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Review Article

Diagnostic Assessment of Progressive Fluctuating Sensorineural Hearing Loss in Children

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Abstract

Deterioration of auditory thresholds in young children is directly associated with negative impact on language development. Early detection of the cause of sensorineural hearing loss eases proper intervention and signalizes valuable prognostic data. Nowadays, the etiology of pediatric hearing loss has been modified, attributable to progresses in gene testing and adequate management of birth infections. This paper updates well known risk factors for progression along with fluctuation of hearing acuity involving health hazard indicators, auditory, laboratory and clinical manifestations of such young patients. This review takes into consideration the most well-known risk indicators associated with an increased likelihood of progressive hearing loss (including but not limited to neonatal intensive care unit admission, family history of hearing loss, various syndromes, prenatal and postnatal infections etc.). Prompt post neonatal monitoring of hearing, leading to early hearing loss identification, is crucial to optimize management and therefore appropriate intervention.

Keywords: Progressive hearing loss; Hearing screening; Gene testing; Children

Introduction

Deterioration of auditory thresholds in young toddlers is of vital interest due to the negative impact on language development. Early detection of the cause of sensorineural hearing loss (SNHL) eases proper intervention and signalizes valuable prognostic data [1]. Nowadays, the etiology of pediatric hearing loss (HL) has been modified, attributable to progresses in gene testing and adequate management of birth infections. The need to further explore risk factors for progression along with fluctuation of hearing acuity involving health hazard indicators, auditory, laboratory and clinical manifestations of such patients is more than urgent so that professionals can intervene in a far more adequate and efficient way [1].

General Concepts Regarding Diagnosis of Progressive Fluctuating Sensorineural Hearing Loss (PFSNHL) in Children

Temporary middle ear disease including Eustachian tube dysfunction and glue ear will need to be excluded as a cause of threshold shifts. That is why both air and bone conduction testing must be done when considering progression, so that the definition of PFSNHL may be applied accordingly. The possibility of non-organic hearing loss presenting as a progressive loss in normal hearing children and children with identified PFSNHL should be always taken into consideration. Moreover, attention should be given to the variation of hearing levels when comparing results of objective hearing tests [e.g. ASSR/ABR] with behavioral hearing thresholds [2]. As some definitions of progressive hearing loss may not consider a particular time window for confirmation of the progression, a minimum audiometric follow-up of 3 months is usually implemented [2].

Etiology of PFSNHL In Children

Taking into consideration the recent advances in the diagnosis and management of infectious etiologies, the rest causes of PFSNHL in children include prenatal, perinatal, postnatal, genetic non-syndromic, and genetic syndromic factors. The most well-known related causations are highlighted right below.

Enlarged vestibular aqueduct (EVA)

EVA is the most frequent innate ear anomaly which can cause SNHL or mixed HL in children [3] and can even induce sudden HL from sudden pressure alterations or insignificant head injury. EVA is defined as a vestibular aqueduct >2.0mm at the operculum and >1.5mm at the midpoint. EVA can occur unilaterally or bilaterally, and associated HL typically fluctuates or progressively worsens from the early childhood. Patients may have reduced hearing at birth, though most are initially diagnosed with HL between 3.5 and 5 years of age. Diagnosis of EVA commonly involves specific high-resolution CT and MRI scans. EVA syndrome is generally resistant to any available intervention and usually redound in HL that is too profound to take advantage from any type of amplification, inevitably necessitating Cochlear Implantation (CI) [3].

Acquired progressive SNHL in infants and young children due to exposure to infectious pathogens

Although exposure to infections during gestation is not uncommon, only a minority of these pathogens can affect the baby. Infections which can induce such a progressive deficit are typically classified as TORCH infections (Toxoplasmosis, Others, Rubella, Cytomegalovirus (CMV), and Herpes simplex viruses). Many other pathogens are considered as equally destructive (such as congenital infections due to Lymphocytic choriomeningitis virus, Treponema pallidum, and nonheritable incidents due to Borrelia burgdorferi, Epstein-Barr virus, Haemophilus influenzae, Lassa virus, Measles virus, Mumps virus, Neisseria meningitides, Non-polio enteroviruses, Plasmodium falciparum, *Streptococcus pneumoniae* and Varicella zoster virus) [4].

