening usually consists of the measurement of oto-acoustic emissions (see below) repeated twice, measurement of oto-acoustic emissions and automated auditory brain stem responses (see below), or measurement of automated auditory brain stem responses repeated twice.[54] Infants who do not pass the screening require appropriate audiological and medical evaluation to confirm the presence of hearing loss, ideally before the age of 3 months. [7] However, passing the neonatal hearing test does not exclude progressive, late-onset and less-severe congenital hearing loss (30–40 dB hearing loss), which is not detected in most neonatal hearing screening programmes. Children who pass neonatal hearing screening but have risk factors for hearing loss or whose parents express concern about their child's hearing abilities need regular follow-up, because hearing loss can develop later in life, depending upon the underlying cause.

Upon referral from neonatal hearing screening, a complete audiometric assessment is required to confirm the presence of hearing loss and to assess its severity and laterality (unilateral or bilateral). The severity of the hearing impairment should be applied to the better hearing ear and averaged over 500, 1,000, 2,000 and 4,000 Hz. Hearing loss is classified based on laterality and severity as mild (20–40 dB hearing loss), moderate (41–70 dB), severe (71–95 dB) and profound (> 95 dB). [55]

The audiometric assessment includes electrophysiological (oto-acoustic emissions, which estimate the function of outer hair cells, and auditory brain stem responses, which estimate of the function of inner hair cells and the integrity of the auditory pathways) and behavioural (audiometry) testing. In clinical practice, the functional integrity of the ear is assessed by different tests to cross-check the results of both physiological and behavioural measures.

Oto-acoustic emissions—Oto-acoustic emissions are sounds caused by the motion of the outer hair cells as they energetically respond to auditory stimulation.[56] Transient evoked oto-acoustic emissions occur after the application of a click stimulus. The oscillatory sound pressure waveform seen in a transient evoked oto-acoustic emissions response corresponds to the motion of the tympanic membrane (eardrum) being pushed back and forwards by fluid pressure fluctuations generated in the cochlea. Transient evoked oto-acoustic emissions responses can give a frequency-specific indication of cochlear status and can be measured by a small probe in the external auditory canal. As their detection requires adequate sound transmission to and from the cochlea, oto-acoustic emissions should not be used as a stand-alone test for assessing normal hearing status, but rather must be interpreted in the context of otoscopy, tympanometry and auditory brain stem responses testing.

Auditory brain stem responses and auditory steady state responses—Auditory brain stem responses are electrical potentials elicited by auditory stimuli that reflect neural activity at several discrete points along the auditory pathway. The activity is recorded from scalp electrodes using computer-averaging techniques. Click- or tone burst-induced auditory brain stem responses are most commonly used and are considered the gold standard for the objective assessment of hearing in infants and children of all ages. The obtained thresholds

are typically within 10 dB of the behavioural auditory thresholds at the higher frequencies (between 2,000–4,000 Hz).

Auditory steady state responses are elicited by AM/FM-modulated tonal stimuli. The stimulus is a continuous signal and can deliver higher average sound pressure levels than click stimuli, making auditory steady state responses useful for obtaining threshold data in children with profound hearing loss (>90 dB). The absence of auditory steady state response thresholds indicates no usable hearing and predicts poor hearing aid performance.[57] For all types of hearing loss, there is a close correlation between click auditory brain stem responses and average auditory steady state responses thresholds at 2,000 and 4,000 Hz, with a difference 10 dB between the thresholds measured with the two methods in the majority of cases.[58] Auditory steady state responses are also useful to estimate the bone conductive hearing thresholds and to distinguish conductive hearing loss from sensorineural hearing loss.

Audiometry—Visual re-enforcement audiometry can be used to test hearing in children between 6–24 months of age. In children with adequate hearing, a new sound source will provoke an orientation reflex towards the sound. Skilled audiologists can obtain reliable results. Play audiometry is used in children 2–4 years of age, by means of conditioning them to respond to an auditory stimulus through play activities.[59] After 4 years of age, standard audiometry is typically used, with an air-conduction transducer (for example, an earphone) or a bone-conduction transducer (or both) (Figure 3). The former tests the integrity of the complete auditory system, whereas the latter vibrates the skull, which stimulates the cochlea directly, bypassing the external and middle ear. Air conduction and bone conduction thresholds, mostly obtained at octave frequencies of 250–8,000 Hz, differentiate sensorineural hearing loss and conductive hearing loss.

Aetiological work up

Once a diagnosis of bilateral permanent congenital hearing loss is established, the search for an underlying aetiological diagnosis is required. The available guidelines include screening for congenital infections, imaging and genetic testing (see below). [28, 60, 61, 62] First line genetic tests are usually limited to screening for mutations in *GJB2* and *GJB6*. The work-up is complemented by ophthalmologic screening to check for ocular signs of congenital infection or syndrome specific details, kidney ultrasonography to check for congenital malformations, electrocardiogram to rule out long-QT syndrome (as is seen in Jervell Lange-Nielsen) and other tests based upon clinical findings. In unilateral hearing loss, the aetiological work-up can be limited to a thorough clinical examination for a syndromic cause of hearing loss, investigation of possible congenital infections and imaging of the inner ear.

Most available guidelines on the aetiological work-up of congenital hearing loss do not incorporate the diagnostic power of next generation DNA sequencing technology and the use of comprehensive genetic testing using gene panels (see below). Comprehensive genetic testing using targeted genomic enrichment with massively parallel DNA sequencing has changed the diagnostic algorithm and in the future, the need for complementary

examinations might be guided by the suspected diagnosis and the results of comprehensive genetic testing. A guideline published by the American College of Medical Genetics and Genomics recognizes the value of this new technology and recommends the use of gene panels. [61] Meanwhile, the use of a sequential diagnostic algorithm (Figure 4) based on the degree of hearing loss is advocated for children with bilateral congenital hearing loss [63] and, through a multidisciplinary approach, an aetiological factor can be identified in about half of the patients. [28]

An aetiological work-up for congenital hearing loss should be conducted for many reasons. It can provide parents with an answer as to why their child has hearing loss, allow accurate and personalized genetic counseling, provide relief from guilt in some cases and aid in management. A genetic diagnosis may provide an accurate estimate of risk for hearing loss in future children and may be helpful for parents in terms of family planning. Identifying the aetiology might help to choose appropriate therapeutic or management options (for example, hearing aids, cochlear implantation or adapted educational needs), might identify coexisting medical problems that need to be treated or monitored (especially when a syndromic genetic cause of hearing loss is found in a child referred as non-syndromic), secure preventable risk factors for future hearing deterioration (for example, aminoglycoside use or head trauma) and might also predict the progression of hearing loss to a certain extent.

Genetic diagnostics—Genetic diagnosis always starts with family history and the creation of a pedigree. This information is essential to define the most probable mode of inheritance, which can in turn limit the list of potential causative genes. A patient without other affected family members might represent a case of autosomal recessive inheritance, but environmental causes of hearing loss must also be considered.

