"Hearing" and Auditory Neuropathy: Lessons from Patients, Physiology, and Genetics

To honor Kimitaka Kaga, scientist-clinician

Arnold Starr

Summary

I review auditory neuropathy (AN), an auditory temporal processing disorder, drawing upon lessons from patients, from temporal bones and peripheral nerves, and from the genetics of the disorder. The auditory temporal processing disorder affects speech comprehension and localization of sounds that can be disabling. Audibility is typically not the majoy problem. The criteria for diagnosis are physiological and include (1) abnormal auditory nerve function reflected by absent or abnormal auditory brainstem responses (ABRs) and (2) normal cochlear outer hair cell functions reflected by cochlear microphonics (CMs) and/or otoacoustic emissions (OAEs). The tests are relatively simple, and the results are typically unambiguous, encouraging the recognition of AN from diverse etiologies. The cochlear sites that are affected include auditory nerve, inner hair cells, or their synapses. Type I AN is a postsynaptic disorder involving both the number and functions of auditory nerves; Type II AN is a presynaptic disorder affecting inner hair cells' ability to form and/or release neurotransmitters. Inherited forms of AN are diverse. Temporal bone studies of postsynaptic forms of AN show a marked loss of auditory nerve fibers with accompanying demyelination whereas both the number and morphology of inner and outer hair cells are preserved. There are as yet no temporal bone studies of presynaptic forms of AN.

Key words Deafferentation, Neural timing, Genetics, Auditory neuropathy

Introduction

A young, 8-year-old girl with a puzzling hearing disorder was referred to me in 1988 by Manny Don and Yvonne Sininger from the House Ear Research Center. She had normal audiometric pure tone thresholds but impaired speech perception.

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doi: 10.1007/978-4-431-09433-3_1,

She was identified as having hearing problems by her teacher when her performance in class declined. She is named, metaphorically, "Eve," as our first patient with "auditory neuropathy." She described her problem as "I can hear but not understand." We studied her in detail for the next 2 years and identified that she had an auditory temporal processing disorder, absent auditory brainstem potentials, and preserved cochlear microphonics, consistent with auditory nerve dysfunction in the presence of normal cochlear receptor hair cells. The article about "Eve" was published in 1991 and needed nine authors to define the condition [1]. Dr. Berlin from the Kresge Hearing Center in New Orleans published a report in 1993 on this same type of hearing disorder and localized the problem to the type I afferent auditory nerve fibers [2]. He organized combining of our efforts and invited our group to come to New Orleans and see some of their patients together. Most of the patients had accompanying neurological disorders that affected their peripheral nerves, and we presumed their auditory nerve was also affected. The exceptions were patients with normal peripheral nerve function, indicating that the dysfunction of the auditory nerve could also reflect a consequence of disorders of inner hair cells and their synapses with auditory nerve. We wrote an article describing their common features succinctly entitled "Auditory Neuropathy" [3].

The unexpected combination of absent or abnormal auditory brainstem responses (ABRs) and normal pure tone audiograms had been noted previously, beginning with Hallowell Davis and S.K. Hirsch, who estimated its incidence was 0.5% in hearing-impaired subjects [4]. Kamitaka Kaga, who is feted in this volume, correctly localized the disorder to the auditory nerve in two elderly patients in 1996 who also had involvement of the vestibular nerves [5].

Auditory neuropathy patients have a wide variety of pure tone hearing loss and in many, speech is impaired out of proportion to the audiometric loss. The finding of absent ABRs when thresholds were elevated to a mild or moderate degree was a paradox because ABRs were being used then, and are still today, as an objective screening test for "hearing." The ABR is more precisely an objective measure of the integrity of function of the auditory nerve and brainstem auditory pathway structures [6]. The information derived from the ABR can provide insights into underlying mechanisms of hearing and its disorders.

The First Lesson: "Time is of the Essence"

The ABR is a measure of brainstem and auditory nerve functions that depends on precise neural encoding of auditory temporal cues. Neurophysiological studies have shown that the neurons in auditory nerve and auditory brainstem structures such as the cochlear nucleus and superior olive are sensitive to microsecond changes of the acoustic signal. The neural code for such temporal events provide signals for such daily processes as speech comprehension and localizing sound sources. The failure to define an ABR in auditory neuropathy (AN) subjects who can hear the clicks may be related to the failure of the auditory nerve to discharge at the

same latency to each stimulus so that the averaged neural response cannot be distinguished from the background potentials, known as dys-synchrony We have modeled the effects of such temporal jitter of nerve discharges on the ABRs in the 1991 report describing Eve [1].

