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Original Article

Auditory N1-P2 Cortical Event Related Potentials in Auditory Neuropathy Spectrum Disorder Patients

Mohamed M. Abdeltawwab

Department of Otorhinolaryngology, Mansoura University Faculty of Medicine, Mansoura, Egypt (MMA)
Department of Otorhinolaryngology, KFMMC Hospital, Dhahran, Saudi Arabia (MMA)

OBJECTIVE: The purpose of this study was to determine whether a group of patients with auditory neuropathy have abnormal changes in auditory N1-P2 and to analyze the results in those patients and compare them with matched group of normal subjects.

MATERIALS and METHODS: Cortical auditory evoked potentials were obtained from nine female and seven male patients with auditory neuropathy, ranging in age from 19 to 48 years. The control group comprised 15 (9 males and 6 females) age-matched, normally hearing adults. Cortical auditory evoked potentials were recorded in both groups. Audiological assessments were performed in both groups, which included pure tone audiometry, speech audiometry, tympanometry, acoustic reflex, distortion products otoacoustic emissions, as well as auditory brainstem potential testing.

RESULTS: N1-P2 amplitudes were reduced and latencies were prolonged in the study group, and these parameters were found to be statistically significant when compared to normal subjects ($p<0.05$).

CONCLUSION: The neurophysiologic measures of auditory processing-i.e., N1-P2 response to tonal frequency stimuli-in auditory neuropathy spectrum disorder patients are found to be different. Hence, arguing a doubt on the affection of hypothesize origin of the N1-P2 potential in ANSD patients.

KEY WORDS: Auditory N1-P2, event-related potentials, auditory neuropathy, auditory dys-synchrony, auditory neuropathy spectrum disorders, auditory evoked potentials

INTRODUCTION

Auditory neuropathy can be defined as a hearing impairment in which otoacoustic emissions (OAEs) and/or cochlear microphonics are normal, despite having no or abnormal auditory brainstem response (ABR) at high stimulus levels [1]. Word discrimination in these patients is impaired and seems to be disproportional to pure-tone thresholds. Auditory neuropathy was considered to be a functional disorder rather than an anatomical abnormality [2].

Although the underlying lesion(s) and the pathophysiologic mechanisms in auditory neuropathy are key points in understanding and treating the disease, the related evidence is still unclear and, in some cases, confusing. Clinical and electrophysiological studies support the hypothesis that it is not a single disease but in fact a spectrum of pathologies that affect the auditory pathways [3].

Auditory neuropathy spectrum disorder (ANSD) is a term recently adopted by the panel of the International Newborn Hearing Screening Conference [4]. It is thought to be a kind of auditory pathology with normal outer hair cell function but disordered neural conduction in the auditory pathway [5].

The exact etiology of auditory neuropathy is unknown. However, a number of factors account for it. These may include gene mutations, infections (measles, mumps), metabolic diseases (diabetes, hyperbilirubinemia, hypoxia), neoplastic processes (acoustic neuroma), and prematurity. It has been hypothesized that various lesions might exist at the level of inner hair cells, the synapse between the inner hair cell, and the auditory nerve or the auditory nerve itself [2, 5]. Adult auditory neuropathy patients typically complain of an impaired ability to understand speech, especially in the presence of noise [6-7].

P1, N1, and P2 are obligatory components of auditory evoked potentials that index detection of the onset and offset of auditory stimuli [8]. The deflection of each has differing underlying neural sources and independent response patterns [9] and is modulated by attention [10]. The primary and association auditory cortices generate the N1-P2 [11].

Corresponding Address:
Mohamed M. Abdeltawwab, Department of Otorhinolaryngology, Mansoura University Faculty of Medicine, Mansoura, Egypt
Phone: 00201002599743; E-mail: matawwab@hotmail.com

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Cortical auditory evoked potentials may not only provide the level or the extent of this so-called "functional pathology" but also the behavioral outcome of auditory rehabilitation provided in ANSD. The purpose of this study was to determine whether a group of patients with auditory neuropathy have abnormal changes in auditory N1-P2 and to analyze the results and compare them with a matched group of normal subjects.

