Review article

Infant hearing loss: from diagnosis to therapy

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Ipoacusie infantili: dalla diagnosi alla terapia

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SUMMARY

Hearing loss is one of the most common disabilities and has lifelong consequences for affected children and their families. Both conductive and sensorineural hearing loss (SNHL) may be caused by a wide variety of congenital and acquired factors. Its early detection, together with appropriate intervention, is critical to speech, language and cognitive development in hearing-impaired children. In the last two decades, the application of universal neonatal hearing screening has improved identification of hearing loss early in life and facilitates early intervention. Developments in molecular medicine, genetics and neuroscience have improved the aetiological classification of hearing loss. Once deafness is established, a systematic approach to determining the cause is best undertaken within a dedicated multidisciplinary setting. This review addresses the innovative evidences on aetiology and management of deafness in children, including universal neonatal screening, advances in genetic diagnosis and the contribution of neuroimaging. Finally, therapy remains a major challenge in management of paediatric SNHL. Current approaches are represented by hearing aids and cochlear implants. However, recent advances in basic medicine which are identifying the mechanisms of cochlear damage and defective genes causing deafness, may represent the basis for novel therapeutic targets including implantable devices, auditory brainstem implants and cell therapy.

KEY WORDS: Children • Conductive hearing loss • Sensorineural hearing loss • Genetic diagnosis • Cochlear implant

RIASSUNTO

L'ipoacusia è una delle principali cause di disabilità nel bambino con conseguenze sulla qualità di vita del paziente e della sua famiglia. La diagnosi precoce ed il tempestivo trattamento sono presupposti fondamentali per limitare (o evitare) gli effetti dell'ipoacusia sul corretto sviluppo del linguaggio e delle abilità cognitive. Negli ultimi 20 anni, l'introduzione dello screening audiologico neonatale universale, ha portato ad una rivoluzione nella diagnosi, anticipando l'epoca di riconoscimento dell'ipoacusia rendendo più precoce ed efficace l'approccio terapeutico. Inoltre, gli sviluppi tecnologici e delle neuroscienze hanno profondamente cambiato la gestione della sordità, con ampia diffusione di innovativi strumenti di diagnosi quali la medicina molecolare, la genetica e le metodiche di imaging. Grazie ad un approccio multidisciplinare si è assistito ad una progressiva riduzione di quelle che erano definite come ipoacusie idiopatiche, a vantaggio di una sempre più accurata diagnosi etiologica. Lo scopo di questo lavoro è quello di raccogliere i più recenti progressi nel campo della diagnosi dell'ipoacusia infantile, cercando di focalizzare gli aspetti strategici dello screening audiologico neonatale, della diagnosi genetica, e dell'imaging. Inoltre, nell'ambito della terapia, vengono considerati i progressi nelle applicazioni degli ausili protesici convenzionali e dell'impianto cocleare, che rappresentano un solido presente terapeutico. Infine vengono analizzate le più promettenti prospettive offerte dalle protesi impiantabili, dall'impianto del tronco encefalico e le prospettive terapeutiche offerte dalle cellule staminali.

PAROLE CHIAVE: *Bambino • Ipoacusie trasmissive • Ipoacusie neurosensoriali • Diagnosi genetica • Impianto cocleare*

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Introduction

Childhood permanent hearing loss has lifelong consequences for both children and their families. Its early detection, together with appropriate intervention, is critical to speech, language and cognitive development in hearing-impaired children. Fortunately, recent interdisciplinary developments and early detection of hearing loss are transforming outcomes by offering more effective opportunities for deaf children.

Hearing dysfunctions in children can be classified by type, degree, configuration, time of onset, aetiology, and finally, consequences on speech development (Table I). More briefly, they can be divided into *conductive, sensorineural, mixed and central types*. *Conductive hearing loss* (CHL) results from interference with the mechanical transmis-

sion of sound through the external and middle ear, and is far more common in children; it can be congenital, as a consequence of anatomic abnormalities, but it can commonly be acquired following middle ear inflammatory pathologies. *Sensorineural hearing loss* (SNHL) results from failure to transduce vibrations to neural impulses in the cochlea, and can be also divided in congenital and acquired, and may otherwise be indicated on the basis of the time of onset as prenatal, neonatal or postnatal. *Mixed hearing loss* involves a combination of these two types. Finally, *auditory processing disorders* refer to defects in the brainstem or higher processing centres of the brain.

Both CHL and SNHL may be caused by a wide variety of congenital and acquired factors that are summarized in Table II. The causes of permanent SNHL are much more widespread than those of CHL. Both permanent conductive and sensorineural HL can be associated with delayed language development and behavioural problems. Although the most common cause of acquired CHL is otitis media with effusion (OME), which has a prevalence of 20% in children at the age of 2 years, this affection is characterized by a high rate of spontaneous resolution, and for some children, effusion does not reduce hearing or negatively impact language development [1].

The prevalence of childhood permanent congenital hearing loss (PCHL) is 1.2 to 1.7 cases per 1000 live births [2], and is essentially due to SNHL. In the US, the rate of PCHL ranges from 1 to 3 per 1000 live births and represents the most common neurological birth defect. Very few studies have been carried out in Italy on the prevalence of deafness. A study performed in Ferrara demonstrated a prevalence of 0.19/1000 in newborns and 2.2/1000 in at-risk children [3]. In Italy, the prevalence of congenital deafness has decreased over the years; the 1.01/1000 ratio observed in the years 1934-1943 dropped to 0.55 in 1974-1988 and to 0.35 in 1989-2003. It is also demonstrated a highly heterogeneous distribution in Southern Italy where a higher prevalence of profound prelingual deafness exceeds the 1/1000 limit by 1.1 and even 1.25, depending on the region.

Evidence on the prevalence of postnatal hearing loss is conflicting. A study from the United Kingdom found the prevalence of hearing loss > 40 dB hearing level (HL) to increase from 1.06/1000 at birth to up to 1.65-2.05/1000 at 9 years of age. This would mean that 35% to 50% of all hearing loss in 9-year-old children is postnatal. A large number of postnatal hearing losses depends on CHL, and specifically on otitis media. Nevertheless, sensorineural hearing impairment in children represents a major cause of permanent disability, and between 20-30% of affected children have profound hearing loss. The prevalence increases up to 6 years of age mainly as a result of menin-

Table I. Hearing loss classification.

Degree	Mild (21-40 dB); Moderate (41-70 dB); Severe (71-90 dB); Profound (> 90 dB)
Type	Conductive; Sensorineural; Mixed; Auditory processing disorders
Onset time	Prenatal; Neonatal; Postnatal
Aetiology	Congenital (genetic or not genetic); Acquired
Speech development	Prelingual; Postlingual

Table II. Classification of congenital and acquired factors involved in conductive and sensorineural hearing loss.

	Congenital	Acquired
Conductive hearing loss	• Aural atresia • Microtia • Ossicular chain anomalies • Syndromic and complex craniosynostosis • (Apert syndrome, Crouzon syndrome, Saethre-Chotzen syndrome)	• Foreign body (cerumen, etc.) • Ear canal exostoses • External otitis • Middle ear infection (acute and chronic suppurative otitis, cholesteatoma) • Middle ear effusion • Ossicular chain disruption • Ear barotraumas • Tympanic membrane perforation
Sensorineural hearing loss	• Syndromic disease (Alport syndrome, Usher syndrome, Waardeburg syndrome, etc.) • Genetic non-syndromic hearing loss (Connexine 26-30, mitochondrial diseases, other genetic disorders) • In utero infections (cytomegalovirus, varicella, herpes, toxoplasmosis, syphilis, rubella, mumps, measles) • Perinatal hypoxia and prematurity • Hyperbilirubinaemia • Ototoxic drugs exposure in pregnancy • Anatomic abnormalities of the cochlea or temporal bone • Neonatal Intensive Care Unit recovery • Low Apgar scores	• Infections • Bacterial meningitis (*Haemofilus influenzae*) • Viral labyrinthitis (measles, mumps, rubella, parainfluenza) • Use of ototoxic drugs (cisplatin, aminoglycosides, furosemide) • Head or acoustic trauma • Autoimmune diseases (Cogan syndrome) • Radiation therapy for head and neck tumours • Chronic otitis media complications

gitis, delayed onset of genetic hearing loss or late diagnosis. Taken together, the estimated prevalence of SNHL in patients younger than 18 years of age is 6 per 1000 [4]. In developing countries, the prevalence is higher because of viral infections, lack of immunization, consanguinity, exposure to ototoxic agents, meningitis and life in extreme poverty [5]; about half of disabling cases of hearing loss are worldwide preventable. Approximately 30% of deaf children have an additional disability, most commonly cognitive impairment. Unilateral hearing loss is present in 3.4-34/1000 children mostly as a consequence of malformation of the inner ear or postnatal pathologies. Affected children can show difficulties in localizing and listening in noisy situations. However, children with unilateral hearing loss have been found to have lower language scores, increased rate of speech therapy, scholastic failures or need for individualized education [6].

Risk factors for the development of hearing loss were established in 2007 by the Joint Committee on Infant Hearing (JCIH) as reported in Table III. Among the most prominent causes are family, history, craniofacial abnormalities, in-utero infections, severe hyperbilirubinaemia, neonatal intensive care unit (NICU) admission for 2 days, respiratory distress, prolonged mechanical ventilation and syndromes associated with hearing loss. However, in 50% of infants with permanent congenital HL there are no known risk factors [7].

In the last two decades, the application of universal neonatal hearing screening (UNHS) compared to the risk factor screening protocols has improved identification of hearing loss early in life and facilitates early intervention. The proven benefits of early identification and intervention (at < 6 months of age) in terms of language outcomes and communication have confirmed the effectiveness and cost-effectiveness of UNHS [3].

Early diagnosis of bilateral SNHL is fundamental to improve both linguistic skills and cognitive development in hearing-impaired children. Audiologic testing can identify the site of the lesion and allow early characterization of hearing loss by distinguishing between dysfunction of cochlear hair cells and nerve fibres. However, the recent advances in genetic testing and aggressive management of perinatal infections represent a challenge for SNHL diagnosis. Developments in molecular medicine, neuroscience and genetics have improved the aetiological evaluation of hearing loss. Once deafness is established, a systematic approach to determining the cause is best undertaken within a dedicated multidisciplinary setting.

Given that half of cases of congenital hearing loss have a genetic aetiology, the identification of the cause by genetic testing may provide substantial benefits, such as determining prognosis, identifying associated risk factors including cardiac conduction defects or associate disabilities and preventing further hearing loss by identifying ototoxic susceptibility (e.g. A1555G mitochondrial mutation) [1].

The main challenge for the otolaryngologist/audiologist remains early rehabilitation of hearing loss. In the last decades, rehabilitation of hearing loss depended on the use of hearing aids that act as sound amplifier, although their effectiveness is limited by the use of a damaged inner ear. In recent years, cochlear implants have changed the outcome of deafness, despite a signal quality that is still impoverished compared to physiological conditions. In perspective, technological improvements will ameliorate performances of cochlear implants. Finally, an exciting challenge is the ability to regenerate the neural epithelium and ganglion neurons by gene therapy, implantation of stem cells or reactivation of the processes of development and maturation of cells formed during embryonic

Table III. Classification of hearing loss risk factors - Joint Committee of Infant Hearing 2007.

