Clinical and Audiological Features in Auditory Neuropathy

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Objective: To medically and audiologically characterize a population of children diagnosed as having auditory neuropathy (AN).

Study Design: Retrospective medical chart review.

Setting/Subjects: We identified 22 patients from a pediatric otology clinic in a tertiary care pediatric hospital setting.

Results: A genetic factor in AN is suggested by our identification of 3 families with 2 affected children and 2 other children with family histories that were positive for hearing loss. Clinical features common among our population included a history of hyperbilirubinemia (n=11 [50%]), prematurity (n=10 [45%]), ototoxic drug exposure (n=9 [41%]), family history of hearing loss (n=8 [36%]), neonatal ventilator dependence (n=8 [36%]), and cerebral palsy (n=2 [9%]). Full clinical and audiological data were available for 18 of the 22 children, including otoacoustic emissions, auditory brainstem responses with cochlear microphonics, and age-appropriate audiometric findings. Significantly, 9 of these 18 patients showed improvement in behavioral thresholds over time, indicating that a subset of children with AN may recover useful hearing levels. Also significant was the success of cochlear implantation in 4 children.

Conclusions: Management of AN in children requires serial clinical and audiometric evaluations, with a prominent role for behavioral testing. Prematurity, genetics, and hyperbilirubinemia appear to be significant factors in the development of AN; hyperbilirubinemia can be associated with spontaneous improvement of hearing thresholds. For those children not benefiting from amplification or FM systems, cochlear implantation remains a potentially successful method of habilitation.


Audiological Definitions

Auditory neuropathy (AN) is a hearing disorder characterized by an absent or severely abnormal auditory brainstem response (ABR), with preservation of the cochlear microphonics (CM) and otoacoustic emissions (OAEs). Clinically, AN is defined as (1) hearing loss, usually bilateral, of any degree; (2) normal outer hair cell function as evidenced by the presence of OAEs and/or CM; (3) abnormal evoked potentials beginning with wave 1 of the ABR; (4) poor speech perception; and (5) absent acoustic reflexes to the ipsilateral and contralateral tones at a 110-dB hearing level. Starr et al. described 10 patients, 5 adults and 5 children, who demonstrated these findings and no other auditory diagnosis on results of clinical, audiological, or radiographic studies. They coined the term auditory neuropathy. The prevalence of AN is not known. Davis and Hirsh reported 1 case of AN (0.5%) in 200 patients with sensorineural hearing loss (SNHL). Other investigators found a higher rate of prevalence, with Kraus et al. reporting a rate of 15% and Rance et al. of 11% of their population with permanent hearing loss.

Cases of absent ABRs in the presence of awareness of sound at moderate or quite low intensities were identified more than 20 years ago. Some individuals who were diagnosed as having SNHL before OAE testing came into common use probably had an undetected AN.

Otoacoustic emissions have been used as an objective test of the integrity of the outer hair cell of the cochlea in patients who are unable to make behavioral responses (eg, infants) or to confirm behavioral audiometric findings. The value of the combination of OAEs and measures of neural function at the level of the eighth cranial nerve and the brainstem has been demonstrated in patients undergoing clinical assessment for AN. Before the recognition of OAEs, presumptive hair cell func-
tion was assessed by recording CMs generated in response to acoustic signals.

The pathophysiology of AN has been suggested to involve an abnormality of the peripheral auditory system localized to the inner hair cells, to the eighth cranial nerve, or to the synapse between them. A disorder at any of these sites could account for normal OAE findings, loss of ABR potentials, and disordered speech perception in the presence of relatively preserved pure-tone thresholds. Based on the finding of normal OAEs, the outer hair cells in the cochlea are presumed to be normal. The status of the inner hair cells alone cannot be assessed with any currently available procedure.

The risk factors for the development of AN are only speculative. Perinatal risk factors such as perinatal intracranial hemorrhage, asphyxia, and hyperbilirubinemia have been implicated. Coincidentally, these factors have also been implicated in other central neurological pathologies. Genetic factors may also be involved in the pathogenesis of AN. Bonfils et al reported on a kindred with a dominant inheritance pattern of a progressive hearing loss with characteristics similar to those of AN.

This report describes the relatively large single-institution experience of the Children's Hospital Medical Center, Cincinnati, Ohio, with children with AN. We herein present the clinical, audiological, and radiographic findings of this distinct population of patients with AN and describe the treatment paradigms used based on the natural history of the disorder.