MATERIALS and METHODS

Participants

This study was conducted in the otorhinolaryngology and audiology clinics in our hospital between January 2012 and October 2013 after approval of the hospital research committee. Written consent was obtained from all participants. Sixteen auditory neuropathy patients were tested (9 females and 7 males) who were in the age range of 19 to 48 years of age (mean=27.8±8.2). Fifteen normal subjects between 19 years and 45 years, mean=29.8±6.8 (9 males and 6 females), served as a control group.

The inclusion criteria of the study group were bilateral sensori-neural hearing loss, speech discrimination out of proportion to the degree and configuration of hearing loss, normal middle ear function with absent acoustic reflexes, absent ABR waves, and preserved OAEs. The inclusion criteria of the control group were normal hearing, excellent speech discrimination scores, normal middle ear functions with normal acoustic reflex, and normal ABR. All subjects included in this study were subjected to the following: pure tone for octave frequencies (250-8000 Hertz), speech audiometry, tympanometry, acoustic reflex threshold testing, OAEs, and ABR measurements.

Apparatus and Procedures

Click ABR, distortion products otoacoustic emissions (DPOAEs), and behavioral hearing assessments were performed in all participants in acoustically treated test rooms with ambient noise levels below 30 dB (A), whereas tympanometry was carried out in a quiet room. ABR was carried out using an ICS CHARTR evoked potential system, version 3.00 (ICS medical CHARTR, IL, USA). The DPOAE testing was carried out using the Scout OAE, version 3.45 (A Bio-logic® Scout Otoacoustic Emissions System, Natus Medical, Inc., USA) to gather DPOAEs.

Tympanometry was conducted using an AT 235 Impedance Audiometer middle ear analyzer (Interacoustics, DK-5610, Assens, Denmark). To ensure that all the middle ear problems were to be detected, 226 Hertz tympanograms and ipsi-lateral and contra-lateral acoustic reflex testing were carried out. The ears were thought to have normal middle ear function when both tympanograms were normal.

The behavioral hearing assessment was carried out with an AC 40 pure tone audiometer (Interacoustics, DK-5610, Assens, Denmark). The thresholds were the lowest level at which at least two consistent responses were achieved. Speech discrimination scores were also tested. The speech reception thresholds were also obtained. All these tests were performed in a sound-treated booth where the ambient noise levels were within permissible limits. The stimuli were presented 40 dB sensation levels with reference to a speech reception threshold monaurally, and the speech recognition scores were calculated by counting the number of words correctly repeated.

Auditory N1-P2 parameters

P1 and N1-P2 were obtained for each participant in this study. They were seated comfortably while obtaining the evoked cortical potential through the ICS CHARTR evoked potential system, version 3.00, coupled with a preamplifier (ICS medical CHARTR preamplifier PA-800), output amplifier, computer, and insert earphones (ICS medical, IL, USA) for both stimulation and recording of the cortical auditory N1-P2 event-related potential testing. The active (positive) electrode was placed on Fz in reference to A2 and A1 (negative), while the common ground electrode was placed at the forehead. The impedance at each electrode site was less than 5 kiloohms, while the inter-electrode impedance was less than 2 kiloohms; 750 Hertz and 1000 Hertz tone burst stimuli with a rise-fall time of 10 milliseconds (ms) and plateau of 50 ms at 40 dB sensation level (supra-threshold) intensity for all participants. Band pass filter was set between 0.1 to 50 Hertz. Artifact rejection was set when the incoming signal exceeded ± 50 microvolt (μV). During the test, we ensured that eye closure was avoided to minimize associated EEG alpha activity, which can contaminate the recording. Time window was 500 ms with 100 ms of pre-stimulus baseline recording time. Responses of 250 stimuli were averaged. The latencies of P1, N1, and P2 and the amplitude of N1-P2 (peak-to-peak amplitude) were measured. Two traces were recorded to ensure reproducibility. The participants were instructed not to pay attention to the stimuli while recording and to watch soundless videos.

Statistical Analysis

Descriptive statistics, including means, standard deviations, and correlations and t-test were used for the control and study groups. The latencies of P1, N1, and P2 and amplitude of N1-P2 were compared for the control group and auditory neuropathy patients. The criterion for statistical significance was set at $p<0.05$.

RESULTS

In this study, the average pure-tone thresholds revealed moderate hearing loss in ANSD patients. Low-frequency loss audiograms were observed in most of the study group (11 patients). The male-to-female ratio was (1:1.28) in the ANSD study group. Thirteen of the ANSD patients evoked the N1-P2 response, while 3 (2 females and 1 male) of the study group had absent waveform.