DNA diagnostics for non-syndromic hearing loss is challenging, as there are numerous possible responsible genes and generally few diagnostic clues based on the phenotype. Thus, for a long time, diagnostic application of the identification of genes associated with hearing loss has lagged behind scientific progress. From 1998–2010, diagnostic laboratories in different countries typically analyzed a handful of genes for non-syndromic hearing loss, including the most frequently mutated *GJB2*. This approach typically identified the responsible gene in only 10–20% of patients with non-syndromic hearing loss. Technological developments, such as next generation DNA sequencing, have enabled the simultaneous analysis of large numbers of genes. Using these techniques, several laboratories are now offering genetic testing for large panels of genes linked to syndromic or non-syndromic forms of hearing loss at an affordable price. Comprehensive genetic testing now has the highest diagnostic rate of any test in the evaluation of hearing loss once it is confirmed by audiometry results. [64]

At present, genetic diagnosis can also assist in predicting the success of specific clinical treatments. For example, in cases of auditory neuropathy spectrum disorder with *OTOF* gene mutations, the function of the auditory nerve is expected to be preserved. However, the finding of cochlear nerve hypoplasia in some patients with auditory neuropathy spectrum disorder associated with mutations in the apoptosis inducing factor, mitochondria associated

1 gene (*AIFM1*) suggests that cochlear implantation in these patients might have limited success. [65] Thus, genetic diagnosis is useful in clinical decision-making.

Diagnostics in acquired congenital hearing loss—Any newborn with signs of congenital infection should be tested for CMV infection, as congenital CMV infection is the leading non-genetic cause of congenital hearing loss in developed countries. This infection should also be considered in children with hearing loss who are otherwise healthy and asymptomatic.[66] Signs and symptoms of CMV infection include intrauterine growth retardation, microcephaly and jaundice, with sensorineural hearing loss present in approximately 30% of symptomatic CMV-infected children.[67] In these instances, a diagnostic evaluation is indicated.[48] Pre-natally, CMV PCR on amniotic fluid can confirm congenital CMV infection (the positive predictive value is close to 100%). [68] After birth, the urine, saliva or throat swab specimens of the newborn should be collected (samples must be collected within 3 weeks of birth, since viral shedding after this time point may reflect postnatally acquired, and not congenital, infection) and analysed. [69] In children undergoing evaluation of the aetiology of sensorineuroal hearing loss beyound three weeks of age, congenital CMV infection can only be confirmed in retrospect, by using stored dried newborn blood spots as the source of template for PCR-based diagnosis. In many developed countries, a blood sample is taken routinely during the first week of life for screening for metabolic, endocrine and other disorders. The remaining blood is stored on dried blood spots. The availability of these samples, however, depends on local storage policies; moreover, these bloodspots have suboptimal diagnostic sensitivity, compared to saliva or urine samples obtained in "real-time".

If congenital CMV infection is suspected, in addition to laboratory tests, brain imaging (cerebral ultrasonography or MRI), visual function assessment and hearing assessment are required. However, in 90% of newborns congenital CMV infection is virtually asymptomatic. These children generally experience fewer neurodevelopmental problems than those who are symptomatic at birth, but 10% will nonetheless develop substantial sensorineural hearing loss sometime in childhood. [24]

A definitive laboratory diagnosis of congenital rubella infection can usually only be made definitively within 12 months from birth. Rubella infection is diagnosed if at least one of four criteria is met [70]: a positive anti-rubella IgM titre (possibly measured with enzyme immunoassays), a substantial rise in anti-rubella IgG titer 2–3 weeks after the acute phase of the infection or high titers persisting beyond what can be expected from passive maternal antibody transfer, the isolation of rubella virus in cultures from throat, nasal, blood, urine or cerebrospinal fluid specimens, or the detection of the virus by reverse transcriptase PCR in throat swabs, cerebrospinal fluid or surgical samples (from congenital cataracts, as the virus can be isolated from the lens).

Despite having neutralizing antibodies, a child infected with rubella can be infectious for months, posing a hazard to susceptible individuals. [71] Occasionally, the virus can be isolated even after 12 months, for example from the cataract, where rubella can survive up to 3 years. In late-onset disease, the virus might also be present in the skin and lungs. Additional laboratory test results that can confirm the diagnosis of congenital rubella infection are

thrombocytopenia, hyperbilirubinaemia and leukopenia. Although congenital rubella infection has become rare in the developed world owing to the eradication of the virus from the Western hemisphere, cases of imported disease can still be observed. Moreover, congenital rubella infection is still endemic in some low-income countries in the developing world, and, therefore, rubella infection should be considered in the diagnostic work-up of unexplained hearing loss if the infection cannot be excluded on historical or epidemiological grounds. [60]

Management

Therapeutic nonsurgical management of pathogen-associated hearing loss currently focuses on two key areas of intervention: specific antimicrobial therapies and anti-inflammatory therapies to mitigate the host's immune response to the infection and thereby reduce the damage to the cochlea. With a better understanding of infectious disease-related hearing loss, however, novel therapies might emerge, such as the use of free radical scavengers[72], anti-oxidants[73] and nanoparticle-based systems[74]. Surgical treatment might be beneficial in select cases in which there is an air-bone gap that is amenable to correction by surgical intervention. Examples of non-medical support are special education and sign language. [75, 76, 77]

Nonsurgical treatment

Cytomegalovirus—Clinically manifest congenital CMV infection with central nervous system involvement requires antiviral treatment. Therapy with intravenous ganciclovir or oral valganciclovir for 6 weeks was initially viewed the preferred treatment option, although neutropenia was recognized as a possible adverse effect. [78] More recently, it has been demonstrated that administration of the oral pro-drug of ganciclovir, valganciclovir, for 6 months starting in the first month of life improves neurodevelopmental outcomes and hearing in infants with symptomatic congenital CMV infection. [79] Other therapeutic options currently being explored include prophylactic vaccination, immunoglobulin therapy and prenatal antiviral therapy.[68, 69, 80] Children with congenital CMV infection require special follow-up with serial audiometry even if hearing is normal at birth, because of they are at substantial risk for late-onset or progressive hearing loss. [81]

Rubella and other infections—Prepubertal vaccination can prevent congenital rubella infection. Live attenuated rubella virus is typically administered in a trivalent formulation, combined with measles and mumps vaccines, or in a quadrivalent formulation that also includes varicella vaccine. Vaccination is recommended for children 12–15 months of age, with a booster at 4–5 years of age, and for women of childbearing age who are not pregnant and have a negative haemagglutination inhibition antibody test.

Only limited data support a role for medical management for other infections that can lead to sensorineural hearing loss (Table 3). Congenital toxoplasmosis, caused by the parasite *Toxoplasma gondii*, is typically associated with intracranial calcifications, chorioretinitis and hydrocephalus.[82] However, the prevalence of hearing loss in congenital toxoplasmosis might be higher than appreciated, because the majority of infected children are asymptomatic at birth.[83] Maternal *T. gondii* infections are treated with spiramycin, and recommended

therapies in infants with congenital infection include pyrimethamine and sulfadiazine. Syphilis, caused by *Treponema pallidum* infection, is causally related to sensorineural hearing loss in both infants who have congenital infection and (albeit more rarely) in children who acquire it post-natally.

All infants born to women with suspected or confirmed Zika virus infection during pregnancy should undergo newborn hearing screening before hospital discharge. Infants with laboratory evidence of congenital Zika virus infection should be referred for hearing evaluation by auditory brain stem responses in the first month of life; if the test is normal, repeat automated auditory brain stem response testing is recommended at 4–6 months of age. [84]

Restoration of hearing

Restoration of hearing is achieved by implantable or non-implantable hearing devices, including conventional hearing aids, cochlear implants and bone-anchored hearing aids; their basic principles and working mechanisms are illustrated in Figure 5.

