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Cochlear implants
Cued speech
Middle-ear muscle reflexes

Abbreviations

ABR: Auditory brainstem response
AN/AD: Auditory Neuropathy/
Dys-synchrony
ANSD: Auditory Neuropathy
Spectrum Disorder
AVT: Auditory Verbal Therapy
CI: Cochlear implant
CM: Cochlear microphonic
ECochG: Electrocochleography
MEMR: Middle-ear muscle reflex
OAE: Otoacoustic emissions

Multi-site diagnosis and management of 260 patients with Auditory Neuropathy/Dys-synchrony (Auditory Neuropathy Spectrum Disorder*)

Abstract

Test results and management data are summarized for 260 patients with diagnoses of Auditory Neuropathy Spectrum Disorder (ANSD). Hearing aids were tried in 85 of these patients, and 49 patients tried cochlear implants. Approximately 15% reported some benefit from hearing aids for language learning, while improvement in speech comprehension and language acquisition was reported in 85% of patients who were implanted. Approximately 5% (13/260) of the total population developed normal speech and language without intervention. Patients were diagnosed at our laboratory (n=66) or referred from other sites (n=194), and all showed absent/grossly abnormal auditory brainstem responses (ABR), often 'ringing' cochlear microphonics, and the presence or history of otoacoustic emissions. Etiologies and co-existing conditions included genetic (n=41), peripheral neuropathies (n=20), perinatal jaundice and/or anoxia and/or prematurity (n=74). These patients comprise 10% or more of hearing impaired patients; their language acquisition trajectories are generally unpredictable from their audiograms.

Sumario

Se resumen los resultados de las pruebas y los datos del tratamiento de 260 pacientes con diagnóstico de Espectro de desórdenes de la Neuropatía Auditiva (ANSD). En 85 de estos pacientes se probó el uso de auxiliares auditivos y 49 pacientes recibieron un implante coclear. Aproximadamente 15% reportaron algún beneficio con los auxiliares auditivos para la adquisición del lenguaje mientras que el 85% de los que recibieron un implante reportaron una mejoría en la comprensión y la adquisición del lenguaje. Aproximadamente 5% (13/260) de la población total desarrolló lenguaje normal sin intervención. Los paciente fueron diagnosticados en nuestro laboratorio (n=66) o referidos de algún otro lado (n=194) y todos mostraron ausencia o anomalía importante de los potenciales evocados (ABR), frecuentemente con una microfónica coclear "timbrante" y con presencia o historia de emisiones otoacústicas. La etiología o las condiciones co-existentes incluidas fueron: genéticas (n=41), neuropatías periféricas (n=20), ictericia perinatal y/o anoxia y/o prematuridad (n=74). Estos pacientes representan 10% o más de los pacientes con hipoacusia; su trayectoria en el proceso de adquisición del lenguaje es generalmente impredecible a partir de sus audiogramas.

*At the Consensus Conference on Auditory Neuropathy/Dys-synchrony coordinated by Drs. Yvonne Sininger and Deborah Hayes (NHS, Como, Italy, June 19–21, 2008), and sponsored by the Bill Daniels Hearing and Speech Center, this nomenclature was recommended by the clinical review panel.

Introduction, Historical and Theoretical Issues

Auditory neuropathy spectrum disorder (ANSD; see terminology discussion in Berlin et al, 2001a, 2001b; Kraus et al, 2000; Rapin & Gravel, 2006) describes a condition in which a patient's otoacoustic emissions (OAE) are (or were at one time) present, and auditory brainstem responses (ABR) are abnormal or absent. In some instances, ANSD is identified on the basis of present cochlear microphonics (CM) and abnormal or absent ABRs (e.g. Berlin et al, 1993; Starr et al, 1996; Deltenre et al, 1999; Rance et al, 1999) with or without abnormalities of OAEs. The patient's pure-tone audiogram, if it can be acquired reliably, may range anywhere from essentially normal hearing sensitivity to a profound hearing loss. Speech recognition ability is generally poor, particularly in noise, although it may be good in quiet in some patients (Rance et al, 2007). In addition, fluctuant listening abilities have been reported, some associated with body temperature and others with no clear precipitant (Starr et al, 1998; Berlin et al, 1999). Prevalence accounts vary from roughly 1% (Foerst et al, 2006) to 10% in schools for the deaf (Berlin et al, 2000; Lee et al, 2001; Cheng et al, 2005) and between 10% in newborns (Sininger, 2002) and 40% in hearing-impaired NICU graduates (Rea & Gibson, 2003).

Probably the first audiological reports of ANSD came from Hinchcliffe et al (1972) well before OAEs (Kemp, 1978) were reported. Subsequent suspicions were raised by Chisin et al (1979), Worthington and Peters (1980), Cacace et al (1983), Kraus et al (1984), Prieve et al (1991), Berlin et al (1993), and (Kaga et al (1996). We (Starr, Picton, Sininger, Hood & Berlin, 1996) labeled this disorder as 'auditory neuropathy' after collectively reviewing our first 10 patients who shared a set of unique auditory problems. One had absent compound action potentials (CAP) during transtympanic electrocochleography (ECoChG) recording (found by Berlin and Hood) and the others had concurrent peripheral neuropathies, which were agreed upon by the two attending neurologists (Starr and Picton). It has been suggested subsequently that the term 'neuropathy' presumes data that we do not always have (Berlin et al, 2003; Moser et al, 2006; Rapin & Gravel, 2006) and should be avoided or at least semantically indexed (Korzybski, 1958²) to allow for the inclusion of inner hair cell losses, as suggested by AmatuZZi et al (2001) and Varga et al (2003), or inner hair cell synaptic disorder Santarelli and Arslan, 2002; Moser et al, 2006; McMahon et al, 2008). At the same time, we must also recognize the 'neuropathy' part of this descriptor and collaborate with our neurology and genetics colleagues to identify and categorize the peripheral neuropathies that have been reported in over one-third of our patients. These neuropathies include absent VIIIth nerves (Buchman et al, 2006), Charcot-Marie-Tooth Disease, and Mohr-Tranebjaerg syndrome (Starr et al, 1996; Merchant et al, 2001) as well as mitochondrial diseases (Corley & Crabbe, 1999; Ceranić & Luxon, 2004; Forli et al, 2006). Additionally, Delmaghani et al (2006) reported mutations in the pejvakin gene in individuals described as having nonsyndromic deafness due to a neuronal defect.

Thus, ANSD may be part of a continuum in which a mosaic of present and functioning inner and outer hair cells and pre- and

post-ganglionic single units of the auditory nerve may lead to various combinations of temporal disruption (Berlin et al, 1993; Zeng et al, 1999, 2005; Starr et al, 2000, 2008; AmatuZZi et al, 2001; Varga et al, 2003; Rance et al, 2004; McMahon et al, 2008). In addition, ANSD patients may differ greatly from one another in their ability to use temporal cues. These factors affect both the methods utilized in evaluation and the issues that must be considered in recommending management for both the patient and family. They also underlie our motivation for this retrospective review of how patients have been treated in the field so far. This paper is written from the historical perspective of the first author (CIB) who saw the first patient in our series in the early 1980s.

