Chapter

Advances in Hearing Loss and Vestibular Disorders in Children

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Abstract

Pediatric hearing loss is a common sensory deficit, affecting nearly 9% of children worldwide. Compared with pediatric hearing loss, vestibular disorders are still not known among the child population. However, vestibular disorders are more and more generally known with time when the measurement of vestibular function is developing. Genetic causes and virus infection are the main causes of pediatric hearing loss, and vestibular migraine is the most common etiological disease of childhood vertigo. This narrative review of the literature discusses the brief etiopathology, the clinical manifestations of hearing loss and vestibular disorders in children, as well as available test protocols to diagnose childhood hearing loss and vestibular dysfunction.

Keywords: hearing loss, vestibular disorders, child, auditory tests, vestibular tests

1. Introduction

Hearing loss is a common sensory deficit in children, nearly 9% of hearing loss occurs in children worldwide [1], and 1–3 out of 1000 deliveries suffer from permanent hearing loss worldwide [2, 3]. Hearing loss has detriment impact on children's quality of life. It may affect children's speech and language development, as well as their learning ability and school performance consequently. Moreover, their cognitive, social, and psychosocial development may be negatively affected [4]. Over the past 30 years, the understanding of the etiology of pediatric hearing loss experienced a steady growth, and the diagnosis and treatment technology for pediatric hearing loss witness a huge development. However, infants with hearing impairment may behavior normally. They soon present hearing difficulty or speech and language delay with time. Therefore, identifying the hearing using newborns universal hearing screening is essential. On the other hand, some children may pass the hearing screening but suffer from delayed-onset hearing loss. Thus, continuous surveillance of their hearing and the speech-language development are essential.

The relationship between auditory and vestibular function is close, children with hearing loss may combined with vertigo or imbalance, due to the anatomy adjacency between the auditory organs and vestibular end-organs. The estimated prevalence of vestibular dysfunction ranges between 0.4 and 8% [5, 6]. Compared with pediatric hearing loss, published medical literature on pediatric vestibular disorders is scant. Vestibular disorders can have significant impacts on children's quality of life. It may lead to delayed motor skills, attention deficit disorder, learning problems,

developmental delay, intellectual disability and emotional disorders [7]. With the increasing awareness of the harm of vestibular disorders in children, more and more studies focus on this field recently. Currently, there are several challenges in the study of childhood vestibular disorders. Firstly, the inability of children to explain the characteristics of the vertigo symptoms make the diagnosis of vestibular disease difficult, especially in very young children. In addition, due to poor cooperation, the vestibular tests are not uniformly reliable in the younger pediatric patients.

We will focus causes of pediatric hearing loss and vestibular disorders, and introduce the advance in the technology of the common auditory, molecular test and vestibular evaluation protocols in children with hearing loss and/or vestibular disorders.

2. Causes of pediatric hearing loss

Pediatric hearing loss is either congenital or acquired. The causes of congenital hearing loss are various, including congenital cytomegalovirus infection, genetic, anatomical abnormalities of the ears. The causes of postnatal acquired hearing loss can be attributed to genetic, trauma, infection, or ototoxic medications [8]. Risk indicators of childhood later-one onset hearing loss include caregivers' concern, family history, findings associated with sensorineural hearing loss (SNHL), hyperbilirubinemia, neurodegenerative disorders and otitis media with effusion [9, 10].

3. Congenital hearing loss

3.1 Virus infection

It is estimated that the 5–20% of congenital hearing loss is caused by congenital cytomegalovirus (CMV) infection [8], which occurs in 0.4–0.64% of all newborns [11, 12]. Clinical spectrum of congenital CMV infection varies widely, 85–90% of infected infants are complete absence of signs of infection (asymptomatic infection). Thus, it is best for all asymptomatic newborns with suspicion of CMV infection undergo either universal or targeted screening of CMV. However, due to the concern of cost, newborn screening for CMV is not widely applied worldwide.

