

Comment

Auditory Neuropathy: A Biologically Inappropriate Label Unless Acoustic Nerve Involvement Is Documented

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Neuropathy means disease due to pathology in peripheral nerves. The term “auditory neuropathy” was introduced quite appropriately by Starr and colleagues who in 1996 described ten individuals with progressive, mostly moderate hearing losses attributable to disease of the VIIIth nerve that had become symptomatic in childhood or young adulthood (Starr et al, 1996). All had preserved cochlear function indexed by recordable otoacoustic emissions (OAEs) and cochlear microphonics; all had absent or very atypical auditory brainstem responses (ABRs) and absent acoustic brainstem reflexes (acoustic middle ear muscle reflexes and contralateral suppression of OAEs). In six of eight individuals tested, speech intelligibility was worse than predicted from their audiograms. Eight of the ten developed a chronic progressive peripheral neuropathy several years later, which provided evidence that a neuropathy of the acoustic nerve was responsible for their hearing losses.

Hearing loss due to an acoustic tumor that compresses the VIIIth nerve causing its subsequent degeneration was documented long ago. Description of progressive hearing loss in some individuals with a genetic neuropathy goes back at least to 1922 (Hicks, 1922). Hearing loss due to an auditory neuropathy had also been described before the Starr report in an occasional case of acute autoimmune peripheral neuropathy (Guillain-Barré syndrome) and a variety of

other chronic genetic disorders of peripheral nerves such as hereditary sensorimotor neuropathies (HSMNs or Charcot-Marie-Tooth disease). Hearing loss also had been reported in some other progressive genetic diseases such as Refsum syndrome, Friedreich’s ataxia, and others that affect both peripheral nerves and central tracts in the brainstem or cerebral white matter and where it is unclear from which site of pathology it arises. In stark contrast, neuropathy does not apply to cases where hearing loss is attributable to pathology of the central auditory pathway alone.

The paper by Starr and colleagues (1996) and a subsequent monograph by Sininger and Starr in 2001 elicited a great deal of interest, resulting in an exponential rise in the number of reports of auditory neuropathy. An unfortunate consequence of this proliferation is that the term “auditory neuropathy” began to be applied without neurologic corroboration, purely on the basis of audiological criteria, including: (1) atypical or absent ABRs, (2) preserved OAEs and/or cochlear microphonic, and (3) worse speech discrimination than typically would be predicted by the behavioral audiogram. Most recently, the term “auditory neuropathy” has been applied to infants who exhibit the first two audiological criteria only. Hence the diagnosis of auditory neuropathy has been made without attempt to differentiate pathology in the VIIIth nerve, that is, auditory neuropathy, from pathology in the other

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peripheral and central portions of the auditory pathway. A glaring example is hyperbilirubinemia of the neonate in whom this diagnosis is made on the basis of ABR and OAEs test results, even though it is well documented that the main site of pathology is the nuclei of the central auditory pathway, vestibular and cerebellar nuclei, basal ganglia, and *not* the VIIIth nerve. It should be noted that the extent of damage to the hair cells and spiral ganglion neurons in neonatal hyperbilirubinemia remains controversial because of the dearth of pathologic material in infants without other potential risk factors for hearing loss; even where hyperbilirubinemia is not the suspect, the diagnosis of AN in infants is problematic (Amatuzzi et al, 2001). ABR and OAE results cannot differentiate between primary involvement of the VIIIth nerve (neuropathy) and secondary degeneration of the VIIIth nerve following damage to the spiral ganglion cells that are the origin of most of its axons, even though the types of pathologies responsible for each may be very different.