Methods

The database at the core of this report is composed of material from patients evaluated at the Kresge Hearing Research Laboratory and the associated Audiology Clinics at LSU Health Sciences Center (n=66) and data submitted by professional colleagues (n=194). No data were submitted or accepted directly from patients without confirmation and clearance from their professional referring agents. Compilation of this database began in 1982 with our first patient and became systematized in 1994 after our first public reports (Berlin et al, 1993). The 260 patients included in this database met strict diagnostic criteria based on acquired copies of the ABR and OAE tracings, which were sufficiently valid to confirm a diagnosis of ANSD. The criteria at the time required a de-synchronized or absent ABR, in the presence of (or one time history of) normal otoacoustic emissions. We would now add elevated or absent middle-ear muscle reflexes, which are incongruent with normal emissions. In order to be included in this database, the test data, including tracings of all OAEs, CMs, and ABRs, were reviewed, and categorization was agreed upon by a team of four of the author-audiologists and researchers who had studied ANSD patients for five or more years (CIB, LJH, TM, and DW). In order to acquire these 260 patients, more than 300 patient files were reviewed. Patients who may actually have had ANSD were excluded where there was insufficient corroborating evidence, for example, just a narrative from others of normal OAEs and/or an abnormal ABR with no tracings. We also excluded patients with a diagnosis of Friedreich's Ataxia (FA) because all of our FA patients had a robust Wave I and normal middle-ear reflexes. This suggested to us that their abnormal ABRs were more traceable to brainstem anomalies than to primary auditory nerve or inner hair cell disorders. Other respected colleagues (e.g. Cacace et al, 1983; Miyamoto et al 1999; Rance et al, 2008) have categorized and treated some FA patients as having ANSD. We remain uncertain in part because of the presence of middle-ear muscle reflexes in our patients and the report of the failure of CI in one FA patient (Miyamoto et al, 1999).

A sample of data from an ANSD patient, which qualified this patient for inclusion in the database, is shown in Figure 1 (bottom). Note the long ringing CM, which could easily masquerade as a normal ABR until or unless tracings to stimuli with polarity reversal were compared. This is contrasted with an ABR from a normal individual shown in the top portion of Figure 1.

OAE data were either transient evoked OAEs (TEOAEs) collected using default test levels and procedures (80 dB peak SPL, non-linear clicks) or distortion product OAEs (DPOAE) typically collected using stimulus levels of L1=65/L2=55 dB SPL. ABRs were obtained using click stimuli, where replicated averages of

²Korzybski's work on semantic indexing teaches that the labels which we use affect our actions. Thus calling this a "neuropathy" may misguide us into believing that the neurons are irreparably damaged or unavailable, and block us from even considering implantation. Hence our suggestion (Berlin et al., 2003) that the term "dys-synchrony" be added to "index" the basic term of "neuropathy" and remind us that, if this might also be "dys-synchrony", implantation is likely to be useful. McMahon et al (2008) and Santarelli et al (2008) later showed physiologically that this is a valid construct, when they separated pre-synaptic from post-synaptic pathology using ECoChG.

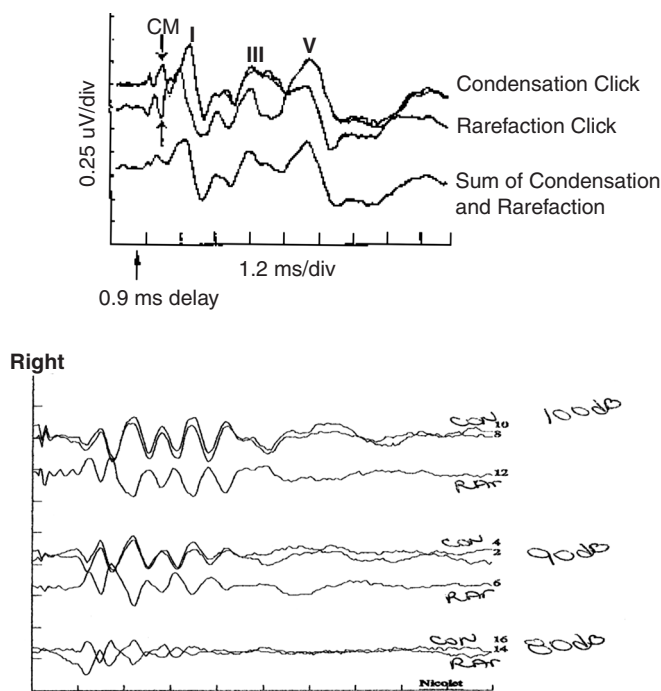


Figure 1. Sample ABR test results in a normal individual (top) and an ANSD patient (bottom). ABRs obtained with condensation and rarefaction polarity clicks are compared in the upper tracings in each panel; the sum of condensation and rarefaction averages are displayed below those tracings.

condensation clicks and averages of rarefaction clicks were compared in order to separate CM from neural components (Berlin et al, 1998). Stimulus intensity levels for the ABR ranged from 75 to 95 dB nHL, with the higher test levels used when no response was seen at 75 dB nHL. Some patients had recordings at multiple levels in order to track CM to its visual detection threshold or to follow Wave V in those instances where a neural (Wave V) response was identified at high intensities. Having multiple-level ABR recordings was not part of the inclusion criteria; however, recordings where the latencies of the waves never changed with intensity were taken as a cardinal sign of the absence of neural synchrony. The CMs were masquerading as neural responses with the predictable latency for some if not all of the waves, but changing their polarity when the stimulus was changed, and not shifting in latency as intensity fell (see lower part of Fig 1). Patients were included when the ABR was completely absent (i.e. no neural response recorded) and also when an ABR was present though low in amplitude, generally with Wave V only and always without a Wave I, and present only at 70 dB nHL or higher. This is typically considered an ‘abnormal ABR’ or ‘abnormal Wave V only’ ABR in definitions of ANSD in the presence of normal OAEs.

Some candidates for the database were rejected because they had salient CM but also had Wave V latency-intensity functions that were likely consistent with transient rather than permanent ANSD (Attias & Raveh, 2007). These patients were not included in the database because of their good neural synchrony (despite the absence of Waves I and III).

Table 1. Demographic information related to age, gender and bilateral versus unilateral ANSD for the 260 subjects included in the analysis.

Age (n=260)	Male		Female	
	Number	Percent	Number	Percent
0-24 months	61	23.46	27	10.38
25-48 months	24	9.23	28	10.77
4-6 years	24	9.23	20	7.69
7-12 years	24	9.23	15	5.77
13-18 years	2	0.77	4	1.54
19-30 years	4	1.54	9	3.46
Over 30 years	7	2.69	11	4.23
Total	146	56.15	114	43.85

Bilateral/Unilateral ANSD	Number	Percent
Bilateral	241/260	92.69
Unilateral	19/260	7.31
Unilateral Male	10/19	52.63
Unilateral Female	9/19	47.37
Unilateral Left Ear	13/19	68.42
Unilateral Right Ear	6/19	31.58

Also, it should be noted that sharply sloping hearing losses in and of themselves can lead to reversals of some if not all of the waves of an ABR (Coats & Martin, 1977). Thus, in our current view, simply the presence of a CM or reversing waves at the beginning of the trace does NOT make a diagnosis of ANSD (Withnell, 2001; Coats & Martin, 1977) without the cross-check of middle-ear muscle reflexes (MEMR)³, OAEs, and an ABR latency-intensity function.

MEMRs were absent or abnormal in all of the 148 patients in whom they were recorded. These data were not part of an inclusion criterion initially, but we recommend them now to validate the diagnosis. They also serve to rule out some Friedreich’s Ataxia patients as primary ANSD patients.

Results

Patient demographics

Table 1 summarizes demographic data on the patients included in the database. The majority of patients are pediatric because mandatory auditory screening is now common in the United States at birth and in the schools. Adults are often identified either because they develop other peripheral neuropathies and/or are unsuccessful hearing-aid users. Other individuals ultimately identified with ANSD often came to us with a misdiagnosis of central auditory processing disorder (CAPD).

