Late-Onset Unilateral Auditory Neuropathy/Dysynchrony: A Case Study

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Abstract

**Background:** Auditory neuropathy/dysynchrony (AN/AD) typically develops early in life and is bilateral in nature.

**Purpose:** Herein, we describe an unusual finding of late-onset unilateral AN/AD based on reported case history and audiometric findings.

**Research Design:** A 64-year-old female presented with a complaint of a progressive unilateral hearing loss that had developed over the past two–three years. She underwent an extensive behavioral/electrophysiological test battery.

**Results:** Magnetic resonance imaging was negative for internal auditory canal mass or lesion. A unilateral notched loss centered at 1000 Hz and other findings were consistent with late-onset unilateral AN/AD: observable bilateral otoacoustic emissions and cochlear microphonics, absent middle acoustic reflexes with stimulation on the affected side, abnormal auditory brain stem response on the affected side, and poorer speech recognition than would be predicted by the audiogram. Middle-latency and long-latency evoked responses were present bilaterally, although with lower amplitudes on the affected side.

**Key Words:** Auditory dysynchrony, neuropathy, sensorineural hearing loss, unilateral

**Abbreviations:**
- ABR = auditory brain stem response
- AN/AD = auditory neuropathy/dysynchrony
- CM = cochlear microphonic
- DPOAE = distortion product otoacoustic emission
- LLR = long-latency auditory evoked response
- MLR = middle-latency auditory evoked response
- NICU = neonatal intensive care unit
- OAE = otoacoustic emission
- SNR = signal-to-noise ratio

More than ten years ago, Starr et al (1996) first described and coined the term *auditory neuropathy/dysynchrony* (AN/AD). Since then it has been generally recognized that an individual with AN/AD typically presents with a neural hearing loss associated with the following profile: preservation of outer hair cell activity as evidenced with observable otoacoustic emissions (OAEs) and cochlear microphonics (CMs), abnormal auditory brain stem responses (ABRs), absent middle ear acoustic reflexes, and poorer speech recognition than would be predicted by the audiogram (Starr et al, 1996; Hood, 1999, 2002; Berlin et al, 2001; Berlin et al, 2003; Rapin and Gravel, 2003, 2006).

While the incidence of AN/AD is not well understood in the general population, some prevalence estimates can be found for special populations. AN/AD was reported in 0.56 percent of infants among those from a neonatal intensive care unit (NICU) with extremely low birth weight (Xoinis et al, 2007). In another NICU, prevalence of the AN/AD profile was found to be 24 percent in 477 infants (Berg et al, 2005). Rea and Gibson (2003) found AN/AD in 40 percent of hearing-impaired infant graduates from a NICU. Among 841 hearing-impaired students aged two to 20 years, prevalence was reported to be 1.55 percent (Lotfi and Mehrkian, 2007). In a cohort of 5190 children aged one to 15 years of age, Foerst et al (2006) report prevalences of 0.94 and 8.44 percent within those at risk for hearing loss and those profoundly hearing impaired, respectively. In another group of children at risk for hearing loss a similar prevalence of less than 1
percent (i.e., one in 433) was reported by Rance et al. (1999). Lee et al. (2001) report a prevalence of approximately 2 percent in children aged six to 12 years attending a school for the hearing impaired in Hong Kong. In a cohort of 183 patients seeking audiologic services in India, a prevalence of 0.55 percent was found (Kumar and Jayaram, 2006). Cheng et al. (2005) report a prevalence of approximately 10 percent in children in schools for the deaf in Florida, Louisiana, New York, and Maryland.

AN/AD typically presents bilaterally and is identified at birth or in early childhood (Berlin et al., 2001; Sininger and Oba, 2001; Hood, 2002; Berlin et al., 2003; Rapin and Gravel, 2006). While onset in early adulthood or middle age is not unheard of, it is unusual. Sininger and Oba (2001), for example, report seven of 59 patients (i.e., 11%) having an onset between 20 and 60 years of age. Some individuals who develop peripheral neuropathies in adulthood display AN/AD with a later onset. Two of ten patients first described by Starr et al. (1996) were reported to have an onset of AN/AD as young adults. One of the patients was diagnosed with Charcot-Marie-Tooth disease, known as hereditary motor and sensory neuropathy. Berlin et al. (2001) report in 100 confirmed cases of AN/AD, 12 with Charcot-Marie-Tooth disease with adult onset.