1. **Caregiver concern regarding hearing, speech, language or developmental delay.**
2. **Family history of permanent childhood hearing loss.**
3. **Neonatal intensive care of more than 5 days** or any of the following regardless of length of stay: assisted ventilation, exposure to ototoxic medications (gentamycin and tobramycin) or loop diuretics (furosemide/Lasix), and hyperbilirubinaemia that requires exchange transfusion.
4. **In utero infections** such as CMV, herpes, rubella, syphilis and toxoplasmosis.
5. **Craniofacial anomalies** including those that involve the pinna, ear canal, ear tags, ear pits and temporal bone anomalies.
6. **Physical findings, such as white forelock, are associated with a syndrome known to include a sensorineural or permanent conductive hearing loss.**
7. **Syndromes associated with hearing loss or progressive or late-onset hearing loss** such as neurofibromatosis, osteopetrosis and Usher syndrome; other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange-Nielson.
8. **Neurodegenerative disorders** such as Hunter syndrome, **or sensory motor neuropathies** such as Friedreich ataxia and Charcot-Marie-Tooth syndrome.
9. **Culture-positive postnatal infections associated with sensorineural hearing loss**, including confirmed bacterial and viral (especially herpes viruses and varicella) meningitis.
10. **Head trauma** especially basal skull/temporal bone fracture that requires hospitalization.
11. **Chemotherapy**.

life [8]. In this scenario, the treatment of sensorineural deafness is closely connected with knowledge of the cause of hearing loss.

This review will focus on innovations in aetiology and management of deafness in children including universal neonatal screening and advances in genetic diagnosis, and will also overview the contributions of neuroimaging and rehabilitation.

Hearing loss classification

Conductive hearing loss

The most common causes of CHL are indicated in Table II. Congenital CHL depends on anatomic disorders that can be classified into major and minor malformations. The development of the external auditory canal (EAC; first branchial cleft) spans from the 4th to the 30th week of gestation, and in this period the auricle and middle ear structures develop independently of each other. Although isolated branchial cleft (EAC) and branchial arch (ossicles) deformities are possible, more commonly the deformity affects more than one area. *Major anomalies* characteristically involve middle ear structures as well as the external auditory canal and pinna. Malformations of the external ear can range from absence or blockage of the external ear canal (atresia auris) to only a slightly reduced pinna and external ear canal (microtia). *Minor anomalies* include abnormalities of a middle ear structure (stapes, incus, malleus, oval window, and round window) in isolation or as a combination of abnormalities involving more than one structure. Although a variety of congenital middle ear malformations responsible for CHL have been described in the literature, stapes and incudostapedial complex are the most commonly-involved structures. External and middle ear malformations can be related to chromosomal defects as a part of syndromes such as osteogenesis imperfecta, Treacher Collins, CHARGE, Klippel-Feil, Goldenhar and Crouzons syndrome. They can be also observed in families affected by mild or moderate non-syndromic CHL having more frequently a dominant autosomic inheritance and linked to maternal pathology, such as TORCH infections, or abuse of alcohol or drugs, such as hydantoin, retinoic acid and thalidomide, and more rarely cretinism [9 10].

The most frequent cause of CHL is *otitis media*, which represents a broad spectrum of disease that includes acute otitis media and otitis media with effusion, followed by traumatic tympanic membrane perforation, chronic otomastoiditis and cholestatoma. *Acute otitis media* usually occurs as the sequelae of a viral upper respiratory infection with disruption of the mucosal barrier allowing bacteria from the nose and nasopharynx to spread to the middle ear. Inflammation of the middle ear may be apparent by local or systemic findings such as ear pain, erythema of the tympanic membrane, fever and cold symptoms [11 12].

Acute otitis must also be distinguished from *otitis media with effusion* (OME), which is defined as fluid in the middle ear without local or systemic illness. In fact, children with the latter do not suffer from acute ear pain, fever or malaise. Hearing impairment is usually mild and often identified when parents express concern regarding their child's behaviour, performance at school or language development. Half or more of cases resolve within 3 months and 95% within a year, but complications such as tympanic membrane perforation, tympanosclerosis, otorrhoea, and cholesteatoma can occur. Inflammation of the middle ear and tubal dysfunction are considered the most important pathogenic factors, and a number of risk factors including infection of upper airway, adenoiditis, seasonality, inadequate antibiotic therapy, genetic and racial factors have been established. Several adjunctive risk factors have been recognized such as allergy, sex, and geographical and environmental factors (e.g. household smoking). There is no evidence to show whether interventions to modify these risk factors reduce the risk of OME. Notwithstanding, a number of treatments have been proposed including local and oral steroids, oral antibiotics, antihistamines plus oral decongestants, or mucolytics, autoinflation, ventilation tubes and adenoidectomy [12 13]. Recurrent otitis media is usually defined as three or more episodes of acute otitis within 6 months or four episodes within 12 months; however, chronic otomastoiditis (COM) typically occurs as a result of long standing Eustachian tube dysfunction. Important complications to consider when evaluating acute otomastoiditis of the temporal bone include coalescent mastoiditis, Bezold's abscess, subperiosteal abscess, dural sinus thrombosis, intracranial abscess, empyema, meningitis, facial nerve involvement, labyrinthitis and petrous apicitis. These same complications can occasionally be superimposed on chronic otomastoiditis [12].

Cholesteatoma occurs in 10% of cases of chronic otitis in children, although congenital middle ear cholesteatoma represents approximately 2% of all cholesteatoma cases. Acquired cholesteatomas predominantly arise following retraction of part of the eardrum in response to middle ear inflammation. Much less frequently they may arise as the result of migration of squamous epithelium through a perforation in the ear drum. Cholesteatoma may also occur as a result of metaplasia of the middle ear mucosa or implantation following trauma [14]. Criteria for diagnosis of congenital cholesteatoma are the presence of a white "pearl" behind an intact tympanic membrane with no history of perforation, otorrhoea or otologic surgery [15 16]. It is now accepted that in some cases of advanced cholesteatoma the natural history tends toward development of tympanic perforation and otorrhoea. In infants, cholesteatoma is considered agressive due to its rapid growth and high rate of recurrence, and is reputed to be more aggressive than in adults [17]. This disease raises two main problems for the surgeon. The first obviously concerns local control, while

the second is the hearing rehabilitation strategy, which is essential to prevent learning difficulties. The optimal surgical technique for obtaining these goals in children is still controversial. Surgical and hearing outcomes may be heavily influenced by immaturity and local anatomical and physiological factors such as Eustachian tube function, middle ear and mastoid space anatomy, restoration of mucosal lining in the middle ear and surgical technique as well as syndromic conditions such as those in Down syndrome. Different surgical techniques and results on residual and recurrence rates and hearing have been extensively reported in literature [18].

Sensorineural hearing loss

As for CHL, SNHL can be classified as congenital and acquired (Table II). Congenital SNHL can be divided in genetic and non-genetic deafness. The latter category can be further classified as syndromic or non-syndromic. The non-genetic category can be prenatal, perinatal and postnatal.

Developmental malformations that affect the otic capsule result in anomalies of both the membranous and bony labyrinth. The specific timing of the insult during otic capsule development determines the resultant type along a spectrum of congenital inner ear malformations. In descending order of severity and developmental time course, these are Michel's aplasia, cochlear aplasia, common cavity, incomplete partition-I (cystic cochleovestibular malformation), cochleovestibular hypoplasia and incomplete partition-II (classic Mondini's malformation). Between 11-41% of children affected by SNHL have inner abnormalities seen on CT and MRI. Imaging findings will be summarized in this review for the impact that radiologic diagnosis has on the surgical aspects and outcome in children undergoing cochlear implantation. Patients with severe inner ear malformations are expected to perform more poorly than patients with normal cochlea because of the likelihood of fewer spiral ganglion cells and the more complex surgery in malformed ears. Nevertheless, different types of electrode arrays have been introduced to improve the placement of device and ameliorate speech performance; in cases of cochlear ossification, the functional effects remain especially controversial. Predictors of good performance include the constellation of incomplete partition of cochlea: enlarged vestibular aqueduct (EVA), dilated vestibule (i.e. Mondini's malformation), isolated EVA and partial semicircular canal aplasia. Children with other cochlear dysmorphologies such as the common cavity or with associated pathologies like the CHARGE association and psychomotor retardation–developmental delay can have poor performance after implantation. Obtaining knowledge of cochlear malformation is especially important in counselling parents before implantation [19].

Hereditary hearing loss can be classified according to inheritance type, age at onset, audiological characters, vestibular phenotype and responsible genetic locus. As previously indicated, about 50% of cases of congenital SNHL can be linked to a genetic cause, with approximately 30% of these considered syndromic and the remaining 70% being non-syndromic. The term "syndromic" implies the presence of other distinctive clinical features in addition to hearing loss, and to date more than 400 syndromic forms of hearing loss have been described. In many syndromes, hearing loss is an inconstant feature, and a complete description of all syndromes associated with hearing loss is beyond the scope of the present review. In Table IV, the main syndromes with associated hearing loss are reported. Genetic hearing loss is a largely monogenic phenotype. Autosomal recessive transmission (DFNB) occurs in about 80% of cases and is typically prelingual, while autosomal dominant (DFNA) hearing loss accounts for about 15-18 % of cases and is very frequently postlingual [20]. X-linked (DFN) or mitochondrial inheritance is observed in the remaining cases [21 22]. An overall summary of mutations reported in 42 genes is shown in Figure 1. The number, mutation and loci of non-syndromic hearing loss are currently reported on the hereditary hearing loss home pages (e.g. http://hereditaryhearingloss.org and http://ghr.nlm.nih.gov).

Other causes of congenital acquired deafness, which are not hereditary in nature, are *prenatal causes* that include: infections, drugs and alcohol consumption by the mother during pregnancy, in utero infections (cytomegalovirus, rubella, syphilis, herpes, and toxoplasmosis), complications associated with Rh factor in blood, prematurity, maternal diabetes, anoxia and finally exposure to toxic substances during pregnancy (e.g. aminoglycoside, radiations, cisplatin). Because children can acquire hearing loss at any age, it is critical for practitioners to be aware of its warning signs, which may be either the inciting event of hearing loss or its manifestations. In Table V, the risk factors for SNHL are indicated for both early age and delayed onset [23]. Among the risk factors indicated by the Joint Committee on Infant Hearing (JCIH), it has been reported that 2-4% of neonates in a neonatal intensive cure unit (NICU) have significant bilateral hearing deficits. Changes in the types of therapeutic interventions and the characteristics of NICU population have resulted in increasing number of risk factors associated with deafness [24].

The *perinatal causes* of hearing loss include ototoxic medication, hyperbilirubinaemia, craniofacial anomalies, syndromes associated with SNHL, low birth weight (< 1500 g), low Apgar score, mechanical ventilation lasting for 5 days or longer, bacterial meningitis, endocranial haemorrhage, hypoxic ischaemic encephalopathy, convulsions, sepsis, administration of ototoxic drugs, ambient incubator noise and perinatal complications (e.g. hypoxia, acidosis). The relationship between birth weight and hearing loss is controversial. In general, infants with

Table IV. Classification of main genetic hearing loss related syndromes.