Nonheritable SNHL in toddlers is mainly induced by bacterial meningitis and can either affect one or both ears, although bilateral involvement is typically more often [4]. Bacterial meningitis most commonly involve Haemophilus influenzae and *Streptococcus pneumoniae* whereas Flavobacterium, Neisseria meningitides, Mycobacterium tuberculosis and E. Coli are found to be responsible in the minority of cases. Although the majority of toddlers who happen to obtain HL do so after 2 days of entering a medical institution, additional carry-through measurement is mandatory since advancement and fluctuation of the auditory impairment frequently takes place [4].

CMV infection is considered as the most significant cause for PFSNHL, being the top prevailing congenital viral infection in the world. The hazard for congenital CMV (cCMV) contamination is utmost in females without previous immunity who firstly develop CMV infection while being expectant. Nevertheless, emerging research suggests that secondary CMV contamination during pregnancy with immunity prior to impregnation (either due to vivification of an inactive virus or re-contamination with a new species of CMV) can further induce a much higher rate of active cCMV than what was used to believe [5].

Genetic progressive SNHL

Non-syndromic hereditary: More than half of neonates with SNHL have an inherited type of HL. In most cases, it is the outcome of a plain Mendelian recessive type of heredity, where both parents have normal hearing and present a sibling with non-syndromic SNHL (75-80% of instances). Besides that, autosomal dominant (around 20%), X-linked (2–5%), and mitochondrial (about 1%) types further add to the load of inherited congenital SNHL [4,6]. Although autosomal dominant and recessive SNHL is quite heterogeneous, GJB2-3-6 mutations, that alter the operation of the connexin encoded protein in the cochlea, account for up to 50% of hereditary occurrences of progressive SNHL in several parts of the world such as USA, most of Europe, Israel, several Asian, Latin American, and African countries and Australia [4,6].

While it is true that in the above-mentioned world populations, up to half cases of persons with progressive, severe to profound autosomal recessive non-syndromic hearing impairment have pathogenic variants in GJB2 (DFNB1), recent studies have shown that the contribution of pathogenic variants in GJB2 to deafness varies considerably by ethnicity [6]. Because molecular genetic testing is by far the single type of test with the highest diagnostic rate and accuracy, it should be implemented first during the assessment of toddlers with presumed hereditary SNHL and deafness. The only exemption applied is when medical history, physical examination, and audiometric testing implicates a specific syndromic form of HL [6].

Syndromic hereditary: More than 400 genetic syndromes which exhibit HL have been already reported [6]. Although syndromic HL reaches up to one third of prelingual hearing impairment, its part to all hearing deficits is relatively poor, proportionate to the prevalence and identification of post-lingual HL. The most frequent type of syndromic hereditary SNHL is Pendred's syndrome [4]. It is a genetic disorder ending up to bilateral SNHL that is congenital in the majority of the occurrences. HL is typically severe to profound, with several instances of mild to moderate PFSNHL. The auditory deficit is linked to an anomaly of the bony inner ear (bilateral enlargement of the vestibular aqueduct with or without cochlear hypoplasia, a combination described as Mondini's malformation or dysplasia). It should be mentioned that goiter may not be present at birth, and can develop later, in early puberty (40%) or even adulthood (60%) [4,6].

Pendred's syndrome is hardly recognized in the period immediately after birth due to the fact that the thyroid abnormality, as already mentioned, is absent in the neonatal period and CT scan of the temporal bone is not routinely considered as part of the neonatal screening arsenal of testings. Besides Pendred's syndrome, Usher syndrome (particularly type III), Refsum disease, Alport syndrome, and Deafness-dystonia-optic neuronopathy syndrome (Mohr-Tranebjaerg syndrome) represent other known causes of progressive, syndromic hearing loss [6], that are characterized by

huge genetic and phenotypic heterogeneity. This extreme genetic heterogeneity highlights the importance of use of multigene sequencing panels for genetic diagnosis instead of single-gene testing, thus greatly improving the diagnostic rate regardless of presumed inheritance pattern or ethnicity.

Auditory neuropathy spectrum disorder (ANSD)

ANSD is mainly audiologically established, involving hearing deficits in the presence of intact outer hair cell function in the inner ear. It is characterized by the existence of otoacoustic emissions or cochlear microphonics, in conjunction with either highly atypical or disappeared auditory evoked brainstem waveforms. ANSD is believed to define nearly 10% of all early permanent auditory deficits, and may be the outcome of a variety of existing pathologies [7]. HL can be either stable for nearly half the cases, or progressive and fluctuating for the rest ones. A group of high-risk entities correlated with the ANSD include prematurity, jaundice, ototoxic medications, infections, various genetic anomalies (including but not limited to otoferlin, connexin 26, and SX010 gene mutation) [7].

