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Auditory function in adrenomyeloneuropathy

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Abstract

Auditory brainstem responses (ABR), ipsilateral and contralateral acoustic reflexes and the masking level difference for speech (MLD) were studied in 29 patients with adrenomyeloneuropathy (AMN). Abnormalities were seen for all ABR components with Waves V and III affected to the greatest degree. For male patients with AMN, the I-III, III-V and I-V interpeak latency intervals were abnormal for a majority of patients. For female patients with AMN, the I-V and III-V interpeak latency intervals were abnormal for a majority of patients with the I-III interval less affected. Contralateral acoustic reflexes were elevated or absent for approximately 50% of ears. Ipsilateral acoustic reflexes were abnormal for 25% of ears. MLDs were significantly reduced in 72% of patients. When considered in terms of the earliest ABR wave abnormality, the earlier components of the ABR (i.e., Waves III and I) were the initial components impaired for the majority of ears. Word recognition in quiet was relatively unimpaired for all subjects. Despite the presence of marked ABR abnormalities, patients with AMN denied the presence of significant difficulty hearing.

Keywords

auditory brainstem response (ABR); acoustic reflex; adrenomyeloneuropathy (AMN); masking level difference (MLD); word recognition; very long chain fatty acids (VLCFA)

Introduction

Adrenomyeloneuropathy (AMN), the adult form of the genetic condition X-linked adrenoleukodystrophy is characterized by involvement of the central and peripheral nervous system, adrenal dysfunction and an accumulation of saturated very long chain fatty acids (VLCFAs) in tissue and body fluids. Elevated VLCFA levels exert a pathogenetic role in several peroxisomal disorders including AMN (1) because the presence of VLCFA results in destruction of the myelin sheath around nerve fibers. AMN is a slowly progressive disorder developing variably over a five to twenty year span. The most apparent characteristic is lower extremity spasticity with difficulty in walking and balance. Symptoms include leg stiffness, progressive paraparesis of the lower extremities, adrenal insufficiency, hypogonadism and sphincter disturbances. Nerve conduction studies reveal the presence of peripheral neuropathy

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(2). Abnormalities in the P100 visual evoked potential were found in 25% of patients with AMN (3).

Peripheral hearing loss is typically not suspected in patients presenting with AMN but has been reported in some patients (4). However, it has recently been reported that the prevalence of hearing loss in patients with AMN does not exceed that found in age and sex matched normative control groups (5). ABR findings typically are markedly abnormal in the majority of patients with AMN (4-6). It has been reported for a limited number of patients with AMN that acoustic reflexes are preserved (6) although acoustic reflex abnormalities have been reported by other investigators in several patients (4).

Audiologic measures other than the ABR that are sensitive to neurological dysfunction have not been utilized to a significant degree in patients with AMN. One such measure is the masking level difference (MLD). The MLD is the difference in thresholds obtained under binaural listening conditions during which the phase is varied between ears. Under one set of conditions (S_0N_0), termed homophasic, the signal (S) and noise (N) are in phase at the two ears. In the antiphase condition (S_0N_π or $S_\pi N_0$), one of the two channels is out of phase at the two ears. Because a 180 degree phase difference produces the largest difference between in phase and out of phase conditions, it is generally used in studies of the MLD. The MLD is mediated by neural units in the pontomedullary region of the brainstem (7) The magnitude of the MLD is typically reduced in patients with lesions of the brainstem auditory pathways (8-10), particularly when the initial abnormalities in the ABR involved waves I, II or III (11). The MLD to speech stimuli has been shown to be more sensitive to brainstem pathology than MLDs to pure tones stimuli (8) although the MLDs to speech stimuli are smaller than the MLDs for pure tones in absolute terms in normally hearing and neurologically intact subjects (12). The purpose of the present investigation is to examine the masking level difference for speech, ipsilateral and contralateral acoustic reflex measurements and the auditory brainstem response in patients with AMN.