Transmission	Phenotype	Genes involved
GENETIC SYNDROMES		
Autosomal dominant	WAARDEBURG (2-5% of infant hearing loss) Sensorineural hearing loss, abnormal pigmentation of the skin and hair, dystopia canthorum, heterochromia iridis and pinched nose	Type I, PAX3 Type II, MITF
	BRANCHIO-OTO-RENAL SYNDROME (2% of infant hearing loss) Sensorineural or conductive hearing loss, cup-shaped pinnae, preauricular pits, branchial cleft fistulae and bilateral renal anomalies	-
	STICKLER SYNDROME Progressive sensorineural hearing loss with cleft palate, abnormal development of the epiphysis, vertebral abnormalities and osteoarthritis; myopathy, retinal detachment and vitreoretinal degeneration in Types 1 and 3.	Type I, COL2A1, Type II, COL11A1 Type III, COL11A2
	TREACHER COLLINS Microtia and malformed ears, midface hypoplasia, downslanting palpebral fissures, coloboma of outer 1/3 of lower eyelids, and micrognathia	Treacle
	NEUROFIBROMATOSIS TYPE II Sensorineural hypocusis with cafè-au-lait spots, meningiomas (intracranial and spinal), ependymomas, gliomas, presenile lens opacities, schwannomas (located in the cranial, spinal and peripheral nerves.)	NF2, SCH
Autosomal recessive	USHER SYNDROME (3-5% of infant hearing loss) Several subtypes based on severity of the deafness, vestibular dysfunction and the onset of retinitis pigmentosa (gradual retinal degeneration leading to decreased night vision, loss of peripheral vision, and blindness	Miosina VIIa (for Uscher Ib only)
	PENDRED SYNDROME Sensorineural hearing loss and abnormal iodine metabolism with euthyroid goitre sometimes detected at birth, but often not clinically evident until 8 years of age	SLC26A4 (PDS)
	JERVELL AND LANGE-NIELSEN SYNDROME Severe-profound hearing loss and prolongation of the QT interval	KVLQT1 KCNE1
X-linked	ALPORT SYNDROME Progressive sensorineural hearing loss in addition to renal disorders (glomerulonephritis, haematuria (and renal failure) and ocular abnormalities	COL4A5
Chromosomic condition (trisomia 21)	DOWN'S SYNDROME Every region of the head and neck can be affected. Hearing loss is usually conductive secondary to the chronic middle ear disease or to ossicular chain abnormalities. Other systems affected include cardiovascular, genitourinary, musculoskeletal and ocular	
CONGENITAL SYNDROME (Unknown cause)		
	GOLDENHAR'S SYNDROME (Oculo-auricolo-vertebral syndrome) Aberrant development of the first and second branchial arches with otologic manifestations include microtia/anotia, and hearing loss (conductive > sensorineural), cardiac abnormalities, ocular abnormalities, hemifacial microsomia and retinal abnormalities	

low birth weight often have several factors that may result in brain damage or hearing loss. There is a growing concern that the administration of aminoglycoside treatment in the noisy environment of the NICU may lead to hair-cell damage and subsequent auditory impairment [24].

Cytomegalovirus (CMV) is the most common congenital infection, and is the most common cause of nonhereditary congenital SNHL. However, perinatal CMV infections transmitted through human milk have been reported, and may be clinically relevant in extremely premature infants.

Symptoms can be detected at birth in 10-15% of the congenitally infected, of which 50-90% will develop sequelae, the most frequent being SNHL, visual defects, psychomotor impairment, mental retardation, cerebral palsy and seizures. Audiological outcomes for CMV infection are still controversial. It is known that children with asymptomatic congenital CMV infection can have late-onset and/or deterioration of SNHL during early childhood, which may not appear until months or years after birth. Although 20% of congenital CMV-infected infants with SNHL have been found to have bilateral hearing loss during the first 6 months of life, the rate of bilateral hearing loss increased to 40% during the first 3 years. However, the frequency of SNHL among infants with asymptomatic congenital CMV has been reported to range from 13 to 24%. In the literature, the rates of delayed-onset SNHL ranged from 11 to 18%, progressive SNHL in 23–62% of cases and improvement of SNHL were reported in 23-47% of these patients [25]. Infants who initially pass a newborn hearing screening test may present with profound hearing loss one year later [26]. Therefore, prolonged and closer follow-up of infected children is important, which should be prolonged until 6 years of age. Development of a CMV vaccine is thus considered to be a major public health priority. At this time, there is no available vaccine for prevention of congenital CMV disease, but a small number of clinical trials of candidate CMV vaccines has reported an efficacy against maternal infection of about 50-60%. The mechanisms by which CMV injures the foetus are complex, and likely include a combination of direct foetal injury induced by pathologic, virally-encoded gene products, an inability of the maternal immune response to control infection and the direct impact of infection on placental function. Notwithstanding, the pathogenesis of hearing loss remains unclear. A recent histopathological study of inner ear lesions in congenitally CMV-infected human foetuses revealed a degeneration of the stria vascularis and cochlear nerve, but CMV infection was not found in the spiral ganglia. In contrast, a diffuse inflammatory reaction was detected in the organ of Corti, cochlear nerve, spiral ganglia and eighth cranial nerve. It has also been demonstrated that endolymph secretion and potassium homeostasis are altered, which causes secondary degeneration of sensory structures [27 28]. There is growing evidence

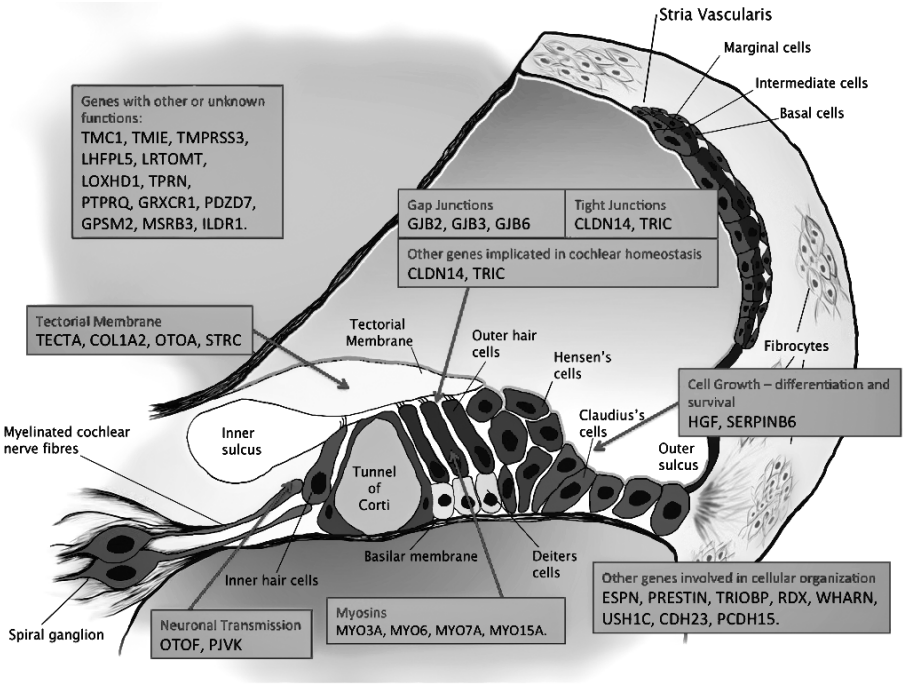


Fig. 1. An overall summary of 42 genes implicated in autosomal recessive hearing loss is presented according to proposed functions of protein products in hearing physiology.

Table V. Classification of risk factors for hearing loss in children by early or delayed onset.

Early onset	• Family history of permanent childhood hearing loss • Neonatal intensive care of more than 5 days • Assisted ventilation • Exposure to ototoxic medications (gentamycin and tobramycin) or loop diuretics (furosemide/Lasix) • Hyperbilirubinaemia that requires exchange transfusion • In utero infections (CMV, herpes, rubella, syphilis, and toxoplasmosis) • Syndromes associated with hearing loss • Craniofacial anomalies and temporal bone anomalies
Delayed onset	• Parental concern about hearing, speech, or developmental delay • In utero infections (CMV, Herpes) • Diagnosis of syndromes associated with hearing loss (neurofibromatosis, osteopetrosis, Usher syndrome, Waardeburg syndrome, Alport syndrome) • Neurodegenerative disorders or sensory motor neuropathies • Culture-positive postnatal infections including bacterial and viral meningitis • Head trauma, especially basal skull/temporal bone fracture • Chemotherapy

that newborns with symptomatic congenital CMV infection may benefit from treatment with either ganciclovir or valganciclovir, the most widely studied drugs in this setting. It is not yet clear if children with asymptomatic or pauci-symptomatic infection at birth would benefit from such treatment [29]. Although congenital CMV infection is a well-known cause of congenital SNHL, very little is known about the consequences of post-natally acquired CMV infections in immunocompetent hosts. Recently, we observed the presence of CMV DNA in the labyrinth fluids of a 15-month-old deaf boy who underwent a cochlear implant one month after a documented primary infection and after disappearance of viral DNA from the blood [30]. Further studies are needed to establish if CMV can cause SNHL when it is acquired post-natally in a normal hearing subject. Moreover, extending the analysis to viral proteins and to the specific serotype might help to shed light on how long and in which state – active or latent – CMV can persist in the cochlea.

Among the *postnatal causes* of hearing loss in this review, we focus our interest on childhood infections (e.g. meningitis and encephalitis), head trauma, noise exposure and ototoxic drugs for their incidence and sequelae. Each year, approximately 1.2 million cases of *bacterial meningitis* occur worldwide, leading to death in 135,000 cases. In the United States and Europe, acute bacterial meningitis is mainly caused by Streptococcus pneumoniae and Neisseria meningitidis. Long-term sequelae are a burden for approximately 50% of survivors from bacterial meningitis. Among these, hearing loss is very common, affecting 26% after meningitidis by Streptococcus pneumoniae, 5%-7% by Haemophilus influenzae and 10% by Neisseria. The severity of hearing impairment in bacterial meningitis can range from very mild to severe and even complete deafness. New insights into the pathology and pathophysiology of meningitis- associated hearing loss have come from animal models of bacterial meningitis. Bacteria reach the cochlea through the subarachnoid space into the cochlear aqueduct inducing a severe suppurative labyrinthitis. Reactive oxygen and nitrogen species, in particular peroxynitrite, seem to be among the crucial mediators of cochlear damage and hearing loss during meningitis. As a consequence of endostial inflammation, osteogenesis cause partial or total obliteration of the lumen progressing apically in the scala tympani, but ultimately involving all scalae from the base to apex [31]. In aggressive cases, total cochlear obliteration may be seen within a few weeks of the original infection. Because of rapid evolution of obliterative osteoneogenesis, early bilateral cochlear implantation for these children is essential and can present surgical problems. However, outcome is difficult to predict and acquisition of speech is possible. The presence of postmeningitic neurologic sequelae and number of active electrodes play a significant role in predicting outcome [32].

