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HEARING LOSS IN CHILDREN (D HORN AND H OU, SECTION EDITORS)

Update on Auditory Neuropathy/Dyssynchrony in Children

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Abstract

Purpose of Review Auditory neuropathy/dyssynchrony (AN/AD) is a form of sensorineural hearing loss characterized by the presence of cochlear outer hair cell (OHC) function and absent or abnormal auditory neural function. This article is meant to update clinicians on best practices for diagnosis and management of AN/AD.

Recent Findings Exciting advances in genetics present opportunities for additional evidence to classify AN/AD based on site of lesion, and may lead to additional understanding of the pathophysiology as well as prognosis. Cochlear implantation continues to be a highly effective intervention for managing AN/AD in pediatric patients.

Summary AN/AD can be a challenging condition to manage given the heterogeneity of its presentation and variety of options for management. Ultimately, clinicians must tailor treatment to the individual child which requires frequent follow-up and communication with families, educators, and other providers. Further research is needed to fully understand this disorder and advance evidence-based care for these children.

Keywords Auditory neuropathy · Auditory dyssynchrony · Cochlear implant

Introduction

Auditory neuropathy/dyssynchrony (AN/AD) is a disorder in which hearing impairment results from a lesion within the cochlea and/or auditory nerve. AN/AD is a distinct form of sensorineural hearing loss (SNHL) with a unique clinical presentation and diagnosis. Typical presentation of SNHL includes loss of outer hair cell function, and in severe cases inner hair cell function, while in AN/AD outer hair cell function is maintained with a site of lesion located within the inner hair cells and/or auditory nerve [1]. This is apparent in the diagnosis of AN/AD, which is characterized by present cochlear microphonic (CM) with absent or abnormal auditory brainstem response (ABR) [2]. Otoacoustic emissions (OAE) may also be present in AN/AD but are absent in approximately 15% of cases and therefore not solely relied upon for diagnosis [3•, 4, 5, 6, 7]. Additional clinical features of auditory neuropathy include speech perception deficits beyond what is expected from a behavioral audiogram, absent middle-ear reflexes, and varying degrees of stable or fluctuating hearing loss [8]. For this auditory disorder, including the term "dyssynchrony" has been proposed versus solely using "neuropathy' given that the auditory nerve may not always be directly implicated in all patients, and to ensure clinicians do not overlook cochlear implantation as a successful option for managing hearing impairment [9]. Patients with AN/AD experience disordered processing of auditory signal timing information that manifests as temporal dyssynchrony [10] which further supports use of this terminology.

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Pathophysiology

There are multiple potential sites of lesion that can result in the clinical presentation of AN/AD, including within the inner hair cells (IHCs, pre-synaptic), the synapse between the IHC and auditory nerve (AN, synaptic), or the AN itself (post-synaptic) [1, 6, 11]. Loss of IHCs [12] or dysfunction in pre-synaptic proteins that are responsible for neurotransmitter release [5, 13, 14] are two possible mechanisms for pre-synaptic/synaptic site of lesion in AN/AD. Within the AN,

demyelination or axonal damage sufficient to impede action potential conduction can present as AN/AD [15].

Prevalence and Risk Factors

Prevalence of AN/AD in the pediatric profound hearing-loss population ranges from approximately 5 to 10% [16–23]. A major risk factor for developing AN/AD is neonatal injury; commonly associated conditions include anoxia, hyperbilirubinemia, kernicterus, and prematurity [8, 24, 25]. The percentage of AN/AD in infants identified with hearing loss increases several-fold within the NICU population, with estimates cited anywhere from 24 to over 40% [26, 27]. Other risk factors include infectious processes (e.g., measles, meningitis), family history of hearing loss, and syndromic conditions (e.g., Charcot-Marie-Tooth disease, Friedreich's ataxia, PHACE syndrome) [8, 28]. However, even within well-baby nurseries alone, there are between 6 and 30/100,000 children with AN/AD that warrant early referral and follow-up [17, 29]. Therefore, it is important that clinicians are adequately screening for AN/AD in all infants and young children.