Subjects

Subjects were 29 individuals with adrenomyeloneuropathy and ranged in age from 19 to 71 years of age (Mean age = 42.53, SD = 14.48). All patients were confirmed to have AMN by elevation in very long chain fatty acids or DNA analysis. Six patients were excluded from the analysis because their hearing threshold levels from 500-2000 Hz at one or more frequencies for either ear exceeded 25 db HL. Thirteen of the remaining subjects were males with AMN (Mean age = 34.49, SD = 13.44, Range = 19-60) and 10 were symptomatic female heterozygotes (Mean age = 49.59, SD = 13.43, Range = 28-71). Subjects were enrolled in an investigation of adrenomyeloneuropathy that included magnetic resonance imaging (MRI) and quantitative measurements of motor skills. Patients were excluded from analysis if they had evidence of cerebral demyelination. The Institutional Review Board of Johns Hopkins University School of Medicine granted approval for the study and all subjects provided informed consent for their participation in the study protocols.

Procedures

Audiometric data were obtained utilizing standard audiometric techniques with a Madsen 922 audiometer. Word recognition performance was assessed in quiet utilizing the W-22 word lists. Subjects were administered the Hearing Handicap for the Elderly – Screening Version (HHIE-S) (13) which is measure of perceived difficulty hearing under everyday listening conditions. Measures of acoustic immittance were obtained utilizing a Madsen Zodiac (Model 901) acoustic admittance measurement unit with a probe tone of 226 Hz. The pump speed for tympanometry was 400 daPa/sec. and the pressure was swept from +200 to -400 daPa.

Measurements of ipsilateral and contralateral acoustic reflexes were undertaken for pure tone stimuli ranging from 500-4000 Hz at ascending levels from 70 to 110 dB HL in 5 dB steps. A repeatable change in admittance of greater than or equal to 0.02 ml was utilized as the criterion for the presence of an acoustic reflex. Acoustic reflexes were defined as abnormal if any threshold at 500, 1000, or 2000 Hz exceeded 100 dB HL or was absent at equipment limits. Auditory brainstem responses (ABRs) were obtained for rarefaction polarity clicks presented at 80 or 90 dB nHL. If waves I, III or V could not be identified in response to clicks presented at 80 dB nHL, measurements were undertaken at 90 dB nHL. The high forehead electrode served as the active electrode and the ipsilateral mastoid as reference with a forehead electrode as ground. Clicks were presented at a rate of 27.7/sec. and 8.4/sec. with a 15 msec. recording window and a passband of 100-3000 Hz. At least two recordings were made at each presentation level. The normality of ABR peaks and ABR interpeak latency intervals (IPLIs) was judged on the basis of the normative data reported previously (14). If a peak could not be identified or was not repeatable upon successive recordings, the peak was classified as abnormal. The MLD for speech was performed utilizing the Tonal and Speech Materials for Auditory Perceptual Assessment compact disk (15). Stimuli were presented at a level of 50 dB HL. The S₀ N₀ condition was always presented first, followed by the S_πN₀ condition. Procedures were followed in accordance with those described in the literature (15). MLDs for speech less than or equal to 5.5 dB were defined as abnormal in the present investigation.

Analysis

For all waves and for each ear, the waves were classified as abnormal if the latency exceeded normative values or if the wave could not be identified. The interpeak latency intervals were classified as abnormal if the intervals (in msec.) exceeded normative values. ABR data for each ear were also categorized as to which ABR component was the initial component abnormal as described by others (11). Comparisons between male and female patients for all ABR waves and interpeak latency intervals were undertaken with t-tests. Because there were no significant differences between ears in the latency of waves I, III or V nor in the interpeak latency intervals, only data for the right ear were analyzed.

Results

Word recognition performance was good to excellent for the right ear (Mean = 95.0%; range = 84-100%) and excellent for the left ear (Mean = 96.7%; range = 92-100%) for speech presented in quiet at 40 dB SL (re: SRT). ABR abnormalities consisted of prolongation of the latency of peaks, prolongation of interpeak latency intervals and absent peaks. ABR waveforms for representative patients are shown in Figure 1. Waveform morphology was within normal limits for Patient A. The Wave I-III, III-V and I-V interpeak latency intervals were prolonged for Patient B. Waveform morphology was markedly abnormal for Patient C as no peaks could be identified.

