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Review

Moderate-Severe Hearing Loss in Children: A Diagnostic and Rehabilitative Challenge

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Hearing loss in children represents a relevant topic, which needs an increasing attention by clinicians and researchers. Unfortunately, most cases of hearing loss still remain idiopathic (most frequently reported causes are genetic, infectious, toxic). An early diagnosis is crucial, as if not properly recognized, hearing disorders may impact negatively on children development and on quality of life. Literature data show that also children with mild-moderate, or even monolateral, hearing loss may present learning or verbal language disorders, if not adequately managed. The diagnostic work-up of hearing loss in children, which starts with universal neonatal hearing screening at birth, is complex, has to define hearing threshold, and, when possible, its etiology, often by multidisciplinary approach. At the same time, the audiological follow-up of those affected by moderate-severe hearing loss must be tight, as it is necessary to verify constantly: (i) hearing threshold levels, (ii) adequateness of hearing aids fitting, and (iii) language development. This review focuses specifically on the diagnostic work-up and the rehabilitative features of moderate-severe hearing loss in children.

KEYWORDS: Cytomegalovirus, hearing rehabilitation, language development, speech therapy rehabilitation

INTRODUCTION

The correct and timely diagnosis of hearing loss in children is a relevant topic as, if not properly recognized, hearing disorders may harmfully impact children development and on quality of life [1]. Universal newborn hearing screening (UNHS) represents a critical instrument for the early detection of hearing loss in infants at birth [1-4]. However, not all cases of hearing loss can be identified by UNHS, especially as late onset or progressive forms of hearing disorders are not evident at birth. Therefore, it is necessary to monitor carefully every child presenting pre-, peri-, and post-natal risk factors for hearing impairment, as already suggested by the *Joint Committee on Infant Hearing* in 2007 [1].

The accurate diagnosis of hearing loss in children and the appropriate rehabilitation is challenging; it is often necessary a stepwise multidisciplinary approach in which several specialists are involved, such as otolaryngologists, audiologists, pediatricians, neonatologists, geneticists, neuroradiologists, speech therapists [5]. It is mandatory to recognize hearing impairment in children, even a moderate loss, as early as possible, and to provide the proper therapeutical and rehabilitative program, in order to guarantee the best opportunities to adequately develop language, cognitive, and relational skills [1].

METHODS

The PubMed, Embase, and Cinahl databases were searched for the last 5 years (from January 2012 up to December 2016). Full-text articles were obtained in cases where the title, abstract, or keywords suggested that the study may be eligible for this review. The medical subject heading (MeSH) terms used included: hearing loss, children, universal newborn hearing screening, cytomegalovirus (CMV), hearing rehabilitation, language development, and hearing aids.

The search was conducted also according to PRISMA criteria/guidelines (http://www.prisma-statement.org/): it was carried out independently and restricted to articles in English (Table 1). Initially, the total number of article identified was 617; other 26

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Table 1. Literature evaluation and selection, according to PRISMA criteria (http://www.prisma-statement.org/)

Total number of articles obtained by PubMed, Embase, and Cinahl search	617
Other papers from references in the published literature	26
Total number of papers identified	643
Paper excluded[1]	479
Article assessed for eligibility	146
Paper excluded[2]	60
Total number of papers finally identified	86

[1]Inclusion criteria were: clinical series, review papers. Exclusion criteria were: not availability of a full text; manuscripts not in the English language; case reports.
[2] Inclusion criteria were: for clinical series, papers with an adequate group of patients studied (n>20); for reviews, papers published on relevant journals and papers showing a rigorous methods and rigorous reporting.

articles were also identified from references in the published literature when all authors agreed about the reliability and importance of these manuscripts, for a total of 643 articles. Inclusion criteria were clinical series and review articles. Exclusion criteria were no availability of a full text, manuscripts not being in the English language, and case reports.

Therefore, authors critically evaluated the 146 selected articles, by reading abstracts and/or texts, to decide whether the identified articles were relevant to this search or not. In this case, inclusion criteria were: for clinical series, articles with an adequate group of patients studied (n>20); for reviews, articles published on relevant journals and articles showing a rigorous methods and rigorous reporting. Finally, 86 articles resulted appropriate for this review according to all authors.

Epidemiology

Hearing loss in children is a relevant health issue, both for its prevalence and for the related social and personal impact. Epidemiologic data reported in literature about the wide prevalence of hearing loss in children, and this fact is due to different reasons, such as dissimilar criteria used to define hearing disorders, different instruments used to define hearing loss, and divergent groups of children considered. However, the reported worldwide prevalence of hearing loss in infancy is 1.12/1000 newborns, considering the congenital forms, and 1.33/1000, also considering those acquired and those with late onset [6].