Newborn Screening

Timely screening and diagnosis of children with all types of hearing loss are critical to ensure early and optimized auditory intervention, and identifying AN/AD requires specific considerations. One common method of audiology referral for infants with AN/AD is through Universal Newborn Hearing Screen (UNHS) programs [30]. In general, there are two currently accepted methods to perform screening, either OAEs or automatic ABR (AABR). The Joint Committee on Infant Hearing (JCIH) recommends that all infants who have received care in the NICU are screened using AABR, given their higher prevalence of hearing loss and risk of AN/AD [31]. In well-baby nurseries, current clinical protocols may allow choosing either OAE or AABR for hearing screening; however, the JCIH states the preferred method is using AABR for initial screen, and a second AABR to rescreen infants that fail initial screening [31], and is the standard practice we have established for newborn hearing screening with our hospital partners. A one-step AABR screening program is more efficient and cost-effective when compared to OAE screening alone or two-step OAE with AABR screening [32]. Highly discouraged is the practice of initial screening with OAE or re-screening with OAE after a failed AABR, as it will miss children with AN/AD and result in delayed diagnosis.

Diagnosis

Full diagnostic testing for AN/AD should be pursued in all cases where there is an absent ABR at screening or absent/abnormal ABR at follow-up testing. Infants with significant family and/or neonatal histories should also be tested for AN/AD, including those with diagnosis or risk for other degenerative neuropathies. For example, older children may present with AN/AD if they have hereditary sensory and motor neuropathies, such as Charcot-Marie-Tooth disease or Friedreich's ataxia [1, 6, 15, 33]. Finally, children with poorer speech perception than would be predicted by pure-tone thresholds should be evaluated for AN/AD, since audiometric findings in AN/AD can range from normal hearing to profound hearing loss [3•].

The diagnosis of AN/AD requires performing an ABR to confirm absent or abnormal neural function with the presence of functioning outer hair cells (OHCs). Testing OHC function for the purpose of diagnosing AN/AD uses cochlear microphonics (CM) instead of OAE [34], as CM is a more stable measure of OHC function [5, 6]. While not used for diagnosing AN/AD, OAE results are useful in the ambulatory clinical setting as part of a comprehensive audiometric evaluation combined with other test results. Middle ear muscle reflexes (MEMRs) are typically absent in children with AN/AD [11, 3•], and also provide a readily available screening method for children with hearing loss in the clinical setting. Children with absent or elevated MEMRs, particularly with present OAEs, should be referred for full evaluation with a diagnostic ABR to test for AN/AD.

Imaging

Children with AN/AD have a high incidence of abnormal radiological findings, and imaging should be considered for patients with both unilateral and bilateral AN/AD [35•]. Nearly two-thirds of children with AN/AD will have at least one abnormality on MRI [36•]. Approximately 20–25% of these abnormalities include cochlear nerve dysplasia, with 15% of children observed having total absence of the cochlear nerve [36•, 37]. While amplification and cochlear implantation may appear to be contraindicated in patients with small or absent cochlear nerves [37], some studies have shown that children with AN/AD may still benefit from these interventions [38, 39]. A temporal bone CT can also be ordered for further evaluation of suspected enlarged vestibular aqueduct or cochlear anomalies, as this method may hold slight advantage over MRI [40]. Clinicians should weigh the risks of sedation in young children for MRI and ionizing radiation for CT with the benefit of yielding a diagnosis [40, 41].

