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The Human Auditory System
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Chapter 28

Auditory neuropathy

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INTRODUCTION

Objective measures of hearing thresholds using auditory brainstem responses (ABRs) were championed by Galambos and his associates four decades ago (Hecox and Galambos, 1974; Galambos and Despland, 1980) and are now used routinely to provide objective measures of auditory nerve and brainstem responses in neonates and adults (Norton et al., 2000).

While the tests were of great benefit for objectively defining "deafness," there were exceptions that tested this assumption. Some subjects with "hearing problems" had relatively normal audiometric thresholds but absent or severely abnormal ABRs (Kaga and Tanaka, 1980; Worthington and Peters, 1980; Hildesheimer et al., 1985; Satya-Murti et al., 1983; Kraus et al., 1984). We identified that their deafness was due to abnormal auditory nerve function in the presence of normal-functioning cochlear sensory hair cells. Figure 28.1 displays measures (audiogram, distortion product otoacoustic emissions (OAEs), ABRs to clicks and to tones, and auditory cortical potentials) from an individual with auditory neuropathy (AN) and a normal-hearing control (normal).

The AN subject in Figure 28.1 had a mild loss of audibility, impaired speech perception out of proportion to the audibility changes, ABRs with absent waves I–III, and barely detectable wave V that was delayed in latency. In contrast, the cochlear hair cell measures (DPOAEs) and cochlear microphonics (CMs) were normal. Cortical N100 potentials were present and delayed in latency (Starr et al, 1991, 1996). The pattern of these results was consistent with a hearing disorder (Starr et al., 1991) due to abnormal auditory nerve functions. Some of the subjects were found to also have cranial nerve (vestibular, optic nerve) and/or peripheral neuropathies, supporting the idea that the auditory nerve was also affected by neuropathic disorders. The term "auditory neuropathy" was used to describe the group of patients we studied (Starr et al., 1996). We also recognized that inner hair cell disorders affecting ribbon synapse function would display similar clinical features.

The hearing disorder of AN affected processing of acoustic temporal cues that are essential for: (1) speech comprehension; (2) localization of sounds; and (3) separating signals from background noise (Starr et al., 1991; Zeng et al., 2005).

Examination of temporal bones from subjects dying with AN showed inner and outer hair cells to be normal in number and appearance, whereas auditory ganglion cells and nerve fibers were both reduced in number and demyelinated (Starr et al., 2003). Loss of auditory nerve fibers would attenuate neural input while demyelination would affect the synchrony of neural conduction. We consider that both the loss of auditory nerve fibers and altered neural transmission contribute to the abnormalities of both ABRs and hearing.

Abnorml ABRs and normal hair cell measures were identified in neonates with otoferlin (OTOF) mutations that affected glutamate neurotransmitter release from inner hair cell ribbon synapses. The locus of the auditory nerve disorder in this mutation was presynaptic and has been shown to affect ribbon synaptic function (Varga et al., 2006; Rodríguez-Ballesteros et al., 2008).

We anticipate that patients with abnormal ABRs and normal cochlear hair measures will also be identified in disorders of neurotransmitter reuptake and auditory dendritic receptor.

We have been asked to comment on other terminologies used for individuals with abnormal ABRs and preserved cochlear hair cell activities. The most common ones are "auditory neuropathy spectrum disorder" and

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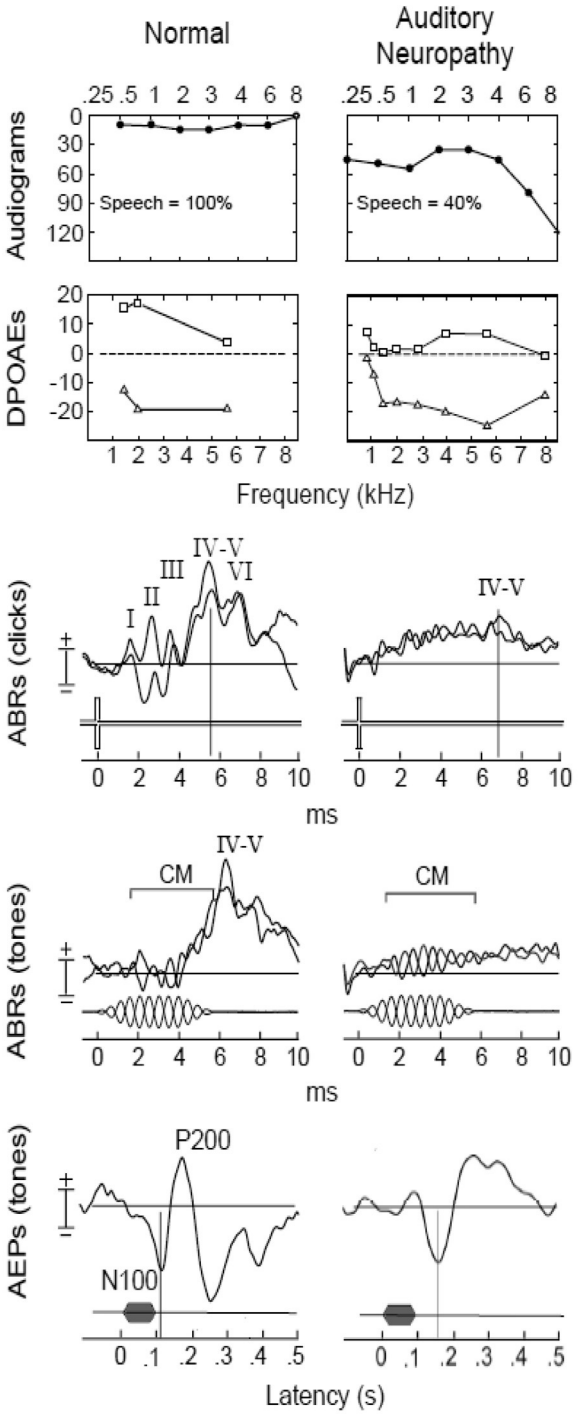

Fig. 28.1. Measures of auditory function in a normal control and a subject with auditory neuropathy. DPOAEs, cochlear hair cell measures; ABRs, auditory brainstem responses; AEPs, auditory evoked potentials; CM, cochlear microphonics.