Conventional hearing aids—In most patients with sensorineural hearing loss, auditory rehabilitation consists of conventional hearing aids. Even in some patients with conductive hearing loss, hearing aids are the principal treatment, especially when medical or surgical options are not feasible. Continued developments in signal processing and increasing miniaturization have increased the performance of hearing aids and their acceptance among patients. [85, 86] For example, the maximum gains for digital in-the-ear, in-the-canal and completely-in-canal aids are about 55–65 dB, 45–55 dB and 35–50 dB, respectively. Nearly all hearing aids are digital and programmable and, therefore, can be customized to the characteristics of the patient's hearing.[86]

Despite these advantages, hearing aids have a number of limitations, including lack of sufficient perceived benefit, high expenses, complications (such as occlusion of the external auditory canal) and cosmetic concerns.[87–89] As a result, only one in five eligible adults actually uses a hearing aid.[90, 91] By contrast, hearing aids use in children is much more widespread, because of the recognized critical importance of early intervention for hearing loss management made possible by universal neonatal hearing screening.[92] The limitations of conventional hearing aids have generated enthusiasm for implantable middle ear hearing technologies that attempt to solve many of the difficulties imposed by conventional aids. Implants couple vibration stimuli directly to the inner ear through multiple ways, thereby offering higher gains and reduced sound distortion than conventional aids However, the need for surgery, high costs and lack of insurance reimbursement have limited their widespread implementation.[93–95]

Cochlear implants—For patients with mild-to-severe sensorineural hearing loss, conventional hearing aids can provide excellent hearing rehabilitation. However, once hearing loss becomes severe-to-profound, these technologies no longer provide adequate clarity of sound for meaningful speech understanding, and cochlear implantation is preferred. Meta-analyses document that unilateral cochlear implants provide improved hearing and quality of life scores in recipients, whereas bilateral cochlear implants lead to

substantial improvements in sound localization and hearing in noise. [96] Furthermore, cochlear implantation is no longer limited to patients with severe-to-profound hearing loss and is now suitable for patients with relatively good low-frequency hearing but poor high-frequency hearing. In these patients, 'hybrid' or 'electro-acoustic stimulation' implants are used, which offer considerably improved sound quality in combination with natural hearing in the low frequencies.[97, 98] These implants are very nearly identical to standard cochlear implants, though have smaller diameter electrode arrays which are only inserted into the basal turn of the cochlea.

Cochlear implantation is now the standard of care for children with profound congenital hearing loss whose parents choose to use oral communication. With the availability of screening and early detection, the age at first implantation has progressively declined and many children are now fitted with an implant before their first birthday. [99] Since bilateral cochlear implantation has shown to be superior to unilateral cochlear implantation in terms of vocabulary outcomes, speech perception and sound localisation, a growing number of countries provide reimbursement for a second implant in children. The outcome of cochlear implantation in children might depend upon the underlying aetiology and associated comorbidities, especially in children with syndromic hearing loss or associated disabilities.[100, 101] Genetic testing is an important tool for predicting the outcomes of cochlear implantation or electro-acoustic stimulation and is useful for choosing the appropriate treatment. [102, 103, 104, 105]

Bone-anchored hearing aids—Improvement or restoration of hearing in conductive hearing loss might be challenging in children with congenital anomalies, such as the spectrum of atresia (abnormal narrowing or absence) of the external auditory canal. Children with atresia of the external auditory canal with minimal or no involvement of the ossicular chain can benefit from microsurgical intervention, though surgery is usually postponed until 6 years of age.[106] In children with complete bony atresia, conventional air-conduction hearing aids are not an option. When surgical reconstruction is not possible or declined by the family, bone-anchored hearing aids are indicated. [106, 107] Compared with adults, however, children have a higher incidence of complications, including non-osseo integration (as high as 15%).[108] A meta-analysis of bone-anchored implant complications has demonstrated skin reactions in 2.4–38.1% of cases, failure of osseo integration up to 18% and revision surgery rates up to 44%.[109] These results are consistent across studies. Underlying cochlear function is an important determinant of benefit with bone-anchored implants; in general, children with pure tone bone-conduction averages better than 45 dB receive excellent benefit from bone-anchored hearing implants, whereas those with averages 45–60 dB have intermediate benefit.

An additional important advantage of bone-anchored hearing aids is their rehabilitation of unilateral sensorineural hearing loss.[110–112] Placed in the hearing-impaired ear, these devices expand the sound field for the patient and significantly improve speech understanding in noise, similarly to a contralateral routing of offside signal hearing aid or a transcranial system. In these situations, the processor placed on the side of the deaf ear acts as a microphone which then directs sound to the hearing ear directly through the skull bone, whereas a contralateral routing of offside signal aid will transmit that sound wirelessly to a

hearing aid worn in the good ear. An increasing body of evidence has clearly demonstrated that the primary benefit is improved hearing in noise, whereas the implants provide little or no objective benefit in sound localization.

Other surgical treatment options—Both implantable and non-implantable hearing devices offer excellent rehabilitative options for patients with hearing loss. Depending on the nature and extent of hearing loss, other surgical options might also be available. For patients who have conductive hearing loss due to abnormalities of the external auditory canal (for example, congenital aural atresia), tympanic membrane (from acute or chronic infections) or ossicles (from congenital or acquired fixation of the ossicles), surgery can be attempted to correct these defects, often with excellent functional results. [113]

Quality of life

Hearing-impaired children who do not receive early intervention and rehabilitation will fall behind their normal-hearing peers in reading skills, cognition and socio-emotional development. This gap might in turn result in modest educational achievements and employment levels in adulthood. [114]

Speech development is impaired by delayed age-at-diagnosis of hearing loss. Children whose hearing loss is identified by 6 months of age have significantly better receptive and expressive skills than children whose hearing loss is identified later.[5] The age of hearing loss identification effect is evident across age, sex, socio-economic status, ethnicity, cognitive status, degree of hearing loss, mode of communication and presence or absence of other disabilities.[115] The positive effect on language outcomes of early confirmation of permanent childhood hearing impairment that is observed in children at primary school age is also found in teenagers. Moreover, the gap in reading skills between children with early confirmed permanent childhood hearing impairment and children with later confirmed impairment widens with age. [116]

Developmental impairment is measurable as early as at 3 years of age. The DECIBEL study compared development and quality of life for children whose hearing loss had been identified through a neonatal hearing screening programme (that is, before 2 weeks of age) and children whose hearing loss had been diagnosed after a distraction hearing programme performed at 9 months of age. Children in the neonatal screening programme received hearing amplification 13 months earlier than children in the distraction hearing screening. Quality of life scores (Pediatric Quality of Life Inventory) at 3–5 years of age were significantly better in children with permanent hearing impairment identified in the neonatal screening programme. [117, 118]

Factors that might contribute to the delay between diagnosis and intervention include: time for reflection requested by the child's parents, cultural considerations, doubts about the degree of hearing loss and the benefits of hearing amplification, acceptance and wearing of hearing aids and practical and technical considerations.

The introduction of hearing aids before 6 months of age will improve subsequent hearing development and is now considered a standard goal in the management of children with bilateral hearing loss. [7]

Outlook

The biggest challenge in the short term in congenital hearing loss is the better prevention of infectious etiologies. In the long term, it is moderating the effects of genetic hearing loss.