Genetics

Clinicians caring for pediatric patients with AN/AD may wish to consider genetic testing, as this may provide additional insight into the site of lesion for a particular care of AN/AD as well as potential prognosis of outcomes with interventions [42•, 43•]. Genes commonly implicated in isolated AN/AD

include OTOF/DFNB9, PJVK/DFNB59, and DIAPH3/AUNA1 [42•, 43•, 44, 45]. There may also be variants resulting in AN/AD as part of a global peripheral neuropathy in MPZ, PMP22 [43• , 42•], FXN [45], and OPA1 [42•, 43•, 45]. Several genetic services offer testing for these specific genes, and in some cases, the AN/AD genes or specific variants may be included in panels that test for several known genetic causes of hearing loss [46, 47]. Other options include comprehensive genetic testing using next generation sequencing (NGS) methods to guide clinical decision making and family counseling through the process of genetic counseling [35•, 48]. Given the variety of genetic testing options, interpretations and interventions, consultation with geneticists and genetic counseling professionals is recommended.

Management Overview

Children with AN/AD demonstrate at least some degree of audiometric hearing loss in 97% of cases, with 30% of these in the profound hearing loss range [3•]. Several options exist for children and their families in managing hearing loss from AN/AD, including amplification via hearing aids, assistive devices such as FM systems, strategies such as preferential seating in classrooms and other noisy environments, and cochlear implantation (CI). The primary auditory interventions for AN/AD are summarized below.

Amplification

Once diagnosed, children with AN/AD showing any degree of hearing loss should be fit with a hearing aid (HA) as soon as possible [49, 50]. Determining appropriate amplification gain is challenging for children with AN/AD who are unable to provide accurate behavioral thresholds, such as very young infants or those with developmental delays, as neither ABR nor OAE can be used as valid behavioral threshold estimates [4, 51, 52]. In these cases, amplification fitting must rely on the observations of both clinicians and parents to closely monitor whether the amplification is adequate to ensure detectability of conversational speech levels. Once behavioral thresholds are obtained, target amplification gain should be fit to the level of hearing loss and adjusted based on the child's behavioral responses to sound with amplification. Providing adequate gain for children with AN/AD is essential; in previous practice, children with AN/AD were routinely fit with mild gain regardless of target gain needs, with the rationale that limiting gain would "protect" the functioning OHCs from acoustic damage. It has since been determined that HA use in AN/AD does not cause OHC damage, and underfitting children minimizes HA benefit and is therefore discouraged [6, 53, 54]. For children with mild hearing loss, low-gain amplification is appropriate to improve auditory attention and perception [55]. Overall, consistent use of appropriately-fit HAs is critical for optimizing device benefit [56, 57]. In cases of AN/AD where hearing threshold fluctuation is confirmed or suspected, monitoring tolerance of amplified sounds is particularly important [55, 58].

Evidence shows that some children with AN/AD can be successfully managed with conventional amplification [4, 49–52, 59–63]. Pediatric AN/AD patients who see benefit from HA use demonstrate increased general auditory responsiveness [4, 60•] and speech perception [4, 49, 51, 60•, 63•], as well as sufficient speech and language development [50, 62, 63•]. These outcomes from HA use can be similar to AN/AD patients who have received a CI [49, 59•, 60•, 62] as well as their age-matched SNHL counterparts using HAs [50, 51, 59•, 63•]. However, there are also studies that report little to no benefit of amplification among AN/AD patients [3•, 55]. HAs provide improved audibility by amplifying sounds, but do not address any aspect of temporal processing impairment. In cases of severe temporal processing impairment in AN/AD, HAs present an amplified version of a temporally distorted signal which minimizes benefit of acoustic intervention [8, 64]. Therefore, children with AN/AD who benefit from HAs tend to have less disordered temporal processing compared to those who are ultimately CI recipients [60•, 62].

