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REVIEW ARTICLE

Auditory neuropathy: Endocochlear lesion or temporal processing impairment? Implications for diagnosis and management

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Hearing aids;
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Summary

Background/Objective: Auditory neuropathy/dys-synchrony, characterized by absent auditory brainstem responses, normal otoacoustic emissions or cochlear microphonics, and word discrimination disproportional to the pure-tone audiogram, may be accompanied by perceptual consequences that could jeopardize language acquisition in affected children. However, the related evidence is constantly changing leading to a serious debate.

The aim of the present paper is to review the current knowledge on auditory neuropathy/dys-synchrony, and to present the therapeutic strategies that can be employed in its management, taking into account the potentially underlying pathophysiology.

Materials/methods: Literature review from Medline and database sources. Related books were also included.

Study selection: Controlled clinical trials, prospective and retrospective cohort studies, nested-based case-control and analytical family studies, laboratory and electrophysiological studies, animal models, case-reports, joint statements and review articles.

Data synthesis: Auditory neuropathy/dys-synchrony, in contrast to what is widely believed, is a very frequent disease, responsible for approximately 8% of newly diagnosed cases of hearing loss in children per year. Hyperbilirubinemia and hypoxia represent major risk factors, whereas generalized neuropathic disorders, or a genetic substrate involving the otoferlin gene, are responsible for the phenotype of auditory neuropathy/dys-synchrony in certain cases. Auditory nerve myelinopathy and/or desynchrony of neural discharges are the most probable underlying pathophysiologic

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mechanisms. Genetic testing may be helpful in cases of non-syndromic prelingual children. Auditory neuropathy/dys-synchrony management aims at restoring the compromised processing of auditory information, either through conventional amplification and/or alternative forms of communication, or by cochlear implantation (combined with intensive speech and language therapy).
Conclusion: Auditory neuropathy/dys-synchrony is more frequent than considered in the past, especially amongst hearing-impaired children. Accurate diagnosis, based on subjective and objective hearing assessment techniques (including the various electrophysiological assessment measures), and timely treatment of the affected children is of paramount importance, with hearing aids, intensive speech and language therapy (and sign language when indicated) providing the mainstay of habilitation, and cochlear implantation representing a valid therapeutic alternative.

Contents

1. Introduction

Hearing provides the pathway through which children normally develop spoken language. It has been demonstrated, however, that speech recognition largely depends on the neural synchrony of auditory perceptions [1], as the latter affects the neural representation of sensory events [2]. Therefore, a desynchronized auditory nerve activity may be accompanied by perceptual consequences, and needs to be timely addressed, in order to ensure a useful language input that could trigger the processes of language acquisition in affected children.

As a clinical entity, auditory neuropathy (also termed auditory dys-synchrony) (AN/AD) is characterized by absent, or grossly abnormal auditory brainstem responses (ABRs), with normal otoacoustic emissions (OAEs) and/or cochlear microphonics (CMs). In addition, word discrimination in these patients is impaired and seems to be disproportional to the pure-tone audiogram [3]. Although this definition is widely accepted in principle, there is still a serious controversy with regard to etiology and management of the AN/AD disorder, with new evidence challenging whatever consensus had been previously achieved.

The aim of the present paper is to review the current knowledge on AN/AD, and to present the therapeutic strategies that can be employed in its management.

2. Materials and methods

An extensive search of the literature was performed in Medline and other available database sources, establishing two main categories of outcomes:

(a) evaluation of the techniques that have been used in the diagnosis of AN/AD in the pediatric population and (b) assessment of the efficacy of different modalities in the management of AN/AD, taking into account the varying pathologic substrates and related pathophysiologic mechanisms.

Using this framework of results, the retrieved studies were critically appraised, according to evidence-based guidelines for the categorisation of medical studies (Tables 1 and 2) [4]. In addition, two secondary end-points were also analysed:

(a) the prevalence of AN/AD, (b) identification of the pathologic lesions and pathophysiologic mechanisms that may be held accountable for the AN/AD phenotype.

During the search the keywords "auditory neuropathy", "auditory synaptopathy", "inner hair cell pathology", "risk factors", "Charcot-Marie-Tooth", "diagnosis", "amplification" and "cochlear

Table 1 Evidence-based categorisation of medical studies

Category of evidence	Origin of evidence
Ia	Evidence from meta-analysis of randomised controlled trials
Ib	Evidence from at least one randomised controlled trial
IIa	Evidence from at least one controlled study without randomisation
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

implants'' were utilized. The keywords ''auditory neuropathy'' and ''auditory synaptopathy'' were considered primary and were either combined to each of the other keywords individually, or used in groups of three. Information from electronic links and related books was also included in the analysis of data. In addition, reference lists from the retrieved articles were manually searched.

Apart from the plain audiologic data and the related diagnosis of AN/AD, every effort was made to investigate and analyse (separate if possible) other neurological disorders that may be involved in the disease process and extent beyond the spiral ganglion neurons or the acoustic nerve [5].