Table 1 shows the average of pure tone air conduction thresholds obtained from the right and left ears of patients with auditory neuropathy, the audiogram shape, the speech discrimination score in percentage for each ear, OAE, acoustic reflex, and ABR test results. Figure 1 shows the mean pure tone air conduction thresholds as a function of octave frequencies in dBHL of the two groups. There were statistically significant differences between both groups ($p<0.05$).

Table 2 reveals the mean latencies in ms and the standard deviation of P1, N1, and P2 and the mean amplitude with standard deviation in μV for normal subjects and auditory neuropathy patients. There were statistically significant differences between both groups ($p<0.05$).

Figure 2 shows the scatter plot of speech discrimination scores as a function of average pure tone air conduction thresholds in ANSD patients. It shows that hearing thresholds decreased as the discrimination scores were lower; nevertheless, discrimination scores were still out of proportion to the degree of pure tone loss.

Table 1. The distribution of the auditory neuropathy patients according to age, gender, pure tone average, audiogram shape, word discrimination scores percentage, OAEs, acoustic reflexes and ABR test

Patient/Sex	Age	PTA (dB)		Audiogram shape	WDS (%)		OAEs	AR	ABR
		Right	Left		Right	Left			
AN1 (F)	18	31.6	38.3	LFL	4	8	+	-	-
AN2 (F)	19	47.5	44.1	Flat	8	0	+	-	-
AN3 (F)	23	28.3	28.3	LFL	40	44	+	-	-
AN4 (F)	31	35.8	34.1	LFL	4	4	+	-	-
AN5 (F)	40	50	51.6	Flat	12	8	+	-	-
AN6 (F)	26	36.6	35	LFL	4	8	+	-	-
AN7 (M)	24	38.3	35	LFL	80	76	+	-	-
AN8 (M)	20	51.6	51.6	Flat	4	8	+	-	-
AN9 (M)	23	19.1	21.6	LFL	44	40	+	-	-
AN10 (M)	29	35.8	35.8	LFL	24	28	+	-	-
AN11 (M)	33	32.5	31.6	LFL	52	48	+	-	-
AN12 (M)	48	49.1	48.3	Flat	20	24	+	-	-
AN13 (M)	37	29.1	29.1	LFL	40	44	+	-	-
AN14 (M)	28	42.5	38.3	LFL	20	16	+	-	-
AN15 (M)	25	40.8	42.5	Flat	24	28	+	-	-
AN16 (M)	21	31.6	27.5	LFL	56	60	+	-	-

+ =present - =absent PTA: pure tone average; AR: acoustic reflexes; WDS: word discrimination scores; LFL: low frequencies loss; dB: decibel; AN: auditory neuropathy; OAEs: otoacoustic emissions; ABR: auditory brainstem responses

Table 2. The mean and standard deviation of the latencies in ms and amplitude in µV for normal subjects and ANSD

	Latencies in ms						Amplitude in µV	
	P1		N1		P2		N1/P2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Normal subjects	62.9	9.4	99.8	14.7	152.9	13.2	6.7	1.4
ANSD	75.07	12.57	135.5	16	194.3	26.7	4	1.5
t-test	p<0.05		p<0.05		p<0.05		p<0.05	

SD: standard deviation; ms: milliseconds; µV: microvolt

Figures 3 and 4 reveal a poor correlation between the pure tone average and the amplitude of N1-P2 in µV (r=-0.1) and the latencies of P1, N1, and P2 in ms (r=0.18, 0.21, and 0.28, respectively) of auditory neuropathy patients, whereas in Figures 5 and 6, there are high correlations between the speech discrimination scores and the amplitude of N1-P2 in µV (r=0.58) and latencies of P1, N1, and P2 in ms (r=-0.69, -0.81, and -0.68, respectively) of auditory neuropathy patients.