Trauma may cause both acquired CHL and SNHL. The forces involved in physical blows to the head may affect the tympanic membrane or ossicular chain. Temporal bone fractures, especially transverse fractures, may damage the cochlea and the facial nerve. All children presenting with signs of hearing loss after physical trauma should receive a full evaluation to determine the precise nature of the damage and plan interventions.

Noise exposure in children is an emerging issue in both Western and developing countries. Environmental noise and exposure to noise in an incubator affect newborns admitted to the NICU. All efforts need to be carried out to reduce noise emissions in this setting. In these children, acoustic trauma is particularly dangerous because it is usually associated with other risk factors for deafness including prematurity, hypoxia and ototoxicity [33].

Children and adolescents are exposed to noise every day in the form of MP3 players, toys, video games and other recreational activities. Such exposure can cause noise-induced hearing loss, tinnitus, hyperacusis and non-auditory effects including depression, anxiety, reduced cognition and poor psychosocial function. Hearing loss for high frequencies can also affect children's speech comprehension of the fricative sounds (e.g. f or s), which can lead to decreased speech discrimination for differentiation of words and overall performance in school. In a recent study, the reported prevalence of hearing loss is about 30% among adolescents aged 12-19 years old [34]. Prevention against noise emission in the NICU and environment may be aided through health education programmes to promote protective behaviours among adolescents, or through legislative measures to limit noise emissions. Recently, the European Commission has indicated that prevention of music and noise-induced hearing loss among children and adolescents is a priority for public health (http://ec.europa.eu/health/ph). In recent years, in our laboratory, the mechanisms and innovative strategy of protection against noise exposure as well as against exogenous factors (i.e. aminoglycosides and cisplatin) have been studied with the goal of developing a translational approach from basic research to clinical applications. Promising results have been obtained with antioxidant treatment, although only a small number of clinical trials have been performed [35-39].

Two major classes of drugs currently in clinical use can cause permanent hearing loss in children. *Aminoglycoside antibiotics* have a major role in the treatment of gram negative infections, tuberculosis and cystic fibrosis, and *platinum-based chemotherapeutic agents* (cisplatin, carboplatinum) are highly effective in the treatment of malignant disease. However, both damage the hair cells of the inner ear, resulting in functional deficits. The mechanisms underlying these troublesome side effects are thought to involve the production of reactive oxygen species in the cochlea, which can trigger cell-death pathways [40-42]. In addition, the A1555G mutation in mitochondrial 12S rRNA facilitates the binding of aminoglycosides and causes hearing loss. The prevalence of the A1555G muta-

tion has been shown to be between 20-30% in deaf individuals in Spain and Asia, of which 15% had a history of aminoglycoside ototoxicity. In Italy, the A1555G mutation is responsible for 5.4% of cases affected with isolated idiopathic sensorineural hearing impairment [42]. Genetic screening for the A1555G mutation is still laborious, and no cost-effective has been demonstrated; thus, the use of aminoglycosides should be limited to very severe infections. Finally, *cisplatin ototoxicity* ranges from 30-70% in paediatric patients. Gender and cumulative dose are important clinical biomarkers of cisplatin ototoxicity. Severity of ototoxicity may be inversely related to age at time of exposure. Furthermore, ototoxicity can have a late onset and risk of hearing loss increases in children undergoing to cranial radiation therapy. In fact, the median time to observation of permanent hearing loss as evaluated by the ASHA criteria is about 6 months. All childhood cancer survivors should undergo yearly evaluation with appropriate audiological evaluation. Patients who receive cranial irradiation are at risk for delayed onset hearing loss that may progress over a period of years, thus necessitating longer follow-up [43 44]. Pre-clinical data indicate that several antioxidants confer otoprotection without affecting cytotoxicity, whereas no confirmed benefit has yet been established for pharmacologic agents developed to prevent or reduce ototoxicity in children. Avoidance of excessively loud noise and ototoxic medications is therefore recommended in children [40 45].

Central auditory pathways diseases

In recent years, there has been an increasing interest in auditory processing in infants (central auditory disorder – CAD or central auditory processing disorders). *Auditory processing disorder (APD)* can be either developmental or acquired. It may result from ear infections, head injuries or neurodevelopmental delays, including those that affect processing of auditory information. In the majority of cases of developmental APD, the cause is unknown. One exception is *acquired epileptic aphasia or Landau-Kleffner syndrome* in which children between 5-7 years old develop an auditory verbal agnosia. There is increasing evidence that dysfunction during a sensitive period may have long-term consequences for auditory development. It should be kept in mind that the developing auditory cortex is highly plastic. As such, the cortex is both primed to mature normally and is at risk for reorganizing abnormally, depending upon numerous factors that determine central maturation.

From a clinical perspective, at least two major components of development can be manipulated: (1) input to the cortex and (2) timing of cortical input [46]. APDs can include problems of sound localization and lateralization, auditory discrimination, auditory pattern recognition, temporal integration, temporal discrimination (e.g., temporal gap detection), temporal ordering, temporal masking, auditory performance in competing acoustic signals and performance with degraded acoustic signals. In all these conditions, the auditory threshold can be either normal or slightly modified, while auditory perceptions are altered due to abnormal directional perception, reduced perception in noise leading to language development or understanding disorders. The problem may be exacerbated in unfavourable acoustic environments. It may or not be associated with difficulties in listening, speech understanding, language development and learning. In its pure form, however, it is conceptualized as a deficit in processing of auditory input. The diagnosis of APD is presently complicated because other types of childhood disorders may exhibit similar behaviours such as attention deficit hyperactivity disorder (ADHD), language impairment, reading disability, learning disability, autistic spectrum disorders and reduced intellectual functioning. Because of these complications, differential diagnosis of APDs requires the systematic acquisition of data that is sufficient to identify an auditory-specific perceptual deficit [47].

There are three possible approaches to the construction of a minimal test battery for APD in school children: (1) behavioural tests, (2) electrophysiologic and electroacoustic tests and (3) neuroimaging studies. A number of questionnaires have been used for screening, but there is a lack of consensus on how the ideal screening procedure should be structured and what tasks it should contain. Combined use of all procedures, in particular electrophysiological and behavioural tests, is needed to improve understanding of the mechanisms underlying the continuum of auditory, phonetic and linguistic processing, and the role of auditory processing in specific language disorders and in children with brain lesions and multisensorial impairment [48].

Auditory neuropathy (AN), recently included into the group of Auditory Neuropathy Spectrum Disorders (ANSDs), shares some analogies with APDs and defines a variety of peripheral disorders due to dys-synchrony of the auditory peripheral system [49 50]. The lesion can involve auditory nerve fibres (pre-synaptic AN), inner hair cells or the synapses interposed between axons and receptors (post-synaptic AN). The modification of the neural discharge frequency leads to the absence of ABR or desynchronization, and to verbal perception impairment that is more pronounced when there is competing noise. In contrast, cochlear microphonic potentials and oto-acoustic emissions are conserved due to outer hair cell preservation. Causes of ANSDs can be environmental, such as severe neonatal hyperbilirubinaemia (kernicterus), neonatal hypoxia or prematurity or genetic. In some cases, AN is just one of several clinical signs resulting from systemic neurodegenerative diseases (e.g. Charcot-Marie tooth peripheral neuropathy, Friedreich's ataxia, mitochondrial disorders). In other cases, it is an isolated entity [50].

Congenital forms interfere with language development, while in the acquired forms severe verbal perception

impairment or regression of linguistic ability can be observed. Mutations in the *OTOF* gene seem to be a major cause of isolated AN in many populations (DFNB9). The *OTOF* gene provides instructions for making a protein called otoferlin. This protein is present in the brain and the cochlea, where it aids in sound processing. Although the exact function of otoferlin is uncertain, it appears to be essential for normal hearing. Recently, different mutations of this gene have been described that confirm the role of the OTOF gene in auditory neuropathy. In the absence of a context of neurological syndrome, the combination of absent ABR and positive OAE responses should lead to a diagnosis of auditory neuropathy and to mutational screening in OTOF [51 52].

Clinical evaluation

Over the past two decades, substantial scientific effort and legislative activity has been directed towards lowering the age of diagnosis of paediatric hearing loss. Indeed, the introduction of universal newborn hearing screening programmes has opened a new era in the early detection of congenital hearing loss. Simultaneously, advances in neuroimaging and molecular genetics have led to a better understanding of the aetiology of paediatric SNHL. Diagnosis of hearing loss needs a multidisciplinary approach starting from audiological-otological, ophthalmological and genetic evaluations as recommended by the 2007 Joint Committee on Infant Hearing.

Universal newborn hearing screening

Two main approaches to screening for bilateral SNHL are introduced: risk factor screening and universal newborn hearing screening (UNHS). In a risk factor-screening programme, newborns with an identifiable risk factor are further screened as indicated by the JCIH (2007) (Table III). However, the correct identification of all at-risk newborns is very difficult to achieve in routine practice, and even when completely successful, risk factor screening programmes are unable to identify all newborns with permanent SNHL as 40% to 60% do not have identifiable risk factors. Universal newborn hearing screening (UNHS) is either recommended or already practiced and legally regulated (nationally or regionally) in many Western countries, e.g., Austria, Great Britain, France, USA, as well as in various countries in Asia. In Italy, it is been recently implemented in some regions.

UNHS programmes offer all newborns an automated hearing screen with the use of otoacoustic emissions (OAE), automated auditory brainstem responses (aABR) or both. In detail, the protocol for UNHS differs depending on whether a newborn baby is healthy or has been admitted to the NICU. For well born babies, a two step procedure is usually performed (TEOAEs/aABR); however, some variations to the protocol have been proposed that affect the timing and modality of screening. In our Hospital, UNHS is performed with the following protocol: TEOAE registration before discharge followed by a second TEOAEs registration at the first month of age and diagnostic auditory brainstem response (ABR) testing in those infants who did not meet TEOAE pass criteria and in those infants at high risk for hearing loss. Combined TEOAE/ABR is the gold standard for NICU infants who are at risk for auditory neuropathy/dyssynchrony. Positive second stage results are usually validated by combined otolaryngological and audiological consultation, diagnostic ABR testing and other electrophysiologic testing performed in a Tertiary Audiology Centre as early as the third month of age [53].

A recent paper by Papacharalampous et al. [54] demonstrated the benefits and limitations of universal newborn screening. These authors described that a total of 676,043 screened children were identified in 20 studies. The average initial referral rate in these studies was 3.89%, while the initial referral rate varied from 0.6 to 16.7%. In the literature, the most alarming problem in the screening procedure is the high rate of infants lost to follow-up, calculated to range from 3.7 to 65%. Despite significant success in lowering the age at which many children with hearing loss are identified, the cost effectiveness of UNHS is still controversial. The undesirable effects of UNHS include parental anxiety, particularly in those whose infants require follow-up testing and the high rate of lost-to-follow-up infants. The expertise of the team and organization, as well as providing correct information to parents, can reduce these effects. Progressive or late-onset hearing impairment seen with congenital CMV infection or in some inherited conditions, is also not detected by a newborn screening programme. The costs of screening vary according to the region from about $10 to $24 per infant, depending on the selected protocol and technology. Without UNHS, infants with hearing loss are typically identified with an established language delay. Although the most recent guidelines outlined in the JCIH (2007) [7] position statement recommend monitoring for post-natal hearing loss, there is significant evidence that with a screening programme implementation, diagnosis and intervention occur earlier and lead to improvement in language outcomes [55].