"auditory neuropathy/auditory dyssynchrony." The term "spectrum disorder" is used when there is both a paucity of objective measures and knowledge of their etiology. Spectrum disorder is inappropriate for AN since we do use objective measures (e.g., ABRs) that can localize the sites of auditory nerve dysfunction as affecting auditory nerve and inner hair cell ribbon synapses (Moser et al., 2013). Most importantly, there are many specific etiologies that have been identified as causing AN (Starr et al., 2001; Santarelli, 2010). We suggest that the term postsynaptic AN be used when there is loss and/or demyelination of auditory nerves. When inner hair cells are affected the term presynaptic AN is appropriate.

The term "auditory neuropathy/auditory dyssynchrony" is used to indicate that there is reduction of neural synchrony of auditory nerve fibers in patients with AN. The concept is attractive but as yet there is no quantitative measure of the degrees of dyssynchrony. We suggest that ABRs may be able to provide such measures of changes of neural synchrony. For instance, in patients with postsynaptic AN the ABR to the initial click could be normal but was then delayed and lost to subsequent clicks in the train (e.g., conduction slowing: Wynne et al., 2013). Dyssynchrony in this instance had a time course of expression. Moreover, both a reduction in signal intensity and a decrease in signal-to-noise ratio in normal-hearing subjects can result in both ABR and psychoacoustic measures that are similar to AN. We now depend on psychoacoustic methods in trained observers to quantify the effects of dyssynchrony of auditory perceptions. Objective measures of both brainstem and cortical potentials may prove a way of quantifying the magnitude change in central auditory processing in normal hearing and in auditory neuropathies (Kraus et al., 2000; Michalewski et al., 2005).

We will review below diagnostic features of AN, including audiologic and psychoacoustics, etiologies (e.g., developmental, genetic, metabolic, degenerative, iatrogenic), their associated pathologies, and the effects of specific therapies.

DIAGNOSIS

The diagnosis of AN relies on electrophysiologic tests with ancillary support from neuroimaging and audiologic assessment.

Electrophysiologic procedures

ABRs in AN are absent or attenuated in amplitude as well as delayed in latency (Table 28.1) (Starr et al., 1996). The conduction velocity of the auditory nerve can be measured only when both waves I and II are present (Butinar et al., 2008). Some of the details of performing these measures are detailed below.

Cochlear hair cell microphonics are typically preserved and can be defined by separately averaging ABRs to condensation and to rarefaction stimuli. Subtracting

Table 28.1

Objective electrophysiologic findings in auditory neuropathy

Test	Results
ABRs	Absent or abnormal
Acoustic evoked middle-ear muscle reflexes	Typically absent
Cochlear microphonics	Normal
Otoacoustic emissions	Normal
Electrocochleography	CAP broad and low amplitude
Neurophonics	Absent

ABRs, auditory brainstem responses; CAP, compound action potential.

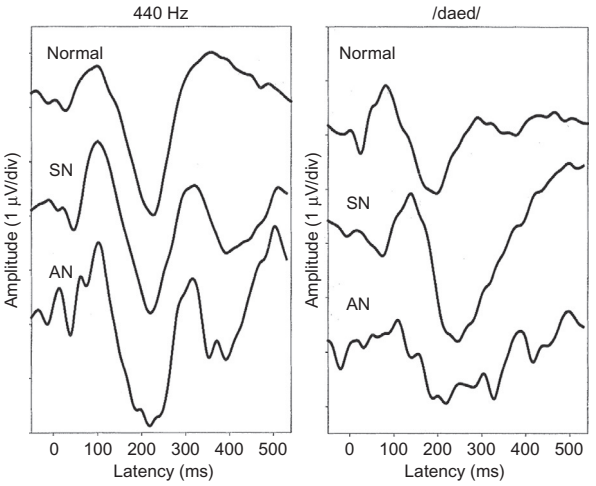

Fig. 28.2. Grand mean cortical event-related potential waveforms in response to tones (left panel) and to speech (right panel) for children with normal hearing (top traces), sensorineural (SN) hearing loss (440 Hz: $n = 17$; /dæd/: $n = 15$, middle traces), and auditory neuropathy (AN) ($n = 11$, bottom traces). Daed is the phonetic representation of the word "dad." (Reproduced from Rance, 2005, with permission.)

the ABR condensation from rarefaction clicks attenuates the neural components, revealing CM that are of opposite polarity to condensation and rarefaction stimuli. Addition of the ABRs to condensation and rarefaction stimuli will cancel CMs and enhance neural components (Starr et al., 1991; Berlin et al., 1998).

Both inner hair cell summating potentials and the compound action potential (CAP) of auditory nerve (wave I of the ABR) can be most clearly identified using electrocochleography (Santarelli and Arslan, 2002). The method helps to localize the sites of auditory nerve dysfunction as involving inner hair cells and/or auditory nerve (Santarelli, 2010). This information can assist the clinician in assessing the likely benefits of cochlear implants. Typically, if the dysfunction is limited to the inner hair cells, cochlear implants will be very beneficial. The technique requires general anesthesia for infants and children but can be done under local anesthesia in adults.

Auditory cortical potentials

A cortical potential can be recorded to the onset of acoustic signals at a peak latency of approximately 100 ms. The potential is of positive polarity in children and changes to a negative polarity by around 8 years of age. The N100/P100 is present in AN even when ABRs are absent. Rance and colleagues (2002) showed that 50% of school-aged children with AN were without an N100 or P100 and its absence was highly correlated with impaired speech perceptual abilities. The presence of a preserved N100 of normal latency provided an objective measure of neural synchrony at the cortical level (Fig. 28.2).

In adults, the latency of N100 to brief tones is also sensitive to the onset of temporal features of the stimulus. N100 latency is prolonged as stimulus onset is slowed (Onishi and Davis, 1968) but is relatively independent of stimulus intensity. In AN subjects, N100 latencies to brief tone bursts, while present, are abnormally delayed in latency (approximately 40 ms) and the magnitude of the delay is independent of audibility changes (Michalewski et al., 2009). Cortical measures can be used to quantify temporal processing deficits of auditory nerve and/or inner hair cell ribbon synapses (Wynne et al., 2013).