In 2007, the *Joint Committee on Infant Hearing* updated the principles of UNHS, which represents the first step of the diagnostic work-up of hearing loss in children, within the first month of life [1]. UNHS allows to identify not only those affected by profound hearing loss but also those affected by moderate-severe hearing loss. When a child fails the UNHS, he/she has to be addressed to an audiological evaluation, in order to organize a proper and individualized diagnostic work-up[1,2]. Unfortunately, the late onset and the progressive forms of hearing disorders are not evident at birth and cannot be identified at the UNHS [7]. For this reason, the *Joint Committee on Infant Hearing* proposed a list of risk factors associated to permanent form of childhood hearing loss, suggesting that every child presenting pre-, peri-, and post-natal risk factors and/or other listed characteristics has to be carefully monitored through audiological assessments within the first years of life (at least until the age of 24-30 months, and of 6 years in case of congenital CMV infection particularly) [1, 8, 9].

Etiopathogenesis of Moderate-Severe Hearing Loss in Infancy

Moderate-severe hearing loss can be congenital or acquired and further classified in pre-, peri-, and post-natal, considering its period of occurrence. Neonatal hearing loss can be due to problems correlated to pregnancy, delivery, and/or the immediate post-natal period [10-13].

Pre-natal hearing loss

During the embryological period, the auditory system is reported to be particularly vulnerable to toxic and teratogenic agents: ototoxic drugs (i.e., aminoglycosides, chemioterapics) used during gestation or drugs/alcohol abuse can be responsible of inner ear alterations, such as mother metabolic disorders (i.e., renal or liver failure, diabetes mellitus) [10, 14]. In particular, fetal alcohol syndrome is a consequence of the alcohol teratogenic effect during pregnancy, and it is characterized by a growth defect, typical facies, microcephaly, skeletal anomalies, mild-moderate mental retardation, behavioral anomalies, congenital heart condition, and hearing loss also [15]. Ototoxicity occurs due to cochlear hair cells and irreversible death; it may also become evident in case of low hematic drug concentration and short therapies for a particular genetic predisposition (a mitochondrial DNA mutation) [16]. Furthermore, ototoxicity increases when other drugs are used in association [17]. Also, gestational infections represent a pre-natal cause of congenital hearing impairment; in particular, CMV infection can be responsible also for late onset of sensorineural hearing loss (SNHL) [18].

Peri- and Post-Natal Hearing Loss

Among peri- and post-natal conditions at risk for neonatal hearing loss, NICU (Neonatal Intensive Care Unit) hospitalization ≥ 5 days plays an important role, as it is reported to increase hearing loss incidence by about 5-10 times, if compared with general newborn population [17]. It may be related not only to NICU equipment environmental noise but also to therapies used, such as ototoxic drugs, or mechanical ventilation for more than 5 days. Prematurity is not reported to be a risk factor itself, but the association of several risk factors may represent a predisposition to develop hearing impairment [17]: very low birth weight (<1.500 g), peri-natal asphyxia, jaundice [1]. Numerous congenital infections have been linked to hearing loss, mono or bilateral, sometimes progressive [10]. Viral infections, such as varicella, herpes, influenza, and mumps, may be responsible for SNHL as much as a bacterial meningitis (*Streptococcus pneumoniae*, *Neisseria meningitidis*) [10]. The most frequent congenital infection is CMV, as vaccines have reduced the incidence of rubella, mumps, and measles. Congenital CMV infection prevalence is estimated in about 0.64% children at birth [19]. It can be a primary or a recurrent infection; only 10% of infected children are symptomatic at birth, and hearing loss may be present in about half of the cases. CMV-related sensorineural hearing defect may be of mild-moderate degree, mono- or bilateral, typically fluctuating and, for most of the cases, with a delayed onset [18-22]. Also, many cases of idiopathic hearing loss in children with a late diagnosis are consequences of an unknown congenital CMV infection. In 2009, Boudewyns et al. [23] tested, through real-time PCR, DNA obtained from neonatal Guthrie cards of infants who failed UNHS and children with non-congenital SNHL, searching for CMV DNA. They found CMV-positive results in 7.3% of the children of the two study groups.