There are only a small number of unilateral cases reported in the literature. Of nine detected cases of AN/AD from 14,807 consecutively screened infants in a universal hearing-screening program, three were reported to be unilateral (Ngo et al., 2006). In nine children between the ages of nine and 46 months with cochlear nerve deficiency exhibiting AN/AD, five were affected unilaterally, and four, bilaterally (Buchman et al., 2006). Of 26 children with AN/AD, Raveh et al. (2007) found a two-and-a-half-year-old child with AN/AD. Konradsson (1996) presented four children (three aged four years old and one seven years of age) with unilateral AN/AD on the left side. Cases of a ten-year-old (Zeng et al., 2001) and an 11-year-old boy (Podwall et al., 2002) diagnosed with unilateral AN/AD have been reported. Additionally, two separate cases of 12-year-old girls with unilateral AN/AD have been documented (Hood et al., 2003; Mallur and Lalwani, 2007). Cheng et al. (2005) note a child of unspecified age, with a compound heterozygote mutation of connexin 26, with unilateral AN/AD. Jerger et al. (1992) describe the case of a 29-year-old female adult with multiple sclerosis with classic signs of AN/AD. Sininger and Oba (2001) report 4 percent of their 59 cases to be unilateral; unfortunately they do not report age of identification.

As described above, AN/AD typically does not develop later in life, and it is not characteristically unilateral in nature. Herein, we describe such an unusual finding of late adult-onset unilateral AN/AD based on reported case history, audiometric, and imaging findings.

METHOD

Patient/Case History

A 64-year-old Asian female was referred to the East Carolina University Speech-Language and Hearing Clinic by her family physician. She presented with a complaint of a progressive unilateral hearing loss with occasional bilateral tinnitus that had developed over the past two–three years. No other significant auditory history was reported. Medically she reported hypertension, elevated cholesterol, and iron-deficiency anemia, all of which was presently managed with prescription. She also reported two to three years of “baby aspirin” intake for her heart but had ceased it for at least one year. On the initial hearing evaluation, a unilateral right sensorineural hearing loss of unknown etiology was confirmed.

Magnetic Resonance Imaging

A subsequent magnetic resonance imaging of the brain and temporal bone with and without gadolinium contrast was undertaken three weeks after the initial audiologic evaluation at the request of her family physician to rule out acoustic neuroma. The attending radiologist reported no evidence of internal auditory canal mass or “enhancing” lesion on either side. Brain imaging was also negative for infarct, hemorrhage, mass, extra-axial fluid, or hydrocephalus. Mild patchy and confluent areas within the cerebral white matter were observed. These were reported by the attending radiologist to be more numerous than expected for the patient’s age and hence abnormal but nonspecific. It was also reported that the findings were most often a result of chronic/benign disorders such as chronic microvascular ischemia; however, the differential would include multiple sclerosis, other demyelinating diseases, hypertension, chronic emboli, Lyme disease, collagen vascular disorders, granulomatous disease, vasculitis, remote trauma, and migraine headaches.

Audiometric Workup

During a second and third auditory evaluation, approximately one month later, an extensive behavioral and electrophysiological test battery was undertaken. A double-wall sound-treated audiometric suite (Industrial Acoustics Company), meeting specifications for permissible ambient noise (American National Standards Institute, 1999), served as the test environment for behavioral testing. A clinical audiometer
(Grason Stadler GSI 61 Model 1761-9780XXE) delivered all stimuli via insert earphones (Etymotic Research Model ER-3A) or soundfield speakers (Grason Stadler GSI 61 Model 1761-9639). A compact disc player (JVC Model XL-FZ258BK) delivered recordings of speech stimulii. Imittance, OAE, and evoked potential measures were recorded in a quiet clinical room with a middle ear analyzer (Grason Stadler TympStar), OAE systems (Otodynamics Echoport ILO292-USB and Bio-logic Scout Sport), and an evoked potential system (Nicolet Spirit), respectively. An insert earphone (Nicolet TIP-300) delivered stimuli for all evoked potentials.