Audiological assessment

Audiologic evaluation of infants and young children includes a thorough case history, otoscopy, and behavioural and neurophysiologic measures. As generally recommended, the audiologic evaluation process must use a battery of tests, which should be adapted to be developmentally appropriate. Methods for diagnosis and characterization of hearing loss for all age groups, general applications and disadvantages are reported in Table VI. As indicated by the American Speech-Language-Hearing

Table VI. Testing methods for diagnosis: objective and subjective diagnostic procedures are summarized by appropriate age, method, clinical application and main disadvantages.

Test	Age	Method	Clinical applications	Disadvantages
Objective tests				
Otoacustic emissions	Since the second or third day of life	It is an acoustic phenomenon that can be measured in the ear canal; it is related to electromotive activity of the outer hair cells of the cochlea, and to re-amplification of the middle ear	• First option test for newborn hearing screening (low cost, fast execution, reliability and validity) • Useful to assess cochlear function when the auditory evoked response are absent (retrocochlear hearing loss)	• No responses obtained in presence of middle ear disease and hearing loss exceeding 30-40 dB • Information only about the normal function of the outer hair cells, but not the type or level of hearing loss • Narrow frequency range studied (1-3 kHz) • Technical limits (positioning the probe, cue obstruction, noise)
Auditory Brain-Stem Evoked Response (ABR)	Infants of 26 weeks gestational age (when myelination begins). This assessment should take place by the age of about 3 months. After 12-18 months, morphology and parameters are similar to those of adults	This type of auditory evoked potentials is a series of five to seven peaks arising from auditory nerve and brainstem structures occurring within 10 msec of the onset of a moderate -intensity click stimulus	• Gold standard for screening of infants with audiological high risk (high reliability, low cost) • Objective estimation of hearing thresholds • Comfortable examination conditions (spontaneous sleep, sedation) • Useful tool in non-cooperative children • Allows differential diagnosis between cochlear and retrocochlear pathologies	• Threshold evaluations (no more than 80-90 dB) restricted to frequencies between 1 and 4 kHz (spectral content of click) • Too small amplitude of Wave I from the auditory nerve • Disorders above the inferior colliculus not identifiable • Caution in the definitive diagnosis of hearing loss in newborns because of the variability of neural maturational processes • Difficult interpretation of responses in children with middle ear effusion
Auditory Steady-State Response	All ages	The ASSR are evoked by continuous tones (carriers) modulated in frequency and / or in amplitude. The response is given by a complex wave linked by a definite phase relationship to the stimulus	• Conjugation between high-intensity sound stimulation and frequential specificity • Reconstruction of a reliable hearing threshold using tonal stimuli • Increased correlation with medium-low frequencies	• Results affected by sleep-wake rhythm, movements of patient and administration of drugs
Electro Cochleography	All ages	Echocochleography studies the electrical responses generated by the cochlea following a massive sound stimulus Evoked potentials are recorded from electrodes placed in or near the cochlea.	• Second option after ABR in the estimation of hearing threshold (high reliability) • Better characterization of hearing loss compared to ABR • Enhancing Wave I of the ABR • Useful in cases of hearing loss with uncertain ABR response or no response	• Invasive method that requires surgery and general anaesthesia • Audiological evaluations restricted to the periphery and frequencies of 1-4 kHz • High cost
Tympanometry	All ages	Test measures in terms of compliance the effects of changes in air pressure on the eardrum-ossicular system	• Non-invasive method that requires no active participation by the patient (easy execution) • Useful to detect middle ear disease especially in children	• Under 6 months of life lower sensitivity of the method for increased distensibility of ear canal • Additional tests are required (otoscopy, reflexes, tone audiometry) for an accurate definition of hearing loss
Acoustic Reflex	All ages	This test refers to the reflexive contraction of the intratympanic muscles resulting from high intensity sound stimulation	• Useful in childhood hearing loss for the evaluation of middle ear function • Assists in the diagnosis of neurological diseases	• Despite numerous attempts, does not identify hearing threshold • Additional tests are required

continues

Table VI. *Follows.*

Subjective tests				
CRIB-O-GRAM	0-6 months	It is based on observation of alarm, postural and psychoemotive reactions after sound stimulus	• Useful preliminary test in infants	• Non-specific evaluation of side • Inter-individual variability • Useful when combined with other tests • Often mistaken interpretation of infant's reactions
Boel-test	6-12 months	This test evaluates unconditioned reflex of gaze direction after sound stimulation	• Multifunctional test that combines visual to sound stimuli	• Non-definitive method that requires additional diagnostic tests
Behavioural Observation Audiometry (BOA)	> 6 months	Relies on the observation of positive or negative behavioural responses of orientation and location of a sound in free field	• BOA can provide useful insight into the quality of the child's auditory responsiveness • The test can predict an audiometric curve which is useful in planning intervention	• Operant discrimination procedure • Behavioural responses to sound may not provide an exact auditory threshold
Visual Reinforcement Audiometry (VRA)	1-3 years	In VRA, conditioned head turns are reinforced by an attractive visual stimulus that is activated near the source of the sound that is presented	• Test that measures binaural hearing thresholds in free field	• Variability in responses due to several factors (age, conditioning of the child, emotional stress caused by environment, technical staff)
Conditioned Play Audiometry (train show, peep show)	2-5 years	Operant conditioning of behavioural responses to sound is an effective approach for older children, with change in response behaviour and in the reinforcement that is used. In this test children learn to engage in an activity each time they hear the test signal.	• Provides a complete hearing test with binaural air and bone threshold and can guide diagnosis	• Variability in responses due to several factors (age, conditioning of the child, emotional stress caused by environment, technical staff)

Association (ASHA, website: http://www.asha.org), audiological assessment for children is designed to: a) determine the status of the auditory mechanism; b) identify the type, degree and configuration of hearing loss for each ear; c) characterize associated disability and potentially debilitating conditions; d) assess the ability to use auditory information in a meaningful way (functional hearing); e) identify individual risk factors and the need for surveillance of late-onset or progressive hearing loss; f) assess candidacy for sensory devices (e.g., hearing aids and cochlear implants). Accurate audiological diagnosis is the basis for an appropriate and early rehabilitation of hearing loss in infants [56].

Neuroimaging

Imaging has come to play an important role in the evaluation of children with hearing loss to assess the anatomy of the middle and inner ears, identify causes of hearing loss and provide prognostic information on potential treatments. The goal standard in imaging for *children* is still controversial. Cochlear malformations have been reported to occur in approximately 20% of children with congenital SNHL. In evaluating children with unexplained SNHL, radiologic studies such as high-resolution computed tomography (CT) and magnetic resonance imaging (MRI) have made it possible to identify a specific cause of auditory impairment.

In general, CT is reserved for the following cases: skull base and inner ear trauma, inner ear bony dysplasia and large vestibular aqueduct syndrome, but it is also indicated in inner ear obstruction to determine whether the process is fibrous or osseous, define the anatomy of the facial nerve, evaluate if the internal auditory canal (IAC) is narrow and if there is a conductive component to the hearing loss, and determine the integrity of the ossicular chain and inflammatory pathologies including cholesteatoma [57]. On the other hand, high-resolution MRI provides excellent resolution of the membranous labyrinth, and lesions of the central auditory pathway in the internal auditory canal, cerebellopontine angle, brainstem and cerebral cortex [58]. Neuroimaging is mandatory in the evaluation of children who are candidates for cochlear implant in order to plan surgery and to predict outcomes. Several relative or absolute contraindications to cochlear implant can be detected by imaging. Cochlear nerve deficiency represents an absolute contraindication to a cochlear implant. Commonly, cochlear nerve aplasia has been associated with narrowing of the inner auditory canal that can be identified by CT. By improving neuroimaging techniques, an increasing percentage of

congenital SNHL has been associated with cochlear malformations. Children with milder inner ear malformations (e.g., vestibular aqueduct enlargement, incomplete partition type II and partial semi-circular canal dysplasias) have better speech performance following cochlear implantation than children with severe malformations (e.g. common cavity or cochlear hypoplasia) or syndromes such as CHARGE syndrome. A number of syndromes are associated with the inner ear malformations that can be detected by neuroimaging, although in some cases no malformations are found (Table VII) [59]. An enlarged vestibular aqueduct has been associated with non-syndromic hearing loss when mutation on chromosome7q31 is present, which is the same gene responsible for Pendred syndrome [60]. Among other aetiologies of acquired congenital hearing loss, congenital CMV is rarely associated with ear malformation but brain abnormalities have been diagnosed in about 80% of deaf children. Labyrinthitis is associated with several conditions, as in meningitis, and is characterized by 3 stages: inflammation, fibrosis and ossification. The fibrosis can be diagnosed by MRI as a loss of normal fluid signal intensity in the membranous labyrinth. However, in the ossifying stage of labyrinthitis cochlear ossification can be distinguished by CT scanning better than with MRI [59].

Table VII. Syndromes associated with SNHL having radiological signs.

Uncommon imaging features	• Alport syndrome • Jervell and Lange-Nielsen syndrome • Stickler syndrome • Usher syndrome
Major or frequent imaging features	• Branchio-oto-renal syndrome • Pendred syndrome • Waardenburg syndrome • CHARGE syndrome

Genetic Hearing Loss Assessment

Major advances in genetics have recently allowed for rapid determination of the genetic origins of deafness in a large number of cases. Diagnosis of genetic hearing loss depends on correlation of genotype, which manifests a particular set of genes and phenotype that represents the organism's observed properties. Additionally, phenotype depends on both inheritance and environmental factors. Syndromic deafness can be diagnosed by associated clinical findings and by family and patient history, physical exam, laboratory tests and imaging to detect syndromic hearing loss. Usually, only one or a few candidate genes are responsible for each syndrome. However, it is very difficult to determine candidate genes for non-syndromic hearing loss, and is often impossible because of the large number of causative genes leading to a relatively undistinguishable phenotype. Based on the outcome of the evaluation, other types of professional expertise may also be needed, especially with syndromal hearing loss (e.g. ophthalmology, cardiology, nephrology, neurology) as in-

Table VIII. General battery of tests suitable for a proper diagnostic approach.