Trauma represents another acquired post-natal etiology of hearing loss; generally, a post-traumatic labyrinth damage can be responsible of a monolateral conductive, sensorineural, or mixed hearing defect [24, 25].

However, about 60% of congenital hearing loss is genetic and it can be syndromic (30% of cases) or non-syndromic (70% of cases) [26-29].

In the last 20 years, genetic diagnosis has experimented many progresses [30]. In particular, the introduction of NGS (next-generation sequencing) and MPS (massive parallel sequencing) for the molecular testing of hearing loss has allowed the examination of large gene panels [31, 32]. Because of the improved diagnostic techniques, about 160 genes have been linked to hearing impairment so far. Many genes have been discovered to be involved in auditory function: mutations of proteins implicated in adhesion between hair cells, ionic transport, neurotransmitter release, and cytoskeletons of inner ear cells may be linked to cochlear disorders [33]. An updated official database of recognized monogenic non-syndromic types of hearing loss is available at the Hereditary Hearing Loss Homepage (http://hereditaryhearingloss.org/) [34]. Every non-syndromic hearing loss (NSHL) is classified considering the time of its discovery and its transmission model. Most cases of NSHL have a recessive transmission model (about 80%); the remaining cases are autosomal dominant, X-linked, and mitochondrial [18, 35-40].

The most frequent recessive form of SNHL (more than 50% of cases and 20%-25% of all causes of congenital hearing disorder [41]) is known as ARNSHL DFNB1A, according to the classification in Hereditary Hearing Loss Homepage [34]; it is linked to mutation of GJB2 (gap junction beta-2) gene, coding for a transmembrane protein called connexin 26 [5, 37, 42-44]. Also, mutation of GJB6, coding for connexin 30, has been reported to be associated to hearing dysfunction (ARNSHL DFNB1B). Generally, GJB2 and GJB6 hearing defects are mild-to-profound SNHL, bilateral, and not necessarily preverbal [45-47].

It has also been reported that some genes, such as GJB2, may have a different pattern of inheritance according to the specific mutation: a particular mutation of GJB2 is linked to an autosomal dominant form of hearing impairment (DFNA3A) [34]. Moreover, some other genes may occur as either non-syndromic or syndromic, such as SLC26A4, which is responsible of a non-syndromic autosomal recessive hearing loss (DFNB4), the second most frequently found after GJB2 [48]. Other common causative genes for autosomal recessive hearing disorder are MYO15A (encoding for myosin XV), OTOF (encoding for otoferlin, whose mutations are linked to an auditory neuropathy/dissynchorny), and CDH23 (encoding cadherin-23, whose mutations may also be responsible of Usher syndrome type 1D) [41, 49].

Hearing loss associated with autosomal dominant and X-linked transmission method are typically postverbal, with a variable hearing loss, generally progressive [30, 50, 51]. These forms can also be easily detected while studying the family tree. Among the most frequently identified genes related to hearing loss with autosomal dominant inheritance, there are: WFS1, TECTA, COCH, and KNCQ4 [41]. POU3F4 is the most frequent genetic mutation related to X-linked non-syndromic hearing impairment commonly associated with cochlear hypoplasia and a bulbous malformation of the internal auditory canal [41].

Mitochondrial mutations are mainly related to moderate-severe hearing loss; the phenotypic expression may be extremely variable, often multisystemic, considering other different factors, genetic, and not [36, 52].

Syndromic hearing loss is associated with dimorphisms and/or signs/symptoms/malformations of other organs [53, 54]. More than 400 syndromes linked to hearing loss have been described so far, but the diagnosis may be difficult as: (i) the genetics of these syndromes is heterogeneous and with a variable penetrance and (ii) different mutations of the same gene may be linked to both non-syndromic and syndromic hearing loss [55]. Waardenburg syndrome (characterized by mono- or bilateral mild-to-severe SNHL, associated with typical hair, skin, and eyes dyschromic manifestations) and branchio-oto-renal (BOR) syndrome (involving branchial arch anomalies; inner, middle, and external ear malformations; hearing loss; and kidney defects [56]) are among the most frequent causes of autosomal dominant syndromic hearing loss.

Pendred syndrome is the most common autosomal recessive syndrome of hearing impairment [55]. It is due to PDS gene mutation, encoding for a protein called pendrin (also known as SLC26A4, solute carrier family 26, member 4), involved in calcium and iodine transport; it has a recessive autosomal transmission modality. Pendred syndrome is characterized by congenital or generally preverbal bilateral profound SNHL, associated with non-endemic goiter, temporal bone anomalies, enlarged vestibular aqueduct, and, sometimes, mental retardation and cerebellar signs. Usher syndrome, with autosomal recessive inheritance, represents the most common form of hearing impairment and vision loss during infancy [55].