**Behavioral Testing**

Thresholds for pure-tone and speech stimuli were determined with standard clinical procedures (American Speech-Language-Hearing Association, 1988, 2005). A Stenger test (Martin, 2002) was performed with 1000 Hz pure-tone stimuli. Tone decay tests (Olsen and Noffsinger, 1974) were performed monaurally with 500, 1000, and 2000 Hz pure-tone stimuli at 20 dB SL. Masking level difference was examined with 500 Hz pure-tone stimuli (Department of Veterans Affairs, 2006) presented at 60 dB HL, as per the protocol recommended by Wilson et al (2003). Word recognition was assessed monaurally, under earphones with a compact disc recording of 50 monosyllabic word lists of the Northwestern University Auditory Test No. 6 in quiet and continuous and interrupted noise (Stuart and Phillips, 1996, 1998), at 30 dB above the spondee recognition threshold. Word recognition in noise was assessed at +10 and −10 dB signal-to-noise ratios (SNRs). Sentence recognition was assessed monaurally and binaurally under earphones with the QuickSIN™ Speech-in-Noise Test (Killion et al, 2004; Etymotic Research, 2006) at 70 dB HL. To evaluate binaural disadvantage/interference, sentence recognition was also assessed in quiet and in competing speech noise with the Hearing in Noise Test stimuli (Nilsson et al, 1994). Stimuli were presented in sound field at 0 degrees azimuth at a level of 50 dB HL. Presentation was made binaurally and monaurally to the good ear while the poorer ear was plugged with a form earplug (E-A-R Classic).

**Physiologic Testing**

Tympanometry was obtained using a 226 Hz probe tone. Pump speed was 600/200 daPa/sec (i.e., pump speed was 600 daPa at extreme pressures and slowed to 200 daPa/sec near the tympanometric peak), with a sweep pressure start point of +200 daPa and an end point of −400 daPa. Ipsilateral and contralateral acoustic reflexes were assessed bilaterally with pure-tone activator stimuli of 500, 1000, 2000, and 4000 Hz.

Primary tones with an f2/f1 ratio of 1.2 and an L1/L2 of 65/55 dB SPL were used to evoke distortion product otoacoustic emissions (DPOAEs). The f2 frequencies ranged from 1000 to 8000 Hz at two points/octave (i.e., 1031, 1406, 1968, 2811, 3983, 5623, and 7966 Hz). DPOAEs were deemed to be present if response amplitude was 3 dB or more above the noise floor.

All evoked potentials were acquired while the patient was resting in quiet. Stimuli were delivered monaurally. Electrocochleography was employed to assess cochlear microphonics (CMs). CMs were evoked with rarefaction and condensation 1000 Hz tonal stimuli presented at 90 dB nHL at a rate of 7.7/sec. The tonal stimuli had a linear rise/fall time of 2 msec with a plateau of 5 msec. Extratympanic recordings with ear canal electrodes (TIPtrode™) were utilized with an ipsilateral/noninverting-contralateral/inverting montage. The forehead (Fz) electrode served as the common electrode. The recorded electroencephalogram (EEG) was amplified 100,000 times and bandpass filtered (5–3000 Hz). EEG samples exceeding ±25 µV were automatically rejected. Analysis time was 15 msec post–stimulus onset. A total of 1024 samples were averaged and replicated for each trial.

ABRs were evoked with rarefaction and condensation click stimuli presented at 90 dB nHL at rates of 7.7 and 77.7/sec. Simultaneous four-channel recordings were obtained with the following (noninverting–inverting) montages: ipsilateral (Cz–M1), contralateral (Cz–M3), vertical (Cz–Nape), and horizontal (M3–M4). The Fz electrode served as the common electrode in all arrays. The recorded EEG was amplified 100,000 times and bandpass filtered (150–3000 Hz). EEG samples exceeding ±25 µV were automatically rejected. Analysis time was 10 msec post–stimulus onset. Totals of 1024 and 2048 samples were averaged and replicated for each trial with the rates of 7.7/sec and 77.7/sec, respectively.