Cytomegalovirus-associated hearing loss

The complex correlations among CMV-induced inflammation, local and systemic host response and the development and progression of sensorineural hearing loss are not adequately understood. Ribosomal profiling has shown that the protein-coding capacity of CMV includes up to 751 open-reading frames (including splice variants), most of which are translated into small proteins of unknown function that are predicted to be shorter than 100 amino acids in length. [119] Because CMV depends on inflammation for reactivation, some of these proteins might simultaneously induce local inflammation and protect the reactivated virus from the host's immune recognition and destruction. [120] CMV genome includes multiple genes associated with immune evasion, which promote persistence of the infection and preclude its clearance. [43, 121] Furthermore, the presence of multiple epitopes across CMV strains means that IgG seropositivity does not completely guarantee protection against re-infection, which increases the challenge of developing a vaccine to completely prevent congenital transmission and its attendant sequelae. [122, 123, 124]

Improving genetic diagnoses

A complete panel of diagnostic tests for hearing loss, which includes a number of laboratory studies, serum chemistries and a variety of imaging tests, is collectively very costly and often only of limited value in establishing aetiology. Comprehensive genetic testing is less expensive than any temporal bone imaging technique and has the highest single-test positive diagnostic rate in the evaluation of non-syndromic hearing loss. As the cornerstone of precision medicine for hearing health care, genetic results can lead to major differences in patient diagnosis and management (that is, Jervell and Lange-Nielsen syndrome, Usher syndromes and mitochondrial DNA-related hearing loss) and therefore makes personalized management possible. However, one of the current problems with comprehensive genetic testing is the challenge associated with the interpretation of a large number of genetic variants. Therefore, high quality comprehensive genetic testing requires careful interpretation of genetic results in light of the phenotypic data by a multidisciplinary panel of experts that should include human geneticists with focused expertise in hereditary hearing loss, bio-informaticians, clinicians, genetic counsellors, research scientists and technicians. In addition to interpreting single-nucleotide variants, this panel should also always provide copy number variant interpretation, as copy number variants have been implicated in up to 20% of diagnoses of non-syndromic genetic hearing loss. [125] One of the factors that complicate the evaluation of the pathogenicity of variants is the ethnicity of the patients, as genetic variants often have different frequencies in different ethnicities. Concerted efforts

should be made to sample multiple distinct ethnicities, as these data are of great importance for assessing possible pathogenicity of identified variants.

Integration of the patient's hearing loss phenotype with the underlying genotype is essential. Except for *GJB2*, no large-scale genotype-phenotype studies have been performed.[20] However, these genotype-phenotype correlations are of great importance for the interpretation of the results of genetic testing, as they provide crucial information about the possible pathogenicity of genetic variants. Complex modelling tools like AudioGene (http://audiogene.eng.uiowa.edu/) offer several enhancements to traditional audiometry and might provide a better tool with which to dissect complex genotype–phenotype interrelationships. [126]

Hearing preservation and restoration

Emerging therapies for hearing loss can be broadly sub-classified as hearing preservation or hearing restoration strategies. [127, 128] Hearing preservation would probably be easier to achieve than hearing restoration; preservation strategies seek to promote hair cell survival and correct protein defects before complete and irreversible hair cell damage occurs. Once hair cells have died, hearing restoration strategies are required, with options depending on the condition of the remaining supporting cells.

Thanks to progress in genetic testing, it is possible to identify groups of patient with gene-specific mutations. Studies aimed at elucidating the broader effects of mutations at the gene level are needed to identify pathways interactions and crosstalk, which in turn are likely to provide novel insights into hearing preservation strategies.

It might be possible to trans-differentiate healthy supporting cells into hair cells in the cochlea. [129] For trans-differentiated hair cells to function properly, however, they must also integrate into their local microenvironment. Thus, even if the hurdle of trans-differentiation were overcome, other substantial challenges would remain. Although trans-differentiation therapy might be successful, several problems have to be resolved before its clinical application is contemplated [128]. For example, trans-differentiated hair cells often are not completely normal and instead exhibit a phenotype intermediate between a hair cell and a supporting cell. With more-severe inner ear damage, the response to trans-differentiation therapy is not very good, suggesting that a better understanding of the mechanism of hair cell death (apoptosis or necrosis, or both) is crucial [130]. Once hair cells are lost, the basilar membrane becomes lined with non-sensory cells, making protective therapies, even at this late stage, important to prevent the transition to a flat epithelium. [128]

Drug delivery and therapeutic targets

Pharmacological treatment to enhance self-repair of hair cells (hearing preservation) and trans-differentiation of supporting cells (hearing restoration) will require high throughput, rapid screening systems to optimize rational drug design and the development of drug delivery systems for the cochlea. Studies have demonstrated the efficiency of zebra-fish models in drug design [131] and middle ear infused, gelatine-based hydrogels appear promising as a means to deliver drugs to the cochlea. [132] A novel intra-tympanic polymer gel delivery system has been evaluated and tested as a strategy for antiviral drug delivery in

a guinea pig model [133] and holds promise for providing antiviral therapy to the CMV-infected cochlea while sparing the patient the substantial toxicities associated with systemic delivery of antiviral agents.

Neonatal hearing screening programmes

Over 50% of cases of permanent childhood hearing impairment can be detected shortly after birth through a programme of neonatal hearing screening. However, passing the neonatal screening does not guarantee normal hearing in childhood and is not a valid reason to disregard parental suspicion of hearing impairment. Progressive or late-onset hearing impairment, as seen with congenital CMV infection or in some genetic conditions, is undetected by neonatal screening programmes. Thus, postnatal identification of childhood hearing loss will remain dependent upon the interaction between parents and professionals. All individuals working with children (for example, teachers and health care providers) should monitor the child's general development and especially language development.

Other limitations of neonatal hearing screenings are related to the sensitivity and specificity of the screening method, coverage and follow-up after a referral from screening. For example, although universal neonatal hearing screening in Flanders, Belgium, has high sensitivity (94.02%) and specificity (99.96%) [134], false positive test results might cause unnecessary anxiety in parents during the vulnerable first weeks of the their newborn infant.

Coverage might be a concern in low-income countries where hearing screening programmes are not available or access to them is limited. In many universal neonatal hearing screening programmes, the progress from screening to intervention is the weakest point of the health care pathway, with the proportion of children lost to follow-up (and treatment) as high as 52% of those referred.[135]

An increasing body of evidence shows that universal neonatal hearing screening is not only beneficial for the child's development and quality of life, but is also cost-effective. The costs of neonatal hearing screenings are comparable with other newborn screening programmes and the benefits are expected to outweigh the costs. [7, 136] An economic analysis has confirmed that both universal and targeted screenings for congenital CMV infection are cost-effective, an observation that should help drive the expansion of screening programmes for this infectious cause of hearing loss in infants. [137]

Acknowledgments

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Box 1. Risk factors for permanent congenital, delayed or progressive hearing loss in childhood

- Hearing, speech, language or developmental delay

- Family history of hearing loss

- 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 hyperbilirubinaemia

- *In utero* infections (toxoplasmosis, rubella, cytomegalovirus, herpes simplex or syphilis)

- 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

- Confirmed bacterial or viral meningitis (in particular if caused by mump, herpes viruses or virus)