Currently it is difficult to distinguish between disorders of auditory dendrites (noise trauma), auditory axons accompanying neurologic disorders (both a form of deafferentation), altered neural conduction, and ribbon synaptic abnormalities. All these conditions affect auditory nerve and brainstem activity, reflected by ABR. We anticipate that further studies of changes of ABR latency and amplitude of ABR components will help to distinguish among etiologies. For instance, AN accompanying degenerative etiology such as Charcot–Marie–Tooth (CMT) will show progressive latency delays and reduction in amplitudes of ABR components (Starr et al., 2003). These measures also may be used to quantify the course of the disorder and provide objective measures of therapies in clinical trials (Rance et al., 2010).

ABR abnormalities (Fig. 28.3) can be helpful in localizing the site of auditory nerve abnormality. Wave I, generated by distal portions of auditory nerve, is typically preserved in proximal disorders of the auditory nerve (e.g., acoustic neuromas) but absent in both presynaptic (OTOF-related ribbon synaptic disorders) and

neuropathic disorders of auditory nerve. Conduction times between waves I and II (the latter generated by proximal auditory nerve; Martin et al., 1995) can reveal abnormal slowing of auditory nerve conduction (Butinar et al., 2008). Prolongation of latency difference between waves I and V (>4.5 ms) reflects slowed conduction between auditory nerve and lateral lemnisci.

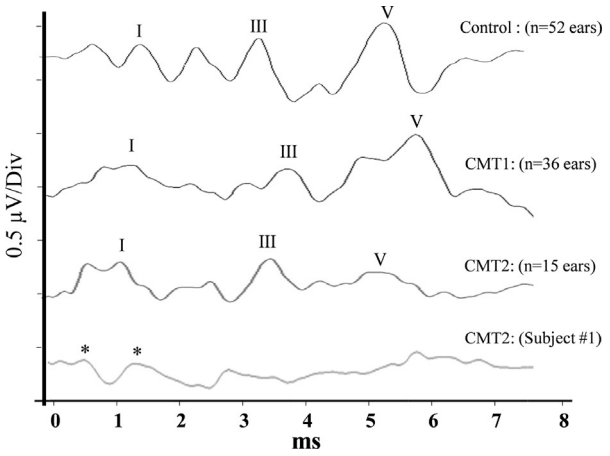

Fig. 28.3. Auditory brainstem response waveforms obtained for children with Charcot–Marie–Tooth (CMT) disease. The top tracing shows the combined waveform for a normal control group. The second is the averaged waveform for children showing slow conduction between waves I (auditory nerve) and III (cochlear nucleus) consistent with demyelination of auditory nerve (CMT1). The third is the averaged waveform for children with CMT2, showing axonal loss and reflected by normal conduction times between waves I and III and V, but reduced amplitude of wave V. The bottom tracing is for a single child who showed no repeatable components I, II, and V to stimuli at maximum presentation levels (90 dB nHL) but whose audibility was impaired. The asterisks in this case are cochlear microphonics. (Reproduced from Rance et al., 2012a.)

The relative amplitude of wave V to wave I is normally >1. When this ratio is less than 0.5, the site of auditory nerve disorder is proximal rather than distal (Starr and Achor, 1975; Rance et al., 2010). Cochlear hair cell activities are normal. These include microphonics (CMs), reflecting outer and inner hair cell intracellular potential changes; OAEs, reflecting contractions of outer hair cells, are present in newborns with AN (Table 28.1). They become absent in approximately 30% of these infants by 2 years of age (Rance et al., 1999). CMs are preserved in those subjects that have lost OAEs (Starr et al., 1998). Thus, for diagnosing AN, the CMs are a reliable measure of preserved hair cell activities (Starr et al., 1991).

Neurophonics or frequency-following responses are field potentials of auditory brainstem structures to low-frequency tones (<500 Hz) that can be recorded using the same ABR recording methods (Fig. 28.3). Their onset occurs approximately 3–5 ms after the onset of CM (Fig. 28.1) and is consistent with brainstem generation. Neurophonics have not been recorded routinely in AN but, in the limited number of subjects tested, neurophonics are absent. An example of one such recording to consonant-vowels by Nina Kraus in a 10-year-old with AN is shown in Figure 28.4. In this subject, neurophonics were absent. The measurement of neurophonics provides an objective measure of low-frequency temporal processing.

Electrocochleography is a method allowing near-field recording of cochlear and nerve potentials using a needle electrode that is passed through the tympanic membrane to rest on the bony cochlea (Eggermont and Odenthal, 1974). The recordings reveal high-amplitude inner hair cell summating receptor potentials, CAPs of auditory nerve, and CMs. The procedure requires local anesthesia in adults and general anesthesia in children and provides

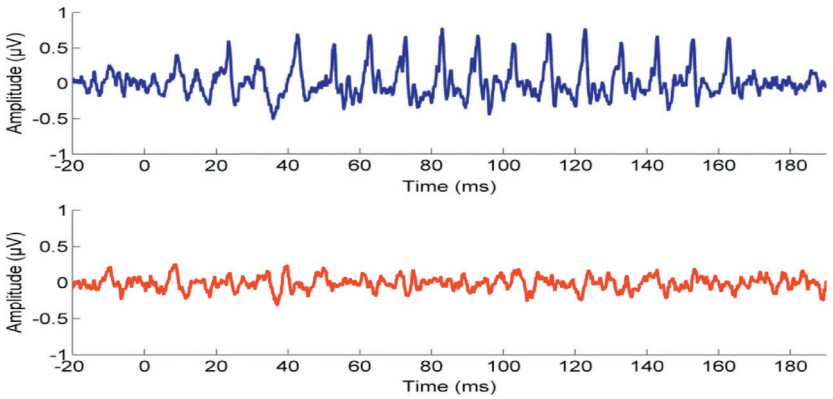

Fig. 28.4. This figure contains auditory brainstem responses (ABRs) to repeated presentations of /da/. The upper trace (blue) is from a normal hearing subject showing averaged potentials over 180 ms. containing repetitive positive potentials occurring at approximately 100 cycles/s. These repetitive potentials are also called "frequency following responses" or (FFRs) and reflect a temporal neural encoding of speech components. The brainstem potentials from an 8 year old subject with auditory neuropathy are in red and do not appear to contain frequency following responses and the child had marked difficulty identifying differences between speech sounds but could hear the speech clearly. We thank Nina Kraus PhD for providing this figure.

objective measures of both inner hair cell summating potentials and auditory neural responses. ABRs do not usually include a summating potential. Figure 28.5 shows electrocochleography from 8 normal and 8 AN subjects. All controls had two distinct negative deflections: the first, an increasingly negative summating potential with onset latency approximately 0.3 ms after CM. The summating potential is interrupted by a second negative/positive potential of high amplitude and short duration, returning to baseline approximately 3 ms after onset of the summating potential.