Middle-latency auditory evoked responses (MLRs) were evoked with click stimuli presented at 90 dB nHL with a rate of 7.7/sec. Simultaneous three-channel recordings were obtained with the following (noninverting–inverting) montages: midline (Cz–M1), ipsilateral (T3–M1 or T4–M2), and contralateral (T3–M1 or T4–M2). The Fz electrode served as the common electrode in all arrays. The recorded EEG was amplified 100,000 times and bandpass filtered (5–1500 Hz). EEG samples exceeding ±50 µV were automatically rejected. Analysis time was 100 msec post–stimulus onset. A total of 1024 samples were averaged and replicated for each trial.

Long-latency auditory evoked responses (LLRs) were recorded to 750 and 4000 Hz tonal stimuli presented at 75 dB nHL with a rate of 1.7/sec. The tonal stimuli had...
RESULTS

Behavioral Testing

The patient presented with normal hearing sensitivity on the left side defined as having pure-tone thresholds at octave and interoctave frequencies from 250 to 8000 Hz of \( \leq 25 \) dB HL (American National Standards Institute, 1996). On the right side a severe notched loss centered at 1000 Hz was evident. Her audiogram is displayed in Figure 1. The Stenger test was negative, inconsistent with pseudohypacusis on the right side. Tone decay was negative bilaterally. The antiphase (SnNo) masking level difference was significantly depressed (i.e., \(<5\%\) of normal listeners [Wilson et al, 2003]).

Spondee recognition thresholds were in good and poor agreement with three-frequency pure-tone averages for the left and right ears (cf. 9 and 30 dB HL vs. 10 and 53 dB HL), respectively (Brandy, 2002). Word- and sentence-recognition performance in quiet and noise as a function of test and ear is presented in Tables 1 and 2. As is evident in these tables, right-ear word-recognition scores were significantly poorer (\( p < .05 \)) than the left for both quiet and noise (Carney and Schlauch, 2007), performance in the right ear was poorer than would be predicted by the articulation index (Popelka and Mason, 1987; Gates et al, 2003), there was no release from masking in the interrupted noise on the right side (Stuart and Phillips, 1996, 1998), and binaural disadvantage/interference was not seen in quiet or noise.

Physiologic Testing

Normal static admittance, tympanometric width, and equivalent ear canal volume were observed bilaterally during tympanometry (Wiley et al, 1996). Ipsilateral and contralateral acoustic reflexes were present with left-ear stimulation of pure-tone stimuli from 500 to 4000 Hz in octave steps. Ipsilateral reflex thresholds were 80 dB HL at 500 and 1000 Hz and 85 dB HL at 2000 and 4000 Hz. Contralateral reflex thresholds were 80 dB HL at 500 and 1000 Hz and 90 dB HL at 2000 and 4000 Hz. All reflex thresholds evoked with the left-ear stimulation would be considered normal (Silman and Gelfand, 1981; Gelfand et al,
Ipsilateral and contralateral acoustic reflexes were absent with right-ear stimulation of the same pure-tone stimuli from 500 to 4000 Hz in octave steps. Maximum presentation levels were 100, 105, and 110 dB HL for ipsilateral stimulus at 4000 Hz; ipsilateral stimuli at 500, 1000, and 2000 Hz; and all contralateral stimuli, respectively.

DPOAEs were observed (i.e., SNR $\geq 3$ dB) bilaterally at all $f_2$ frequencies except at 3983 and 5623 Hz on the left side and 3983 Hz on the right side (see Figure 2). The observed DPOAE amplitudes were bilaterally symmetrical and exceeded the tenth percentile for a normal distribution (Gorga et al, 1997).