- Head trauma, especially of the basal skull, or temporal bone fractures, that require hospitalization
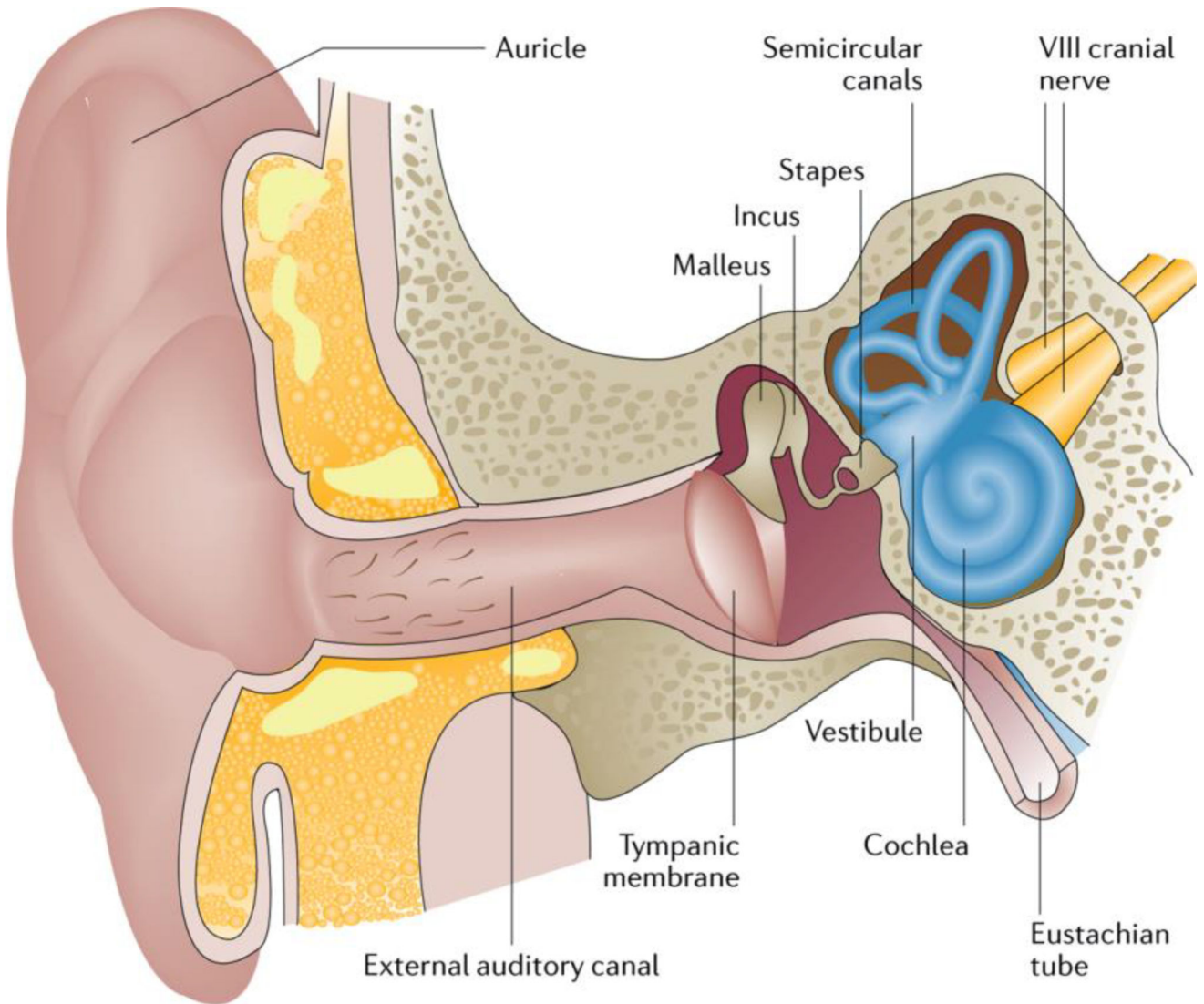
- Chemotherapy

Source: the American Academy of Pediatrics[7]

Figure 1. Cross-section of the outer, middle and inner ear
The ear is composed of three major parts, the outer, middle and inner ear. The outer ear includes the auricle and external auditory canal, and is separated from the middle ear by the tympanic membrane. The middle ear, a mucosal-lined air-filled space, houses three bones (ossicles) — the malleus, incus and stapes — and bridges the external and inner ear. The inner ear is divided into two parts: the vestibular portion, which includes the vestibule and the three semicircular canals, and the cochlear portion, which contains the outer and inner hair cells of the sensory epithelium. The footplate of the stapes covers the oval window of the inner ear. The VIII cranial nerve (the auditory or cochlear nerve) links the inner ear with the brainstem. The Eustachian tube links the cavity of the middle ear to the pharynx, permitting the equalization of pressure on each side of the tympanic membrane. The ear converts the vibratory mechanical energy of sound into the electrical energy of nerve impulses. Sound is transmitted through the external auditory canal to the tympanic membrane and middle ear ossicles. Here, air vibration is translated and amplified to mechanical vibration. At the level of the footplate, these mechanical vibrations are

transmitted to the cochlea, resulting in movement of the cochlear fluids. The movement of the cochlear fluids moves and alters the shape of the outer hair cells of the cochlea. This process mediates sound amplification and increases frequency specificity. The movement of the inner hair cells of the cochlea stimulates the adjacent nerve fibres and transmits the electrical signal to the brain.
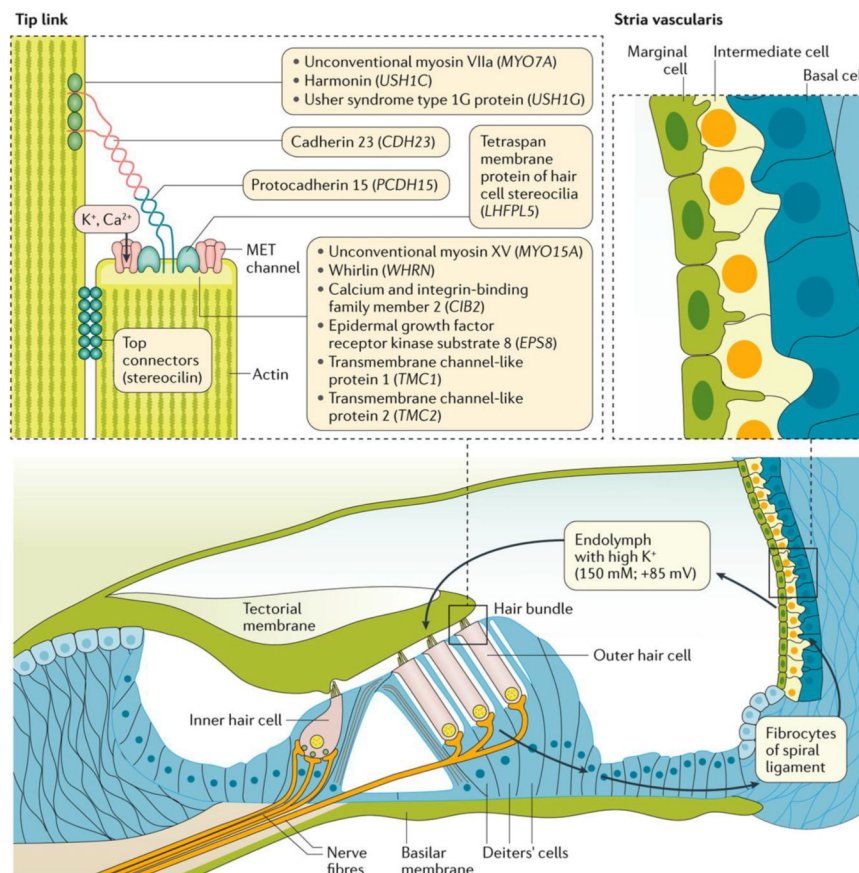
Adapted from Jentsch, T. J. Neuronal KCNQ potassium channels: physiology and role in disease. *Nat. Rev. Neurosci.* **1**, 21–30 (2000), Macmillan Publishers Limited. Inset of figure adapted with permission from Fettiplace, R. & Kim, K. X. The physiology of mechanoelectrical transduction channels in hearing. *Physiol. Rev.* **94**, 951–986 (2014), American Physiological Society