3. Results

Seven controlled clinical trials, 17 prospective cohort studies, 14 retrospective cohort studies, seven nested-based case-control studies, nine analytical family studies, three laboratory studies, 18 electrophysiological studies, seven animal models, 19 case-reports, one guideline, one joint statement and 12 review articles met the defined criteria and were included in study selection.

4. Discussion

4.1. Epidemiology

It was not unusual for most ENT doctors until recently to consider AN/AD a very rare disease, with little (if any) chance to be encountered in their clinical practice. However, current evidence largely supports the opposite—the disease is much more frequent than initially anticipated.

Hence, AN/AD is currently held accountable for as much as 8% of newly diagnosed cases of children with hearing loss per year [6], representing a rather alarming figure, as AN/AD is relatively recently acknowledged, therefore may have been seriously underestimated and undertreated in the past. The prevalence of AN/AD is estimated to range between 0.23% and 0.94% in infants ''at risk'' for hearing impairment [7,8], whereas an ever higher prevalence of 1.96% was reported in a study that involved neonatal intensive care unit graduates [9]. Among children with confirmed diagnosis of permanent hearing loss the prevalence reaches 7%, or even 11% [7,8,10].

With regard to the age of symptom onset, AN/AD is categorized in two distinct groups; an early-onset form, typically associated with a neonatal insult, and a delayed-onset form, which is usually accompanied by generalized neuropathy. However, only 25% of AN/AD cases are older than 10 years when the symptoms of the disease initially occur [11], whereas generalized neuropathic disorders are present at about 80% of patients with symptom onset occurring after the age of 15 [10].

4.2. Pathology—pathophysiology

Although the underlying lesion(s) and the pathophysiologic mechanisms in AN/AD are key-points in understanding and treating the disease, the related evidence is still unclear and, in some cases confusing. In depth study of the most recent data, concerning clinical and electrophysiological research in this field, support the hypothesis that AN/AD is not a single disease, but a spectrum of pathologies that affect the auditory pathways [12].

It has been repeatedly found that there is a strong association of AN/AD with neonatal risk factors for hearing loss, such as prematurity, hyperbilirubinemia, hypercholesterolemia, hypoxia, neural ischemia and central nervous system immaturity, separately or in combination, along with low-birth weight and idiopathic conditions [8,13—15]. Administration of certain antibiotics and diuretics in neonatal intensive care units has also been implicated in the development of the AN/AD profile [14]. Hyperbilirubinemia and hypoxia seem to prevail among the risk factors [6,8,16—18]. More than 50% of early-onset AN/AD cases reported in the literature so far, have a medical history that

Table 2 Cochlear implantation outcomes in AN/AD children

Type of study	Authors	Ev. lev.	Implant type	Studied groups	Reported advantages	Reported disadvantages	Remarks
Prospective control [81]	Gibson and Sanli	IIa	Nucleus Cochlear	AN/AD-EABR normal/ abnormal experimental/ SNHL EABR normal control	(a) Speech perception in AN/AD children with normal EABR is better than their SNHL peers and (b) speech perception in AN/AD children with abnormal EABR is worse than their SNHL peers	Not all studied groups showed normal distribution	Only 25% of children fitting the AN/AD profile seem to have an actual neuropathy
Retrospective cohort [115]	Shehata-Dieler et al.	IIb	wnr	AN/AD children not responsive to hearing aids	(a) Children developed open-set speech discrimination, (b) children utilized oral language, and (c) children were able to discuss with familiar persons	None reported	Cochlear implantation should be utilized if conventional amplification fails
Case-reports [28]	Rouillon et al.	III	Nucleus cochlear	DFNB9 deafness	(a) Considerable to remarkable identification of open-set words, (b) considerable identification of open-set sentences, and (c) highly satisfying MAIS scores	Age at implantation and idiosyncratic factors influence implantation outcomes	Hereditary, non-syndromic, prelingual deafness
Retrospective control [109]	Buss et al.	IIa	Clarion	AN/AD experimental/ SNHL control	(a) All implanted children performed at a comparable level to their SNHL peers, regarding speech production and (b) all children demonstrated synchronous neural response to the stimulation delivered through the implant	Post-implantation behavioral data in one child remained variable	The possibility of true variability in auditory processing abilities in some AN/AD children cannot be disregarded

Retrospective cohort [6]	Madden et al.	IIb	Clarion/ nucleus cochlear	AN/AD children with bilateral profound HL	(a) Significant improvement in auditory and communicative skills and (b) significant closed- and open-set discrimination scores	None reported	(a) Longer period of waiting before cochlear implantation than SNHL peers and (b) not available data for all implanted patients
Retrospective cohort [110]	Shallop et al.	IIb	Nucleus cochlear	AN/AD children with severe to profound HL	(a) All implanted children moved from category 1 ESP preoperatively, to category 4 postoperatively, (b) all implanted children showed significant improvement in speech awareness, (c) children tested with GASP demonstrated open-set word recognition, and (d) children were able to talk to the telephone	Less than optimal results were encountered in one child	Children did not have additional neurological deficits
Case control [57]	Miyamoto et al.	III	Nucleus Cochlear	Post-lingual progressive deafness-Freidreich's ataxia experimental/ post-lingual progressive deafness control	(a) Closed-set vowel recognition comparable to controls	(a) Closed-set consonant recognition lower than controls and (b) open-set word recognition lower than controls	(a) Post-lingual deafness and (b) modest benefits after cochlear implantation

ev. lev.: evidence level, AN/AD: auditory neuropathy/dys-synchrony, SNHL: sensorineural hearing loss, EABR: electric auditory brainstem responses, ESP: early speech perception, MAIS: meaningful auditory integration scale, GASP: Glendonald auditory screening procedure, and wnr: was not reported.