Test	Reason for test	Possible consequences if missed
History	Illness, trauma, drugs	Depends on what missed
High-resolution CT	Anatomical abnormalities	SNHL progression, other diagnosis
MRI	Anatomical abnormalities	SNHL progression, other diagnosis
TORCH titres	Congenital infection	No possible treatment
Electrocardiogram	Long QT interval	Sudden death (Jervell and Lange-Nielsen)
Complete blood cell count	Anaemia	Depends on anaemia type
Urinalysis	Haematuria, Proteinuria	Renal failure, Alport syndrome
Antinuclear antibody, sedimentation rate (eventually Western Blot)	Autoimmune diseases	Depends on diagnosis
BUN and creatinine levels	Elevate levels	Renal failure, Alport syndrome
Fluorescent treponema antibody	Syphilis	No possible treatment
Glucose level	Diabetes	High
Thyroid function test	Hypothyroid	High
Perchlorate test	Pendred syndrome	Depends
Liver function tests	Liver abnormalities	Depends
Connexin 26	Genetic hearing loss	Aetiological diagnosis
Genetics consultation	Others genetic hearing loss	Aetiological diagnosis Long-term prognosis
Neurology evaluation	Associated diseases	Educational consequences
Ophthalmology evaluation	Retinitis pigmentosa, others	Double handicap (Usher syndrome)

dicated in Table VIII. If a form of syndromic deafness is suspected, gene-specific mutational screening can be obtained in many cases, and a growing number of genes can currently be identified. However, if non-syndromic deafness is suspected, CMV testing should be performed; if the pedigree suggests autosomal dominant or recessive or mitochondrial DNA inheritance, the candidate gene can be studied as indicated in Table IX [61].

The identification of a small number of genes that frequently underlie non-syndromic forms of deafness, despite the extreme phenotypic heterogeneity of these forms, has significantly improved the possibility of genetic diagnosis. Firstly, the connexion 26 (Cx26) gene has been found in about 50% of all cases of prelingual, autosomal recessive hereditary hearing loss. Moreover, one particular Cx26 mutation, 35delG, represents 70% of all Cx26 mutations although more than 100 mutations have been described. Today, GJB2 represents the most widely studied gene at the epidemiological, genetic and biochemical levels because of the high frequency of mutations, the small length of the gene and the ease of sequencing DNA. However, correlation between genotype and phenotype remains controversial due to the high variability of hearing loss in the same genotype described [52 62 63]. In recent years, other genes for different connexins have been mapped. In particular, a deletion in the *GJB6* gene (associated with Connexin 30) has been described as the second most frequent mutation in prelingual deafness, suggesting that mutations in the complex locus that contains *GJB2* and *GJB6* genes can result in a monogenic or digenic pattern of inheritance in this type of hearing loss [64].

Secondly, mutation in the mitochondrial 12S rRNA gene, A1555G, has been shown to underlie both an isolated form of sensorineural deafness and deafness induced by aminoglycoside treatment, and occurs relatively frequently. Variability in clinical findings may be due to the presence of variable numbers of mitochondria containing mutations in different tissues of the body (heteroplasmy) [22]. Further studies are needed to confirm the role of these mutations in susceptibility to hearing loss induced by exogenous factors (i.e. noise exposure) and aging.

The most common form of syndromic hereditary SNHL is Pendred syndrome, which is characterized by SNHL, bilateral dilatation of vestibular aqueduct with or without cochlear hypoplasia and goitre. Pendrin is a protein that is located in the inner ear and thyroid gland, encoded by the SLC24A4 gene. It is a transmembrane protein and a member of the solute carrier family, a group of anion transporter-related proteins that includes prestin, an inner ear protein (65), along with other proteins. Mutations in this gene justify not only a recessive non-syndromic deafness, but also a syndromic pathology. In some cases, clinical diagnosis plays a pivotal role because genetic tests are only rarely available as a clinical test mainly due to the extremely high cost. For example, mutations in COL4A3, COL4A4, COL4A5, and MYH9 are known causes of Alport syndrome; however, renal biopsy and/or skin biopsy are currently necessary for diagnosis, and gene testing is very costly and not routinely performed [4 61].

With remarkable advances in genetics, and increases of sensitivity and specificity and decreases of costs for genetic analysis are projected, in the future an increasing number of genes can be tested. In the future, the genetic screening could be applied with the possibility to perform prenatal diagnosis. However, this perspective opens to ethical issues that need to be considered. The early identification of hearing loss provides information for adequate planning of clinical follow-up, including fitting of hearing aids and candidate children for cochlear implants. Additionally, prevention of deafness should include avoiding specific drugs or specific activities in genetically-susceptible patients, such as those with the A1555G mitochondrial mutation who must avoid the risk of aminoglycoside ototoxicity or acoustic trauma [61]. Finally, a negative mutation screen must not be taken to mean that the deafness is

Table IX. Systematic genetic tests for deafness.

SNHL features (onset age)	Causative mutations
Bilateral SNHL by appropriate hearing tests (0-15 years)	GJB2
Bilateral SNHL by appropriate hearing tests (0-50 years)	A1555G&A3243G mitochondrial DNA
Monoallelic pathological GJB2 mutation (0-15 years)	GJB3, GJB6
Auditory neuropathy by OAE and ABR (0-4 years)	OTOF
Enlarged vestibular aqueduct by ear CT (0-50 years)	SLC26A4
SNHL at low frequencies (0-30 years) Dominant, mild-moderate	WFS1 exon 8
SNHL at middle frequencies (0-20 years) Dominant, mild-moderate	TECTA ZP domain
SNHL at middle frequencies (0-4 years) Recessive, severe	TECTA
SNHL at high frequencies (0-40 years) Progressive, dominant, mild-severe	KCNQ4 pore region
Rapidly progressive, recessive (5-15 years)	TEMPRSS3 exon 4-12
Progressive, dominant, mild-severe (30-50 years) Balance disorder	COCH LCCL domain
Maternal inheritance, progressive HL, mild-severe (0-50 years)	12S rRNA; tRNA Ser (UCN) tRNA Leu(UUR); tRNA Lys tRNA Glu

not genetic. Identification of genetic causes provides a key to understand the mechanism of hearing loss, leads to better management of hearing loss, facilitates functional recovery by effective rehabilitation and improves compliance of parents who can be informed with regards to diagnosis.

Strategy of deafness identification

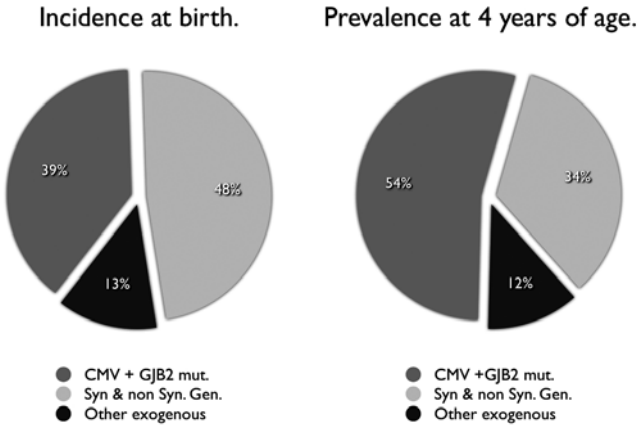
Early identification and appropriate treatment of hearing loss in infants is critical for normal child development. In addition, early detection of hearing loss and early use of hearing aids or cochlear implants are critical for the development of speech, language and communication skills in children with hearing loss. It is well known the goals of the *Healthy People 2010* indicate that all deaf children should have audiological evaluation within 3 months and should be enrolled in appropriate intervention services within 6 months. Traditionally, targeted surveillance has been proposed by the Joint Committee on Infant Hearing (JCIH) as the primary method to identify congenital hearing loss and monitor children with risk indicators associated with congenital and delayed-onset/acquired/progressive hearing loss (Table IX) [7].

The most recent guidelines, outlined in the JCIH (2007) Position Statement, made significant amendments to the 2000 statement and recommend monitoring at-risk children at 6-month intervals, placing an extraordinary burden on both families and audiology services. In fact, any child who presents with one of these risk factors should receive at least one diagnostic audiological evaluation within 24 to 30 months of age (JCIH 2007) [7]. In addition to risk-factor monitoring, it is recommended that the family doctor monitor all children for developmental milestones, auditory skills, and caregiver and parent concerns about the child's speech and language abilities [7]. Therefore, a long term screening for postnatal hearing loss has been suggested [7].

There is sufficient evidence that infants who are included in UNHS programmes are identified earlier and receive earlier intervention. Although several issues such as the feasibility of screening, the optimal technology for screening, the personnel that should be performing the screening and cost-effectiveness are still a matter of discussion [53]. In addition there is a cautious optimism on the possibility that emerging technologies including genetic and viral diagnostic tools (i.e. DNA mapping and PCR assay) can lead to aetiological diagnosis.

The advent of rubella vaccine in 1969, and more recently a vaccination programme for Haemophilus influenza type B, have dramatically decreased the frequency of infectious causes of SNHL. However, current guidelines recommend a comprehensive approach including imaging studies, GJB2 and GJB6 testing, developmental and ophthalmological evaluations, ECG, thyroid function tests, glucose, serology for syphilis, viral serology for CMV (or TORCH) and urinalysis in all children with severe to profound bilateral hearing loss. Table IX summarizes the tests to consider in evaluation of SNHL in children. Because of high costs, extensive testing of all patients should be avoided and diagnostic tests should be tailored to each patient depending on the physician's expertise [4]. Interestingly, Morton and Nance (2006) described the epidemiological features in newborns and infants (Table X) [66]. Namely, CMV infection and GjB2 mutation in newborn and infants represent about 40 % and 50%, respectively, of all SHNL, and summarizing all genetic causes and CMV infection more than 80% of SHNL are further included. These data confirm that at present, CX26 mapping are strongly recommended when associated with genetic counselling and CMV serology [66].

Table X. Incidence and prevalence of aetiologic factors by group age.



Neuroplasticity and consequences of hearing deprivation

In contrast to the cochlea, which is mature by 26 weeks of gestation, the auditory cortex is immature at birth and is highly plastic during the developmental period. Auditory cortex plasticity refers to a dynamic process by which changes in synapses, neurons and neuronal networks depend on behavioural, environmental or neural processes, in addition to injury. The expression of neuronal plasticity increases from the cochlea to the cortex. Plasticity is based in part on changes in synaptic function (synaptic plasticity), on changes in synchronization in neuronal networks and on changes in inter-neuronal connection patterns within neuronal networks [1].

Two different developmental phases of cerebral cortex can be differentiated: the first is synaptogenesis, which is independent on inputs (i.e. depends on genetic patrimony) and is completed during intrauterine life. This phase terminates when the thalamic afferents reach the cerebral cortex. The second phase is driven by sensory afferents that remodel synapses by increasing synaptic connectivity and excitatory synapses. According to Hebb's law,

synchronous activation of neurons pre-and post-synaptic induces a strengthening of connections, while activation in "phase" tends to reduce their effectiveness. Therefore, developmental plasticity refers to changes of neuronal function evoked by sensory stimulation, and auditory perceptions are referred to auditory events. In the developing auditory system, the sound experience leads to the organization of tonotopic maps. Consequently, auditory experience has a shaping influence on the functional maturation of the auditory system [67].