Our database contains slightly more males than females (56% versus 44%). This is not considered significant at present as other reports showed slightly more females than males, though the number of patients was much smaller (e.g. Starr et al, 2000). The majority

³MEMRs were absent or abnormal in all of the 148 patients in whom they were recorded. These data were not part of an inclusion criterion initially, but we recommend them now to validate the diagnosis. They also serve to rule out some Friedreich’s Ataxia patients as primary ANSD patients.

Table 2. Patient history and risk factors in the pediatric population of the database (by number and percent of subjects). Note that only 38.5% report normal birth and neonatal history. Thus, many patients had multiple risk factors, such as premature birth, hyperbilirubinemia, exchange transfusions, anoxia, etc., and therefore the percentages overlap considerably.

	Number	Percent of 153
History and risk factors (subjects aged 0–18 years; n = 153)		
Normal history	28	18.30
Normal pregnancy	31	20.26
Premature birth	73	47.71
Hyperbilirubinemia	74	48.37
Exchange transfusion	31	20.26
Anoxia	26	16.99
Respiratory distress	23	15.03
Artificial ventilation	35	22.88
Ototoxic drugs	44	28.76
Low birth weight	11	7.19
Anemia	6	3.92

of our sample have ANSD in both ears, with only 19 of 260 (7.3%) showing unilateral ANSD. Reports of unilateral ANSD are common (e.g. Konradsson, 1996; Podwall et al, 2002; Buchman et al, 2006). Interestingly, 13 of 19 unilateral cases involved the left ear, while only 6 patients had right unilateral ANSD. At present, this number of unilateral patients is too small to determine whether this is any more than a sampling effect.

Patience history information

Patient history and risk factors are shown in Table 2. Review of all records showed that sufficient history information was available for 153 of the patients in the database in the age range of birth to 18 years. Older patients were first seen as teenagers or adults, and we did not have verifiable birth history information for many of them. Thus, the factors related to the birth and postnatal period are shown for only 153 patients in Table 2.

Other history information, which sometimes included late onset of ANSD, was available for 197 patients in all age groups. Thirty-two patients have other family members with ANSD, suggesting a genetic cause. Underlying genetic causes, such as mutations in the otoferlin gene, have been confirmed in some of these patients (Varga et al, 2003). Six of our patients reportedly have mitochondrial disorders. In addition, some patients showed concurrent neuropathies, including Hereditary Motor Sensory Neuropathy (HMSN) that may encompass Charcot-Marie Tooth Disease (3), optic nerve atrophy (4), cerebral palsy (13), and kernicterus (3).

Otoacoustic emissions and middle-ear muscle reflexes

As part of the Kresge Laboratory audiological test battery, we recorded OAEs, tympanograms, and MEMRs on all our new patients. This strategy has been strongly recommended to others and has uncovered underlying ANSD in many of the patients referred to us from outside sources. This strategy, of course, has prevented us from missing ANSD when the evaluations originated with us. These data are shown for the patients in the ANSD database in Table 3.

Table 3. Otoacoustic emissions (OAE) and middle-ear muscle reflex (MEMR) test results.

	Total	Percent
Otaoacoustic Emissions (number of ears)*		
Left Ear		
Present	176/233	75.54
Absent	40/233	17.17
Partial/Questionable	17/233	7.30
Right Ear		
Present	167/224	74.55
Absent	39/224	17.41
Partial/Questionable	18/224	8.04
Middle Ear Muscle Reflexes (number of subjects)**		
Absent MEMRs (all absent)		
Bilateral ANSD	125/148	84.46
Unilateral ANSD	7/148	4.73
Total Absent	132/148	89.19
Abnormal (combination of elevated and absent)		
Bilateral ANSD	14/148	9.46
Unilateral ANSD	2/148	1.35
Total Abnormal	16/148	10.81

*OAE data exclude non-ANSD ears in unilateral cases and ears with no data.

**MEMR data only include ears with normal tympanograms.

OAE data were reviewed for all 260 patients. Usable OAE data were available for 233 left ears and 224 right ears. Reasons for exclusion included the non-ANSD ears of the 19 patients with unilateral ANSD, patients for whom OAE data were not available (diagnosis based on CM data), and/or high noise levels in the recordings. It can be seen from Table 3 that approximately three-fourths of the patients had present OAEs while the remaining one-fourth had either partial or absent responses. Some of these abnormalities may have been due to on-going or previous middle-ear problems in the younger patients.

Middle-ear muscle reflex data were extracted for 148 patients who had normal tympanograms and/or present OAEs. MEMRs were absent for all frequencies and conditions tested in 90% of the patients. Ten percent showed some MEMR responses; however, it should be noted that no ANSD patient had normal MEMRs at all frequencies. Those with reflex responses showed elevated thresholds and/or combinations of present (elevated) and absent reflexes. Some of these data were previously published (Berlin et al, 2005) based on 136 of these 148 ANSD patients.

Audiogram and speech recognition results

Pure-tone responses ranged from normal or nearly normal to absent (Table 4). Degree of hearing was calculated based on averages of thresholds for 500, 1,000, and 2,000 kHz. Behavioral audiograms were often reported with 'poor reliability' of responses. Audiograms were submitted for only 155 patients and were acquired through earphones for about 70% of the patients included. Symmetry of thresholds was compared for the 103 patients with bilateral ANSD and test results under earphones. Approximately three-fourths of patients demonstrated symmetric responses from the left and right ears.

Table 4. Audiometric test results, based on data from 155 subjects. Degree of pure tone behavioral hearing loss is based on pure-tone averages for 500, 1,000 and 2,000 kHz.

	Total	Percent
Pure Tone Test Data (number of subjects)		
Bilateral ANSD—Left and Right Ears		
Unilateral ANSD—Left Ear	103/155	66.45
Unilateral ANSD—Right Ear		
Sound field	6/155	3.87
	2/155	1.29
	44/155	28.39
Left and Right Ear Symmetry (number of subjects)*		
Symmetric Thresholds	79/103	76.70
Asymmetric Thresholds	24/103	23.30
Degree of Pure Tone Behavioral Hearing Loss (number of ears)**		
Within Normal Limits	8/258	3.10
Normal-Moderate	6/258	2.33
Mild	10/258	3.88
Mild-Moderate	42/258	16.28
Mild-Severe	19/258	7.36
Mild-Profound	8/258	3.10
Moderate	25/258	9.69
Moderate-Severe	37/258	14.34
Moderate-Profound	11/258	4.26
Severe	16/258	6.20
Severe-Profound	37/258	14.34
Profound	39/258	15.12

*Based on bilateral ANSD subjects tested via earphones.

**Based on data from left ears, right ears and sound field.

Speech recognition scores for monosyllables in quiet were available from only 25 patients in the database aged four years and older. It should be noted that speech audiometry was attempted in 95 patients in this age range; only 25 had word recognition ability in

quiet and only 5 in noise. Word recognition in quiet was 0% in the remaining patients (Table 5 and Figure 2). For the 25 patients with speech recognition ability only in quiet, their scores averaged 45.1% for the left ear and 47.8% for the right ear. Five subjects had word recognition ability both in quiet and in noise. These subjects represent our 'best performers' in relation to ability to utilize auditory information, and this is also reflected in their recognition scores, averaging 86–87% in quiet and 48–64% in noise tested by us with 25-word PB lists at a S/N ratio of +10 for four of the patients and +8 for the remaining patient. The background noise was white noise.