The increasing number of papers describing patients diagnosed entirely on the basis of the three audiological criteria described above indicates that some professionals are applying the term “auditory neuropathy” inappropriately, suggesting to us that the fields of audiology and otology seem to have lost track of what the term “neuropathy” means biologically. We recently reviewed in detail the anatomic and electrophysiologic criteria (see figure 1 and table 1 in Rapin and Gravel, 2003) required for a diagnosis of auditory neuropathy in the strict sense of the term, that is, pathology that

demonstrably involves the spiral ganglion neurons or their axons. This cell type, like other peripheral nerves, is myelinated by Schwann cells up to its entry into the brainstem. The neurons of the central auditory pathway, starting at the brainstem cochlear nuclei and up to the cortex, are myelinated by oligodendroglial cells whose biology and pathology are entirely distinct from those of Schwann cells. Central tracts in the white matter of the brain, cerebellum, brainstem, and spinal cord are not “nerves,” and their pathologies are not “neuropathies.”

BRIEF REVIEW OF THE CONSEQUENCES OF NERVE CELL PATHOLOGY

There are two main types of neuropathies, demyelinating and axonal (see Table 1). “Primary demyelinating neuropathies” spare axons but slow or interrupt axonal conduction and thus impair function of the involved nerves. (Demyelination of central white matter in the brain or spinal cord slows or precludes conduction along central sensory tracts, but these are not “neuropathies,” although some of their consequences, in particular for hearing, may be similar.) Partially demyelinated nerves may continue to conduct, but conduction becomes asynchronous because it is variably slow in demyelinated axons and normal in spared axons. This situation tends to have particularly detrimental effects for those aspects of audition that depend on well-synchronized volleys (Berlin et al, 2002). Very longstanding demyelination eventually results in axonal dysfunction and eventually

Table 1. Simplified Consequences of Various Loci of Nerve Cell Pathology

Anatomic site of nerve cell damage	Consequences for nerve conduction
Myelin sheath: axon survives for a time. Longstanding demyelination → axonal dysfunction (mixed neuropathy) or death	Nerve excitable, but slow, dys-synchronous nerve conduction velocity.
Axon: low-level axonal pathology → myelination spared in unaffected neurons. Severe axonal pathology or death → disintegration of the myelin sheath (mixed neuropathy) and retrograde death of neuronal cell body	a) Conduction velocity in nerve's still myelinated axons normal → conduction <i>not</i> dys-synchronous. b) End-stage → nerve inexcitable
Both axon and myelin sheath: end result of either chronic demyelinating or axonal pathology	Conduction slow and dys-synchronous as long as nerve still excitable
Neuronal cell body: prompt death of axon and dendrites and disintegration of the myelin sheath	Axon inexcitable, no conduction

in inexcitability and death of the axon. A number of authors use the term “auditory dys-synchrony” to mean auditory neuropathy or, more broadly, to mean any of the disorders in which ABRs are absent and OAEs are present. This usage is not appropriate. Auditory neuropathy is not the only peripheral disorder that can affect hearing and the ABR with recordable OAEs as these same findings might arise from selective pathology of the inner hair cells (IHC) sparing the outer hair cells (OHC). Hearing loss associated with auditory dys-synchrony that arises in the brain stem auditory pathway does not affect the OHC and is not an auditory neuropathy. Finally, dys-synchrony accounts for only a subset of the possible effects of auditory neuropathy.

“Primary axonal neuropathies” are characterized by degenerated axons’ failure to conduct, with normal conduction in spared axons. The consequence is that although nerve function is variably impaired, conduction velocity is unaffected in surviving axons, again until there is so much degeneration that the nerve becomes unexcitable. Axonal neuropathies often start at the most distant end of the axon and only slowly progress in retrograde fashion to eventually reach the neuronal cell bodies from which the axons originated, which then undergo secondary degeneration.

Both chronic demyelinating and chronic axonal neuropathies eventually become “mixed neuropathies” as the biologic relation of axon to its myelin sheath is intimate. When the primary site of pathology is the neuronal cell bodies, both their axons and dendrites

degenerate and perish within days, resulting in total loss of function.