We learned what effects impaired auditory neural temporal processing had by examining what these patients could hear and what they could not hear. Eve taught us that rapid time sequences could not be processed: she was impaired on detecting two stimuli presented in rapid sequence. She could not integrate temporal cues presented to each ear, so that localizing signal sources in the environment was deficient. In contrast, intensity discrimination was preserved [1]. My colleague at Irvine, Fan Gang Zeng, made detailed psychoacoustic measures in a number of other AN subjects showing that the common denominator underlying their auditory perceptual deficits is impaired auditory temporal processing [7].

The Second Lesson: "Diagnosis Is Only a Beginning"

The physiological criteria for defining abnormal auditory nerve functions in the presence of preserved receptor activities are a short list [3].

1. Absence or marked abnormality of the ABR, beyond what would be expected for the audiometric threshold elevations.
2. Preserved cochlear receptor functions evidenced by presence of otoacoustic emissions (OAEs) and/or cochlear microphonics (CMs), both generated by outer hair cells. The summating potential (SP), generated primarily by inner hair cells, is of relatively small amplitude and difficult to resolve in the ABR [8].

We also noted that acoustic middle ear muscle reflexes were absent or markedly elevated, and this measure can serve as an adjunct for diagnosing AN [3]. We did not include perceptual measures of temporal processes for diagnosis because cooperation by the subject is required and so many of the patients with AN are infants and children. The identification of these youngsters reflected the widespread use of ABRs and OAEs as objective screening measures of auditory function in the newborn nursery.

AN and its physiological measures can change over time. In approximately one-third of the patients, the disorder progresses to also involve the mechanical properties of cochlear outer hair cells, reflected by the loss of otoacoustic emissions, whereas cochlear microphonics typically persist [9]. Neonates with hypoxia or bilirubinemia can show improvement over time of both ABRs and behavioral measures of hearing. Adults with Guillain–Barrré syndrome, an acute immunological disorder, can temporarily lose their hearing as a result of acute demyelination of the auditory nerve [10]. Later in this chapter I discuss adults who are encountered with criteria for AN (absent ABRs and normal otoacoustic emissions) but who are asymptomatic. AN is clearly diverse in both etiology and time-course, and relationship to perceptual disorders requires vigilance to appreciate its dynamic features.

Our appreciation of underlying mechanisms of AN has utilized studies of temporal bones from AN patients after death. At least five temporal bones are examined [11–15]. Three of the earliest temporal bones, studied by Hallpike and Spoendlin, preceded the recognition of AN, but their descriptions of the hearing disorder are compatible with AN. All the patients to date had hereditary neurological disorders affecting peripheral and cranial nerves. Their temporal bones showed marked loss of auditory neural ganglion cells, axons, and dendrites. The inner and outer hair cells were normal in appearance. Some of the remaining auditory nerve fibers show varying degrees of demyelination. Similar changes were found in both affected peripheral and vestibular nerves [13,16], even though there were no clinical symptoms of vestibular nerve involvement [16]. The vestibular neuropathy is "asymptomatic," an alert that auditory neuropathy also can be "asymptomatic". There is a temporal bone study in premature infants with absent ABRs (unfortunately OAEs or CMs were not examined) showing in some a selective loss of inner hair cells without loss of auditory nerves. The incidence of this finding in the 12 temporal bones examined was 25%. As far as I am aware, an isolated loss of inner hair cells is not described in adult temporal bones. The difference between neonates and adults may reflect a particular sensitivity of inner hair cells to anoxia in the developing cochlea [17].

The Third Lesson Is from Genetics: "AN is a Many-Splendored Thing"

AN is similar to other medical conditions by involving multiple etiologies and multiple mechanisms. Genetics provide clear examples of this diversity. I have reviewed the literature (see Table 1) and our own experiences here at Irvine and classified AN. The classification is organized around the synapse that links inner hair cells (presynaptic site) with the auditory nerve (postsynaptic site). Such a model has been successful in defining disorders of neuromuscular function. The classification includes (1) anatomical sites affected (inner hair cell, auditory nerve, their synapse); (2) whether peripheral or optic nerves are involved; (3) type of functions affected (nerve activity, transmitter formation, release, and reuptake, receptor actions); and (4) site of action of the affected gene action (mitochondrial or not). The latter distinction appears to have particular phenotypes involving both optic and auditory nerves accompanying mitochondrial dysfunctions.