Hearing aids and cochlear implants

Hearing-aid outcome data were provided on 85 patients, while CI data came from 49 patients (Tables 6 and 7). Hearing aids, verified with real-ear measurement for our patients at Kresge Lab, were fit by just one of us (CIB) using an audibility criterion. That is to say, the most stable and repeatable behavioral audiogram was used and first converted to SPL. Then a 40 dB input signal was amplified by the program until the real-ear measures or DSL with RECD showed the output to exceed the target threshold by 5 dB or more. Then the input was changed to 60 and finally 75 dB to assure compression and output levels matched the expected maxima predicted from the curves. Aids were tried in 27 of our patients, to establish candidacy for cochlear implantation. In retrospect, it is clear that hearing aids alone helped language acquisition in relatively few of those patients in our sample.

A total of 11 of the 94 patients who tried hearing aids in this sample learned language with hearing aids sufficient to reach second and third grade, and reportedly compete successfully with normal-hearing peers. The categories were established by parent and audiologist's report (see Table 6). Thus we should not be quoted as suggesting that hearing aids *will* not work with these patients, but only that they have not in the *past* been salutary for the majority of this limited sample.

This observation should be viewed in context with 13 patients in this sample (13/260=5%) whose ANSD was so mild as to require *no* intervention for hearing or developing speech and language³, although all reported trouble hearing in noise.

Table 5. Speech awareness, reception, and recognition test results, based on data from 95 subjects. Note that only 25 subjects of this number had word recognition ability in quiet greater than 0%, and only 5 subjects had any word recognition ability in quiet *and* noise.

Results for Subjects with Measurable Word Recognition in Quiet <i>Only</i>		
Number of subjects over 4 years of age	25	
Left ear mean score (Quiet)	Mean: 45.1%	St. Dev.: 27.5%
Right ear mean score (Quiet)	Mean: 47.8%	St. Dev.: 27.4%
Results for Subjects with Measurable Word Recognition in Quiet <i>and</i> Noise		
Number of subjects over 4 years of age	5	
Left ear mean score (Quiet)	Mean: 86.0%	St. Dev.: 12.8%
Right ear mean score (Quiet)	Mean: 87.2%	St. Dev.: 8.7%
Left ear mean score (Noise**)	Mean: 48.0%	St. Dev.: 15.8%
Right ear mean score (Noise**)	Mean: 64.0%	St. Dev.: 22.1%

*SRTs were typically obtained using a very limited set of spondees.

**Speech in noise testing was typically at a +8 or 10 signal-to-noise ratio.

³Four patients came from other clinics initially.

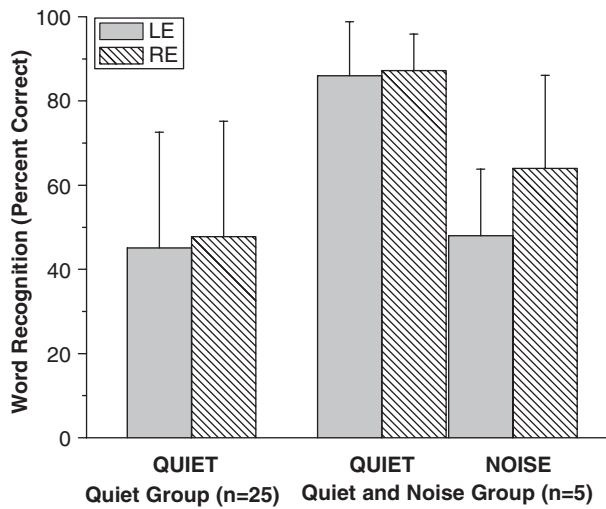


Figure 2. Speech word recognition test results. Data were derived from 68 subjects, four years of age or older, when formal testing could be completed. Of these, 25 subjects had measurable word recognition in quiet *only* (shown on the left portion of the graph), and five subjects had measurable word recognition in quiet *and* noise (shown on the right portion of the graph).

Table 6. Outcomes with hearing-aid use.

Outcome with Hearing Aid Use	Number	Percent
Good benefit-functional interaction		
4–6 years	1	
7–12 years	1	
19–30 years	1	
Total with good benefit	3/85	3.53
Some benefit (helped with language acquisition)		
0–24 months	3	
25–48 months	1	
4–6 years	2	
7–12 years	1	
19–30 years	1	
Total with some benefit	9/85	10.59
Little benefit (helpful with environmental sounds)		
0–24 months	2	
25–48 months	6	
4–6 years	5	
7–12 years	5	
Over 30 years	3	
Total with little benefit	21/85	24.71
No benefit		
0–24 months	6	
25–48 months	12	
4–6 years	10	
7–12 years	13	
13–18 years	3	
19–30 years	4	
Over 30 years	4	
Total with no benefit	52/85	61.17

Table 7. Outcomes with cochlear implant use.x

Patients with Cochlear Implants	Number	Percent
Age Group (number of patients)		
0–24 months	10	
25–48 months	12	
4–6 years	11	
7–12 years	14	
13–18 years	1	
19–30 years	1	
Total	49	
Outcome with Cochlear Implant (all database patients)		
Successful	42/49	85.72
Slow progress	1/49	2.04
Uncertain	2/49	4.08
Too soon to tell (recently implanted)	4/49	8.16
Outcome with Cochlear Implant (only patients seen at Kresge Lab)		
Successful	14/14	100.00

Discussion

It should be stressed that we are reporting what has happened to these patients, not what we felt at the time were the best management procedures to follow. We also can offer little in the way of experimental data on the majority of these patients because they were often too young to participate in psychophysical studies and were not part of a prospective Kresge Lab-based experiment. However, elsewhere (Berlin, Hood & Morlet, 2008), we offer what we believe to be a distillation the most effective management strategies that have been reported from this multi-site source of data.

Patient variation across a continuum

The data suggest that patients vary across a continuum, with auditory abilities of the patients ranging from mild to severe (Figure 3). Patient characteristics and outcomes follow both unpredictable and, in part, unexpected courses. Some individuals with ANSD went unidentified or had no complaints about hearing until sometime between puberty and adulthood (similar patients are reported by Shivashankar et al, 2003). Others have shown good neural plasticity and accommodate to their condition, developing speech and language and usually communicating well in quiet, but report that

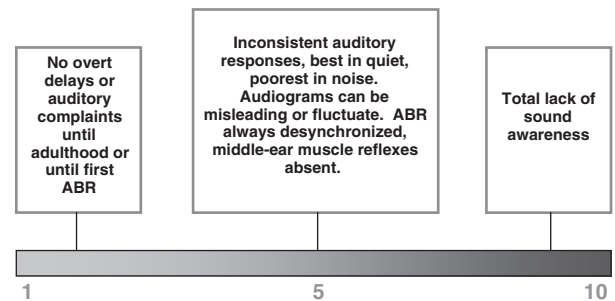


Figure 3. A continuum of ANSD.

they hear poorly in even the slightest background noise. At the other extreme, some patients have very poor or non-existent sound awareness and never develop auditory abilities, auditory based language, or speech. Some patients have missing VIIIth nerves that may remain undiscovered until after a failed CI (Buchman et al, 2006). By contrast, some of these patients and/or their parents report that they are comfortable and well served in Deaf Culture if they neither benefit from nor respond well to hearing aids or Auditory Verbal Therapy, while others say they do well with just lip-reading and/or cued speech. Others, whose parents desire verbal communication, have become ideal candidates for cochlear implantation, which usually promotes neural synchrony. In some cases, there may be a combination of ANSD and more central hearing losses (particularly in patients with other conditions in addition to ANSD); this increases the difficulty of predicting success of management and outcomes. We continue to learn about many, but not all, of these patients and monitor their concerns and issues, albeit informally.⁴