Figure 2. The stria vascularis and sensory hair cells

The stria vascularis is the highly specialized tissue that produces the endolymph; it is situated on the lateral wall of the endolymphatic duct in the cochlea, [138] and consists of marginal, intermediate and basal cell layers. On the apical membrane of the marginal cells, ion channels secrete K^+ into the endolymph against a concentration gradient. Endolymphatic K^+ flows into sensory hair cells when mechanotransduction (MET) channels on the apical surface of the stereocilia open. The K^+ influx depolarizes the hair cells and triggers electrical activity in the fibres of the auditory nerve. The hair cells subsequently release K^+ via channels in the basolateral surface and K^+ is recycled through one of several pathways back towards the stria vascularis (arrows). [138, 139]

The acellular tectorial membrane overlies the sensory hair cells; mutations in genes coding for its various constituents can all cause hearing loss, although not all of these forms of genetic hearing loss are congenital in onset. [140, 141, 142143] The tip link connecting two adjacent stereocilia is located between the apical surface of the shorter one and the lateral surface of the taller one, whereas stereocilin connects the sides of the two stereocilia (top left inset). Mutations in the genes encoding components of the tip links and their interacting proteins might cause syndromic and non-syndromic forms of congenital hearing loss. Unconventional myosin-VIIa, a motor protein that moves along the stereociliary actin

filaments, interacts with the PDZ-domain-containing protein harmonin, Usher syndrome type-1G protein and cadherin-23. [144] Cadherin-23 is a long transmembrane molecule that homodimerizes, and its large extracellular domains interact with homodimers of protocadherin-15. [145] These five tip link proteins form the 'Usher interactome' and mutations in their coding genes are responsible for Usher syndrome type 1 (Table 1), the most common cause of the dual sensory impairment of hearing and vision loss. Protocadherin-15 forms the lower half of the tip link. Its anchor includes a complex of the motor protein unconventional myosin-XV, its cargo whirlin, epidermal growth factor receptor kinase substrate 8 and calcium and integrin-binding family member 2 (which is also associated with Usher syndrome type 1). [146, 147, 148, 149]. The MET channel at the lower tip link density might interact directly with protocadherin-15 (reviewed in Fettiplace & Kim). [37]
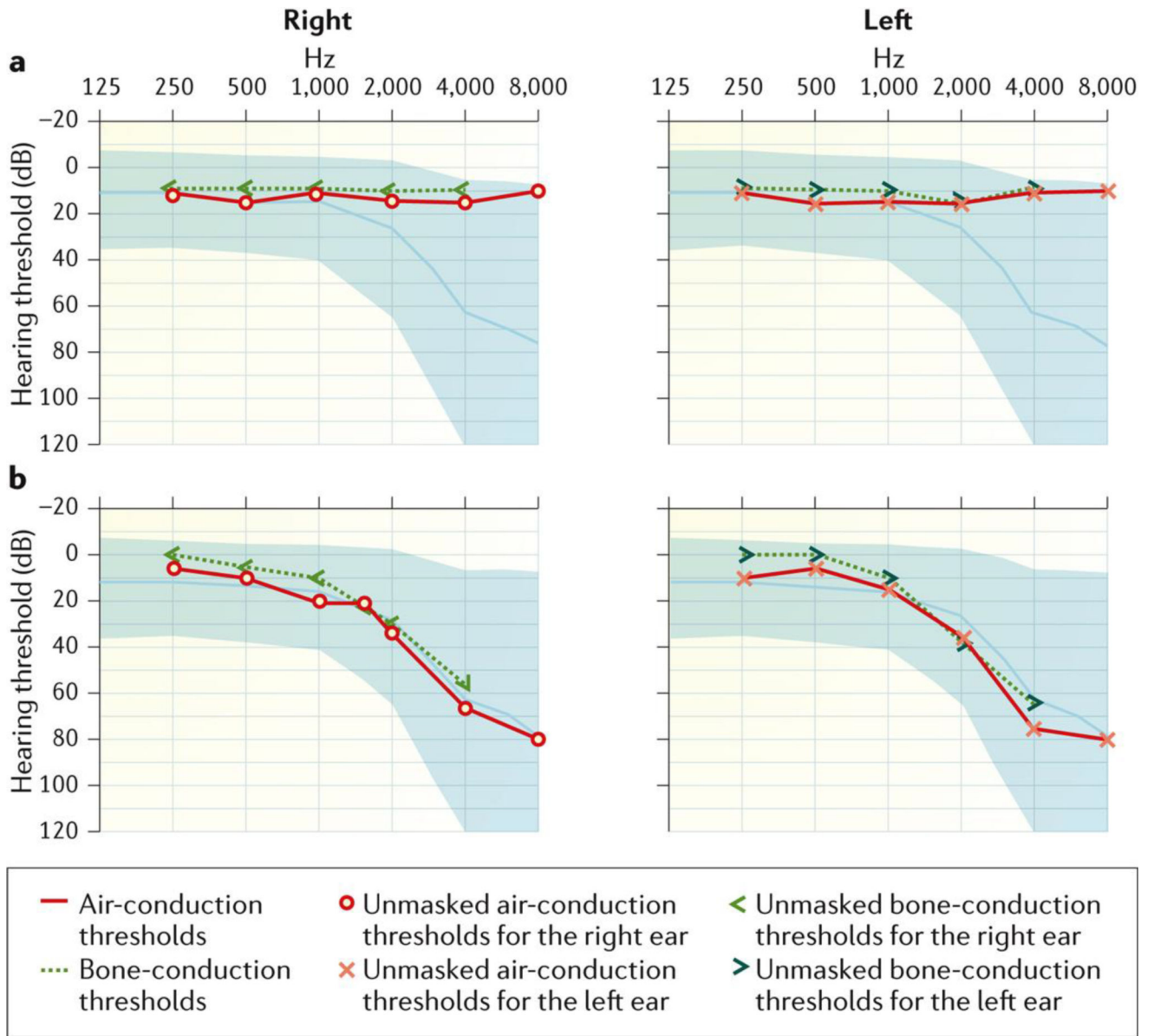
Figure 3. Audiometry assessment