Regular assessment and close follow-up of progress in auditory skill, speech, and language development are necessary during HA use in AN/AD to evaluate whether the child would benefit from changes in intervention approach, including consideration of cochlear implantation. To assess development of auditory skills, our clinic uses the LittlEars Auditory Questionnaire (LEAQ, MED-EL Corp., Innsbruck, Austria). The LEAQ is a brief questionnaire designed to assess progressive auditory milestone development of sound detection, comprehension, and expressive-vocal behaviors, and is standardized to normal-hearing children up to 24 months of age [65]. LEAQ scores obtained at HA fitting and then at 3-month interval are used to evaluate progress in auditory skill development during the HA trial. Over time, the LEAQ score trajectory will indicate any plateaus in development, allowing clinicians to modify intervention strategies. Assessment of speech and language development should be conducted every 6 months by qualified professionals such as Speech-Language pathologists to ensure development is progressing or to alert the team if delays are emerging. Speech perception should also be evaluated using validated measures as soon as the child is able [10, 51, 66] with speech perception testing in noise taking place once the child is older than 3 years [62, 67]. While there are no specific quantitative criteria for using these measures to determine cochlear implantation candidacy in AN/AD, the multidisciplinary team should communicate frequently with each other and families of children with AN/AD to monitor for any delays in development and to inform timely clinical recommendations of all interventions, including cochlear implantation candidacy.

Frequency Modulation Systems

Temporal processing impairment in AN/AD leads to significant challenges understanding speech in background noise, even in children who did not require intervention at early ages and showed normal speech and language development [3•, 30, 67, 63•]. A frequency modulation (FM) system can be used by children in noisy environments such as classrooms to help minimize the background noise and facilitate speech perception [68, 69]. Depending on the child's hearing needs, FM systems can be used independently or as an accessory with a HA or CI.

Cochlear Implantation

Cochlear implantation (CI) is a viable option for managing AN/AD. Unlike SNHL, children with AN/AD who have mild to moderate hearing loss may not benefit from conventional amplification alone [4, 3•, 51]. Additionally, approximately 30% of children with AN/AD have severe-to-profound hearing loss, and patients in this audiometric category should be considered for CI candidacy [3•]. While acoustic hearing interventions solely provide amplification, direct electrical stimulation of the auditory nerve provided by CIs can restore neural synchrony in addition to increasing access to speech sounds [8, 64]. Children with AN/AD should have both CT and MRI imaging prior to implantation [37, 36•] and be assessed for potential contraindications, such as an absent auditory nerve or severe peripheral or central neuropathy (e.g., severe kernicterus, Friedreich's ataxia). If no contraindications are present, cochlear implantation should be considered for a child with AN/AD who is showing lack of progress or delays in auditory, speech, and language skill development despite using appropriately-fit HAs [3•].

Outcomes of cochlear implantation in children with AN/AD indicate this as a successful management approach in many cases. A large multi-center study evaluating management strategies for children with AN/AD found that 86% of implanted children demonstrated successful outcomes with CI as determined by audiologist and parent report, with 12% uncertain/too early to tell, and 2% slow progress. In contrast, HA outcomes were determined as 'good' or "some" benefit (i.e., functional interaction, help with language acquisition) for 14% of children, and little or no HA benefit for 86% [3•]. Improvement of speech perception and language development in AN/AD patients has been shown to match those of SNHL controls [70–77, 59•], although variability in outcomes in the AN/AD population also includes some with poorer outcomes [61]. CIs also improve speech perception in noise for children with AN/AD [70, 72, 76, 60•], and parents report higher satisfaction in subjective measures, as well as improved psychosocial factors [78–80]. Given the heterogeneity of the disorder, it is unsurprising that several studies report variability in performance outcomes after CI [58, 81, 82]. Yet, this variability has also been shown not to differ significantly from patients with CI due to other forms of hearing loss [59•]. Larger-scale and longer-term studies can further explore the efficacy of CI as a treatment for AN/AD [52, 64, 83].