PATIENTS AND METHODS

We performed a medical chart review of the hospital's hearing loss database for an 8-year period. Criteria for inclusion in the study were as follows: (1) permanent SNHL, (2) the presence of a CM with a severely abnormal or absent ABR waveform, and (3) the presence of a transient evoked or distortion-product OAE at the initial presentation. Complete reviews were made of the otologic and audiological charts to confirm all database information. All patients underwent computed tomography of the temporal bones and a comprehensive laboratory and medical evaluation. The latter included ophthalmologic and genetics consultations, electrocardiography, renal and thyroid panels, urinalysis, and measurement of the sedimentation rate and the levels of glucose, syphilis IgG and IgM, cholesterol, and triglycerides.

Age-specific pure-tone audiometry for the standard frequencies from 250 to 8000 Hz was performed for all children using conventional, play, or behavioral means. Tympanometry was also performed at the time of testing. Click-evoked distortion-product OAEs were measured at click levels of 65- and 55-dB peak sound pressure for the f1 and f2 components. The noise floor for the distortion-product OAEs was 8 dB, with waveform reproducibility in at least 3 octave bands of more than 75%.

Auditory brainstem evoked potentials were recorded in a single-electrode configuration, in a channel running from the forehead to the ipsilateral ear using a band-pass filter between 100 and 3000 Hz. Click stimuli consisted of 1 run of condensation followed by 1 run of rarefaction clicks presented monaurally at rates of 21.1 per second and at intensities of 80-dB and when necessary at 95-dB HL. Two averages were made at each test signal, and the presence of reproducible components were defined. Patients underwent assessment in a sound-treated room, in a state of natural or chloral hydrate--induced sleep.

Audiometric thresholds were analyzed at 500, 1000, 2000, and 4000 Hz individually and for a pure-tone average at these frequencies. Statistical analysis comparing audiometric improvements between patients with and without hyperbilirubinemia was performed using the Wilcoxon rank sum test.

RESULTS

From our database of 428 children with hearing loss, 22 had a diagnosis of AN. In 20, the diagnosis was based on positive OAE findings with an absent ABR finding or with only a CM on ABR findings. Two additional patients were identified with an obvious CM on ABR findings, but they failed to demonstrate robust OAEs. Full data were available on 18 of the 22 children with AN; the remaining 4 children had received a recent diagnosis.

The mean age at presentation was 17 months (range, 1-60 months), with 9 male and 13 female children. The mean age at diagnosis of hearing impairment was 4.5 months (range, 3 days to 19 months). The racial demographic data showed 18 white and 4 African American patients. The overall prevalence of AN in our population with known SNHL is 5.1%. All but 1 patient with AN had received the diagnosis after OAEs began to be routinely used in our institution, in 1996, so a more useful gauge to the frequency of this disorder was to evaluate this time period. Since 1996, the incidence of the diagnosis of AN was approximately 10% per year in our population with SNHL.

RISK INDICATORS

Predisposing factors associated with AN were varied and often found in combination. Overall, 15 children with AN (68%) had a complicated perinatal course. This included hyperbilirubinemia in 11, prematurity in 10, the use of gentamicin sulfate or other ototoxic medications in 9, and the need for mechanical ventilation in 8 children. Cerebral palsy was noted in 2 patients. A genetic influence appeared to be a factor in the development of AN in up to 8 patients (36%) in our series. A recessive inheritance pattern can be hypothesized because of the presence of 2 sets of sibling pairs and 1 set of twins. The other 2 patients had remote family histories of idiopathic hearing loss without any formal genetic pattern. All 8 of these patients had a severe or profound hearing loss and had no evidence of improvement compared with the remainder of our study population.

Results of electrocardiography, comprehensive laboratory analysis, and ophthalmologic and genetic evaluations were all unremarkable in these patients, except in the affected sibling pairs. Radiological evaluation, including computed tomography of the temporal bone or magnetic resonance imaging, revealed no evidence of dysplasia of the inner ear or internal auditory canal. We found no historical or clinical evidence of peripheral neuropathy in any of our patients, and peripheral neuropathy has not developed in any child to date.

CHANGES IN TEST RESULTS OVER TIME

Of the 18 children with full audiological data, the initial mean of the pure-tone average at 500 Hz and 1, 2, and 4
kHz was 101 dB, and the final mean threshold was 67 dB (Figure 1). The initial audiogram showed that most children (16/18 [89%]) presented with a severe or profound loss (Figure 2). The final audiogram from our follow-up of these children shows a more even distribution, with 11 (61%) of the 18 children with a severe or profound loss (≥90 dB), 1 (6%) with a moderate impairment (41-74 dB), and 6 (33%) with mild to borderline hearing (20-40 dB). All audiograms had a flat configuration, and none of our patients had a unilateral SNHL. Two patients (a pair of siblings) lost their OAEs after undergoing amplification during a 2-year period. Their CMs remained unchanged. No patient had any discernible pattern on their ABRs, and this did not change with time. Results of tympanometry showed normal middle ear pressures.