includes exposure to either one (or both) of these factors [10].

Bilirubin neurotoxicity results from the detrimental effect of prolonged exposure of the auditory system to excessive unconjugated bilirubin fraction, at different stages of neurodevelopment [19]. Bilirubin selectively damages the brainstem auditory nuclei, and may also damage the auditory nerve and spiral ganglion containing cell bodies of the primary auditory neurons [20]. As a result, the paucity of large caliber neurons undermines the temporal coding of auditory information, which is a prerequisite for neural synchrony [21].

In addition, animal experiments have also demonstrated that in contrast to the effects of acute anoxia, in which all the aspects of cochlear function appear to be simultaneously lost, the susceptibility of the inner and outer hair cell systems to mild, long-term hypoxia seems to differ. Thus, the functional unit of inner hair cell/cochlear afferent system is vulnerable to long-term, mild hypoxia, whereas the outer hair cell function shows little or no changes (consistent with the pattern of AN/AD) [22].

It should be pointed out, however, that hearing thresholds can spontaneously improve in certain cases of neonates with AN/AD. Hyperbilirubinemia may be associated with such a transient behavior of the disease [17], whereas higher birth weight, among low-birth weight AN/AD sufferers, is associated with less likelihood for spontaneous recovery [23].

Although the above-mentioned risk factors are present in a large number of isolated AN/AD cases, hereditary, non-syndromic disorders may also account for the disruption of the functional complex between the hair cells and the spiral ganglion neurons, which is manifested as AN/AD. The transmission patterns in these genetic disorders are quite heterogeneous, being predominantly autosomal recessive [17,24,25]. X-linked recessive and autosomal dominant patterns have also been described and associated with a more delayed symptom onset [26,27]. Thus, the DFNB9 subtype of prelingual hearing impairment (autosomal recessive form of inheritance) shows a quite typical AN/AD pattern, characterized by the absence of ABR waveforms [24,25,28] in the presence of recordable OAEs which, however, may deteriorate over time [24,28,29]. Genetic research has linked a mutation of the OTOF gene, which encodes the protein otoferlin at the molecular level, with the ensuing hearing impairment. Otoferlin is present in the inner hair cells of the mature murine cochlea, and is potentially involved in the synaptic vesicle-membrane fusion and the membrane trafficking that is activated by increased local Ca^{++} concentration [25,30].

Impaired Ca^{++} influx in auditory synapses may, by itself, be involved in the pathogenesis of the AN/AD disorder, as demonstrated in animal models showing Ca^{++} channel deficiency. Indeed, Ca^{++} channel deficient mice are characterized by a complete block of inner hair cell synaptic transmitter release and an associated reduction in the number of spiral ganglion neurons, whilst outer hair cells at the basilar turn of the cochlea preserve their morphology. This in turn results in the absence of ABR, whilst high-frequency DPOAEs are produced, in a similar manner to the observed findings in AN/AD [31]. However, even though this form of synaptic defect may account for the observed AN/AD phenotype in certain cases, it seems that a deficiency in the presynaptic active zones of the mature inner hair cells (synaptic ribbons) might be more critical in reducing fast synaptic vesicle exocytosis and synchronous synaptic activation of spiral ganglion neurons, thus minimizing neural output, despite an apparently intact outer hair cell function [32]. Indeed, data also deriving from mutant mice models (Bassoon and Piccolo mice) suggest that synaptic dysfunction (auditory synaptopathy), caused predominantly by a reduction in synapse-anchored inner hair cell ribbons, might compromise synchronous auditory signalling, and the ability of auditory brainstem neurons to detect submillisecond interaural time differences [33], as these functions rely on precisely timed release of several synaptic vesicles at the mature afferent inner hair cell synapse, which in turn requires the presence of the ribbon. Moreover, temporally precise sound coding is impaired in these animals. Interestingly, however, the mutant mice are not completely deaf, indicating that the remaining fast synaptic vesicle exocytosis and the presence of slow exocytosis in ribbon-deficient synapses support some residual auditory signalling, and providing an alternative pathomechanism for the observed AN/AD pattern in some cases.

Isolated neuropathy of the auditory nerve per se cannot also be excluded in certain cases [34—37], and especially cochlear nerve deficiency has been reported in 18% of children with electrophysiological characteristics of AN/AD in a study by Buchman et al. [38]. In terms of pathophysiology, a perisynaptic synchronization disorder may result from the abnormal hair cell/VIIIth nerve functional unit, leading to temporal processing deficits [39,40].