In contrast to the controls, AN subjects had either absent CAP or a low-amplitude CAP (identified in only 2 AN subjects, #3, 4, circled in Fig. 28.5), whereas a summating potential was present in all. All AN subjects showed a prolonged negative potential of large amplitude, even when the CAP was absent. The generators for the abnormally prolonged negative potentials in AN may reflect dyssynchronous generation of summating potential and/or dyssynchronous discharges of nerve fibers.

Usually the onset of the CAP at high intensity is similar in both normal and AN subjects, whereas the CAP is broad and of low amplitude in AN subjects.

Neuroimaging

Magnetic resonance imaging (MRI) of the brainstem and auditory nerve can assist in localizing the site(s) of auditory nerve involvement. Congenital atrophy of auditory nerve occurs in neonates and children with normal cochlear hair cell measures (Buchman et al., 2006). The degree of atrophy may be a factor affecting the outcome of a cochlear implant. MRI and computed tomography scans are now the methods of choice for detecting structural abnormalities of auditory nerve causing AN, such as acoustic neuromas and brainstem tumors (see Chapter 29).

Audiology and psychoacoustics

Audiologic measures

Diagnostic features of AN include: (1) impaired speech perception out of proportion to audibility changes; (2) impaired ability to detect rapid changes in intensity; (3) inability to utilize interaural differences of temporal cues; and (4) abnormal ability to process acoustic signals in the presence of noise masking (Starr et al., 1991, 1996;

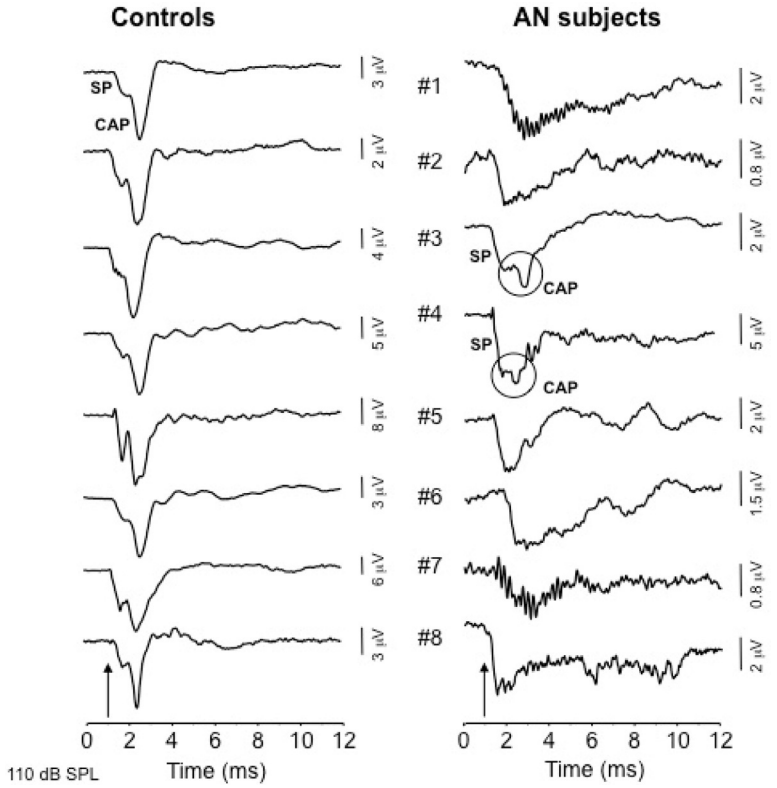

Fig. 28.5. Electrocochleography in normal-hearing (left column) and auditory neuropathy (AN) subjects (right column). Summating potential (SP) and compound action potential (CAP) in response to high-intensity clicks (110 dB) recorded from 8 controls (left) and AN subjects (right). The separation of the CAP from the SP is clear in controls, while a CAP can only be identified in 2 AN subjects (#3, #4; circled). In the remaining AN ears the SP continues and a boundary between CAP and SP cannot be identified. Arrows at the bottom indicate CM onset. (Reproduced from Santarelli et al., 2008.)

Rance et al., 1999; Zeng et al., 2005). Details of hearing abnormalities are described in the section on new directions, below.

ETIOLOGY

The etiologies of AN phenotype are multiple (see Starr et al., 1998, for review). These include developmental disorders (e.g., hypoplasia of auditory nerve: Buchman et al., 2006), toxic-metabolic disorders (e.g., hyperbilirubinemia: Shapiro, 2003); infections (e.g., meningitis), inflammation (e.g., siderosis), neoplasms (e.g., acoustic neuroma), genetic mutations affecting neural functions (e.g., CMT disease: Starr et al., 2003) and ribbon synapse function (Moser et al., 2013), optic neuropathy (e.g., Huang et al., 2009), mitochondrial disorders such as Friedreich's ataxia (Cacace and Pinheiro, 2011), autoimmune disorders (e.g., Guillain–Barré syndrome), nutritional disorders (Attias et al., 2012), and degenerative changes accompanying aging (Masuda and Kaga, 2011).

Neurologic examinations can identify neurologic and medical conditions that are associated with AN. These disorders include genetic mutations affecting the optic nerve (Opa1 gene) and/or vestibular nerve (Fujikawa and Starr, 2000; Santarelli et al., 2008; Huang et al., 2009), disorders of peripheral nerves (e.g., Starr et al., 2003; Butinar et al., 2008), metabolic disorders causing neuropathies (e.g., Acar et al., 2012), immune disorders e.g., Guillain–Barré syndrome (Ueda and Kuroiwa, 2008), and inflammatory disorders such as rupture of aneurysm producing siderosis (Nadol et al., 2011) or as a consequence of meningitis (Celis-Aguilar et al., 2012).