Other less common causes of PFSNHL in children

Numerous publications have reported that a lot of usual, commercially accessible toys may deliver electronic sounds which are extremely loud [8]. Noise induced fluctuating audiometric threshold shifts are constantly reported in toddlers, with the presumed inclination reaching just below 10 percent in young children [8]. Meniere's disease (MD) in young children is quite uncommon, representing only 2% of MD patients in general [9]. Nevertheless, the inner ear dysfunction in children's MD did show a significantly declining order from the cochlea, to the saccule, utricle and semicircular canals, mimicking the sequence in a typical adult MD, thus producing fluctuations along with progressive threshold shifts [9]. One third of these children have a family history of MD, that can assist in the early diagnosis and proper intervention.

Haemoglobinopathies can also be associated with PFSNHL [e.g. sickle cell anaemia]. Moreover, ototoxic interventions in young children (including but not limited to radiotherapy and platinum compounds like cisplatin/carboplatin administration in children with severe head and neck cancer) [10] may also cause PFSNHL. Besides that, a past history of aminoglycoside use should be specifically investigated. In such cases targeted audiologic re-evaluations is a prerequisite for early detection and appropriate management of ototoxicity. Rarely, cochlear otospongiosis presenting as pure SNHL should be considered as a part of the differential diagnosis in older children exhibiting PFSNHL [11]. Finally, PFSNHL can also occur as a part of multisystem autoimmune conditions e.g. SLE, Cogan's syndrome or it could be the only presenting feature of an immune-mediated inner-ear disorder.

Laboratory Investigation Of PFSNHL

Besides clinical history and full body clinical examination, ophthalmic assessment and genetic evaluation may be necessary as several corresponding conditions may cause PFSNHL [2]. Parents' and siblings' audiograms may be also helpful in interpreting genetic test results [2].

MRI of Internal Auditory Meati / brain or CT scans of Petrous Temporal Bone

MRI is the method of choice for PFSNHL offering an enhanced footprint of the cochlea-vestibular nerve, its cochlear division, along with the central auditory pathways and cortex. The inner ear structure such as inner ear fluids, fibrosis, and interscalar defects are most visible on MRI. CT on the other hand is optimal for little patients suffering from HL with a stable conductive component (besides meningitis). Both illustrative modalities are helpful in bacterial meningitis where neither imaging technique by itself is adequate in exhibiting anatomical modifications due to fibrosis or ossification [2]. In rare cases of children with PFSNHL, high resolution CT can manage to identify potential progressive cochlear otospongiosis [11]. Appropriate intervention and if needed amplification should be initiated in these young patients while monitoring the progression of the disorder.

CMV testing

CMV testing should be routinely carried out for all children with progressive HL. If mother's CMV IgG/IgM are both negative, congenital CMV (cCMV) infection is excluded and venepuncture in the child can be avoided. If maternal antenatal sample is addressable, mother's IgG low avidity measurements can indicate recent CMV infection [2]. If the infant is less than one-year old urine or saliva samples should be sent for CMV DNA PCR. In case of saliva samples, meticulous care to postpone breast-feeding for the preceding 1 hour must be taken in order to diminish the propability of false positive measurements due to CMV contamination from breast milk [2]. If the infant is less than 3 weeks old during testing, a positive result from either the saliva or the urine sample may be considered as sign of cCMV infection. If the infant is more than 3 weeks old, the neonatal dried blood spot should be respectively sent for CMV DNA measurement to establish the diagnosis of cCMV infection [2].

It should be mentioned that although a positive outcome for CMV DNA PCR on the dried blood spot taken in the first 3 weeks of life validates the diagnosis of cCMV, a negative test does not reliably omit cCMV. Dried umbilical cord can be utilized respectively to demonstrate cCMV infection [2]. Moreover, most recently, a targeted screening program for cCMV was established for neonates who fail the initial newborn hearing screening as a mean to early identify HL and prevent potential developmental and cognitive delays [12].