Diagnostic Work-Up of Moderate-Severe Hearing Loss in Children

The diagnostic work-up of hearing loss in children is often difficult and requires a multidisciplinary approach [5, 57-60].

Particularly, the identification of the hearing impairment etiology, when possible, is important. After an accurate personal and familiar history taking and an otoscopic evaluation, a complete physical examination is the first step in the approach to the diagnosis of hearing loss in children [1, 61-63]. In case of external ear malformations (i.e., auricle abnormalities, external auditory canal atresia, or stenosis) which may be isolated or associated with other physical anomalies (therefore configuring a syndrome), it is mandatory to evaluate the auditory function. In presence of preauricular pit or tag, which can occur sporadically or inherited, and can be associated with a syndrome (such as BOR syndrome), the assessment of hearing function is still controversial [64]; audiometric testing has been recommended in case of syndromic forms, but there is no consensus on hearing investigation in sporadic cases, as the role of isolated preauricular pits as a risk factor for auditory impairment is still unclear [65-67].

During the general evaluation, it is also important to evaluate the presence of other abnormalities, such as skin dyschromia, eye irregularities, renal dysfunction, particularly when suspecting syndromic forms and in case of familiarity for hearing loss [1, 2, 68].

Family history of hearing impairment represents a risk factor to be considered during the diagnostic work-up [69]; a history of hearing impairment is mentioned as risk factor for both congenital and post-natal hearing loss by the *Joint Committee on Infant Hearing* [1, 70]. It has been recommended to accurately analyze at least three generations in the family tree, especially in the suspicion of an autosomal dominant hearing loss [67, 71].

Likewise, a genetic assessment is important, as about 60% of cases has a genetic origin. Even more important is the genetic investigation in case of hearing loss occurring in an inbred family, as it increases the prevalence of recessive forms [30]. The genetic evaluation is often long and difficult and it is based on genetic tests performed in programmed stages, on the basis of clinical suspects [18, 36, 72, 73]. The first step is always represented by a clinical genetic evaluation; therefore, in order to plan the appropriate molecular studies, auxologic parameters and family tree are registered [69]; facial dysmorphisms and major (such as labiopalatoschisis) and minor anomalies (such as little auricle, fifth finger clinodactily, pit, tag, renal malformations, branchial arch development anomalies) are searched [18, 36]. Frequently, a diagnosis is suggested by facial features, typical phenotypes of syndromic dysmorphisms [74]. Also, a unilateral hearing loss could suggest a genetic etiology [75, 76]. For every child with a negative GJB2/GJB6 mutation or a negative CMV test, a clinical follow-up has been recommended in order to assess periodically potential dismorphological patterns that could relate to a particular syndrome [74].

The NGS and MPS technology has improved the genetic approach to hearing loss [77]. There are important factors to be considered when choosing a genetic test, such as patient's history and phenotype [78]. The identification of a genetic hearing disorder is important as it may improve prognostic accuracy and may allow a correct genetic counseling for the affected patient and relatives at risk [79, 80]. Also, the genetician may provide information to parents among inheritance modalities and the pre-natal diagnosis if available [81, 82].

Neuroradiologic examination is another necessary diagnostic stage: temporal bone CT (computed tomography) scans and brain, brainstem, pontocerebellar angle, inner ear and central auditory system MRI (magnetic resonance imaging) are recommended in all permanent hearing loss in children and, frequently, they are complementary examinations [83]. CT scans are essential in case of cranial trauma, but also in case of pre-surgical evaluation before cochlear implant surgery, in case of cholesteatoma, or in case of suspected middle ear malformation [84-86]. MRI has a high degree of definition of labyrinth fluid contents; it is suitable in the inner ear and central auditory system evaluation [83].

A serological assessment is always important; when a congenital CMV infection is suspected, also, a retrospective diagnosis is possible through viral DNA PCR research in Guthrie card blood spots or in urine sample. In order to differentiate a pre-natal CMV infection from a peri- or post-natal infection (which are not associated to a significant risk of hearing impairment), the CMV DNA research has to be performed within two weeks of birth [23, 87, 88]. An early diagnosis of congenital CMV infection is fundamental in order to set up the appropriate antiviral therapy [89-91]. Anti-CMV vaccine is currently under evaluation and may become available in the future.