Underlying mechanisms in ANSD

An outstanding and admirable review of underlying mechanisms in ANSD has recently been published by Starr et al (2008). Our current understanding of inner-ear physiology suggests that the outer hair cells are low-level pre-amplifiers rather than fully sensory cells (e.g. Dallos & Fakler, 2002; Dallos et al, 2006). The inner hair cells, which have a limited 65–70 dB dynamic range, are the drivers for the primary neural elements. Thus, the presence of normal OAEs and a ‘corner’ audiogram in the presence of an MRI showing a normal VIIIth nerve, would suggest serious impairment of at least inner hair cells with possible concomitant anterograde loss of afferents and synaptic connections. This type of patient might be classified as having total dys-synchrony first, which might accompany a genetic cause (e.g. otoferlin) or neonatal anoxia (Amatuzzi et al, 2001) with inoperative inner hair cells. Spontaneous language learning in congenital non-temperature-sensitive otoferlin patients has not been documented. Thus, cochlear implantation, as soon as the parents wish, seems wise to prevent anterograde neural degeneration traceable to the lack of afferent stimulation.

Separating neural from inner hair cell dysfunction

Trans-tympanic electrocochleography, which can separate pre-synaptic from post-synaptic dysfunction, is now our most powerful clinical tool. Despite our having promulgated ECoChG in the 1970s (e.g. Cullen et al, 1972), we have not used it on more than a few of our own ANSD patients, including one patient we presented in the Starr et al (1996) paper. Pre-synaptic dysfunction implicates the inner hair cell and its environs, while post-synaptic dysfunction implicates neural elements themselves. Gibson) and Sanli (2007), (McMahon et al (2008), and Santarelli and Arslan (2002) have shown that pre- and post-ganglionic disorders might be separated from one another. These are essential data and might be ultimately collected on all new patients to understand the nature of their auditory disorder and provide more accurately targeted management.

⁴through a Parent’s List Serve owned by Elaine Blackford, RN at www.AuditoryNeuropathy@Yahoo.com. Nurse Blackford’s son was among the first 16 ANSD patients we diagnosed at LSUHSC, and she established this List Serve to supply parent-friendly information to other families who receive the ANSD diagnosis.

Speculations on what, if anything, the audiogram might tell us about the underlying pathophysiology?

This section presents speculations based on literature reports of true neuropathy patients (e.g. Starr et al, 2003), studies of post anoxia patients (Amatuzzi et al, 2001), and the experiences of some of our own patients with confirmed otoferlin mutations (e.g. Varga et al, 2003, 2006). All of these speculations depend upon a stable behavioral audiogram, which is often difficult to acquire on ANSD patients.

We suspect, based on our data and the literature, that very poor audiograms indicate that inner hair cells are generally absent or malfunctioning (Amatuzzi et al, 2001; Moore, 2004; Rance, 2005; Rapin and Gravel, 2006) or the V IIIth nerve is absent (Buchman et al, 2006). The better the audiogram, the more likely we are to have some functioning inner hair cells and some compromised neural elements (Starr et al, 2008). Combinations and mosaics no doubt abound, but, at the extremes, ANSD and normal OAEs in the presence of a ‘corner’ audiogram are most probably associated with complete inner hair cell loss (Amatuzzi et al 2001; Varga et al 2003, 2006) or absent auditory nerves (Buchman et al, 2006). In contrast Starr et al (1996) and Merchant et al (2001) have shown that a mild-to-moderate audiometric loss has been associated with considerable residual inner hair cells but compromised nerve fibers. This constellation has been predicted by Rapin and Gravel (2006) from most of the same literature.

Possible relationships between clinical characteristics and underlying mechanisms

We present two case examples highlighting the variation in clinical characteristics and possible relationships to underlying mechanisms.

Patient A. This patient, who has mutations in the otoferlin gene, was part of the Varga et al (2003) study. She presented with a corner audiogram (Figure 4), which we now associate with completely absent or malfunctioning inner hair cells. Of course one might argue that she might have absent endocochlear potentials (e.g. Loundon et al, 2005), but this argument does not hold in view of her normal OAEs (Figure 5). She is also patient A in the Shallop et al (2001) paper on CIs in ANSD. Her brother inherited the same gene mutations and also has ANSD. Her CI, originally done at age four years and recently upgraded to bilateral implants, has been very successful in part because of her pre-implant language education with cued speech. She now shows excellent speech and language and is mainstreamed in a normal school, outperforming virtually all of her normal-hearing peers in reading levels and vocabulary.

From the temporal bones Starr et al (2003) studied, we reason that along with good audiograms come more usable inner hair cells and that only a small number of healthy nerve fibers are needed to transmit that information (Kiang et al, 1986; Burkard et al, 1997). However, these conditions need not be mutually exclusive, and it is probable that, in some mild-to-moderate losses, a mosaic of problems might co-exist. Thus, as Amatuzzi et al (2001) have already shown in the temporal bones of anoxic infants, there can be parts of the cochlea that show normal outer hair cells and absent inner hair cells, and within just a few millimeters the condition can reverse, with normal-looking inner hair cells and absent outer hair cells. In support of the notion that as long as there are viable inner hair cells there will be some audiometric sensitivity, we again cite Starr et al (2000, 2003), who show the temporal bones of patients with a familial neural disease, intact inner hair cells, and sparsely

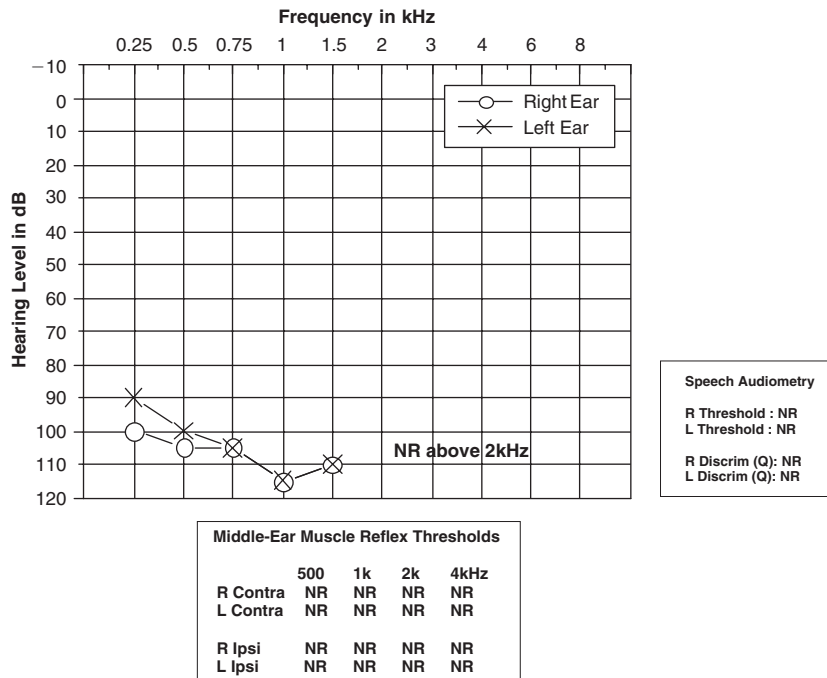


Figure 4. Test results for ANSD patient A. Pure-tone thresholds were consistent with a profound hearing loss in the lower frequencies bilaterally and no response in the higher frequencies. No speech reception (threshold) or recognition (discrim) ability was demonstrated. Middle-ear muscle reflexes were absent for ipsilateral and contralateral stimulation at the usual clinical test limits (90–95 dB HL ipsi and 100–110 dB HL contra). NR=no response.

myelinated auditory nerve fibers. CIs have already been shown to be effective in such patients despite the neuropathies, probably by synchronizing the available neural elements. As we cited earlier, (McMahon et al (2008) have shown that pre-synaptic and post-

synaptic ANSD can be differentiated by ECochG and aid in the separation of what we called ‘dys-synchrony’ from ‘neuropathy’.