A. Pure tone audiometry obtained in a child with bilateral normal hearing thresholds across all frequencies. B. Pure tone audiometry obtained in a child with bilateral and symmetric sensorineural hearing loss. Hearing thresholds are normal up to 1,000 Hz. A ski-slope audiometric configuration is recorded at higher frequencies, showing mild hearing loss at 2,000 Hz that increases to severe hearing loss at 8,000 Hz.
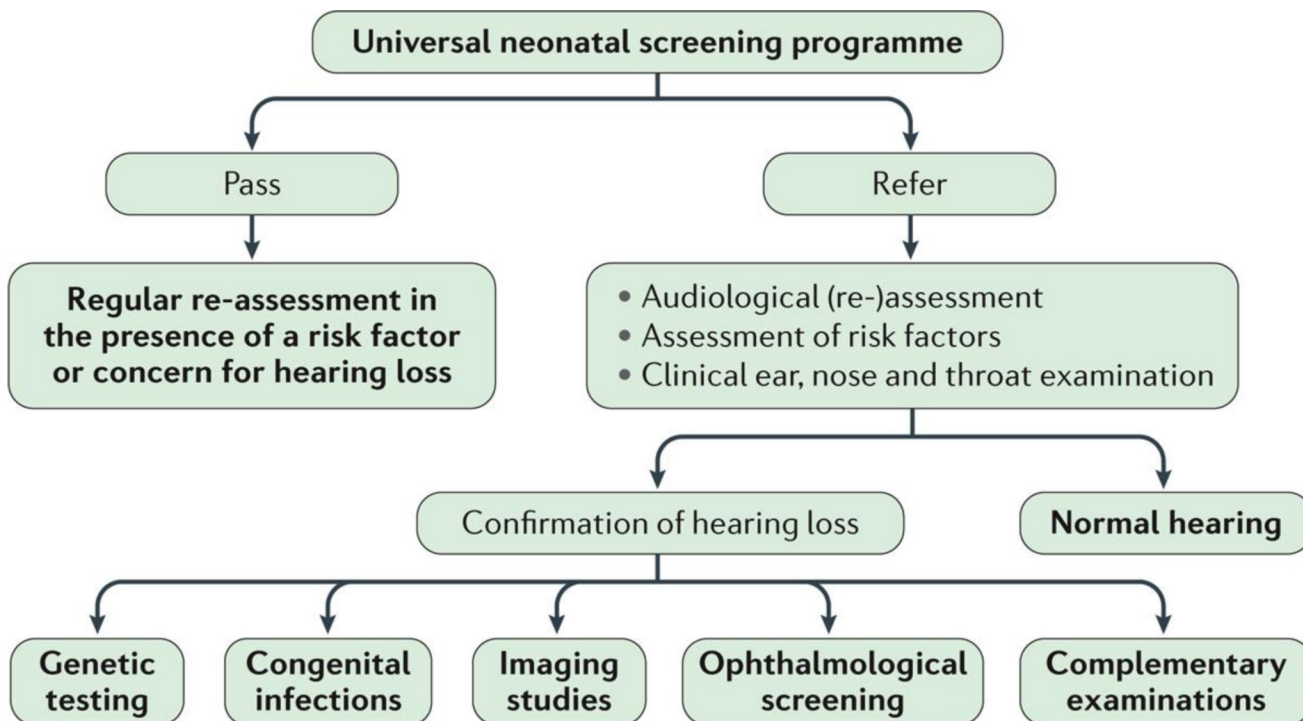
Figure 4. Multidisciplinary algorithm for the assessment of hearing function in infants
Newborns who pass the neonatal hearing screening should undergo regular follow-up when risk factors for hearing loss (as defined by the Task Force of the American Academy of Pediatrics) are present. [7] If a newborn fails the screening and bilateral congenital hearing loss is suspected, a comprehensive audiological and aetiologic work-up is required. Audiological tests can confirm the presence of hearing loss and determine its type (conductive, sensorineural or auditory neuropathy spectrum disorder), laterality and severity. Genetic testing is an integral part of the aetiological work-up, as are the exploration of perinatal insults and the presence of congenital infections as possible causative agents. In particular, timely investigation for congenital cytomegalovirus (CMV) infection is essential, as it is the most common infectious aetiology of hearing loss. Virological identification of CMV must be made in the first 3 weeks of life to ensure that the infection was truly congenital and not post-natally acquired. Imaging studies are recommended in all cases of bilateral hearing loss 60 dB or with craniofacial malformations. [62] Imaging exams can rule out the presence of structural inner ear anomalies, which might occur as an independent entity, be part of a syndrome, or have therapeutic implications. Certain inner ear anomalies might place the child at increased risk for sudden hearing loss (for example, enlarged vestibular aqueducts) or meningitis and require appropriate counselling. Imaging studies are a prerequisite before cochlear implantation to assess cochlear anatomy and confirm the presence of a cochlear nerve. A detailed assessment of the test results by a paediatric ophtalmologist is recommended, given the high prevalence (40–60%) of ophthalmologic problems in hearing impaired children. [150] Other complementary investigations include, for example, electrocardiogram and renal ultrasonography. ENT; ear, nose and throat.
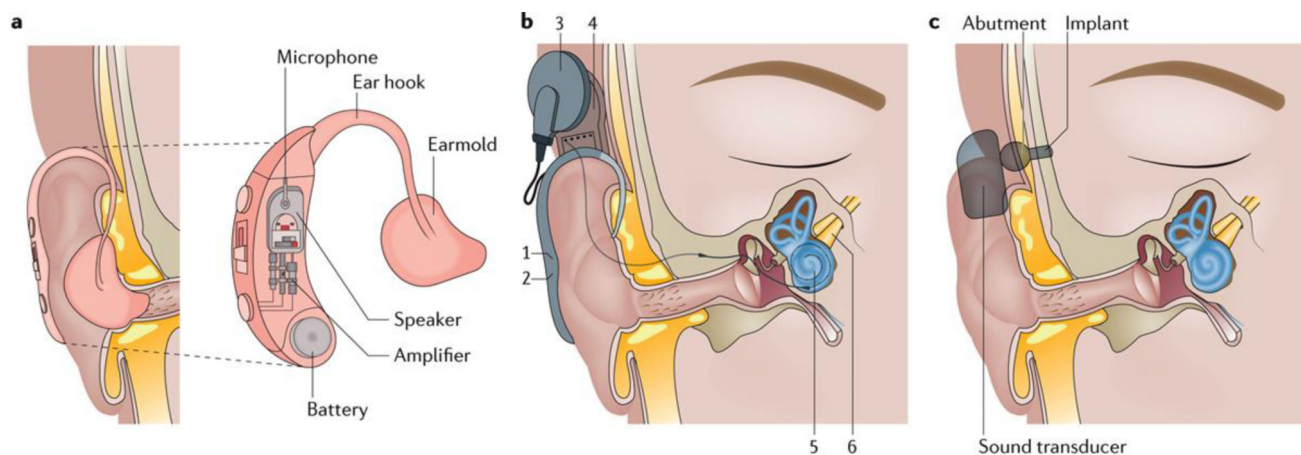
Figure adapted with permission courtesy of Cochlear Ltd