PATHOLOGIES OF AUDITORY NEUROPATHY

Auditory nerve

Examination of human temporal bones ($n = 5$) from subjects with hereditary disorders of auditory neural function (Spoendlin, 1974; Hallpike et al., 1980; Merchant et al., 2001; Starr et al., 2003; Bahmad et al., 2007) showed marked loss of auditory nerve ganglion cells, nerve fibers and demyelination of many of the remaining fibers (Fig. 28.6). Both the number and appearance of inner and outer hair cells were normal (Fig. 28.7). The neuropathology is consistent with deafferentation and impaired neural conduction to affect both the magnitude of auditory nerve input and the synchrony between fibers (Wynne et al., 2013). Patients with AN due to compression from acoustic neuromas also have loss of nerve fibers and demyelination in proximity to the region of compression. The pathology would lead to neural

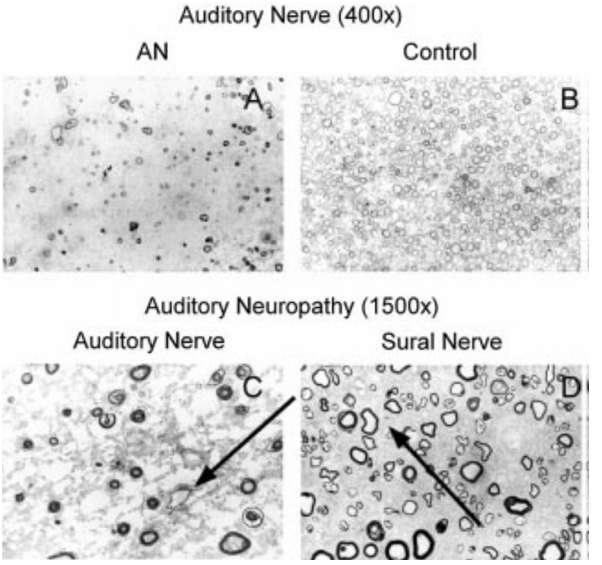

Fig. 28.6. Auditory nerve adjacent to brainstem in the top panel from auditory neuropathy (AN) subject (**A**) and age-matched control (**B**) (osmium tetroxide, ×400). Lower panel from the AN subject shows high-power view (×1500) of auditory nerve (**C**) and sural nerve (**D**). The arrows are directed to thinly myelinated fibers in both nerves, reflecting incomplete remyelination. (Reproduced from Starr et al., 2003, with permission.)

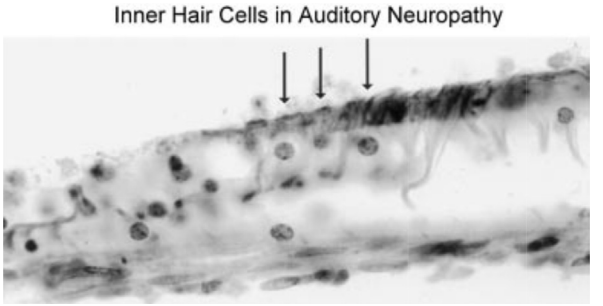

Fig. 28.7. Intact inner hair cells (arrows) as seen between the inner sulcus and inner pillar cells in a section cut on the bias (osmium tetraoxide, hematoxylin and eosin, ×650). (Reproduced from Starr et al., 2003, with permission.)

conduction blocks and could possibly compromise cochlear blood supply to affect hair cell function (Matsunaga and Kanzaki, 2000).

Inner hair cells, but not ganglion cells, have been shown to be selectively depleted in temporal bones of some premature infants (Amatuzzi et al., 2011). This selective inner hair cell loss, if expressed in term infants, would be expected to show absent or marked attenuation of inner hair cell summating receptor potentials but intact neural potentials to electric stimulation of auditory nerve.

Auditory nerve damage accompanying acoustic trauma

Attention to details of cochlear damage accompanying excessive noise exposure has revealed immediate damage to auditory nerve dendrites relative to the expression of noise damage to hair cells and auditory nerve dendrites (Furman et al., 2013; Moser et al., 2013). The dendritic effects result from excessive neurotransmitter release causing prolonged excitation of the dendrites and their subsequent retraction from inner hair cells by neurotransmitter release (glutamate) from inner hair cell ribbon synapses. These effects are of greater magnitude with high- than low-threshold auditory nerve fibers. Noise exposure can cause both delayed damage to auditory ganglion cells and inner hair cell ribbon synapses. These data suggest that noise-induced hearing disorders such as tinnitus are due, in part, to AN affecting both auditory nerve dendrites, a postsynaptic AN, and inner hair cells, a presynaptic disorder AN.

Inner hair cell ribbon synapses

Physiologic studies of experimental animals with homozygous OTOF mutations have marked impairment of glutamate neurotransmitter release (Moser et al., 2013). A compound mutation of OTOF mutations in humans is expressed as a temperature-sensitive deafness (Starr et al., 1998; Varga et al., 2006; Marlin et al., 2010). Experimental animal models accompanying gene mutations also have impaired inner hair cell neurotransmitter release (Jing et al., 2013). In humans with temperature-sensitive AN due to OTOF mutation, auditory nerve activity is reduced during continuous sound stimulation accompanied by abnormally rapid adaptation of loudness to continuous auditory signals (Wynne et al., 2013).

In summary, the clinical picture of dysfunction of auditory nerve (absent/abnormal ABRs in the presence of preserved cochlear hair cell measures (OAEs and/or CMs) has been shown to accompany: (1) disordered presynaptic release of neurotransmitter by ribbon synapses (Starr et al., 1998; Marlin et al., 2010); (2) deafferentation accompanying loss of auditory nerve fibers (Starr et al., 2003); and (3) conduction blocks (Wynne et al., 2013) accompanying demyelination of nerve fibers.

The distinction between both etiology and site of the disorder affecting auditory nerve function requires expertise in several disciplines, including audiology, genetics, neurology, psychoacoustics, and speech processing.

CLINICAL EXPRESSION OF AUDITORY NEUROPATHY

The prevalence of AN in adult populations is difficult to determine as the physiologic assessments used to identify the condition (ABR/CM/OAE) are not routinely undertaken unless there are specific clinical indicators for retrocochlear abnormality (asymmetric hearing/unusually poor speech understanding) or a prior diagnosis of genetic disorder involving peripheral neuropathy (e.g., Freidreich's ataxia, CMT disorders). In pediatric populations, on the other hand, electrophysiologic assessment is the cornerstone of infant hearing testing and universal screening has revealed that AN is a relatively high-incidence condition, particularly amongst babies in the neonatal intensive care unit. Data from our laboratory over a 5-year period (1991–1996), for example, found that 1 in every 423 (0.23%) special care unit graduates presented with the AN result pattern (Rance et al., 1999). We estimate that AN and ribbon synapse disorders accounts for approximately 10% of all permanent pediatric hearing loss.