Patient B. Success with CIs in such patients is supported by our observations in another ANSD patient (Patient B) with the

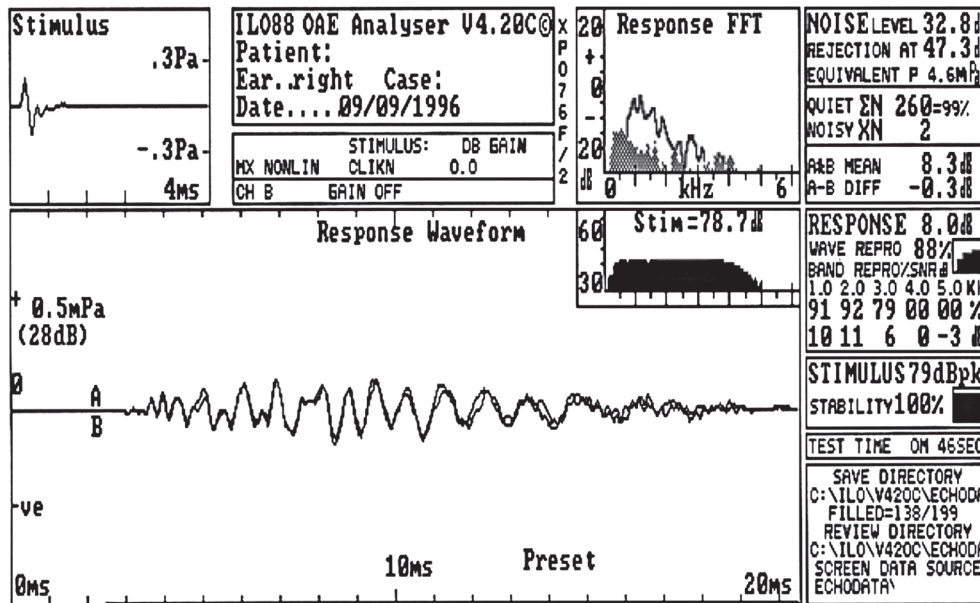


Figure 5. Transient OAE right-ear test results for ANSD patient A. OAEs were present with good reproducibility, particularly in the 1–3 kHz range. Similar results were obtained for the left ear.

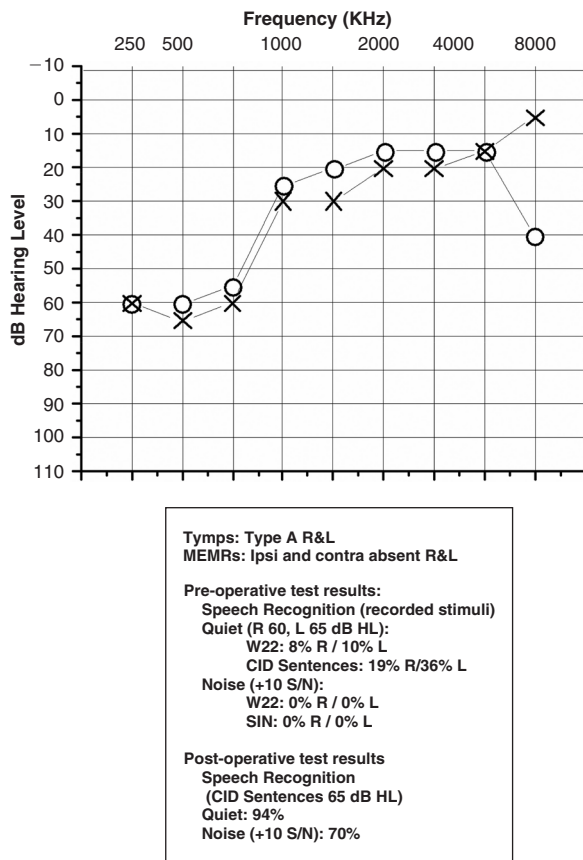


Figure 6. Test results for ANSD patient B. Pure-tone thresholds were consistent with a moderate hearing loss in the lower frequencies bilaterally rising to the normal hearing range in the higher frequencies. Middle-ear muscle reflexes were absent for ipsilateral and contralateral stimulation at 90–95 dB HL ipsi and 100–110 dB HL contra. Speech audiometric test results in quiet and in noise are shown before and after obtaining a cochlear implant.

audiogram shown in Figure 6, normal OAEs, absent MEMRs, and de-synchronized ABR (Figure 7). Initially, we were reluctant to implant this patient because of her nearly normal audiogram for 1 kHz and higher frequencies, but she was losing useful vision due to optic nerve atrophy and systemic peripheral neuropathy. Her post-implant results were, to say the least, excellent, wherein she showed 8–10% word recognition in quiet before her implant and 70% in noise after her implant.

In this case, cochlear implantation was so successful for the 16-year-old daughter that she encouraged her similarly-afflicted father to have the surgery. The CI was equally successful for him. This father and daughter clearly demonstrate a systemic neuropathy, presumably in the auditory system as well, with reduction in axonal function rather than totally inoperative inner hair cells. Such patients, who often have neurological disorders such as Charcot-Marie-Tooth disease, or sometimes hyperbilirubinemia and kernicterus, have not shown ‘corner’ audiograms in our sample. Other patients have audiograms that fluctuate with body temperature, a common report in multiple sclerosis for example, again supporting a primarily neural locus for them (Varga et al, 2006).

There are clearly cases in the literature that suggest cochlear implantation is *not* always successful. Miyamoto et al (1999), for example, showed an unsuccessful implant in a patient with Friedrich’s ataxia, and Buchman et al (2006) showed why MRIs are critical in evaluating ANSD patients. Many of their patients exhibited either *no* VIIIth nerve or morphologically small or sparse innervation. This would presumably lead to poorer cochlear implant results than in patients with abnormal inner hair cells for example. Having studies of pre- and post-synaptic responses to sound as McMahon et al (2008) and Santarelli et al (2008) have proposed, might better predict success in ANSD patients.

Issues in evaluation of ANSD

We face an increased incidence of the diagnosis ANSD because of the widespread use of screening programs at birth and because of the increased survival of premature infants under 30 weeks gestation. If only *one* test is used for screening, two errors will occur. OAE screening programs or programs that screen for hearing loss with OAEs will miss ANSD. For such programs locked in to OAEs, we have recommended elsewhere (Berlin et al, 2005) the addition of MEMRs to screening programs if possible and follow up with ABRs on any patient who has normal OAEs and absent MEMRs. Programs that only use ABRs for both screening and diagnosis, and do not add OAEs, have in the past and will continue to miss normal outer hair cell function (Hall et al, 2004). It has been argued that more norms are needed before we can rely on immittance audiometry to aid in the diagnosis of ANSD in infants (Sutton, 2007). However, the presence of reflexes at levels near 90 dB HL per se in neonates and infants up to six months of age would seriously question a diagnosis of ANSD. See Hall et al (2004) for a full discussion. Sutton himself may be modifying his criticism (2009).