Up to 10–15% children with CMV infection exhibit apparent infection manifestation (symptomatic disease), among them, some infants may present with potentially life-threatening disseminated disease [11, 13]. The common presentation of the CMV infection in symptomatic children are petechiae, jaundice, hepatomegaly, splenomegaly, microcephaly, and other neurologic signs. Among infants who develop CMV-related SNHL, hearing loss may occur at birth or later [14]. Moreover, about 50% of children with SNHL following CMV will continue to have further hearing loss deterioration or progression [15, 16]. Therefore, it is important for all infants with congenital CMV infection, whether they having hearing loss or not, receive serial audiological monitoring throughout the first year of life to allow for early detection of possible SNHL. Other known congenital infections that may cause neonatal hearing loss are TORCH microorganisms (toxoplasmosis, other organisms, rubella, CMV, herpes) [9].

3.2 Genetic causes

The majority of congenital hearing loss, up to 60% of cases, is due to a genetic etiology [17]. The genetic phenotypes of SNHL can be defined as syndromic or

non-syndromic. 70% of newborns Hearing loss is non-syndromic. Up to now, 124 genes are found to be associated with non-syndromic hearing loss [18]. Most of the patients with non-syndromic SNHL have the disease-causing variant in the gene GJB2, which encodes the protein connexin 26 [19]. Hearing loss due to GJB2 deficiency was first reported in 1997. Now, various gene variances are reported to be related to the onset of hearing loss. 80% of non-syndromic genetic hearing loss is caused by autosomal-recessive (AR) inheritance, predominantly occurs prelingually and frequently results in severe hearing loss [20]. On the other hand, autosomal-dominant (AD) inheritance accounts for most of the other 20% of non-syndromic genetic hearing loss and more often result in variable level of progressive hearing loss and occurs between 10 and 40 years old [21].

The remaining 30% of congenital hearing loss present with syndromic form and is associated with structural or functional anomalies of other organs and systems [22]. Patients with mitochondrial inheritance predominately have variable severity of progressive SNHL, with onset aged between 5 and 50 years [23]. X-linked and mitochondrial inheritance accounts for only 1–2% of non-syndromic hearing loss [20].

More than 40 known genes are related to syndromic hearing loss [18]. Syndromic hearing loss may also be transmitted as an AR, AD, X-linked, or matrilineal trait [18]. Pendred, Usher, and Alport syndromes are the most common syndromic hearing loss among children. Pendred syndrome, cause by recessive variants in the SLC26A4 gene, is characterized by thyroid dysfunction, goiter, enlarged vestibular aqueduct, and incomplete partition type II cochlear abnormality (Mondini). Usher syndrome is associated with at least 9 genes and present with hearing loss, vestibular dysfunction, and vision loss. Alport syndromeisan X-linked (80%) or recessive disorder (depending on the gene) exhibit kidney failure, ocular abnormalities (anterior lenticonus, retinopathy), and progressive SNHL. It is noteworthy for patients with suspected syndromic hearing loss, it is even more important to identify the genetic cause, as many of the comorbidities can be more severe [24]. In brief, if a child has a three-generational family history suggestive of AD inheritance, a genetic cause is essentially established [25]. In addition, a comprehensive and thorough medical history collection and physical examination are needed for all hearing loss newborns to identify the insidious and harmful comorbidities.

4. Acquired hearing loss

Genetic causes, trauma, infection, or ototoxic medications are the main causes of acquired hearing loss. Genetic hearing loss, may occur later in childhood. For children with delayed hearing loss, genetic causes should always be considered, especially if other causes are excluded.

Environment causes leading acquired hearing loss include trauma, infection, exposure to ototoxic medications, chemotherapy and radiation therapy and noise. Of all of these, environmental noise is the most common cause of hearing loss [25].

Infectious causes of hearing loss can occur both before and after birth. As we mentioned previously, CMV is a substantial cause of delayed hearing loss in children. Other infectious causes of SNHL include measles, mumps, varicella zoster, Lyme disease, bacterial meningitis, and otitis media. Several groups of drugs are the well-recognized causes of SNHL, including aminoglycoside antibiotics, systemic chemotherapy (especially cisplatin), macrolides, and loop Kenna diuretics [26].

Furthermore, it is worth mentioning that otitis media is a common cause of pediatric hearing loss. OME is a middle ear disease that affects 90% of children at least once before they reach school age [27]. Although OME is very common in children, permanent SNHL caused by OME is rare. Persistent middle ear effusion is frequently found in children after the resolution of acute inflammation in acute otitis media.