Neurons chronically deprived of excitatory inputs may undergo transsynaptic degeneration so that a slow cascade of degeneration may occur along several relays of a denervated pathway. This has been well documented in the central auditory pathway of experimentally deafened animals and in a few human cases when appropriate anatomic studies were performed.

RECOMMENDATIONS ON NOMENCLATURE

From a biologic point of view, the indiscriminate use of the term “neuropathy” for disorders of the spiral ganglion cells and their axons myelinated by Schwann cells as well as for those of the central auditory pathway myelinated by oligodendroglial cells is as inappropriate as not making a distinction between “conductive hearing loss” and “sensorineural hearing loss” (see Table 2). Therefore, we propose that: (1) hearing impairments due to disorders of the hair cells be referred to as “sensory hearing losses”; (2) those which through comprehensive behavioral, electrophysiologic, and pathologic investigation can be specifically attributed to pathology of spiral ganglion cells and their VIIIth nerve axons be referred to as “auditory neuropathies”; and (3) disorders of the central auditory pathway (cochlear nucleus, inferior colliculus, medial geniculate body, auditory cortex) be referred to as “central hearing losses.” When it is not clear whether the pathology affects

Table 2. Proposed Anatomically Based Nomenclature of Nonconductive Hearing Losses

Anatomic site of pathology	Proposed nomenclature
Hair cells	Sensory hearing loss
Spiral ganglion cells/VIIIth nerve	Auditory neuropathy
Central auditory pathway (cochlear nucleus → inferior colliculus → medial geniculate body → auditory cortex)	Central hearing loss
Spiral ganglion cells/VIIIth nerve and/or central auditory pathway (when the locus of pathology is undetermined)	Neural hearing loss
Hair cells and/or spiral ganglion cells/VIIIth nerve and/or central auditory pathway (when the locus of pathology is undetermined)	Sensorineural hearing loss

the auditory nerve, the central auditory pathway or both, the term “neural hearing losses” applies to indicate that the hearing loss involves the central or peripheral nervous system and not the hair cells. This new recommendation is a modification of the suggestion we made in our more detailed 2003 review of auditory neuropathy and is similar to that of Marsh (2002). In our 2003 paper, we suggested that the term “auditory neuropathy” be limited to cases for which the locus of pathology has been pinpointed to the spiral ganglion cells, their processes, or the VIIIth nerve, and “that the term neural hearing loss be used for pathologies that affect all higher levels of the auditory pathway from the brainstem to the auditory cortex” (p. 708). However, on reflection, it seems more logical and avoids any anatomic ambiguity to use the term “neural hearing loss” only for hearing losses that cannot be differentially diagnosed as a sensory (hair cell) hearing loss, an auditory neuropathy sensu stricto, or a central hearing loss (as defined above). Adoption of these conventions will bring the audiologic/otologic nomenclature into conformity with that which neurology applies to other disorders of the brain and peripheral nerves.

Electrophysiologic criteria (see table 1 in Rapin and Gravel, 2003) and imaging of the brain as well as the cochlea and VIIIth nerve are now available for making these distinctions. Consequently there is, in our opinion, no excuse for the continued biologically erroneous and confusing use of the term “auditory neuropathy” for cases where there is tenuous or nonexistent evidence that the pathology involves the spiral ganglion cells and VIIIth nerve selectively. When there is clear evidence that the hearing loss is not *sensory*, and when the locus of the disorder cannot yet be specified because of less than comprehensive functional testing or lack of neuropathologic evidence, we suggest that the use of “neural hearing loss” is preferable to “auditory neuropathy” as it is currently applied. Finally, until the site of pathology has been clarified, the familiar term “sensorineural hearing loss” would apply if all that is known is that the hearing loss is not conductive. We include here the many cases in which ABR and OAE data do not differentiate between auditory neuropathy and inner hair cell impairment. We cannot stress strongly enough that these distinctions

are not just biologically important, they are critical to ensure that an individual patient receives comprehensive diagnosis and appropriate management including consideration of candidacy for cochlear implantation.

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