ABR abnormalities were most prevalent for Wave III and V and less prevalent for Wave I for both male and female subjects. In terms of the interpeak latency intervals, ABR abnormalities were present for the wave I-III, III-V and I-V intervals with the highest prevalence for the Wave I-V interpeak latency interval. As shown in Figure 2, abnormalities were seen in all waves and interpeak latency intervals for both male and female patients with AMN. While there was no significant difference in the latency of Wave I between male and female patients with AMN, there was a significant difference ($t = 2.78$; $p < 0.02$) in the latency of wave III between male (Mean = 4.34; SD = 0.25) and female patients (Mean = 3.99; SD = 0.32). There was also a significant difference ($t = 3.70$; $p < 0.002$) in the latency of Wave V between male (Mean = 6.95; SD = 0.46) and female patients (Mean = 6.26; SD = 0.40) with AMN. In terms of the interpeak latency intervals, there was a significant difference ($t = 4.21$; $p < 0.0007$) in the

I-V interval between male (Mean=5.46; SD= 0.44) and female patients (Mean= 4.71; SD= 0.33). For the wave III-V interpeak latency interval, a significant difference ($t= 3.10$; $p < 0.007$) was observed between male (mean= 2.69; SD= 0.35) and female patients (Mean= 2.27; SD= 0.24); there was also a significant difference ($t= 2.84$; $p < 0.02$) between male (Mean= 2.72; SD= 0.18) and female patients (Mean= 2.44; SD= 0.25) in the I-III interpeak latency interval. No significant differences were found in the frequency of MLD, ipsilateral or contralateral acoustic reflex abnormalities or in the mean MLDs between male and female patients with AMN.

As shown in Figure 3, acoustic reflex abnormalities consisting of absent or elevated reflexes for two or more frequencies were relatively common for contralateral reflex elicitation. Ipsilateral acoustic reflexes were abnormal for 25% of ears. However, in no case were acoustic reflexes elevated or absent for all conditions for ipsilateral and contralateral stimulation of both ears. The MLD was abnormal in 72% of patients.

ABR data were considered in terms of the initial wave abnormality as described by others (16). For each ear, the earliest ABR component that was prolonged in latency or absent was determined. Results are shown in Figure 4 and indicate that the early components of the ABR (i.e., wave I and III) were initially impaired for the majority of ears.

With a criterion of a score of 10 or greater on the HHIE-S indicating subjective hearing difficulty, none of the subjects indicated any difficulty on the HHIE-S. The HHIE-S scores ranged from 0-6 (Mean =1.27; SD= 2.27).

Discussion

Several studies measuring ABR latencies in AMN have shown significantly prolonged absolute peak latencies and interpeak intervals (4-6,17). In our study, all waves were delayed or absent with wave V being the most delayed, then wave III and wave I. The I-III, III-V and I-V interpeak latency intervals were significantly more prolonged in the male patients with AMN than in the female patients. This outcome is not surprising given that AMN in affected females develops later in life with milder symptoms than those experienced by affected males (18). In addition, the age distribution of the women in the present investigation is consistent with the later development of symptoms in symptomatic women with AMN. There were no significant differences in the frequency of acoustic reflex, MLD abnormalities or the mean MLDs between female and male patients with AMN. While ABR abnormalities were found for virtually all patients with AMN, acoustic reflex and MLD abnormalities were comparatively less evident. The hit rate for the ABR exceeded 90% for the Wave I-V interpeak latency interval, whereas the hit rates for the ipsilateral acoustic reflex, contralateral acoustic reflex and MLD were 25%, 50% and 72% respectively. The presence of acoustic reflex abnormalities is suggestive of pathology involving the lower brainstem in some patients with AMN. The acoustic reflex is unaffected by cortical pathology (19) but is typically impacted by disorders affecting the trapezoid body or superior olivary complex of the brainstem (20). The contralateral acoustic reflex may reflect brainstem pathology when ipsilateral reflexes are intact as was the case frequently in the present investigation. Contralateral acoustic reflex abnormalities, which were present in 50% of the AMN patients in this study, have also been reported in patients with a variety of neurological conditions including patients with multiple sclerosis (21). It should be noted that while abnormalities in the acoustic reflex were found, in no case were reflexes entirely absent for stimulation of both ears for all reflex conditions. Other investigators (6) have observed preservation of acoustic reflexes in AMN. This is in contrast to other disorders (e.g., auditory neuropathy) with marked impairment in speech processing and ABR abnormalities in which acoustic reflexes are generally absent for all patients (22).