In addition, auditory nerve myelinopathy is another possible pathologic mechanism accountable for certain cases of AN/AD [41]. Indeed, inadequate myelination of neural fibers, though ultimately capable of conducting action potentials, is characterized by delayed excitation and impaired ability to transmit high-frequency neural signals, due to

prolonged refractory periods of transmission [42—44]. Such fibers also conduct the neural signals at different velocities [43], thereby potentially affecting the synchrony of the overall nerve discharge. Hence, in cases of repetitive stimulation of the auditory neurons by acoustic stimuli at critically short interstimulus intervals, a conduction block might develop [43]. The impaired insulation of the auditory neurons in AN/AD was also confirmed by case-reports, in which a conduction block of the auditory nerve has developed, when the core body temperature of the patients has risen [45,46]. Moreover, axonal neuropathy of the auditory pathways was also suggested as a potential pathologic mechanism in cases of AN/AD, even though axonal and myelin-related neuropathies are rather indistinguishable in clinical practice [10].

Myelin and axonal impairments that can result in the development of AN/AD often occur as part of generalized neuropathic disorders, and especially in Charcot-Marie-Tooth disease. This hereditary motor and sensory neuropathy usually begins in late childhood, and has been associated with AN/AD cases typically exhibiting a delayed onset of symptoms. The disease represents a rather heterogeneous group of polyneuropathies, with different patterns of inheritance (autosomal dominant, autosomal recessive, and X-linked dominant), sharing a common clinical phenotype [47]. The basis of this phenotype is a length-dependent axonal degeneration, or a demyelinating neuropathy, although both pathologies co-exist in certain cases. Whilst the peripheral portion of the auditory nerve is the most likely site of lesion associated with the auditory symptoms [48], studies in Slovene, Italian and Bulgarian gypsy families have suggested a mutation in the chromosome 8 (genetic locus 8q24.3) inherited in an autosomal recessive pattern as the genetic basis of the associated AN/AD phenotype [49—52]. In addition, AN/AD also occurs in the most common form of the disease, the mutation in the genetic locus 17p11.2, inherited in an autosomal dominant fashion [53,54]. Histopathologic evidence indicates cochlear hair cell survival, despite the loss of spiral ganglion cells, and demyelinating processes in the VIIIth nerve in these patients [55].

AN/AD has also been reported in cases of Friedreich's ataxia [37,56,57], a hereditary neurodegenerative disease, in which the main lesion site is restricted to the brainstem and cerebellar parenchyma. The histopathologic evidence of an essentially intact organ of Corti with easily identified hair cells, and the pronounced loss of nerve fibers and spiral ganglion cells [58], correspond to the observed AN/AD pattern of abnormal ABRs and normal OAEs in these patients [56].

The audiological and electrophysiological features of AN/AD have also been reported in patients, in which the hearing deficits developed in the context of mitochondrial myopathies [59], or systemic sclerosis [60].

The observed clinical benefit after corticosteroid treatment in two out of six patients reported in the study of Xing et al., suggests that immunologic damages of the hearing system might also play a role in the pathophysiologic mechanisms of AN/AD [61]. In addition, the occurrence of AN/AD after Stevens—Johnson syndrome insults [37] further supports the immunologic basis of this condition in specific cases. Finally, various reports suggest that infectious processes associated with measles, mumps, or meningitis, might also account for the development of AN/AD [8,38,62].

Irrespective of the cause of the AN/AD phenotype it seems that a common pathophysiologic mechanism prevails—the desynchrony of neural discharges, which in turn causes severe impairment in the patients' temporal processing abilities, without affecting the amplification function of the inner ear. However, axon-related neuropathies and inner hair cell lesions, which are also thought to be the underlying pathologies in some AN/AD cases and do not primarily affect the synchronization of the auditory nerve, might actually result in a reduced number of neural elements available for signal transmission, and hence a hearing deficit of a more sensorineural nature.

4.3. Diagnosis

AN/AD by definition includes the presence of normal OAEs and/or CMs, the absence of ABR waveforms, and impaired speech perception, disproportional to the pure-tone audiogram. It is, therefore, of paramount importance in young children to assess a rough estimate of auditory thresholds using behavioral audiology, although the latter cannot measure speech perception, which as a task is quite impossible to perform in very young children. It is also rather predictable that even though ABR and ASSR (auditory steady-state responses to multiple simultaneous stimuli) correlate well with auditory thresholds in cases of normal hearing and sensorineural hearing loss [63—66], this does not apply in AN/AD cases [3,67,68].

Although the definition of AN/AD is widely accepted in principle, and may have actually been the only part of the disorder that had not changed with time, there are still some exceptions and variations in electrophysiological testing. Indeed, approximately 20% of AN/AD subjects may have a low-amplitude wave V in their ABRs, indicating that

neural synchrony can be partially preserved in some subjects with this disorder [69]. Moreover, OAEs may be absent in up to 30% of ears with confirmed diagnosis of AN/AD [69].