Figure 5. Non-medical treatments for hearing loss

A conventional hearing aid converts environmental sounds to amplified sounds. A hard case is worn behind the auricle and contains all the electronic parts (microphone, amplifier and battery). A sound is picked up by a microphone and converted to an electrical signal that corresponds to the pressure variation produced by the sound. This signal is then amplified and delivered to a speaker that converts the amplified electrical signal back to sound. The speaker sends the sound signal to the tympanic membrane by a slim tube connecting the hearing aid to an earmold that fits in the external auditory canal. B. A cochlear implant converts sounds to electrical signals and is composed of different parts. A microphone (1) picks up environmental sounds and transmits them to a speech processor. Through a magnetic coil (3), acoustic signals are transmitted from the speech processor to a subcutaneously implanted receiver/stimulator (4) that converts the acoustic signal into electric impulses. An electrode array (5) placed in the scala tympani of the cochlea directly stimulates electrically the auditory nerve (6). C. A bone-anchored hearing aid converts a sound signal to micro-vibrations: it uses the principle of bone conduction to directly stimulate the cochlear fluids by vibrating the skull behind the ear at auditory frequencies. A titanium screw (the implant) is surgically anchored in the bone and becomes fixed through a process called osseo-integration. The implant is connected to a sound transducer by means of an abutment (connector). The sound transducer captures the sound, converts it to vibrations and sends them to the implant. The implant then transmits the vibrations through the bone directly to the inner ear. In the most recent bone-anchored hearing aid systems, the abutment is replaced by a magnetic connection. Copyright permission obtained from Cochlear Limited ©

Table 1

Common syndromic forms of hearing loss

Syndrome	Proteins involved (coding genes)	Clinical characteristics[*]
Jervell and Lange–Nielsen	Potassium voltage-gated channel subfamily E member 1 (KCNE1) and potassium voltage-gated channel subfamily KQT member 1 (KCNQ1)	Cardiac arrhythmia (long QT interval)
Usher	Usher syndrome type 1: Unconventional myosin-VIIa (MYO7A), harmonin (USH1C), cadherin-23 (CDH23), protocadherin-15 (PCDH15), Usher syndrome type-1G protein (USH1G) and calcium and integrin-binding family member 2 (CIB2) Usher syndrome type 2: usherin (USH2A), adhesion G protein-coupled receptor V1 (ADGRV1) and whirlin (WHRN) Usher syndrome type 3: clarin-1 (CLRN1)	Retinitis pigmentosa
Alport	Collagen alpha-3(IV) chain (COL4A3), collagen alpha-4(IV) chain (COL4A4) and collagen alpha-5(IV) chain (COL4A5)	Glomerular kidney disease and eye abnormalities
Branchio-oto-renal	Eyes absent homolog 1 (EYA1), homeobox protein SIX1 (SIX1) and homeobox protein SIX5 (SIX5)	Branchial cysts or fistulae, external and middle ear anomalies and renal abnormalities
Waardenburg	Paired box protein Pax-3 (PAX3), microphthalmia-associated transcription factor (MITF, endothelin-3 (EDN3), endothelin B receptor (EDNRB), zinc finger protein SNAI2 (SNAI2) and transcription factor SOX-10 (SOX10)	Pigmentary abnormalities of skin, hair and iris
Pendred	Pendrin (SLC26A4)	Enlarged vestibular aqueduct and thyroid goiter
Stickler	Collagen alpha-1[151] chain (COL2A1), collagen alpha-1(IX) chain (COL9A1), collagen alpha-2(IX) chain (COL9A2), collagen alpha-1(XI) chain (COL11A1) and collagen alpha-2(XI) chain (COL11A2)	Skeletal and joint abnormalities, myopia and vitreoretinal degeneration
Treacher Collins	Treacle protein (TCOF1), DNA-directed RNA polymerases I and III subunit RPAC1 (POLR1C) and DNA-directed RNA polymerases I and III subunit RPAC2 (POLR1D)	Characteristic facies caused by underdevelopment of facial bones (malar and zygomatic hypoplasia, small jaw), cleft palate, eyelid colobomata and external and middle ear anomalies

[*] Aside from the manifestations that affect the ear or the auditory system.

Table 2

Congenital infections associated with acquired hearing loss

Infectious agent	Type (mode of acquisition)	Transmission	Epidemiology of symptomatic congenital infection	Early clinical manifestations[*]	Late clinical manifestations[*]	Diagnosis (prenatal in mother or in amniotic fluid	Diagnosis (postnatal in newborn)
Toxoplasma gondii	Intracellular protozoan (foodborne)	Higher risk of transmission in later gestation. More-severe symptoms in earlier gestation [152]	1–10 per 100,000 live births[153]	Intracranial calcifications, hydrocephalus and chorioretinitis Asymptomatic in >60% of cases	Retardation, seizures and SNHL	Maternal serology Amniotic fluid PCR	*T. gondii* specific IgG, IgM and IgA and PCR in blood and CSF
Rubella virus	RNA virus Togaviridae (inhalation)	Highest in first trimester [42]	0–598 per 100,000 live births[154]	Cataract, SNHL, cardiac defects and microphthalmia	Retardation	Maternal serology	Rubella IgM and PCR in blood, nasopharyngeal swab, urine and CSF [153]
Cytomegalovirus	DNA-herpes virus (bodily fluids and sexual contact)	Transplacental	0.65 per 1,000 live births [41]	Retinitis and intra-cranial calcifications [80] Asymptomatic in 85% of cases	Mental retardation, cerebral palsy and seizure disorders [80]	Maternal serology and amniotic fluid PCR	PCR in blood, urine and saliva Specimens must be obtained <21 days of age to reliably diagnose
Herpes simplex virus	DNA-herpes virus (bodily fluids)	Intrapartum	0.3 per 100,000 live births[155]	Microcephaly, intra-cranial calcifications, skin andocular findings[155]		Maternal serology	HSV1-2 surface cultures and HSV1-2 PCR in blood and CSF
Treponema pallidum	Spirochete (sexual contact)	Highest in third trimester[156]	8.7 per 100,000 live births[157]	"The great mimic". Diverse array of symptoms in any major body system [153]	Interstitial keratitis, SNHL and notched teeth[158]	Maternal serology (nontreponemal and treponemal)	Non-treponemal test in blood

CNS Central Nervous System; CSF Cerebrospinal fluid; PCR polymerase chain reaction; SNHL Sensorineural hearing loss.

[*] Other than those associated with the infection (for example, rash, thrombocytopenia, anaemia, lymphadenopathy and hepato-splenomegaly)

Table 3

Characteristics of infectious congenital hearing loss

Infectious agent	Pathophysiology (presumed)	Prevalence	Unilateral/bilateral	Severity	Progression	Treatment
Toxoplasma gondii	Inflammatory response to the tachyzoite form of *T. gondii* induces CNS necrosis[159]	0%[160]	unknown	unknown	Unknown	The effect of pyrimethamine and sulfadiazine on hearing loss is unknown[160, 161]
Rubella virus	Direct damage and cell death in the organ of Corti and stria vascularis[52]	58%[42]–66%[153]	Bilateral[42]	Mild to severe[42]	Possible	There is no specific treatment available
Cytomegalovirus	Viral labyrinthitis and inflammatory injury[43]	15% (industrialized countries) 33% (developing countries)[162, 163]	Unilateral or bilateral	Mild to profound	Common	Ganciclovir or valganciclovir slow the progression and stabilize hearing loss Established hearing loss is generally irreversible even with antiviral therapy
Herpes simplex virus	Only in association with confounding factors associated with SNHL[164]	Unknown	Unilateral or bilateral[164]	Mild to severe	Absent[164]	The effect of acyclovir[155] on hearing loss is unknown
Treponema pallidum	Obliterative endarteritis[165]	Unknown	Bilateral	Profound	Possible	The effect of intravenous penicillin on hearing loss is unknown[156]

CNS, central nervous system; SNHL, sensorineural hearing loss