On the basis of the ability to differentiate sounds, children learn to abstract stimuli by learning to "recognize" a phoneme, and then the word and background noise. Taken together, data confirm that language development is based on the interaction with the sound environment and linguistic input. It has been recognized that there is a "sensitive" period in which neural systems are particularly responsive to relevant stimuli, and which are more susceptible to change when stimulated. Sensitive periods have more flexible onsets and offsets, and appear to be strongly influenced by experience. The concept of a sensitive period must be defined in relation to the concept of a "critical" period in which behaviours and their neural substrates do not develop normally if appropriate stimulation is not received within a restricted period of time [68]. The critical period has relatively rapid onset and offset, and appear to be largely under endogenous or genetic control. Studies of congenitally deaf children who later receive cochlear implants show that they never develop normal cortical responses to auditory stimuli if implantation occurs after a critical window around age 3-4 years [69-71].

After this critical period, the re-organizational capacity of the auditory system is reduced, the neural network consolidates and its modifications rarely occur. Peripheral damage affects significantly auditory brainstem nerve pathways. Large population studies in congenitally deaf children have shown that these children benefit most when cochlear implantation takes place within the first 3.5 years of life, when the central auditory pathways show maximal plasticity. The latency of the P1 component of the cortical auditory evoked potential (considered a biomarker of cortical maturation) decreases rapidly, and reaches the normal age range in children who receive an implant before 3.5 years of age. In contrast, children who receive implants after the age of 7 years show abnormal cortical responses, even after many years of cochlear implant use [72-74].

At the cortical level it is always true that one "uses it or loses it". Deafferentation leads to a reduced development in both volumetric and organization (hierarchic and functional) of the auditory cortex [67]. Accordantly, cortical development continues after birth, and the auditory cortical system develops until 4 years of age and completes maturation in adulthood. Auditory perception and sound discrimination are innate, while the child acquires senso-motorial, perceptive and cognitive abilities until two years. If the auditory input is deficient, verbal perception cannot be developed [69]. On the other hand, at the cortical level cross-modal interaction between different sensorial areas is established. If the auditory input is deficient, multi-modal interactions are modified leading to language and cognitive disorders.

Auditory sensorial deprivation during the acquisition of native language does not allow the development of the complex neural mechanism based on the synchronization and connections between different cortical areas. Finally, the top-down control of the associative cortex on the primary auditory cortex has not been determined [75]. It has been demonstrated that deaf signers of American Sign Language (ASL) shows extensive activation of homologous areas within the right hemisphere, indicating that the specific processing requirements of language may also, in part, determine the organization of language systems of the brain and support the hypothesis that delayed and/or imperfect acquisition of language leads to an anomalous pattern of brain organization for that language. In such patients, the auditory performances remain lower even after CI [76 77].

In conclusion, during auditory deprivation the plastic capacity of the auditory system shows two different appearances. The first, less important, concerns the ability of auditory perception in the primary auditory cortex to restore the tonotopic organization when sensorial input is resumed. The second, more defined and limited temporally, is related to the multi-modal cortical organization, which leads to auditory system efficiency about language perception as shown by PET and MRI. Taken together, studies in neuroplasticity and in children fitted with cochlear implants have established the existence of, and the time limits for, a sensitive period for cochlear implantation. The optimal time for cochlear implantation is under 2 years of life when central auditory pathways show the maximum plasticity to sound stimulation [1 73 78].

Therapy

Early treatment of hearing loss can allow many infants to develop normal language skills. Treatment of CHL including *acute otitis media* is still discussed and an extensive literature has been produced. Briefly, recent guidelines indicate amoxicillin–clavulanate and ceftriaxone as the most effective antibiotics against penicillin-resistant pneumococcus and β-lactamase producing bacteria. Immunization with the pneumococcal conjugate vaccine and influenzae vaccine appears to decrease the frequency of acute otitis media. Other medical and surgical treatment including the use of systemic or topical decongestants and the administration of steroids or antihistamines is not indicated. Myringotomy and tympanocentesis or insertion of tympanic tube and adeneoidectomy and/or tonsillectomy are recommended in treatment of otitis media effusive;

however, appropriate selection of patients and surgical approaches are still controversial. Finally, surgical management for complication of otitis media and treatment of chronic otitis media and cholesteatoma can be performed with several surgical options and are widely discussed in the literature [12 17 21 79 80].

Therapy remains the major challenge in paediatric management of SNHL. Current approaches are represented by hearing aids and cochlear implants, although recent advances in human genomics and molecular biology have led to the identification of mechanisms and defective genes causing deafness, which represent novel putative therapeutic targets. This review addresses an overview on the main findings of treatment of SNHL.

Conventional hearing aids

As a result of newborn hearing screening programmes, deaf infants are identified at earlier ages and usually receive amplification devices between 3-6 months of age or even earlier [7]. Conventional hearing aids are indicated in children with moderate to severe hearing loss inducing delayed speech or articulation disorders. Throughout the world, there are considerable variation in practices in the management of children with mild and unilateral hearing losses. Few studies have systematically addressed the effectiveness of hearing devices (hearing aids or frequency modulation [FM] system) in the treatment of this population. In several states in the USA, such as the state of Colorado, amplification is provided for children with these hearing losses. In contrast, in the United Kingdom the target disorders include moderate to profound bilateral hearing loss [81 82]. Consistent with our experience the amplification in children with mild hearing loss should be carefully considered in cases of multiple handicaps and/or syndromic children (i.e. visual impairment, mental deficiency) having permanent CHL or SNHL. Indication for hearing aids in children with bilateral severe SNHL is also discussed in relation to the cochlear implant and depends on the benefits of amplification. However, all children with severe to profound hearing loss should be considered for cochlear implantation. The decision should be make also with family and parental counselling is recommended in these cases. Commonly, the effectiveness of conventional hearing aids depends on the degree and configuration of hearing loss. The prescription is a crucial component of intervention because the benefit of amplification can be achieved by consistent and appropriate hearing aid use. Modern hearing aids are digital, which means that the analogue signal picked up by the microphone is converted to digital form before being amplified or otherwise processed in order to best meet the needs of the hearing aid user. While some receivers require the digitally processed sound to be converted back into an analogue signal before delivering the sound to the ear, others produce the analogue signal directly from the digitally processed sound. The use of digital technology makes it possible to combine many special features into the rather small hearing instruments. This is achieved through very complex signal processing schemes. Several types of hearing aids are available; the appropriate type depends on the child's individual needs and skills. The behind-the-ear (BTE) hearing aid is commonly recommended for infants and young children. BTE instruments are suitable for all degrees of hearing loss. They can usually be easily connected to an FM system so they are ideal for children in school. Children have special needs because they have smaller ears than adults, they have limited ability to provide behavioural/verbal responses to stimuli in a reliable manner, and they rely on amplification to develop speech and language and to acquire knowledge of the world around them. Therefore, amplification in children requires careful evaluation, both in selecting technology and in fitting hearing aids. Current hearing aids offer a variety of sophisticated technologies including compression, wireless transmission, directional microphones, feedback management, noise reduction and frequency suppression. However, in younger children the application of these methods can be extremely complicated and some features can be implemented in older children. Furthermore, the hearing aids fitting has become increasingly complicated with many styles and parameters to choose from. These concerns have been discussed in detail in the specific literature. Among the prescriptive algorithms the National Acoustic Laboratories of Australia introduced the NAL-NAL1 and -NL2, a threshold-based procedures, that prescribe gain-frequency responses for different input levels, or the compression ratios at different frequencies, in wide dynamic range compression hearing aids. The aim remains to maximize speech intelligibility for any input level of speech above the compression threshold, while keeping the overall loudness of speech at or below normal overall loudness. In the very early stage, fitting is mainly based on hearing thresholds obtained by ABR and Acoustic reflex, even if further information can be obtained by behavioural observation. Effectiveness of amplification for young children is best determined by evaluating aided performance using subjective reports and objective electrophysiological measures depending by the child's age *(www.nal.gov.au*). Only a small number of papers have reported the outcome of hearing amplification, but more recent guidelines stress the importance of establishing parent-professional partnerships and training related to fitting processes. The main issues of amplification include proper positioning/wearing of the device, adjustment of controls and use of special features. The evaluation of prosthetic gain is critical in the management of the deaf child and depends on the technical expertise and both parent and teacher collaboration. The outcome measures include labora-

tory evaluations as well as information about real world intelligibility that can be obtained by patents, teachers, auditory-verbal therapist and caregivers. Monitoring of communication skill development plays a key role in the decision to pass from hearing aids to cochlear implant in children that have reduced performances.

Bone-anchored hearing device (BAHD)

The principle of a bone-anchored hearing aid (BAHA) is based on sound conduction through bone via a percutaneous osseointegrated implant. In the paediatric population, the indications for BAHA include congenital aural atresia and microtia, and unilateral profound and mixed hearing loss. BAHA has also been used in children with chronic suppurative otitis media, chronic otitis externa and traumatic ossicular chain disruption after failure with conventional aids [83]. The most common devise is Cochlear™ BAHA® which is available since 1987. In the BAHA, a titanium prosthesis is surgically embedded into the skull with a small abutment exposed outside the skin. A sound processor sits on this abutment and transmits sound vibrations to the titanium implant. Similarly, Oticon Medical™ has introduced Ponto® which is a bone-anchored hearing aid system. In traditional two-stage surgery, the fixture is inserted in the skull at the first stage. After a period of time to allow for osseointegration, the second stage is comprised of a skin graft, soft tissue reduction and abutment placement. However, recently a one stage surgery has been suggested also in children. One major complication in paediatric BAHA is the soft tissue reaction. In order to reduce this side effect, the Sophono™ has been recently introduced which uses a metal disc to magnetically couple to the internal component that delivers auditory stimulation through closed skin. The benefits of BAHD in congenital aural atresia and microtia are well documented. In a recent investigation, Marsella et al. described that the main indications for BAHA are a minimum age of 3 years at the time of implantation and/or cortical bone thickness ≥ 3 mm as documented by CT [84]. These authors studied 47 children affected by ear dysplasia that was syndromic or not, and in agreement with other reports [85], they showed that functional gain was significantly better with BAHA compared to conventional bone-conduction hearing aids. Moreover, BAHA may also be indicated in children with profound unilateral hearing loss following a trial period wearing a BAHA headband for several weeks with the child's active participation. Finally, sequential bilateral implantation requires complementary investigations and appears to provide improved perception in noise. In conclusion, this type of hearing aid provides an improvement in the quality of life of children, which should be further improved as a result of recent technical developments.

Implantable middle-ear devices

These devices stimulate the ossicles and improve comfort by allowing the ear canal to remain open and not occluded. Currently, implantable middle-ear devices are indicated for patients aged 18 years or older, as an alternative to conventional hearing aids for individuals who are either unable to wear hearing aids or reject them for a variety of reasons [86]. Several devices have been introduced (i.e. Carina®, Vibrant Soundbridge®, Envoy®: which is first totally implantable system), but functional results are still controversial as only a very small number of cases have been reported. Most current devices are designed for patients with mild-to-severe SNHL. Patients with severe SNHL often have difficulty with feedback because of the amount of gain required.

Cochlear Implants

The first paediatric cochlear implant programme was established at the House Ear Institute in 1980. Currently, more than 80,000 children are CI recipients worldwide produced a real revolution in the treatment of severe-to-profound bilateral SNHL, being the most effective way to correct a severe acoustic damage not amendable with conventional hearing aids. A CI is essentially composed of two components: the first, an external or sound processor, collects and processes environmental sounds and sends them to the second component, the implanted part, through which it conveys the stimulus directly to nerve fibres in the form of electrical signals, bypassing the no longer functioning cochlear receptors.