With regard to the latter observation, however, no statistically significant relation between the presence or absence of OAEs and behavioral hearing levels has been established in AN/AD children [8,69]. Furthermore, OAEs may disappear during the course of AN/AD [69,70], yet this fact alone is not necessarily associated with the presence of potentially contributing factors, such as middle ear disease, or the provision of amplification [11], and behavioral audiograms do not seem to deteriorate if the OAEs disappear [70].

By contrast, the lack of efferent suppression of OAEs with the use of contralateral white noise is considered more specific for the differential diagnosis of AN/AD [34,71—76].

Electrocochleography (ECochG) is a measure of the electrical potentials that are generated in the inner ear as a result of sound stimulation. From the three response components recorded in ECochG (cochlear microphonics — CMs, summating potential — SP, compound auditory nerve action potential — AP) the AP was the only that reportedly had good threshold sensitivity, therefore could be used for the assessment of hearing acuity [77]. However, the CMs, through their ability to reflect the integrity of cochlear hair cells, seem to play a significant role in the identification of ears with AN/AD [10,78]. In fact, Rance et al. reported that approximately one half of their AN/AD subjects were accurately diagnosed by the presence of CM responses, despite the absence of recordable OAEs [8]. Nonetheless, Starr at al. suggest that the obtained CMs correspond to the normal age-adjusted ranges in only 60% of AN/AD patients, which are actually older than 10 years old [69]. Moreover, outer hair cell integrity should not necessarily be inferred from the presence of CMs, and outer hair cell pathology cannot be excluded, especially in the absence of recordable OAEs [79].

Therefore, caution is warranted in the case that CMs may be applied as the primary identification method of the AN/AD profile. It seems that the combination of OAEs and CMs as objective indicators of outer hair cell function in patients with absent (or grossly abnormal) ABR waveforms, might be a better option for the improvement of diagnostic accuracy. The presence of an atypical waveform representing an early positive summating potential (abnormal positive potential—APP), on round-window electrocochleograms should also be carefully evaluated in these cases [80]. Indeed, evidence suggest that when APP findings are combined with an absence of intraoperative electric ABR responses, the affected children are most likely experiencing a true neuropathy [81].

In addition, more delayed electrical auditory potentials, such as the cortical event-related potentials (ERPs) were also shown to be present in 50% of children with AN/AD and may offer a means of predicting perceptual skills in newly diagnosed youngsters, since these skills cannot be reliably estimated by the behavioral audiogram [82].

The audiometric findings in children with AN/AD vary significantly, with behavioral thresholds ranging from normal to profound levels [8]. The average pure-tone threshold loss in AN/AD subjects in a study by Starr et al. was 57 dBHL [69]. Hence, hearing thresholds in AN/AD might not necessarily fall within the mild to moderate hearing loss range [35,71,72], but actually display a more even distribution across the audiometric range [6]. Approximately 40% of patients with AN/AD reported by Rance et al. showed severe to profound hearing loss in their behavioral audiograms [8], whereas a higher proportion (60%) was found in a study by Madden et al. [6].

The shape of the audiometric curves tends to vary, according to the degree of hearing loss. Thus, ears with normal (or near normal) hearing show similar acuity at each of the test frequencies. Ears with thresholds in the mild to severe hearing loss range, on the other hand, display an up-sloping pattern in the majority of cases, whereas flat configuration audiograms may also be observed (Table 3). Finally, flat or corner audiograms have

Table 3 Hearing loss configuration in children with AN/AD

Study	Shape of the audiometric curve		
	Up-sloping (*n* = number of ears)	Flat (*n* = number of ears)	High-frequency (*n* = number of ears)
Shivashankar et al. [87]	4	2	1
Madden et al. [6]	—	7	—
Rance et al. [8]	11	7	—
Doyle et al. [37]	7	4	4

Note: ears with normal hearing, or profound hearing loss have been excluded.

been reported for ears with profound hearing loss [8].

Significant fluctuations in the audiometric findings during the course of the disease are not uncommon in AN/AD. Thus, Rance at al reported that only nine of the 14 children in their study, for whom three or more reliable audiograms were available, showed hearing thresholds, which were stable over time, whereas the remaining five demonstrated significant hearing level fluctuations up to a difference of 45 dB [8]. Significant improvement in behavioral thresholds over time can also occur in children with AN/AD. Nine out of 18 children in the study of Madden et al. showed audiologic evidence of hearing improvement, during a period of 1—12 months after the diagnosis of AN/AD, with the mean improvement time estimated at 4.5 months [6]. Interestingly, Aldosari et al. also reported a case of a 9-month-old infant girl, who despite her initial AN/AD hearing loss profile, which was combined with absent visual fixation at the age of three months, showed significant improvement in both her hearing and her vision (confirmed by reproducible ABR waveforms) at the age of 9 months [83].