Other important examinations that can facilitate the identification of hearing loss etiology are electrocardiogram and QT evaluation, thyroid and kidney function tests, and echography and ophthalmologic assessment [68, 92].

The definition of the hearing threshold level is mandatory since the first evaluation of the child. Audiometric tests are chosen on the basis of patient age [1, 2]. From birth to up to 4 to 6 months, objective tests are preferred: (i) otoacoustic emission (OAE), in association with automatic ABR (auditory brainstem response) in children at risk for hearing loss; (ii) ABR with threshold assessment and, when possible, (iii) ASSR (auditory steady-state responses) evaluation, which can provide useful threshold information among middle frequencies; (iv) tympanometry and acoustic reflex threshold; (v) electrocochleography, in selected cases and when available. From the age of 6 to 7 months, subjective audiometric tests (behavioral tests), such as COR (conditioned orientation reflex) and VRA (visual reinforcement audiometry), can be used with a variable level of reliability. From the age of 2 to 3 years, testing with play audiometry and peep show can be performed; in this period of life, in case of collaborative children and without particular comorbidities, a pure tone laminar audiometry and a vocal audiometry with age-appropriate verbal sets can be tempted [1, 2].

Hearing and Speech Therapy Rehabilitation

Within the first 2 years, neuroplasticity increases rapidly and continues until the age of 3 to 4 years. As a consequence of a cochlear damage during infancy (and, above all, during the first 6 to 8 months), the development of auditory pathways and cortical areas can be impaired [93-95]. If an adequate auditory stimulation is restored (i.e., by hearing aids, to rehabilitate a moderate-severe hearing loss), a reactivation of the neural synaptic connections may be possible, ensuring a regular auditory pathway development [93]. Hence, the early identification of hearing impairment in children and in particular within the first 3 months of life, is really important in order to set the proper and earliest therapeutical-rehabilitative plan [1, 96, 97]. If hearing loss is not recognized and corrected, it has been reported that scholastic learning and social activities may also be compromised, as well as emotional and psychological development [1, 98].

The efficacy of hearing aids is related to their fitting and particularly to the quantity of speech and spectral information transmitted to the central auditory system [99]. Since (i) the earliest diagnosis of hearing disorders, and (ii) the availability innovative technologies (particularly in terms of advanced hearing aids solutions), a progressive improvement of the rehabilitative results achieved in children affected by moderate-severe hearing loss has been observed in the last years [37]. Hearing aids in infancy have been recommended in case of bilateral SNHL, and in case of persistent conductive or mixed hearing loss [1, 96, 100, 101]. Increasing evidences suggest a benefit of hearing aids use also in children with unilateral SNHL[102, 103] and in some cases of auditory neuropathy [104].

A tight audiological follow-up of the hearing-impaired children then allows (i) to fit hearing aids amplification at best, each time, and therefore (ii) to achieve the best verbal perception conditions [1, 105, 106]. Also, a periodic evaluation by speech therapists could help in defining the development of verbal language milestones [1, 2, 107]. Specific attention should be paid to bilingual children, as they are exposed to different language stimuli and have to learn different perceptive characteristics and rules [108, 109].

CONCLUSION

Hearing loss in children represents a diagnostic and rehabilitative challenge. Its early identification is crucial not only to ensure an adequate

language development of children but also to allow the development of their cognitive, relational, social, and even scholastic skills [1, 98, 99, 107]. The diagnostic work-up is often complicated either in order to define the hearing threshold level, either to the identification of the hearing loss etiology, when possible [1, 110]; the latter could indicate, more appropriately and when possible, the best therapeutical-rehabilitative process. For this reason, a stepwise approach to the diagnosis hearing loss during infancy often requires a multidisciplinary team and may involve specialists such as otolaryngologists, audiologists, pediatricians, neonatologists, geneticists, neuroradiologists, and speech therapists [5].

It is otherwise important to remember that not all children with a language disorder present a concomitant hearing defect; sometimes, language skills deterioration may be the sign of a neurological condition, such as an autism spectrum disorder [111]. Also, epileptic encephalopathies, a group of severe cerebral diseases, characterized by epilepsy which may be responsible of a psychomotor regression and, in particular, of a cognitive and communicative impairment should be ruled out [112].

A tight audiological follow-up of children affected by moderate-severe hearing loss is always recommended in order (i) to verify constantly hearing threshold levels as well as the improvement of auditory and perceptive abilities, and (ii) to fit consequently hearing aids at best [1, 105-107].

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