5. The test batteries for diagnosing pediatric hearing loss

5.1 Auditory tests

For all newborn infants, neonatal hearing screening is essential. In 2000 and 2007, The Joint Committee on Infant Hearing (JCIH) recommended universal newborn hearing screening (UNHS) for newborn infants, in order to early detection of and intervention for infants with hearing loss [9]. Now, UNHS is applied in most developed countries, and these countries have formulated guideline for newborn hearing screening. Diverse screening protocols may be adopted in different countries. All these protocols are based on the 1-3-6 benchmark (screening completed by 1 month, audiological diagnosis by 3 month, enrolment in early intervention by 6 month) set in the earlier editions of the JCIH recommendations. Although UNHS is applied widely, many countries still do not have UNHS included in their health agenda, partly due to its high cost or doubt of its value [28].

The most common available newborns hearing screening tests to date include otoacoustic emissions (OAE), that is further classified as transient-evoked otoacoustic emissions (TEOAE) or distortion product otoacoustic emissions (DPOAE), and automated auditory brainstem response (aABR).

Children who fail the hearing screen should undergo further auditory test. Frequency-specific audiometry and tympanometry are considered to be the basic hearing tests for pediatric patients. However, additional behavioral and objective measures are essential to evaluate the hearing, and cross-check of subjective and objective hearing tests is needed to ensure an accurate and timely diagnosis. This is particularly important in the pediatric population [29].

Once the children are diagnosed with hearing loss, they will refer to the otorhinolaryngology specialists and audiologists to identify the etiology and receive treatment.

One problem must be considered is that a passed UNHS does not exclude a future delayed hearing loss onset, particularly in children with risk factors [30]. Therefore, it is necessary to continuously monitor their hearing and behavior, and children who have delayed speech and language development should be subjected to new hearing tests.

5.2 Molecular test

Any infant or child with bilateral congenital hearing loss of unknown etiology requires a genetics consultation and undergo genetic tests. For children with a suspicion of AR NSHL, genetic testing for GJB2 by Sanger sequencing is recommended [31]. In addition, serologic testing in both mother and infant is advised upon the suspicion of a congenital infection of CMV, toxoplasmosis, rubella, herpes simplex and syphilis [32].

At first, the only available genetic testing for hearing loss was single-gene testing. Now, comprehensive genetic testing (CGT) is becoming the new standard, this

technology improves the genetic diagnostic yield by applying massively parallel sequencing or next generation sequencing (NGS), which make the cost of sequencing decrease and avoid multiple tests [33, 34].

Whole Genome Sequencing (WGS) is an emerging tool with the potential to generate an incomparable variety and quantities of genetic information. Although WES has shown to be a potential tool for DNA diagnostics of hearing loss, its sensitivity is lower than the targeted resequencing methods [35]. Moreover, the cost of WGS is relatively high, which limits its clinical application. Now, as the cost WGS is decreased, it is expected to be the standard diagnostic tool in clinical practice within 5 years [36].

Currently, the testing of congenital CMV infection in most highly resourced countries is based on clinical suspicion alone. This means a large proportion of CMV infections are underdiagnosed. Universal or targeted screening of CMV contributes to identify CMV infection, however, due to the cost concern, only infants with suspicious CMV undergo screening in most countries.

When pediatric patients are diagnosed with hearing loss. Standard examinations include history taking, physical examination and other examination can be selected according to their corresponding clinical manifestations. For example, computed tomography imaging or magnetic resonance imaging of temporal bone can be taken into consideration to exclude structural inner ear or neurological anomalies. Upon the suspicion of other syndromic hearing loss, different additional corresponding examinations can be performed according to the diagnosis, such as an electrocardiogram for Lange-Nielsen syndrome or a urine analysis and renal ultrasound for branchio-oto-renal syndrome [37, 38]. Ophthalmic examination is also necessary since the prevalence of ophthalmic problems in children with hearing loss is 40 to 60% [39]. In addition, vestibular evaluation should be performed in case of a negative result for both genetic and serologic tests in the sporadic cases or patients with a suspicion of AR SNHL [40].