CMs were observed bilaterally and inverted with the reversal of the stimulus polarity (see Figure 3). ABRs were only observed on the left side (see Figure 4). Absolute and interpeak latencies were within acceptable clinical normal limits, as were wave V/I amplitude ratios. Appropriate wave V latency shift occurred with the increased stimulus repetition rate. Figure 5 presents ABRs evoked with rarefaction and condensation click stimuli presented at 90 dB nHL with a rate of 7.7/sec recorded from the ipsilateral ($C_z$–$M_i$) montage. Evidence of a “ringing” CM in the left ear and its reversal with stimulus polarity reversal is noted four to five msec after the cessation of the click stimuli. The Pa/P41 wave components of the MLR were observed bilaterally with little interaural differences in latency, although with lower amplitudes on the right side (see Figure 6). LLRs were reliably recorded to 750 and 4000 Hz tonal stimuli bilaterally. Replicable P1, N1, and P2 components were observed bilaterally again with lower amplitudes on the right side (see Figure 7).

**DISCUSSION**

Although unilateral case studies of AN/AD have been previously reported in the literature (e.g., Jerger et al, 1992; Konradsson, 1996; Zeng et al, 2001; Podwall et al, 2002; Hood et al, 2003; Mallur and Lalwani, 2007), to the best of our knowledge, this is the first reported case of a late adult-onset (i.e., greater than 60 years of age) unilateral AN/AD. Cases of unilateral deficits are unique, in that the patient’s good side can be used as an internal control. The patient presented with all the classic signs of AN/AD on the affected side relative to the normal unaffected side: normal outer hair cell activity as evidenced with observable OAEs and CM, absent middle ear acoustic reflexes, abnormal ABR, abnormal masking level difference, and poorer speech recognition than would be predicted by the audiogram. Consistent with previous reports (Squires and Hecox, 1983; Widen et

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**Table 2. Percent Correct Soundfield Sentence-Recognition Performance in Quiet and Noise as a Function of Test and Ear**

<table>
<thead>
<tr>
<th>Test Condition</th>
<th>Left</th>
<th>Binaural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quiet</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Continuous Noise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+10 dB Signal-to-Noise Ratio</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>0 dB Signal-to-Noise Ratio</td>
<td>74</td>
<td>86</td>
</tr>
</tbody>
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*Note: Right ear was plugged with a form earplug. Hearing in Noise Test stimuli were presented in sound field at 0 degrees azimuth at a level of 50 dB HL.*

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**Figure 2.** The patient’s DPOAEs evoked to primary tones with an $f_2/f_1$ ratio of 1.2 and with L1/L2 of 65/55 dB SPL. The $f_2$ frequencies ranged from 1000 to 8000 Hz at two points/octave.

**Figure 3.** Electrocochleograms evoked with rarefaction (R) and condensation (C) 1000 Hz tonal stimuli presented at 90 dB nHL at 0 degrees azimuth at a rate of 7.7/sec. Extratympanic recordings with ear canal electrodes were utilized with a horizontal montage ($A_i$–$A_c$) referenced to $F_z$. Clear reversal of the cochlear microphonic with stimulus polarity reversal is seen bilaterally. Confirmation that the recording was cochlear in origin is seen in the bottom tracing where the insert tubing was disconnected from the transducer, which remained in place, and no acoustic stimuli (NS) were delivered to the ears.

**Figure 4.** ABRs evoked with rarefaction click stimuli presented at 90 dB nHL at a rate of 7.7/sec. Simultaneous four-channel recordings were obtained with (A) ipsilateral ($C_z$–$M_i$), (B) vertical ($C_z$–Nape), (C) contralateral ($C_z$–$M_i$), and (D) horizontal ($M_c$–$M_i$) montages.
al., 1995; Hood, 1999; Kraus et al., 2000; Pearce et al., 2007), despite the absence of the ABR, MLRs and LLRs can remained largely unaffected. It has been suggested that the MLR and LLR reflect different neural synchrony than is needed to produce the components of the ABR (Squires and Hecox, 1983; Hood, 1998, 1999; Kraus et al., 2000; Rapin and Gravel, 2003, 2006).