Speech perception in children with AN/AD is disproportional to the expected from the audiometric findings (in cases of mild to moderate thresholds) [6,84,85], therefore it cannot be reliably estimated from the behavioral audiogram [8,37]. Thus, even though the behavioral hearing thresholds of the AN/AD children in a study by Rance et al. varied from mild to profound levels, they had all demonstrated poor open-set speech perception abilities in unaided listening conditions [84].

Listening in background noise is also extremely difficult for AN/AD children [45,84,86] and there is evidence of significantly poor performance on the dichotic digit test (competing situation), in children that are able to handle auditory stimuli in quiet conditions [87]. The perceptual disruption in children with AN/AD is largely attributed to timing-related perception characteristics, whereas psychophysical measures show minimal effects on intensity-related perception [88,89]. The degree of temporal disruption can be correlated to the speech discrimination score, whereas frequency discrimination ability is also affected in AN/AD patients with poor temporal resolution [89]. The extent to which the perceptual difficulties that these children face are associated to generalized neurological disorders which may become apparent later on, and/or the lack of appropriate auditory stimulation during critical developmental periods [70] has not been fully clarified so far.

The classic clinical triad of findings in AN/AD is combined with the absence, or threshold elevation of middle ear reflexes to both ipsilateral and contralateral tones [45,73,75,85]. Evidence concerning the pediatric population in a study by Berlin et al., extracted by a database of 136 patients that had undergone middle ear reflex measurements, revealed that none of the evaluated children showed normal reflex at all frequencies tested. Based on the overall findings of their study, the authors suggested an ipsilateral middle ear reflex test, at least at 1 and 2 kHz, in any perinatal hearing screening that depended solely on OAEs [90]. Sutton, however, has questioned the validity of the previous report in children younger than 6 months [91].

The results of vestibular function tests reported by Sheykholeslami et al. indicate that in patients with isolated auditory neuropathy, the vestibular branch of the VIIIth cranial nerve may also be affected [92]. However, since these data refer to adult patients, albeit the early onset of their disorder, no significant correlation between the severity of AN/AD and vestibular-evoked myogenic potentials could be established for children with AN/AD. Additional data also support the idea that AN/AD and vestibular neuropathy reserve their independence to some extent [93].

Laboratory studies have also attempted to correlate increased serum bilirubin levels, which may serve as a contributing factor to the development of AN/AD, and biochemical indices, such as the neuron-specific enolase, in order to detect potential neuronal damages that may be linked to AN/AD. Even though a firm correlation is yet to be established, there is a trend among children with AN/AD towards higher enolase values, which might in turn help as a marker in the closer follow-up of these children [94].

Even though C/T and MRI findings in children with AN/AD are typically normal [73,95—97], there are suggestions to incorporate an MRI evaluation to the assessment algorithm of all children diagnosed with AN/AD [38]. Indeed, Buchman et al. reported that up to 18% of children with electrophysiological characteristics of the AN/AD profile who were given MRI, showed evidence of cochlear nerve disorders [38]. This may be especially true for syndromic pediatric patients [38], or children that demonstrate unilateral AN/AD, in which cases the clinician should be highly suspicious and focus on analysing the neurophysiologic characteristics and imaging examinations [95] before proceeding to the available therapeutic options.

Finally, especially in cases of prelingual children that develop the AN/AD phenotype in the absence of a neurological syndrome, genetic testing for mutations of the OTOF gene may be proposed, as such

cases of non-syndromic AN/AD can be detected at a molecular level [24,25,28,98].

It should also be noted that in order for timely diagnosis of AN/AD to be established, screening of high-risk cases along may not prove sufficient [99,100], because as much as one third of AN/AD cases may not actually have any high-risk factor.

4.4. Treatment

The development of auditory and communication skills in children with prelingual onset of AN/AD may be particularly compromised, to the extent that no safe predictions can be made. Therefore, the management of children with this disorder should be individualized [8] and modified according to the child's progress.

The initial step in helping a child with AN/AD is to inform parents about the child's condition and present them with all the available diagnostic and therapeutic options. The parents should be informed that appropriate management should take into account the variation among patients, and the changes that may appear in some children's audition over time [68]. They should also be informed that in cases not responsive in a satisfying degree to auditory inputs in order to develop spoken language (i.e., after conventional amplification, or cochlear implantation), visual language should be considered as a temporary or constant means of communication (baby signs, sign language, cued speech, or speech reading), depending on the age of the child, the age of symptom onset, and the child's progress.

Usually the main objective set by parents and professionals after the diagnosis of AN/AD is the development of spoken language. However, this may involve a lengthy (re)habilitation process with variable results. Conventional amplification may be the first intervention that can be attempted towards this direction, even though there is still a lot of debate, regarding its use. Thus, skepticism has been expressed with regard to the safety of hearing aid use for AN/AD children, and potential noise-induced damages to cochleas with evidence of outer hair cell function [37]. A reasonable basis for this skepticism is that the possibility of acoustic trauma through overamplification is potentially greater in ears with ''normal'' endocochlear function, especially to the extent that these ears cannot be adequately protected by middle ear reflexes [45,73,75,85].