In newborns in neonatal intensive care units (NICU) there is increased incidence of AN in the presence of metabolic disorders (e.g., acidosis, hypoxia) and infections. The latter may reflect the common use in the ICU of antibiotics with cochlear toxicities. MRIs of the brain commonly show diffuse periventricular brain lesions. ABR abnormalities in many of these neonates do resolve.

In healthy neonates abnormal ABRs occur at increased incidence in families with a history of hearing loss. If measures of hair cell function are preserved, AN is a likely diagnosis. Several genetic mutations have been identified as causal in these children. Atrophy of the auditory nerve, either unilaterally or bilaterally, has been identified by MRI and is a cause of AN (Buchman et al., 2006).

In school-age children audiograms may show normal or mild hearing loss in the presence of impaired speech comprehension. Many of these children utilize lip reading without their realization and definition of the disorder requires awareness of this compensatory adjustment.

In adults the hearing disorder affects speech comprehension out of proportion to the audiogram loss. These patients are aware of their deficits and that they become exaggerated by background noise. Neurologic exam can identify the site of the disorder as being neural by the finding of neuropathies affecting other peripheral or cranial nerves (most commonly, vestibular and/or optic) that may be asymptomatic.

In an aging population AN is common and may be related to the frequent occurrence of other cranial (particularly vestibular, optic) and peripheral neuropathies. These patients typically have abnormal cochlear outer hair cell measures (OAEs, CMs) consistent with a sensory hearing loss. When abnormalities of speech comprehension are beyond that seen with cochlear

hearing loss, AN may also be likely. The clinical and objective assessment of peripheral and other cranial nerve functions may help identify the hearing disorder as being affected by neural disorder. Cochlear implantation has been shown to be of benefit for speech comprehension in these elderly subjects (Orabi et al., 2006; Poissant et al., 2008; Carlson et al., 2010).

Noise-induced hearing loss is a form of AN initially affecting auditory nerve dendritic connections with inner hair cells.

HEARING DISORDERS ACCOMPANYING AUDITORY NEUROPATHY

Among the various hearing difficulties experienced by AN patients, two are particularly important: sound detection thresholds and speech perception.

Sound detection thresholds

Hearing threshold levels in individuals with AN vary across the audiometric range independently of whether the ABR is present or absent. Sound detection thresholds in both adult and pediatric populations are evenly distributed and range from normal to profound levels (Rance et al., 1999; Sininger and Oba, 2001; Berlin et al., 2010).

Importantly, discrimination of complex acoustic signals (e.g., speech) is not significantly correlated with audibility in individuals with AN (Zeng et al., 2001; Rance et al., 2002). In contrast, our experience has been that perception in cases with sensory hearing loss is closely related to audibility, with those individuals presenting with profoundly impaired sound detection thresholds showing the poorest perception (Yellin et al., 1989; Rance et al., 2002). AN listeners with hearing thresholds in the profound range also suffer extreme discrimination deficits, but so do individuals with normal or near-normal sound detection (Starr et al., 1996; Zeng et al., 2005; Rance et al., 2008). As such, it is often the degree to which the neural representation of sound is distorted rather than audibility in this group that determines perceptual ability.

Speech perception

Speech comprehension difficulty is a consistently reported feature of AN. Most affected adults have shown perceptual deficits greater than predicted from their audiogram (Starr et al., 1996, 2000; Zeng et al., 2001; Rance et al., 2008). Results in children have been more variable. At best, young listeners with AN show speech perception test results comparable to their peers with sensory (cochlear) hearing loss. At worst, they show

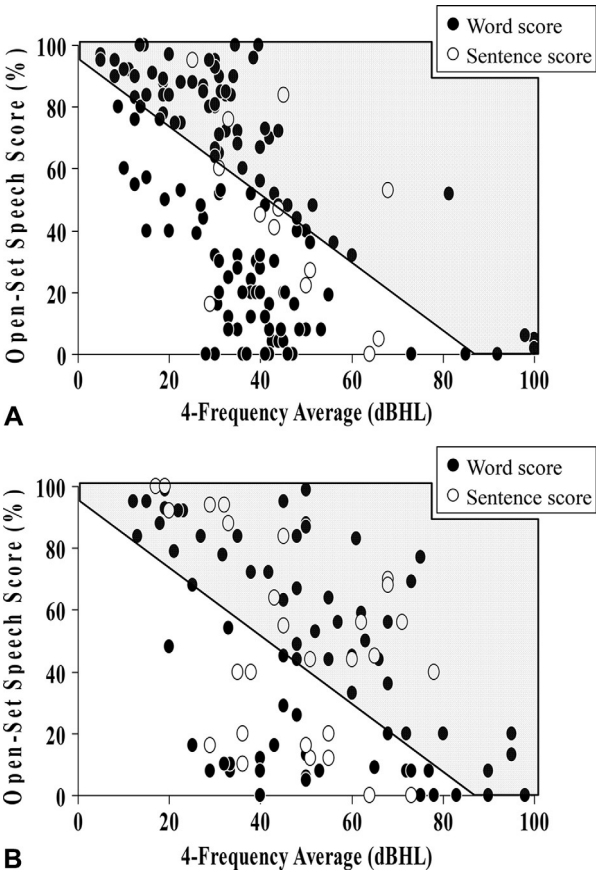

Fig. 28.8. Open-set speech perception scores (in quiet) plotted against average hearing level (HL) for adults (**A**) and children (**B**) with auditory neuropathy who have been presented in the literature. The filled data points represent findings from open-set word tests and the open points show open-set sentence test results. The gray area represents the expected performance range for ears with sensory hearing loss. (Reproduced from Yellin et al., 1989, with permission.)

no functional hearing ability at all despite (in many cases) enjoying complete access to the normal speech spectrum. Figure 28.8 shows this broad spread of perceptual performance, reflecting the lack of a significant relationship between speech understanding and audibility in both adults and children with AN. As can be seen from these data, approximately 50% of AN cases show perceptual ability poorer than the expected minimum for sensory hearing loss of equivalent degree.