6. Disease spectrum of pediatric vestibular disorders

The reported prevalence and etiologies of vestibular disorders are various depending on the medical institution which children are referred to, the referral criteria, the age range when they tested and the type of the vestibular testing they undergo [41]. According to a systematic review conducted by Brodsky et al., the top 4 diseases resulting in childhood vertigo were vestibular migraine (VM) (23.8%), benign paroxysmal vertigo of childhood (BPVC) (13.7%), idiopathic (11.7%), and labyrinthitis/vestibular neuronitis (8.47%). Less common etiological diseases included Meniere disease and central nervous system tumors [42]. Another recent clinical study also showed that the most common etiological diseases are VM and BPVC, followed by vestibular neuritis [43]. However, Gedik-Soyuyuce et al. pointed out that benign paroxysmal positional vertigo (BPPV) was the most common cause (49%), followed by VM (41%), BPVC (4.5%), vestibular neuritis (4.5%) and psychogenic vertigo (4.5%) [44].

Božanić Urbančič et al. investigated 257 vertigo/dizziness children and reported that central diseases accounted for 19.1%, peripheral vestibular diseases 12.4%, hemodynamic diseases 10.9%, and psychological diseases 5.8%. None of the symptoms were attributed to visual problems. 40.8% children with central vertigo had BPVC and 8.2% had migrainous vertigo. The etiology could not be identified among

112 children (43.6%) [45]. Moreover, they found the most common etiological central diseases is BPVC, other diseases such as epileptic, infectious, neoplastic, vascular, postoperative vertigo, vertigo due to hydrocephalus, degenerative/hereditary vertigo can also lead to vestibular symptoms.

To sum up, VM and BPVC are reported to be the most common causes of vertigo in children. VM is a subtype of migraine and is also common among adults. The speculated cause of migraine is the dysfunction of thalamocortical networks, which is vulnerable to trigger factors, including stressful life events, visual stimuli, hormonal changes, hypoglycaemia, or sleep deprivation [46]. In the developing brain, migraine may have a different phenotype than it does in the adult brain. For example, the duration of migraine attacks can be shorter in children, and the head pain is most often bilateral instead of unilateral. In some cases, children with migraine may not even exhibit headache [47]. BPVC is the early stage of VM, the reported prevalence of BPVC is variable, ranging from 6–20% [48]. Recently, the Committee for the Classification of Vestibular Disorders of the Bárány Society put forward the diagnostic criteria for Vestibular Migraine of Childhood [49]. The clinical presentation of BPVC is episodes of vertigo that typically last for minutes at a time and resolve spontaneously without any postictal symptoms.

Other reported common causes of pediatric vertigo include trauma, ocular disorders (such as vergence insufficiency, ametropia, anisometropia), congenital malformations and syndromes (Large vestibular aqueduct syndrome and Cogan syndrome), superior semicircular canal dehiscence, chronic otitis media and cholesteatoma, psychiatric disorders, central nervous system disorders (epilepsy, multiple sclerosis and episodic ataxia) and posterior fossa lesions (Vestibular schwannoma and Meningiomas) [50].

Persistent postural-perceptual dizziness (PPPD) is not as common in childhood as in adult age, Wang et al. Retrospective review 53 pediatric patients with a diagnosis of PPPD, and they reported that Common diagnoses in addition to PPPD included benign paroxysmal positional vertigo (64.2%), vestibular migraine (56.6%), and anxiety (28.3%) [51].

7. Vestibular function assessment for pediatric population

The children's vestibular function development is as follows. The vestibular function and specifically the vestibulo-ocular reflex is present at birth, although its time constants are about half of normal adult values at 2 months old [3]. The absence of a VOR by 10 months of age should be considered abnormal. The development of children's postural stability is that they first control the head, then the trunk, and finally the postural stability when standing. Regarding balance control, unlike adults, infants and children prefer visual inputs to vestibular information rather than somatosensory inputs in achieving postural equilibrium. At 3–6 years of age, children begin to use somatosensory information appropriately. In adolescents around the age of 15, the coordination of adult-like postural responses can be assumed due to complete maturation of the three sensory systems and the ability to solve intersensory conflict [52].