Indications for cochlear implantation are constantly changing and are influenced by developments in technology, disease knowledge and experience of the physicians involved. The Guidelines adopted by most European centres are those issued by the National Institute for Health and Clinical Excellence (NICE, UK, 2009) [87]. In this report, the unilateral CI is recommended for children with severe-to-profound hearing loss, defined as a hearing threshold higher than 90 dB HL at frequencies of 2-4 kHz without hearing aids, and without an adequate benefit from hearing aids, defined for children as no achievement of speech, language and listening skills appropriate for age, developmental stage and cognitive abilities. As part of the assessment, children should also have had a valid trial with a conventional hearing aid for at least 3 months. The timing for surgery is still controversial: in the US, the FDA requires waiting until the child is one year of age, while NICE does not establish a lower limit of age. According to the literature, the age limit below which the CI guarantees the development of language skills and understanding closer to those of normal hearing subjects is around 18 months of age [1 88-90].

Bimodal stimulation is the use of both electrical stimulation through the CI in one ear and acoustic stimulation via conventional hearing aids in the non-implanted ear. This possibility is allowed by the presence of residual hearing in the contralateral ear. The benefits of bimodal stimula-

tion compared to the use of the CI alone are represented by better speech perception in quiet and in the presence of background noise, as well as better spatial localization and overall improvement of sound quality [91]. The use of a hearing aid, also providing stimulation of the contralateral auditory system, reduces the amount of auditory deprivation. The current clinical approach is to propose unilateral CI with bimodal stimulation in all cases, at least until it is possible to obtain some amplification of residual contralateral hearing [92].

The rationale for a bilateral CI indication is to restore physiological binaural hearing, which allows using information such as differences in intensity and interaural delay, which are especially important for sound source location and discrimination of speech in noisy environments. The European guidelines (NICE, 2009) recommend sequential bilateral CI in children as a viable option only if there are medical conditions supporting it, and caregivers who can provide a favourable functional outcome [86]. Simultaneous bilateral CI is recommended as an option in all prelingual children with severe-to-profound bilateral hearing loss who do not benefit from hearing aids. Furthermore, it is recommended for deaf children with visual impairments and those at risk of cochlear ossification (e.g. after meningitis) [93].

The most recent European Bilateral Pediatric Cochlear Implant Forum Consensus Statement recommends that an "infant or child with unambiguous cochlear implant candidacy should receive bilateral cochlear implants simultaneously as soon as possible after definitive diagnosis of deafness; an atraumatic surgical technique designed to preserve cochlear function, minimize cochlear damage, and allow easy, possibly repeated re-implantation" [94]. However, in the literature, the opportunity of bilateral CI is still discussed on the basis of auditory results. Studies of bilateral cochlear implantation in children has shown that sound localization is improved about 20% of cases with an average of 20% improvement in the ability to hear speech against background noise [1]. Concerns remain regarding cost-effectiveness, given that the cost of CI in Italy ranged between €39,000 and €68,000 similar to other countries [95], with lifetime costs that approach about €90,000. Considering the high cost for CI, the benefits of bilateral implants remained to be established.

Surgery for cochlear implantation is a safe procedure, currently well codified, without significant risk of bleeding and performed under general anaesthesia. The major short term complications include anaesthetic risks that must to be particularly considered in children under 1 year of age. Minor complications include seroma and suture extrusion CSF leak bleeding, while major complications are facial palsy or facial stimulation, device failure and infections [90 96].

Fitting of the CI may be defined as a set of procedures that have the purpose of reaching optimal adjustment of the device, in such a way that this is "tailored" for the patient. Follow-up is therefore fundamental in the deaf recipient child, and it can be considered as important as speech therapy rehabilitation to ensure proper development of perceptual and linguistic skills of the young patient. In paediatric preverbal patients, known to be poorly cooperative, fitting of the individual electrodes (12 to 22 depending on the model) is facilitated by techniques involving the measurement of "objective" parameters that do not require the cooperation of the patient, which are based on the registration of a phenomenon "evoked" by electrical stimulation. Examples of objective methods are the recording of E-ABR, which is the electrical evoked potentials of the brainstem, and the recording of E-SRT, namely the electrically evoked cochleovestibular stapedial reflex threshold. These methods are also effectively used in the intraoperative monitoring of electrodes to evaluate the correct insertion in the cochlea and their function. Given the incomplete reliability of objective measures to determine the best map, fitting experts cannot ignore behavioural methods, consisting in the observation of the patient's reactions to electrical stimulation.

After a suitable period of adaptation to the CI, the child must also be "conditioned" or trained to perform a simple task (e.g. putting coloured bricks in a box) in response to sound stimulus. Interestingly, pitch has been recognized as the most important factors affecting cochlear implant performance. Poor pitch resolution has been shown to have negative implications for speech perception in noisy listening conditions, and it is also implicated in less accurate melody recognition by implanted patients compared to normal-hearing subjects [97 98]. Implanted children, like adults, show poor music perception skills: they can understand the rhythm of songs, but perform significantly worse than normal-hearing peers when challenged with tasks of familiar song recognition, and, most of all, of melodic pattern identification. It is reasonable to assume that music perception by paediatric cochlear implant recipients could benefit from training that is specifically designed to enhance pitch perception [99 100].

Auditory Brainstem Implant (ABI)

The auditory brainstem implant (ABI) is similar in terms of design and function to a CI except that the electrode is placed in the cochlear nucleus in the brainstem. ABI is designed for individuals with hearing loss due to a non-functional auditory nerve such as those affected by VIII nerve aplasia, temporal bone fractures, bilateral vestibular schwannomas (from neurofibromatosis type 2; NF2) or severe ossification of the cochlea and modiolus. Limitations for good performance of ABI are represented by the lower stimulation selectivity due to the positioning of the electrode on the surface of the brainstem that allows large electric field interactions between electrodes. In addition, the tonotopicity is lost from the brainstem to the cortex. In terms of speech perception,

good results have been demonstrated in non-NF2 adult patients, while there is limited data in children.
A new ABI has been proposed with penetrating microelectrodes to improve selective stimulation and pitch sensation, although there are few data on the safety of this device. Furthermore, the speech ability after ABI is different among patients. The FDA approved this device for individuals 12 years of age or older who have been diagnosed with neurofibromatosis type 2. In reality, only 75 children have received the ABI [101]. One of the first reports on a child implanted at 14 months of age described a significant improvement in both auditory performance and verbal production [102]. Nevertheless, the outcomes in children undergoing ABI are still less favourable compared to a CI, and not all children achieve speech development. Several ethical issues remain opened because of the relative risk of the surgery compared with benefits [101]. Further technological improvement in ABI design and surgery are expected in the next years.

Audiologic rehabilitation and speech-language therapy

Rehabilitation represents a very important tool in the management of deaf children. Audiologic rehabilitation is the process of providing training and treatment to improve hearing for children who are hearing impaired. With infants and children, audiologic or hearing rehabilitation services are sometimes called "habilitative" rather than "rehabilitative." In fact, the term "rehabilitation" focuses on restoring a skill that is lost. Instead, in very young children a skill, such as talking, may not have been present in the first place. The services provided will depend on each child's individual needs and are based on the following factors: age of the child, age of onset of the hearing loss, age when hearing loss was discovered, degree of hearing loss, type of hearing loss and age of child when hearing aids were first used [103].
The audiologic habilitation plan for children is guided by the type of communication method the family is using with the child. A variety of communication methods are available: listening and spoken language (also referred to as auditory-verbal or auditory-oral), cued speech or cued language (this method utilizes specific hand shapes and placements around the face to clarify the ambiguity of lip-reading) and sign language [71]. Finally, hearing rehabilitation of children includes different skills: developing language, training in listening and proper use of hearing aids and hearing assistive devices [104].

Pharmacological therapy from the present to the future

As discussed in this review and on the basis of the reported aetiological findings, three different approaches could be addressed in the future: pharmacological intervention, gene therapy and stem cell application. The goal standard of therapy for SHNL is now represented by cochlear implant, but some limitations of speech perception depend on the loss of spiral ganglion neurons in almost all SNHL. In perspective, further advances of translational medicine will change the role of the CI as "multifunctional" in which to integrate electrical stimulation with the application of molecules and drugs to improve performance by restoring or preventing loss of spiral ganglion neurons or regenerating cells [1]. In fact, hair cell death is an irreversible process that can be induced by exogenous factors and several mechanisms are now well established, while the impact of genetic aetiology and susceptibility are still not completely understood [38 105].
Several experimental drugs have been proposed for treatment of SNHL, although few clinical trails have been conducted. Our group has extensively studied antioxidants for treatment of hearing loss due to hypoxia, acoustic trauma, aminoglycosides or cisplatin therapy [36-38 106]. Clinically, antioxidant strategies can be used as add-on neuroprotective therapy after perinatal oxidative stress, but they hare not studied in preventing deafness [107]. Corticosteroids have been proposed for the treatment of the trauma after the insertion of a cochlear implant electrode and in preventing sequelae of meningitis [108]. Antiviral therapy has been proposed in the treatment of CMV: ganciclovir, valganciclovir, foscarnet, cidofovir and CMV hyperimmune globulin are effective in treating or preventing CMV infections in the immunocompromised host, but require close monitoring for associated toxicities. Treatment for congenital CMV is associated with significant toxicity and uncertain effectiveness [109].
Finally, knowledge of molecular mechanisms of developmental processes (i.e. Sox 2, Atoh1 and Notch signalling pathways) or genes involved in differentiation (i.e. espin, myosin VII, whirlin) offers hope for the treatment of inner ear diseases. Gene transfer by viral vectors or nanoparticles represents a promising and novel approach for delivering therapeutic genes or molecules into the inner ear. Stem cells have been the subject of intense speculation and controversy for many years as they open radically new therapeutic possibilities. It has been observed that transplantation of neonatal or embryonic stem cells, adult mouse inner ear stem cells and stem cells from the central nervous system differentiate into cells containing hair cell markers and proteins. Promising results were recently published by Rivolta's group demonstrating that embryonic stem cell transplanted into an auditory neuropathy model, otic neuroprogenitors engraft, differentiate and significantly improve auditory-evoked response thresholds [109]. Many ethical and biological (i.e. immunological, cancerogenic, teratogenic) obstacles remain before applications can be fully realized [81 111 112].

Conclusions

Hearing and speech are essential for children in learning, playing and developing social skills. In fact, children learn to communicate by imitating sounds. In the presence of hearing loss, children can show impaired speech/language development, social problems and academic difficulties. Diagnosis of deafness in children must be early, accurate and, possibly, aetiological.

Most hearing losses can be aided with modern technology, medical therapy or surgical procedures. As already mentioned, the most effective treatment consists in early intervention. Early diagnosis of severe or profound deafness, early fitting of hearing aids or cochlear implant and an early start in special education programmes can help maximize auditory abilities. This one gives the children the best chance for successful speech and language development. Furthermore, thanks to technological advances, deaf children and their families now have a variety of exciting options available.

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