In addition to these perceptual limitations in quiet, speech understanding in noise is a particular problem for listeners with AN-type hearing loss (Zeng and Liu, 2006; Rance et al., 2008). As demonstrated in Figure 28.9 (which shows speech perception findings for a group of patients with Friedreich ataxia), even those individuals with AN who enjoy relatively normal perception in favorable (quiet) conditions struggle to

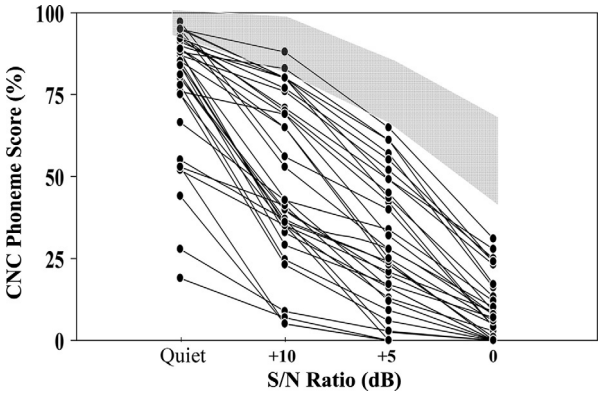

Fig. 28.9. Speech perception in Friedreich ataxia. Results were obtained in quiet listening conditions and in background noise at three signal-to-noise (S/N) ratios. The shaded area represents the 95% confidence range for a matched control group. CNC, Consonant-Nucleus-Consonant. (Reproduced from Rance et al., 2008, with permission.)

discriminate speech in background noise. For instance, signal-to-noise ratios of around 0–3 dB are typical and accepted in "real-life" listening environments such as school classrooms and open-plan offices. In contrast, the majority of AN subjects report comprehension difficulties when exposed to the typical signal-to-noise ratios of <3 dB that affect most of their day-to-day interactions. Psychophysical studies have shown the same degree of impaired comprehension in both simultaneous (where the signal is presented within the noise) and non-simultaneous (where the noise occurs immediately before or after the signal) masking experiments (Kraus et al., 2000; Zeng et al., 2005; Vinay and Moore, 2007). As such, it appears that listeners with AN are less able to separate sounds occurring successively, a temporal processing disorder. In an everyday listening context, where the level of background noise fluctuates, this temporal processing deficit might impair the listener's ability to use brief gaps in the noise to optimize speech understanding (Fig. 28.9).

AUDITORY PROCESSING IN AUDITORY NEUROPATHY

The mismatch between audibility and speech understanding in listeners with AN suggests that distortions of suprathreshold cues is the limiting factor in perceptual performance (Starr et al., 1996, 2000; Rance et al., 1999, 2002, 2012a). Speech perception ability in fact appears closely related to the degree of neural disruption in VIIIth-nerve and central auditory pathways (Kraus et al., 2000; Rance et al., 2002; Zeng et al., 2005). Psychophysical studies investigating the ways in which this disruption affects basic auditory processing have revealed that AN produces a pattern of effects quite distinct from that caused by sensory hearing loss. For example, as the cochlea is responsible for the initial processing of spectral cues (through the precise tonotopic arrangement of signals along the basilar membrane), sensory hearing loss is usually associated with impaired "frequency resolution" (the ability to perceive (resolve) the frequency components of a complex sound) (Rance et al., 2008). Listeners with AN on the other hand (who typically show evidence of normal cochlear (outer hair cell) function) generally enjoy normal cochlear frequency processing for high but not low frequencies (Cacace et al., 1983; Starr et al., 1991; Rance et al., 2004; Zeng et al., 2005; Vinay and Moore, 2007). Similarly, intensity discrimination (the capacity to detect level differences between sounds) which is also largely determined by cochlear-level processing, is relatively normal in AN listeners (Zeng et al., 2005).

Temperature-sensitive forms of AN due to mutations of OTOF (Starr et al., 1998; Marlin et al., 2010; Wynne et al., 2013) show clinical features that vary in degree as body temperature changes. When afebrile, their temporal processing ability (e.g., gap detection threshold) and speech comprehension may be normal. However, for sustained stimuli they experience marked adaptation of loudness similar to that described for acoustic neuromas. When body temperature rises their ability to comprehend speech is markedly impaired. It appears that temperature-sensitive AN degrades ribbon synaptic neurotransmitter release to be both reduced and dyssynchronous, even at stimulus onset, and then both impairments increase during continuous stimulation. In contrast, neural forms of AN show normal adaptation to sustained stimulation (Wynne et al., 2013). Abnormal adaptation is a hallmark of presynaptic AN due to ribbon synaptic disorder. (Santarelli et al., 2008) The impairment of neurotransmitter release likely participates in affecting speech perception in noise.

In contrast, by disrupting the integrity of the temporal neural code, AN affects perception based upon timing cues. In particular, temporal resolution (the ability to perceive rapid changes in auditory signals over time) and the temporal aspects of pitch discrimination can be severely compromised. In AN, temporal resolution deficits have been demonstrated both in "gap detection" tasks where listeners with AN typically require a silent period 2–5 times longer than normal controls before they become aware of a change in a continuous signal (Starr et al., 1991; Zeng et al., 2005) and in "amplitude modulation detection," where they show an impaired ability to track rapid signal envelope changes (Rance et al., 2004, 2010, 2012a; Zeng et al., 2005).

As well as demonstrating monaural temporal processing limitations, individuals with AN show impaired ability to integrate binaural difference cues. Abnormal masking-level difference (MLD) results, for example,

are a consistently reported finding (Starr et al., 1991, 1996; Hood, 1999). MLD assessment measures the release from masking obtained when a signal or noise is presented out of phase with a competing signal in the contralateral ear. Normal subjects typically show an MLD (with dichotic phase inversion) of ≈ 10 dB, indicating that phase information from each ear has been accurately represented at the level of the lower brainstem (Licklider, 1948). AN subjects, in contrast, typically show little or no masking release, suggesting an inability to accurately combine the neural code from each ear. This impaired ability to generate normal neural responses to monaural signals also accounts for their marked impairment to judge sound direction. When a sound emanates from any point other than directly in front of, or behind, the listener, the signal travels an unequal distance to each ear, giving rise to subtle (<1 ms) interaural time differences. Furthermore, the head acts as a barrier when the source is not directly in front or behind, which results in interaural level differences (of ≈ 10 dB). These difference cues are initially processed in the superior olivary complex of the brainstem where neural impulses originating in left and right auditory nerves converge on the same neural elements. These neurons are tuned to subtle binaural time and intensity differences essential for location (and movement) (Riedel and Kollmeier, 2002). While localization based on intensity cues is unimpaired in AN listeners, a number of studies have found that even gross interaural timing differences (>0.5 ms) are not interpreted as changes in sound direction (Starr et al., 1991; Zeng et al., 2005).