Urine examination

Urine examination for microscopic hematuria and proteinuria is essential, particularly to a family history of renal disease, and should be repeated at least on one occasion as abnormalities may be missed with a single sample. Renal ultrasound can also be a part of the routine examination perspectively. Moreover, as a recent study on a large scale mentioned [13], universal urine screening

likely identifies subclinical symptomatic cCMV further contributing to early diagnosis and intervention. Urine examination can also be useful in rare cases of chemical exposure-induced ototoxicity, especially in early-life exposure to particular heavy metals from specific waste areas [14]. Evidence suggests that increased urine measurements of lead (Pb) and cadmium (Cd) levels, leading to corresponding blood DNA methylations of Rb1, CASP8 and MeCP2 may induce epigenetic modifications to the hearing acuity of preschool children [14] supporting an epigenetic type of PFSNHL.

Genetic tests

As a general rule, blood tests for GJB2/GJB6 and for mitochondrial HL (1555A>G mutation) are advisable in all cases of bilateral progressive HL, where etiology has not yet been determined. Genetic testing is usually performed by sequencing. The chain-termination method of sequencing enables analysis of a small amount of genes, predetermined, according to the initial clinical findings and the professional judgement of the health care professional involved [15]. In contrast, next-generation sequencing permits analysis of a far greater amount of genes related to HL [15]. Proper genetic testing enables family counselling, documents related comorbidities that may need to be further addressed, allows early and proper intervention and finally assists in the development of novel therapeutic approaches [15]. The evolution of Next Generation (Massively Parallel) sequencing, where vast numbers of genes can be sequenced quickly and relatively thrifty, represents the immediate present and future in genetic evaluation of PFSNHL [6].

Serology for other infections

Mothers may be screened for infections causing PFSNHL during pregnancy. When their immune status is unknown then the following conditions should be routinely checked as many of the affected babies can be asymptomatic at birth.

Congenital toxoplasmosis: If child is <1 year of age, testing should include maternal toxoplasma IgG: In case of negative result, congenital Toxoplasma infection is excluded. In case of positive outcome, congenital toxoplasma cannot be ruled out. In this scenario, if child's Toxoplasma IgM is positive, this points towards congenital infection. When both Toxoplasma IgG/IgM are negative, congenital toxoplasmosis can be safely excepted [2]. If child is >1 year of age, should child's and mother's Toxoplasma IgG are negative congenital Toxoplasma infection is excluded. When both are positive, extra evaluation of child's and mother's plasma (along with antenatal maternal blood when present) may be needed [2].

Congenital Rubella: <6 months old, when child's Rubella IgM is negative congenital rubella is rare. Further confirmation is needed with a rubella IgG exam at one year (prior to MMR). Earlier than this age detectable IgG can originate from the mother. When positive, further evaluation necessitates, as positive predictive value of a single IgM test is low [2]. >6 months of age, Child Rubella IgG at one year old (strictly prior to MMR); when negative, it leaves out congenital rubella infection. when positive, Rubella may be likely diagnosed [2].

Congenital Syphilis: IgM-positive neonatal serum can be regarded as evidence of congenital infection. TPHA and FTA-ABS tests [IgG] can be alternatively utilized to leave out congenital syphilis if the tests are unclear in an infant <12months old who has not received intervention [2].

Congenital HIV: Testing may be advised in 'at risk' pregnancies when the maternal HIV status is not clear [2].

Investigation of autoimmune diseases

Given the potential for treatment and importance of early intervention, blood tests for autoimmune/ immunological conditions should be offered to children with PFSNHL. Tests can involve antinuclear antibodies, antineutrophil cytoplasmic antibodies, DsDNA, RA factor, antiphospholipid, anticardiolipin, antithyroid antibody, antibodies to Sm, C3 and C4 [2]. General inflammatory markers i.e. ESR, CRP and FBC may also be useful [2].

Vestibular investigations

Vestibular dysfunction is seen in several conditions that cause PFSNHL e.g. CMV, EVA, Usher 3, Cogan, and meningitis. All corresponding children may undergo a clinical vestibular evaluation and if feasible vestibular testings, including calorics, VEMPs, video Frenzel's glasses and vHIT testing [2].

Epilogue

Universal newborn hearing screening can nowadays provide precise data on the progression of HL in young children. Before that, such drift was difficult to assess because of inadequate information on HL onset. Recent findings [16] emphasizes that almost 50% of children diagnosed with mild bilateral HL showed a decrease in hearing in a period of 1 year and more. Taking into consideration the most usual risk indicators associated with an increased likelihood of progressive HL [1] (including but not limited to neonatal intensive care unit admission, family history of HL, various syndromes, prenatal and postnatal infections etc.), close post neonatal monitoring of hearing following early HL identification is crucial to optimize amplification and/or other appropriate intervention [1].

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Conflict of Interest

No Conflict of Interest.

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