Undetected mild forms of ANSD

Some forms of ANSD are so mild as to need no intervention; our very first patient in 1982 is just such a patient (see next paragraph). Other combinations, in which pure-tone hearing loss generally exceeds 70 dB HL on the audiogram, lead to conditions currently called ‘dead zones’ in the cochlea and suggest that amplification in that zone will not be helpful (Turner et al, 1999; Moore et al, 2000, 2004). Thus we should consider that many of the patients who have, in the past, failed to progress well with hearing aids and auditory verbal therapy (AVT) may have all along been unidentified ANSD patients. In those who have been implanted unilaterally, we have already found some with residual normal OAEs in the unimplanted ear, and there are likely others where emissions have disappeared with time (Deltenre et al, 1999; Rance et al, 1999; Starr et al, 2000; Berlin et al, 2001a). Using a pre-hearing aid triage with positive and negative polarity clicks included in the ABR, plus OAEs and MEMRs, to rule out ANSD might be considered for CI teams that currently require hearing-aid trials before implantation. Currently, hearing aids are often used and recommended as a requirement before implants can be considered; our data show this practice should be monitored carefully because it has sometimes served to delay the ability to eavesdrop on language. Cued speech or signs to aid visual eavesdropping have been a powerful adjunct to avoid language delays, especially if hearing aids are chosen or used for any length of time.

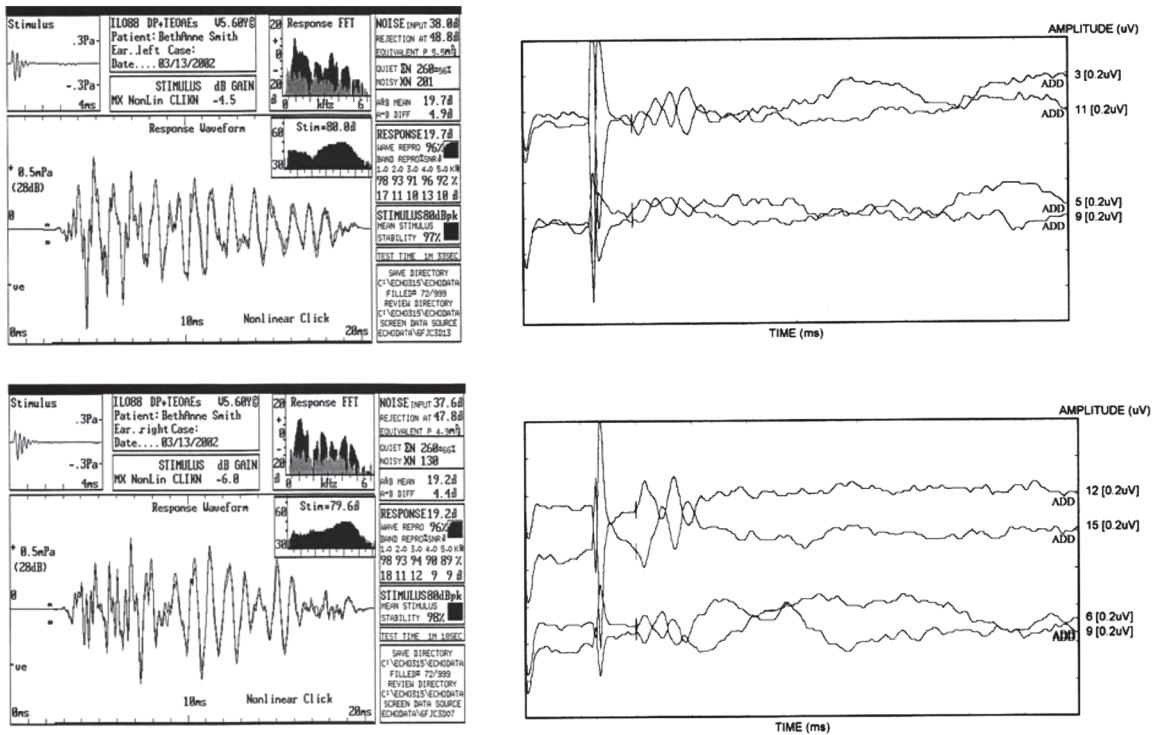


Figure 7. Transient OAE and ABR test results for ANSD patient B. Robust OAE responses were obtained for each ear (left top, right below). ABRs display only cochlear microphonics, shown by comparison of condensation and rarefaction polarity clicks at two intensities (left top, right below).

Some patients (5% in our current sample) develop adequate speech and language with little or no intervention needed. The first patient (Patient C) we ever saw with this syndrome had a normal audiogram with absent MEMRs (which at the time we considered

to be an insignificant variant; Silman and Gelfand, 1981) and had *no complaints at all*. He was a volunteer ‘normal’ subject for an ABR normative study carried out by one of our colleagues. We saw him again 22 years later to confirm the presumptive diagnosis of

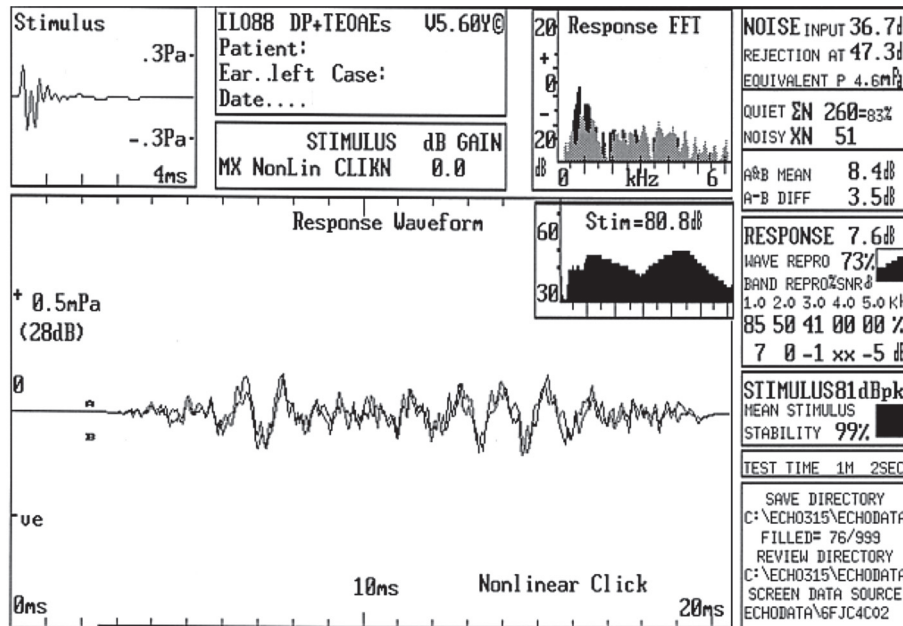


Figure 8. Transient OAE left ear test results for ANSD patient C. OAEs were recorded only for the lower frequency bands.