The following groupings of AN are proposed:

a. Type I postsynaptic AN: plus vestibular and peripheral neuropathies
b. Type I postsynaptic AN: plus optic nerve disorders accompanying nuclear and mitochondrial mutations affecting mitochondria
c. Type II presynaptic AN: inner hair cell and transmitter disorders
d. AN unspecified: affected sites unknown

Table 1. Genetic varieties of auditory neuropathy (AN)

Groupings	Gene	Inheritance	Sites affected	Other features
Type I: AN postsynaptic: ganglion cells, axons, dendrites:				
With sensory/motor neuropathy (Charcot–Marie–Tooth, CMT)	Nuclear		Neurons Nerves	
i. HSMN-Lom	NDRG1	R	Schwann	Roma
ii. HSMN-myelin protein zero	*MPZ*	D	Axon	
Pathology: Loss of ganglion cells and VIII nerve; hair cells normal				
iii. HSMN-peripheral myelin protein	*PMP22*	R	Schwann	
iv. HSMN-neurofilament light	*NF-L*	D	Axon	Asymptomatic
v. Gap junction protein	*GJB1, 2,*	R	Axon	Connexin
vi. AUNX1	q23-q27.3	X-linked	?	
With optic neuropathy	Nuclear and mitochondrial			Mitochondrial functions
i. Optic atrophy 1	*OPA1*	D	Terminals	Nuclear
ii. Leber's optic atrophy	Various			Mitochondria
iii. Friedreich's ataxia	FXN	R	Axons	Variable phenotype
Pathology: Loss of ganglion cells and VIII nerve; hair cells normal				
iv. Multiple systems atrophy	?	R	?	
v. Wolfram 1	WFS1	R	Axons	Variable phenotype
vi. Mohr-Tranebjaerg	*(DDP/TIMM8A*	R	Axons	Variable phenotype
Pathology: Loss of ganglion cells and VIII nerve; hair cells normal				
Auditory neuropathy alone				
i. Perjvakin	DFNB59	R	?	OHC?
ii. AUNA1	13q14–21	D	?	AN young OHC old
Type II AN: presynaptic:				
1. Inner hair cell				
i. Otoferlin	*OTOF*	R	IHC	Temperature sensitive
ii. Gap junction proteins	*GBJ6*	R	IHC	Connexin

OHC, outer hair cells

The Fourth Lesson: "Be Hopeful for AN"

Cochlear implants (CI) work in AN to improve speech perception and psychoacoustic measures of temporal processes [18,19]. Eve has a CI and depends on it to assist lip reading, which has been the major adaptation to her limitations. Eve is a good lip reader and becomes even better when using the implant.

I am of the opinion that learning to hear is lifelong and not restricted to "critical periods." The current trend to implant children with AN during the first year of life so as to be within one of the "critical periods" may not be without flaws. We know that the tests used to diagnose AN can improve in some children [20]. Moreover, adults fulfilling the criteria for AN can be asymptomatic [21] or only symptomatic under certain conditions [22,23]. Such exceptions test the rule that implants should be used in AN without behavioral evidence of impaired auditory temporal processing. The ABR is a brainstem measure and will not reflect brain processes that can adapt to the temporal processing disorder. There are new cortical potential methods of auditory temporal processing that can be used to examine infants as objective measure of cortical processes related to behavioral measures. I suggest that to wait for this evidence is in the best interest of the patient. Observation and new data will help to resolve the issues. As we begin to define the variety of mechanisms of AN, we will have the opportunity to develop appropriate therapies that will be focused and specific for different types of AN.

AN has taught me to listen to my patients. Each one provides unique insights. It is also necessary to make sense of their diversity, to find their common features. Sometimes we do have success, but the real joy is in the process of trying to understand.

This study was supported by Grant #DC 02618 from the National Iustitute on Deafness and Other Communicative Disorders.

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