While findings in the present investigation shown in Figure 2 as well as an earlier paper (5), suggest Wave V and Wave I-V interpeak latency intervals are typically affected to the greatest degree in AMN, the alternative approach shown in Figure 4 to analysis of the ABR results is revealing (16) and showed that, particularly for the male subjects with AMN, waves III and I tend to be the first abnormal ABR component. Findings suggest that for many patients with AMN, there is dysfunction in the auditory nerve and low brainstem impacting on the ABR.

The MLD has been found to be insensitive to cerebral lesions (7,23,24) while sensitive to brainstem disorders (9). The hit rate for the MLD obtained in the present investigation (72%) is comparable to that obtained in other studies in patients with brainstem disorders (25,26), although other studies have reported poorer sensitivity (9).

Abnormal auditory CNS function in individuals with AMN may be accompanied with peripheral hearing loss. Data from six subjects were excluded in the present investigation due to the presence of hearing loss in the 500-2000 Hz frequency region. Although hearing loss was present among some of the remaining subjects in this study in the higher frequency region, peripheral auditory sensitivity was within normal limits in the majority of patients in spite of the presence of marked ABR abnormalities. Previous studies have shown that the prevalence of hearing loss in AMN does not exceed that found in age and sex matched control groups (5). These findings are in agreement with other studies that have reported that peripheral hearing loss is not commonly found in disorders impacting on the auditory pathways at brainstem levels (8). It had been reported previously in AMN that the ABR might be absent despite the presence of normal audiometric findings and a normal slow cortical evoked potential (6) which is in agreement with our findings. Subjects with AMN in the present investigation reported no significant difficulty hearing and were found to have good to excellent word recognition abilities in spite of the presence of marked ABR abnormalities. Nevertheless, it is appropriate to question whether more subtle deficits in auditory processing may be present that were insensitive to the measures utilized in the investigation. Such deficits in central auditory function as well as subjective complaints of hearing difficulty have been reported in neurological disorders associated with ABR abnormalities such as multiple sclerosis (MS) (27) as well as in other variants of adrenoleukodystrophy (28). ABR abnormalities suggestive of auditory pathway involvement have been shown to be consistent with the presence of disproportionate difficulty in speech processing in individuals with hearing loss (29,30) and in cochlear hearing loss, a significant relationship has been found between the latency of Wave I and II and word recognition performance (31). Word recognition performance is significantly correlated with ABR wave V amplitude in patients with acoustic neuroma (32). However, the finding that AMN patients in this study generally reported no significant difficulty with their hearing is in contrast to findings obtained in patients with other forms of neurological disease and marked ABR abnormalities (27). For example, a significant number of patients with MS (40%) reported the presence of difficulty when asked to self assess their perceptions of hearing handicap (27) whereas no individuals with AMN in the present investigation indicated the presence of any difficulty hearing. This result is in agreement with Kaga et al. (32) who demonstrated that for more difficult materials than utilized in the present investigation, nonsense syllable identification is not invariably impaired in brainstem disorders; particularly if Wave I was preserved or if the Wave I-V interpeak latency interval was only moderately prolonged (33). Findings in the investigation indicate that patients with AMN do not have significant difficulty with hearing despite the presence of abnormal ABR morphology.

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Figure 1. Auditory brainstem response waveforms in response to rarefaction clicks presented at 80 or 90 dB nHL at a rate of 8.4/sec. for three individuals with AMN. All individuals were diagnosed with AMN. Waveforms for the individuals depicted in (a) were judged normal, (b) significantly prolonged and (c) absent.

Figure 2.

Percent of ears abnormal for wave I, III, and V and for the I-III, III-V and I-V interpeak latency intervals for male and female patients with AMN.

Figure 3.

Percent of ears abnormal for the ipsilateral and contralateral acoustic reflex and percent MLDs abnormal for male and female patients with AMN.

Figure 4.
First abnormal ABR component (in percent) for ears of male and female patients with AMN.