Currently, some vestibular tests are introduced as childhood vestibular function evaluation. The available vestibular function tests applied in children include cervical vestibular evoked myogenic potentials (cVEMP), ocular vestibular evoked myogenic potentials (oVEMP), video head impulse test (vHIT) and calorie test.

It is documented that rotatory chair, cVEMP and vHIT tests are feasible for children aged 0 ~ 2 years; for children aged 3 to 7 years, vHIT, cVEMP and oVEMP have satisfactory compliance; Children over 8 years old can cooperate well to complete vHIT, calorie test, cVEMP and oVEMP test. All these tests are well tolerated by children and relatively easy-to-use, and simple to operate. Additionally, it should be noted that the test procedure requires an individualized process, that is the protocol should be adjusted according to the condition of each subject [53].

Dhondt et al. conducted vestibular tests for 58 healthy children between 5 months and 6 years of age, and found that most subjects can complete the vestibular tests, the completion rate from high to low was cVEMP, oVEMP, vHIT, rotatory test and caloric test [54]. Similar result was demonstrated by Verrecchia et al., and they found that the best compliance was achieved for HIT (97.1%) and least for cVEMP (68.6%) in pediatric cochlear implants candidates [55].

Some causes may lead to a low compliance of vestibular test in children. For example, due to lack of attention or interest for the target or their gaze diversions, a naturally depressed vestibular function [56] and gaze fixation [57] may present in very young children (<6 months), so their HIT can result falsely pathological results. In VEMP, due to various procedural biases in VEMP recording, the risk for false pathological results is also common, because it is difficult to keep a stable and sustained neck muscle activation in unconstrained children [55].

vHIT is the most widely used tool for pediatric vestibular function assessment. In terms of the diagnostic value of vHIT, recent studies showed that the vHIT test is a sensitive and efficient vestibular test in the pediatric population [58, 59], although the sensitivity of vHIT may be lower than caloric test in vestibular dysfunction detection, particularly in the pediatric population [59]. Moreover, due to the low compliance of caloric test in young children, vHIT is selected to be a regular vestibular test for young children. Regarding balance tests, it is reported that children with unilateral vestibular impairment showed normal balance function, which indicates that vestibular compensation enables them to rely on vestibular input to keep balance. As a result, it is difficult to judge the extent of vestibular dysfunction by using balance tests alone [60].

8. Vestibular dysfunction in pediatric patients

Children with vestibular diseases can present with the same vestibular function abnormalities as adults who suffer from the same diseases. For example, pediatric patients with VM have higher values of gain compared to asymptomatic patients [61]. In addition, children with Meniere disease exhibit a significantly vestibular function declining sequence from the cochlea, to the saccule, utricle and semicircular canals [62].

Vestibular dysfunction may also occur in children affected with some auditory diseases but without vertigo symptoms. Children with SNHL can exhibit vestibular impairment, given the embryological and anatomical connection between the cochlea and vestibular end-organs and their shared sensory microstructure and genetics [63]. Another example is otitis media with effusion, previous studies revealed that approximately 30% of the children with OME have some degree of vestibular impairment documented with vestibular test [64, 65]. Moreover, the vestibular impairment among OME patients may be not severe. A study results showed that the mean vHIT gains and gain asymmetry values of pediatric with OME and dizziness and healthy

children were comparable. However, covert saccades were observed in 57% of the patients with OME and dizziness, but none patients had overt saccades [66].

Some researchers have described vestibular hypofunction in children with cytomegalovirus infection, vestibular neuritis, complicated cholesteatoma, post traumatic vertigo, motion sickness and auditory neuropathy [67–73].

One hotpot of pediatric vestibular disorders is the evaluation of post-cochlear-implantation vestibular function. Recent evidence has demonstrated a relatively wide range of patients suffered from vestibular dysfunction after cochlear implantation [74–76], and the total equilibrium score was also significantly reduced in implanted children than the non-operative controls [77]. Different mechanisms have been proposed to explain this phenomenon, including electrical stimulation by the prosthesis, direct trauma following electrode placement, foreign body reaction or labyrinthitis, and endolymphatic hydrops [76, 78–80].

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