Several key findings were critical to the diagnosis of AN/AD with this patient. First was the observation of OAEs and the CM consistent with normal outer hair cell function. The presence of the CM alone is not indicative of normal outer hair cell function (Withnell, 2001), and it is certainly possible that the response seen to the 1000 Hz tonal stimuli may be generated by more basal areas of the cochlea (Patuzzi et al., 1989; Ruggero et al., 1997). The observation of the long ringing of the CM observed with the ABR and its reversal in polarity with reversal of the click polarity is collaborative, however (Berlin et al., 1998). Absent middle ear reflexes, while stimulating the affected side, were also important (Berlin et al., 2005). An additional hallmark of AN/AD was the absent ABR on the affected side.

We were concerned about the less-than-normal DPOAEs on the left side considering the normal thresholds from 250 to 8000 Hz. The DPOAEs were repeated three times across a three-month period with two different devices, so we were confident that they were not a result of artifact or equipment/operator error. Certainly some individuals with AN/AD have demonstrated a selective loss of their OAEs while the CMs were preserved (Deltrenre et al., 1999; Berlin et al., 2003). The symmetry of the DPOAEs (see Figure 2) leads us to believe, however, that some cochlear dysfunction unrelated to the AN/AD is contributing to the loss/reduced amplitude of the emissions in the f2 frequency range of 4000 to 6000 Hz. Significant red flags in the patient’s history were long-term aspirin use and iron-deficiency anemia. There are some reports on the short-term effects of aspirin on DPOAEs in humans (Long and Tubis, 1988; Wier et al., 1988; Brown et al., 1993) but not long-term effects. The symmetrical loss of loss/reduced amplitude of the emissions may be related to the reported long-term use of aspirin. Abnormal DPOAEs have not been reported in younger adult patients (i.e., mean age 27.5 years, SD = 9.7) with iron-deficiency anemia (Cetin et al., 2004), however.

One final observation is the patient’s poor word-recognition performance in interrupted noise. While listening in interrupted noise, relative to continuous noise, individuals typically experience a perceptual advantage or “release from masking.” This phenomenon reflects the temporal ability of the listener to resolve speech fragments or get “glimpses” or “looks” of speech between the dips or gaps of noise that facilitates the identification of specific speech stimuli (Stuart and Phillips, 1998). Demonstrations that listeners with noise-induced hearing impairment (Phillips et al., 1994), those with multiple sclerosis with demyelinating lesions in the auditory system yet normal peripheral hearing sensitivity (Rappaport et al., 1994), older normal-hearing listeners, and older normal-hearing listeners with presbycusis (Stuart and Phillips, 1996) exhibited poorer performance in interrupted noise compared to young normal-hearing listeners suggest that the paradigm is sensitive to auditory temporal deficits in the periphery and central auditory system. The patient’s performance in the good ear is typical of normal-hearing listeners (i.e., a 48% improvement in interrupted noise at the –10 dB SNR). There was no evidence of improved performance in interrupted noise on the affected side. This finding is consistent with the previously demonstrated reports that individuals with AN/AD suffer from a severe temporal processing impairment (Zeng et al., 1999; Zeng et al., 2005). That is, intensity-related processing and frequency discrimination at high frequencies are normal, but
tasks that require temporal encoding of stimuli (e.g., gap detection, temporal integration, lateralization with interaural timing differences, and temporal modulation transfer function) and frequency encoding requiring phase locking (a temporal phenomenon) are severely impaired.

Finally, with regard to the patient’s management, following our evaluation we recommended a referral for a neurologic evaluation to rule out any other neuropathies and/or related conditions. We also recommended an annual audiological evaluation. Considering her good binaural performance (i.e., no evidence of disadvantage/interference) and her reported limited listening difficulties, we have not recommended any rehabilitative measures other than modified listening strategies (e.g., preferential seating, reducing or eliminating background noise, etc.) and hearing conservation.

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NOTE

1. Enhancing lesions are those abnormalities with blood–brain barrier permeability that allow large-enough gadolinium leakage to be detected visually (i.e., inflammation and tissue damage are seen as bright areas). The evidence of enhancing lesions is often used to characterize the extent of tissue injury caused by multiple sclerosis.

REFERENCES