There are several prognostic factors that can help gauge who will most and least benefit from cochlear implantation in AN/AD. As for children with SNHL, early age at implantation [77, 84–86, 59•, 60•] as well as length of use [60•] are considered positive factors in performance for AN/AD. Additionally, distal sites of lesion—for instance, at the inner hair cells or dendrites of spiral ganglion (SG) cells in the auditory nerve—are thought to result in more favorable CI outcomes compared to more proximal lesions affecting the soma and axon of SG cells [5, 45, 43•], which has implications of outcomes in AN/AD relative to the site of lesion. AN/AD patients with OTOF mutations likely have a pre-synaptic site of lesion within the IHCs and generally show excellent outcomes after CI [44, 87–89] as the CI stimulation bypasses the defective IHCs cells to stimulate a presumably functional auditory nerve [43•]. However, clinicians must be mindful to evaluate the whole child, as genetic site of lesion assessment does not necessarily rule out other potential factors that impact CI use. For example, one study presented two siblings with AN/AD and the same OTOF variant who showed very different CI speech perception outcomes and auditory nerve responses [44]. Cochlear nerve dysplasia (CND) may manifest as a diagnosis of AN/AD, and can impact cochlear implant outcomes [38, 90–92]. Cognitive or developmental disabilities predict poor performance with a CI [73, 93, 94], and should be part of a comprehensive CI assessment in AN/AD. Overall, these comorbidities may not preclude CI as patients with AN/AD may still show benefit [93, 95], but these factors need to be considered along with those described above when counseling families on appropriate expectations.

CI programming and binaural listening configuration options should be considered to provide optimal listening for patients. A programming option for an implanted child with AN/AD who may not be performing well with a CI may be to slow the stimulation rate of the sound processing strategy [93]. If a child has aidable hearing in the ear contralateral to the CI, a bimodal listening configuration (i.e., hearing aid in the contralateral ear) should be considered as the amplification may provide additional benefit above the CI alone [91, 94, 96]. Bilateral cochlear implantation should be considered for children with bilateral severe-to-profound hearing loss, and may be indicated if concerns of speech and language development persist after unilateral CI [94]; additional benefits to bilateral CIs include improved sound-source localization [97].

Other Considerations

Neural Maturation

For SNHL, age of cochlear implantation continues to decrease in the pediatric population, with some infants being implanted as early as 4 months to optimize speech and language development during this critical period [98–101]. In AN/AD, children with risk factors of prematurity and low birth weight should be closely followed to assess nervous system development during the first 12 months of life prior to moving forward with cochlear implantation [30, 99, 102–104]. If an absent/abnormal ABR is due to neural maturation, this is expected to resolve by around 12-month adjusted age. Therefore, ABR testing for premature infants should be repeated at 12-month adjusted age and prior to cochlear implantation.

Temperature-Sensitive AN/AD

One type of AN/AD is temperature-sensitive auditory neuropathy (TSAN), where patients can experience moderate to profound hearing loss when febrile [89, 105–107]. Children with TSAN generally present with normal to mild hearing loss when afebrile, but report fluctuations in their hearing [89, 105], speech perception worse than predicted by audiometry [107], difficulty hearing in noise [106, 107], and delay in language acquisition [105, 106]. TSAN has been linked to homozygous and compound heterogeneous OTOF mutations [89, 105] and genetic testing should be considered if a child is suspected to have TSAN. There is little evidence on effective treatment. Some patients develop normally with no intervention [106], and preliminary studies show hearing loss may recover with age [89]. Hearing aids may help with audibility [105], but HA use needs to be closely monitored to ensure appropriate sound output during fluctuations. Cochlear implants have been successfully used in one case [89].

Conclusion

AN/AD can be a challenging condition to manage given the heterogeneity of its presentation, varied outcomes, and differing sites of lesion. To optimally manage AN/AD and support the children and families requires a multidisciplinary team, close monitoring, and frequent communication among all involved in the child's care. The exciting developments in technology, diagnostic testing, and understanding of AN/AD will certainly bring new insight and opportunities to further improve providing the best care for these patients.

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Compliance with Ethical Standards

Conflict of Interest Alexandra N. Roman The author declares that she has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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