Overall, 9 (50%) of the 18 children with severe or profound hearing loss showed audiological evidence of a spontaneous improvement in their hearing (Figure 2). This occurred 1 to 15 months after their diagnosis, with a mean improvement time of 5.8 months. In 3 of the 9 patients with spontaneous improvement, the audiograms showed only a low-frequency gain initially. We compared improvement rates in children with (10/18 [56%]) and without (8/18 [44%]) neonatal hyperbilirubinemia. The children with jaundice were more likely to have a more profound initial hearing loss but showed a greater tendency to improve spontaneously and to end with a better hearing outcome (Figure 3A). When analysis of the frequency-specific data was performed, a statistically significant difference between children with and without jaundice was observed at the following frequencies: 500 Hz (P = .02), 1 kHz (P = .04), and 2 kHz (P = 0.04) (Figure 3B). Children achieved a stable audiogram by a mean age of 18 months (range, 11-25 months), with clinically meaningful improvement (ie, the decision for cochlear implantation) occurring by a mean age of 12 months.

The audiological improvements in these children were better than would be predicted on the basis of development. Of these 9 children, the initial ABR test results corresponded to abnormal findings on behavioral audiometry. Initial behavioral audiometric testing was not performed until at least 6 months of age. We found no significant difference in the timing of the initial audiogram between patients with and those without hyperbilirubinemia. The mean age at initial testing for children with hyperbilirubinemia was 8.8 months, (range, 6-23 months); for those without, 10.4 months (range, 6-20 months).

Total bilirubin levels in those affected ranged from 12.3 to 40.0 mg/dL (210-684 µmol/L), with a mean level of 19.4 mg/dL (332 µmol/L). Hyperbilirubinemia lasted 4 to 10 days, with a mean of 6.8 days in duration. Hyperbilirubinemia was noted on postpartum day 2 or 3,

Figure 1. Mean pure-tone thresholds at presentation (top) and the last audiogram (bottom). Mean initial hearing loss was 101 dB; current, 67 dB.

Figure 2. Tendency to spontaneous resolution in patients with auditory neuropathy, initial vs final audiogram. Data are expressed as number of children.

Figure 3. Comparison of improvements of the hearing outcomes in children with and without hyperbilirubinemia. A, Mean values for hearing level are expressed in decibels. B, Change in hearing level for each frequency. Asterisk indicates statistical significance (Wilcoxon rank sum test).
and the therapeutic intervention was appropriate to the level of bilirubin, ranging from no intervention to phototherapy to exchange transfusion when needed. No correlation of the bilirubin levels and the extent of improvement of the audiogram was noted.

**SENSORY AIDS**

Hearing aids and/or an FM system were used in 16 (73%) of the 22 children. Four children (18%) needed cochlear implants. Four children (18%) were observed and did not require any amplification because of spontaneous improvement. Two of our most recent patients younger than 6 months are undergoing observation, but their need for auditory assistance cannot be determined at this time.

The 4 patients who needed cochlear implants included a pair of siblings. They all presented with a bilateral profound SNHL, and no evidence of a spontaneous resolution was noted during a 1-year follow-up. They received no benefit from our standard amplification with or without FM assistance. Our patients undergoing cochlear implantation were aged 1 to 3 years, with a mean age of 2 years. All 4 patients tolerated the implantation procedure well, with no complications noted. Our first 2 patients have documented significant improvement in their auditory and communicative skills after implantation, with age-appropriate open-set speech discrimination scores of better than 70%. The next 2 patients underwent implantation within the past 6 months, and their preliminary data so far suggest a potential for similar improvement.

**COMMENT**

Patients with AN have normal outer hair cell function as measured by OAE findings and the presence of a CM on results of ABR testing, but a lack of neural synchrony as demonstrated by absent ABR waveforms. Although the population with presumed AN is heterogeneous, they consistently exhibit a constellation of findings that suggest that the outer hair cell function is normal and that the inner hair cell and/or eighth cranial nerve functions are impaired. Findings on pure-tone audiograms in these patients range from normal to profoundly impaired. Most of the patients complain of difficulty understanding speech, particularly in the presence of noise. Patients diagnosed as having AN tend to have word recognition abilities that are disproportionately poorer than would be predicted by audiometric thresholds. Speech intelligibility scores in retrocochlear disorders (ie, acoustic neuromas) are reduced beyond what would be expected for the loss of sensitivity. The hearing loss may be stable or may fluctuate over time. A variety of audiograms have been described with no clear predominating shape and pattern. Our study confirms the heterogeneous clinical findings in AN. The medical impact of the hearing loss on these patients remains significant. Patients in our study with significant and persistent hearing loss have responded well to conventional rehabilitation with amplification and cochlear implantation.