Sound localization has obvious benefits, alerting the normal listener to possible information sources and environmental dangers. In addition, sound localization cues may be used to improve perception in background noise when a target signal (such as speech) and competing noise arise from different directions (Micheyl et al., 2007) and or different spectral sources. AN affects the ability to selectively attend to a particular voice based on its location and, as a result, affected listeners typically require much higher signal-to-noise ratios (or lower noise levels) than their normal peers to comprehend speech and communicate effectively (Rance et al., 2012b).

TREATMENT OF AUDITORY NEUROPATHY

There are two main approaches to reducing the functional hearing deficit in individuals with hearing impairment. The first is to improve the listening environment. The second is to amplify/modify the signal reaching the listener's ear to maximize access to its salient cues.

Signal clarity

Listening-in-noise difficulty is a cardinal feature of AN, and as such, any approach that improves the signal-to-noise ratio (i.e., the relative loudness of speech to background noise) is likely to be important. Simple "listening tactics," whereby the individual physically structures the communication environment to reduce ambient noise and maximize the clarity of the speaker's voice, may be beneficial for general communication. Sound-field amplification systems, which amplify the speaker's voice (via loudspeakers), may also be useful for structured listening situations such as the school classroom or auditorium (Johnstone et al., 2009).

Another approach involves the use of "FM-listening" systems. These devices, which have been used extensively in children and adults with sensory hearing loss, transmit speech signals (detected by a lapel-worn microphone) via radio waves to ear-level receivers worn by the listener. As a result, the listener obtains a signal-to-noise ratio advantage from the proximity of the speaker's mouth to the transmitter microphone. Recent data from our laboratory have demonstrated significant speech perception and general communication benefits in a group of children and adults with AN due to Friedreich ataxia (Rance et al., 2010).

Amplification (hearing aid)

The basic function of conventional hearing aids is to amplify sound. As such, they can make environmental sounds and speech louder (allowing access to AN listeners with impaired sound detection) but they cannot improve the clarity of the sounds. Amplification outcomes in patients have been mixed. Some children (perhaps those with lesser degrees of temporal disruption) have responded well to hearing aids and have shown aided speech perception abilities consistent with their sensorineural counterparts (Rance et al., 2002; Roush et al., 2011; Ching et al., 2013). In many youngsters and almost all affected adults, however, conventional amplification has been of little or no benefit (Starr et al., 1996; Rance, 2005; Berlin et al., 2010). As a result, digital signal processing hearing aids designed to accentuate temporal and/or amplitude differences in the acoustic signal have been considered (Zeng et al., 2001; Narne and Vanaja, 2008) and may, in the future, improve outcomes in some cases.

Digital signal processing hearing aids can be programmed to process complex sounds (such as speech) in real time. They are not limited to making sounds louder, but can additionally (or alternatively) enhance the acoustic information that contributes most to intelligibility for people with a hearing impairment. Furthermore,

they can reduce the deleterious effects of unwanted background noise. For people who have specific difficulties with the perception of temporal information, sound-processing schemes have been devised that make timing cues more salient. For example, exaggerating the changes in level that occur in natural acoustic signals over a relatively short time scale can enhance temporal information. This process is known as amplitude expansion.

Cochlear electric implants

Cochlear implantation is currently the intervention option of choice for AN patients with severe auditory processing difficulties but not for children less than a year. Most reported cases have shown significant perceptual benefits and speech perception performance equivalent to that obtained by implantees with cochlear hearing loss (Trautwein et al., 2001; Madden et al., 2002; Shallop, 2002; Mason et al., 2003; Zeng and Liu, 2006; Teagle et al., 2010). These findings may seem counterintuitive, as the signal provided by the implant must still pass through a pathologic inner hair cell and/or a pathologic auditory nerve. Of the >200 AN cases reported, only a handful have had poor outcomes (Miyamoto et al., 1999; Rance et al., 1999; Teagle et al., 2010; Roush et al., 2011). Significantly, most subjects with cochlear implants show normal ABRs to electric stimulation (where previously to acoustic stimulation they had not). This suggests either an increase in the number of neural elements contributing to the evoked response (perhaps as a result of bypassing peripheral abnormality and stimulating the spiral ganglion and/or first node of Ranvier in auditory dendrites directly) or an improvement in the synchrony of neural firing. Whatever the explanation, it would seem that cochlear implants offer a viable means of improving functional hearing in most individuals with AN.

In the selection of candidates for cochlear implantation, the first criterion is the preservation of a normal-sized auditory nerve, as shown by MRI.

The audiologic measures in cochlear implantation candidates usually fall into two categories:

1. Those with hearing thresholds in the severe/profound range. In such cases the benefit of a hearing aid is limited and implantation should be undertaken as soon as reliable sound detection thresholds can be obtained. In children this is typically possible from ≈8 to 12 months of age.
2. Those with hearing thresholds in the normal to moderate range, but in whom poor discrimination may pose a problem. In children with AN, speech perception ability cannot be reliably evaluated until ≈3–4 years of age. This is obviously later than desirable. Research is needed to develop objective measures that can predict long-term auditory capacity and allow cochlear implantation candidature decisions to be made in infancy. In contrast, adults with AN who have impaired speech perception but relatively normal audiograms should be considered for implantation.

NEW DIRECTIONS

The quantification of auditory function in AN may be useful biomarkers of changes in function of certain hereditary or metabolic disorders affecting cranial or peripheral nerves (e.g., Friedreich's ataxia (Rance et al., 2008, 2012b) and CMT (Rance et al., 2012a)). The ABR measures of latency are stable and the effects of variables such as core temperature, gender, or cochlear damage are well known. The ability to define conduction times between the distal and proximal portions of the auditory nerve (Butinar et al., 2008) and between auditory brainstem structures (Starr and Achor, 1975) enhances the detection of slight alterations of function before symptoms or neurologic signs of progression occur.

The use of cortical electrophysiologic measures (Wynne et al., 2013) may provide information as to the capacity of the central auditory system to reorganize and deal with the disordered ribbon synapses and auditory nerve fibers.

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