However, neither any significant deterioration in behavioral hearing thresholds of AN/AD children, fitted for at least 12 months according to the guidelines for sensorineural hearing loss of equal degree, has been reported [82], nor evidence of deterioration of hair cell function due to hearing aid use has been obtained so far [10,101].

In addition, Rance et al. demonstrated that there seems to be no significant relationship between the hearing levels of ears with and without OAEs, or between speech perception performance and the presence or absence of OAEs [8]. Thus, there is no evidence that outer hair cells contribute to the hearing abilities of children with AN/AD and even if overamplification resulted in outer hair cell damage, we do not know for a fact that such damage would have had any serious effect in children with AN/AD.

Following a cautious amplification strategy Hood proposed high quality, low gain and wide dynamic range compression hearing aids for these children, with careful monitoring of their OAEs [102]. However, OAEs can disappear prior to the fitting of hearing aids [70], therefore, monitoring the effects of amplification with the use of OAEs in these ears may be misleading. As an alternative, hearing aid fitting may be limited to children without OAEs, or those who had lost their OAEs in the course of the disease [70]. Nonetheless, by following the latter strategy a significant proportion of children may remain unaided or underamplified and lose the intervention benefits that may be related to the early access into the normal auditory spectrum [103,104].

The second main reservation with regard to hearing aid use from children with AN/AD, is associated with the pathophysiologic substrate of the disease and the concern that conventional amplification may only provide a louder, yet equally distorted signal [10]. This concern was in large part extrapolated by the poor acceptance of amplification among adult AN/AD sufferers, in terms of little or no benefit [3,37,70,99,105]. More robust evidence presented by Cone-Wesson et al. [106] confirmed that 14 out of 29 AN/AD children in their series (48%) who had received amplification, had actually stopped wearing their hearing aids, thus indicating little or no amplification benefit, whereas three (10%) showed improvement in hearing thresholds and speech perception, and five (17%) were in an intermediate situation, demonstrating threshold improvements despite the absence of measurable perceptual benefits. By contrast, Rance et al. [82] demonstrated significant open-set speech perception improvements in 50% of AN/AD children who were fitted, and were able to correlate these improvements to the presence of cortical event-related potentials, which may serve (if further confirmed by additional studies) as an index to predict which children could actually benefit from amplification in the future. The authors furthermore

suggested that the provision of amplified sound in AN/AD children may grant them with increased access to speech elements, and/or improve neural synchrony, by recruiting all residual neurons available [82]. Consistent behavioral thresholds obtained over two or more test sessions, may determine the level of amplification recommended for the young patients. Similarly, the use of FM systems at home or at school settings might offer a low-risk option, with the potential benefit of improving the signal-to-noise ratio, whilst presenting minimal risks to surviving outer hair cells, at minimal amplification levels [6]. Hence, it seems that the provision of conventional amplification in AN/AD children may benefit a yet undetermined, but existing subpopulation, and therefore can be justified as a management option, either for enhancing clear speech, or during a trial period of candidature for cochlear implantation [8,37].

Cochlear implantation is the final step, towards restoring the compromised processing of auditory information in children with AN/AD. Indeed, a growing body of evidence suggests significant advantages for cochlear implantation in the management of AN/AD [6].

In theory, the electric signals from the cochlear implant may improve synchronization within the auditory pathway [48,107—109], thus ameliorating temporal processing in AN/AD patients. The preoperative, intraoperative, and postoperative evoked potential measures show that the restoration of neural synchrony may actually occur at multiple levels of the auditory pathways in patients with AN/AD [110]. However, caution is warranted in the signal processing strategy of the implant, as data from demyelinated fibers suggest that time constants depend not only on the types of the demyelinated axon, but also on the methods of fiber stimulation [111], and high stimulation rates in a dysfunctioning auditory nerve might lead to conductivity fatigue and worse than expected results. By contrast, the discrete, pulsatile nature of signals emitted from modern devices may further contribute to the synchronization of neural activity [112]. In addition, in cases of lesions of endocochlear origin, the direct stimulation of spiral ganglion neurons might by-pass the reduced number of inner hair cells, thus contributing to the improvement of auditory function.

Hence, there seems to be a valid rationale for cochlear implantation in children with AN/AD and the results obtained postoperatively in these children, may not be different from the general population of pediatric implant patients [109,113]. Thus, Shallop et al. reported that the five children with AN/AD that were implanted at Mayo Clinic showed significant improvements in sound detection, speech perception abilities and communication skills, without demonstrating any postoperative complications [114]. The results of Shehata-Dieler et al., regarding three children that were implanted after failing to get any benefit from conventional amplification, were also encouraging, as these children actually developed open-set speech discrimination and were able to use oral language for communication [115]. These findings seem to apply also for tonal languages, such as Chinese. Hence, the mandarin-speaking child of Lin et al. also showed significant improvement of speech perception skills after receiving the cochlear implant [116].