**OTHER PERIPHERAL NEUROPATHY**

Some of the patients initially diagnosed as having AN in other studies demonstrated indications of a peripheral neuropathy, or these indications developed. Patients with similar audiometric findings have been diagnosed as having hereditary motor sensory neuropathy (Charcot-Marie-Tooth disease type 1). Friedreich ataxia, or Guillain-Barre syndrome. Therefore, a neuropathic process may also affect the auditory nerves and thus account for the hearing disorder, which developed in patients before the clinical neuropathy. Spoendlin described the temporal bones of 2 individuals with Friedreich ataxia. He noted that the organ of Corti was normal, but that damage to the spiral ganglion cells had occurred in these patients. Hallpike et al also found normal hair cells with degeneration of spiral ganglion cells and auditory nerve fibers in a patient with hereditary hearing loss, poor speech comprehension, and peripheral neuropathy. No patient in our study had any clinical evidence of a neuropathy. Neuropathy was excluded by results of routine developmental evaluation by the pediatrician or the neurologist. The mean follow-up for these patients is 32 months, and the oldest child is now aged 10 years. Rance et al found no evidence of neuropathy in their study of 20 children with AN. However, in long-term follow-up studies, Starr et al demonstrated peripheral neuropathies in 80% of children with AN who were older than 15 years. None of these children exhibited evidence of a peripheral neuropathy at younger than 5 years. Longitudinal studies in our cohort will be required to examine the prevalence of any neurological conditions.

**GENETICS**

Roma (gypsy) families have demonstrated hereditary auditory, vestibular, motor, and sensory neuropathies in a number of reports. Results of sural nerve biopsies on some adults showed systemic demyelination and also the loss of a number of axons. The locus of the gene in these cases of a demyelinative neuropathy was located on the long arm of chromosome 8 (8q24). In our study, several families had 2 offspring with AN and no other apparent clinical disease. A genetic sensitivity to clinically low levels of bilirubin and AN has been postulated (C. I. Berlin, PhD, oral communication, February 5, 2000). This may explain why our patients with a history of hyperbilirubinemia had higher or worse initial hearing thresholds but did better than children without hyperbilirubinemia, with better thresholds overall. Further studies in our families will be required to better delineate these genetic factors.

**HYPERBILIRUBINEMIA AND OTHER RISK INDICATORS**

Hyperbilirubinemia occurred in 50% of our population. Infants and children who demonstrate paradoxical audiological findings have been well described in the literature with hyperbilirubinemia or have been described with AN. In a study of 13 neonates with hearing loss due to hyperbilirubinemia, Chisin et al found CMs in 9 of the 13 children with absent or disordered ABRs,
suggesting sparing of the hair cells. This finding suggests an association between hyperbilirubinemia and the occurrence of this unique form of hearing impairment, particularly in premature and low-birth-weight infants. Prematurity and perinatal anoxia predisposes infants to bilirubin encephalopathy (kernicterus),\textsuperscript{15,16} and both conditions were present in 7 (64\%) of our 11 patients with hyperbilirubinemia. Severe SNHL and central nervous system deficits such as choreoathetotic cerebral palsy, seizures, and mental retardation were once relatively common sequelae of hyperbilirubinemia. Improvements in medical therapy have significantly reduced the occurrence and severity of kernicterus in full-term infants. The toxic effects of low and moderate levels of bilirubin on the central nervous system of premature and low-birth-weight infants may account for these cases of AN. In premature and low-birth-weight infants, the risk for kernicterus and permanent sequelae may be much higher at serum bilirubin levels below those thought to be safe for term infants.\textsuperscript{3} Successful treatment before the development of kernicterus may account for the “spontaneous” improvement in these children’s hearing thresholds. Children with neonatal hyperbilirubinemia appear to represent a unique subpopulation of patients with AN. Because of the common incidence of milder forms of hyperbilirubinemia, future studies may examine the presence of AN in a large-scale, otherwise healthy, newborn population.

**IMPLICATIONS FOR NEWBORN HEARING SCREENING**

This study illustrates the value of the combined use of OAEs and ABRs in hearing loss screening. We recommend routine OAE testing in all children diagnosed as having SNHL. Absent OAEs require clinical evaluation of the patient’s middle ear status, followed by tympanometry and measurement of the middle ear muscle reflexes to rule out a hidden middle ear disease. Checks of ABR and/or CM should be considered in high-risk newborns who undergo OAE testing as their primary screening tool. Physicians and audiologists should include AN in their differential diagnosis of SNHL in children. A subset of these patients with a history of hyperbilirubinemia shows distinct audiological improvement during the first year of life. Although the appropriate treatment strategies have yet to be confirmed, selective amplification and cochlear implantation appear to be successful.

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