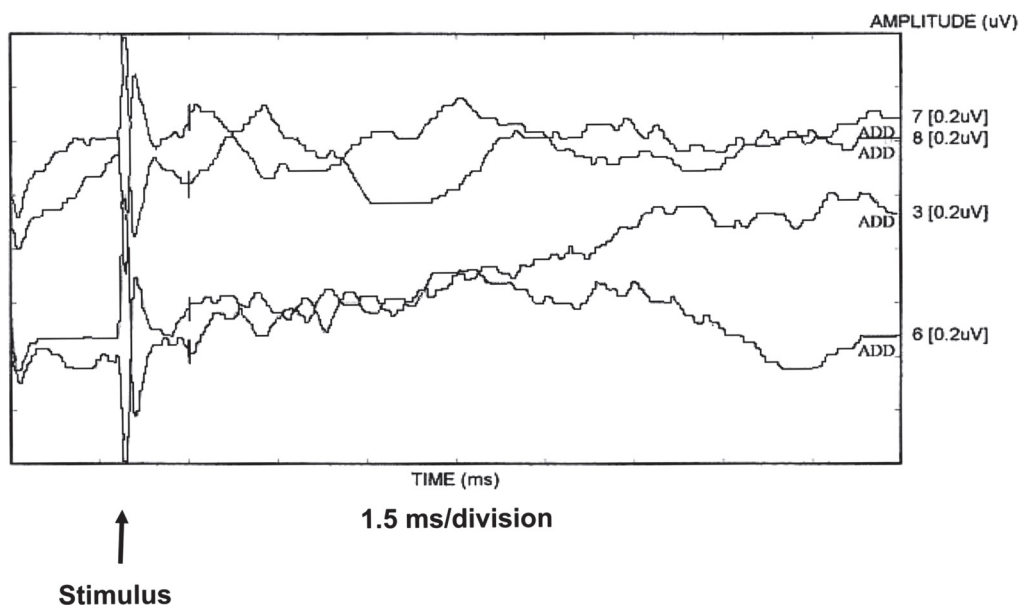


Figure 9. ABR Test results for ANSD patient C. ABRs show cochlear microphonics, defined by comparison of condensation and rarefaction polarity clicks for each ear and no synchronous neural responses.

ANSD, at which time we found normal OAEs (Figure 8), no ABR (Figure 9), and this new audiogram (Figure 10), for which he told us hearing aids suggested by others were never satisfactory.

The other 95% of ANSD patients have constituted potential enigmas for management groups that depend primarily (as we did initially) upon the pure-tone audiogram for their guidance.

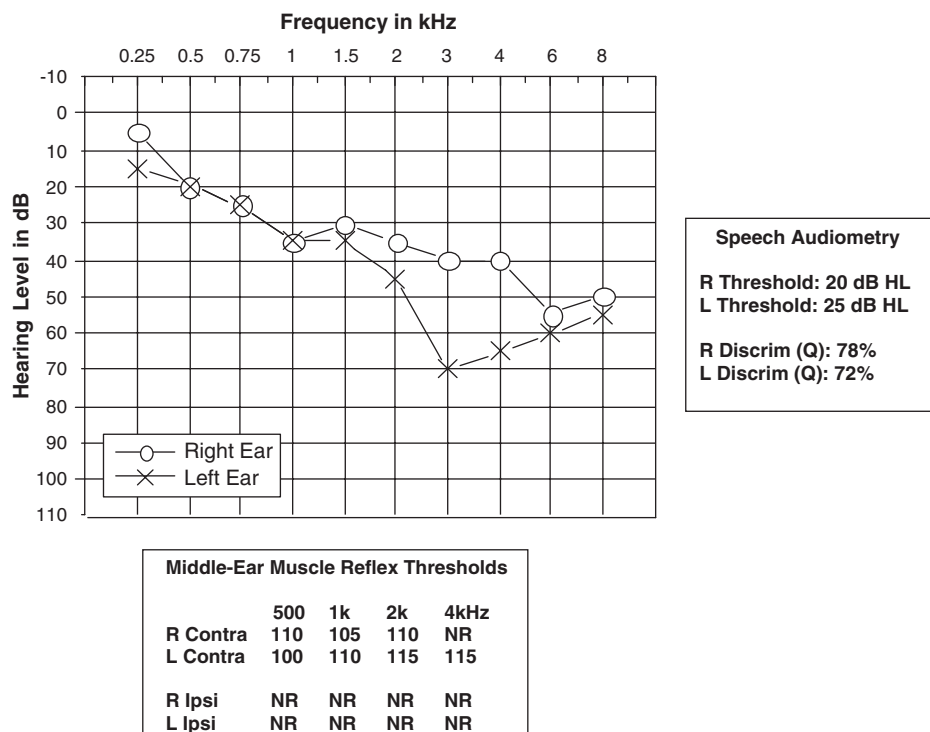


Figure 10. Test results for ANSD patient C. Pure-tone thresholds were consistent with normal hearing in the lower frequencies bilaterally sloping to a mild-to-moderate hearing loss in the higher frequencies. Speech-reception thresholds were in the borderline normal range, and word recognition (discrim) ability was 78% in the right ear and 72% in the left ear. Middle-ear muscle reflexes were present at elevated threshold levels for contralateral stimulation and absent for ipsilateral stimulation. NR=no response.

Potential weakness of multi-site reports

Much can be learned from careful compilation of information such as we have here, but some potential weaknesses must be recognized. First, because of confidentiality rules, and the 23-year period of our data acquisition from 1982 to 2005, we have little idea of how many of these patients have also been reported in the literature by our colleagues who published their papers before this paper was accepted for publication.

Second, there are no experimentally controlled or collected data here on the psychophysical or perceptual nature of ANSD. The data obtained from our database provide a view of practices and experiences in our purview, using information about outcomes obtained through case reviews and collaborations. Reports with more extensive direct experience will come, as the number of identified patients continues to grow and from countries (e.g. India and China) with large populations.

Another weakness of reports such as these is always in the paucity of population data and the failure to control all the testing methods. The few patients we report here by no means constitute the majority of the patients in the population. The data also address what *has* happened in the past and been reported to us, and are not presented as harbingers of what will happen in the future with any individual patient. While these patients have been with us for years, the life-saving methods with some premature and medically compromised infants likely will be producing more such newborns.

Note also that some patients who have already been implanted because of failure to develop adequate speech and language by 'traditional methods', including AVT and hearing aids, may well be unrecognized ANSD patients. In those who have had only one CI, we have already found some with residual normal OAEs in the unimplanted ear, and there are likely others where emissions have disappeared with time (Deltenre et al, 1999; (Rance et al, 1999; Starr et al, 2000; Berlin et al, 2001a).

Conclusions

ANSD patients make up at least 10–15% of children in schools for the deaf, although some report a much lower incidence. There are likely to be many patients who have already been implanted because of failure to succeed with hearing aids and AVT. Only in retrospect, after years of depending upon it, can we see that the audiogram has not generally been valuable in these patients as a management tool for hearing-aid fitting. Success with hearing aids in quiet as reported by others (Deltenre et al, 1999; Rance et al, 2008) has not led to age-appropriate language acquisition in the majority of patients in our report. We recommend obtaining tympanometry, MEMRs and OAEs as a pre-audiometric screening to see if the audiogram can and should be trusted as a valid picture of 'hearing' for patients like these. If OAEs are normal and MEMRS are absent, an ABR will help disambiguate the results and clarify the diagnosis. In audiograms that imply hearing loss of more than 40 dB but accompany normal OAEs word recognition in noise has not been well predicted from the audiogram. Collaboration with speech-language pathologists, neurologists, and teachers of the deaf is of great value to the patients and their families. Although the audiologist is likely to be among the first professionals to encounter a patient with ANSD, management should focus on the global communication skills and abilities of the patient to acquire language, become literate, and be self-sufficient.

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Declaration of interest: We have no financial or related ownership of Parents List Serve on yahoo.com

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