Furthermore, patients with non-syndromic recessive AN/AD can also be adequately helped by cochlear implantation [25]. Thus, cochlear implants in cases of mutations in the OTOF gene reportedly yield satisfying results [24] and the implanted children present a good quality of clinical responses and electrophysiological tests postoperatively [28,117].

On the other hand, even though all four of the implanted children in the study by Madden et al. [6] showed improvement in auditory and verbal development, that improvement was variable. Other reports also imply that caution is warranted when considering cochlear implantation for children with AN/AD, as less than optimal results may be encountered. Thus, the case-report presented by Miyamoto et al. showed improvement in vowel recognition 1 year after the implantation, which as a result was only slightly lower, compared to the child's sensorineural peers, but scored significantly lower with regard to consonant and open-set recognition [60].

Intraoperative electrophysiological measures, such as the electric ABR, may be used to predict the expected outcome of cochlear implant surgery in AN/AD children [81]. Indeed, cochlear implant candidates presented with abnormal round-window electrocochleograms indicating AN/AD (large CMs and APP) show better speech perception scores than their sensorineural peers at 1 and 2 years postoperatively when intraoperative electric ABR waveforms appear normal ($p < 0.01$ and 0.05, respectively). However, when the latter results appear abnormal the implanted children score significantly worse ($p < 0.01$ and 0.0005, respectively) [81]. As many as 25% of children with electrocochleagraphic abnormalities indicative of AN/AD may belong to the latter category and seem to experience a true neuropathy (yet still not precisely determined in nature), whilst in the majority of them (75%) the outer hair cells are 'dys-synchronising' the output of the remaining inner hair cells, by providing inappropriate tuning of the basilar membrane [118]. The

finding that the latter category of pediatric implantees performs better than the control group also suggests that the higher cortical areas are not adversely affected in these children.

We should also take into account the fluctuating course of AN/AD in certain cases, which in effect may have not given an adequate chance to the child to spontaneously recover useful hearing levels [6], and the fact that the maturation process of the auditory system in infant cochlear implant candidates with AN/AD may still be in progress [23,83]. Thus, in the study of Madden et al. the AN/AD children had reached a stable audiogram by a mean of 18 months of age (range, 11—25 months), with clinically meaningful improvement (i.e., decision for cochlear implantation) occurring by 12 months of age [6]. Hence, though cochlear implants may yield better results when applied early [119,120], this might not be always true in cases of AN/AD. Therefore, cochlear implantation should be considered as a therapeutic option only if repeated measures have proven persistent AN/AD, and repeated constant behavioral measures of the child's hearing have been obtained [13], along with his/her aided speech perception ability [10].

In addition, although it may seem reasonable to consider AN/AD children with severe to profound hearing loss as cochlear implant candidates, a significant proportion of cases demonstrates lesser degrees of hearing loss. Cochlear implant candidature for these children should be evaluated cautiously, and include the co-existing conditions (demyelinating diseases, neuropathies, etc.), as well as preoperative electrophysiological measures (event-related potentials, promontory testing, and round window electrocochleography).

5. Conclusion

AN/AD is more frequent than considered in the past, especially amongst hearing-impaired children. Hyperbilirubinemia and hypoxia are major risk factors for this disorder, whereas a genetic substrate involving the OTOF gene is responsible for the AN/AD phenotype in certain cases. Auditory synaptic deficiency, auditory nerve myelinopathy and/or desynchrony of neural discharges are the most probable underlying pathophysiologic mechanisms, causing severe impairment in the patients' temporal processing abilities, and putting the processes of language acquisition in jeopardy.

Therefore, accurate diagnosis is of paramount importance and should include a combination of OAEs and CMs in patients with absent (or grossly abnormal) ABR waveforms. During diagnostic evaluation it should be kept in mind that significant fluctuations in the audiometric findings are not uncommon in children with AN/AD, whilst genetic testing can also be added to the diagnostic battery.

The management of children with this disorder should be not only timely, but also individualized and modified according to the child's progress. It is consisted of a three-step process, which starts with parental information. Conventional amplification, intensive speech, and language therapy (and sign language when indicated) provide the mainstay of habilitation. Indeed, hearing aids, despite the reservations expressed regarding their safety for AN/AD children, and the concern that they might only provide a louder, yet equally distorted signal, seem to benefit a yet undetermined, but existing AN/AD subpopulation, and therefore can be justified as a management option, either for enhancing clear speech, or during a trial period of candidature for cochlear implantation. The latter represents the final step towards restoring the compromised processing of auditory information, by improving synchronization within the auditory pathway. A growing body of evidence suggests that cochlear implantation is a valid therapeutic alternative in the management of AN/AD, however, patient selection should be cautious and take into account potential co-existing conditions (demyelinating diseases, neuropathies, etc.) and electrophysiological measures that may predict the expected outcome of surgery.

Finally, in light of the recent knowledge on AN/AD, universal newborn hearing screening protocols that rely solely on OAE recordings may need to be revised, in order to ensure more timely diagnosis of this disorder, which in turn can lead to optimal therapeutic outcomes.

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