DISCUSSION

The diagnosis of auditory neuropathy is commonly based on evidence of normal cochlear function but abnormal cochlear nerve action potential testing. Cortical auditory evoked potentials may, however, still be evident and can be recorded in those patients. Recently, the auditory neuropathy was found to be not a single disease but a spectrum of pathologies affecting the auditory pathways [3]. In the present study, the mean age for ANSD patients was 27.8 years, and the participants' hearing thresholds ranged from mild to moderate hearing loss. Low-frequency/rising audiometric contours were observed in 68% of the study group, while 32% had flat audiograms, and the male-to-female ratio was 1 to 1.28.

In spite of auditory neuropathy patients having abnormal or absent ABRs, they may show N1 and P2 auditory cortical potentials to tones [12], speech signals [13], and silent gaps in continuous noise [14]. However, these cortical potentials typically may be prolonged in latencies compared to normal hearing subjects.

Early studies of auditory cortical potentials to tones in normal hearing subjects showed that N1 latency was remarkably stable over a wide range of intensities [15]. The mere fact that some patients had N1-P2 auditory evoked potentials and some of them did not increase supports that auditory neuropathy describes a variety of auditory dysfunctions and should not be thought of as a single disorder. In this study, N1-P2 was absent in 3 out of 16 patients, whereas, Rance et al., 2002, found N1-P2 to be absent in 50% of their study, and the absence of these potentials was related to impaired speech perception [16].

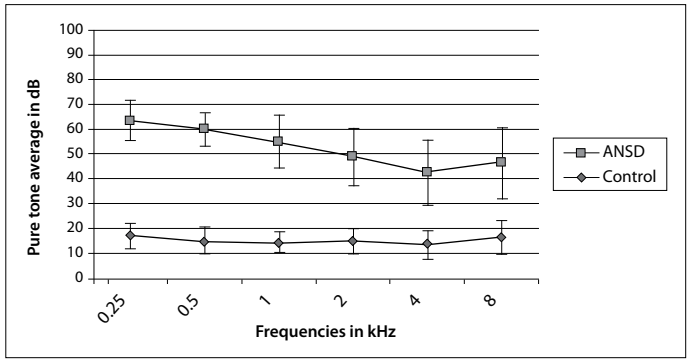

Figure 1. The mean pure tone air-conduction thresholds in octave frequencies in the two groups. Error bars represent 1 standard deviation above and below the mean
dB: decibel; kHz: kilo Hertz

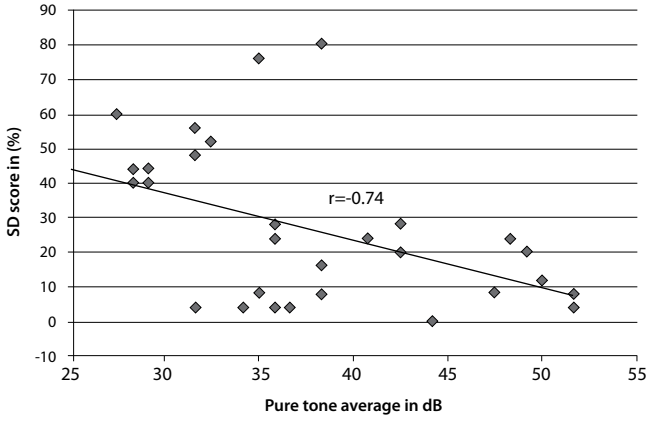

Figure 2. Scatter plot of speech discrimination scores as a function of pure tone air-conduction thresholds in octave frequencies in ANSD patients
SD: speech discrimination; dB: decibel

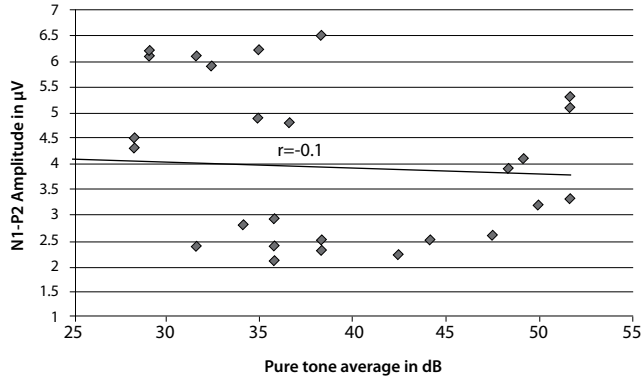

Figure 3. Scatter plot of N1-P2 amplitudes as a function pure tone air-conduction thresholds in octave frequencies in ANSD patients
µV: microvolt; dB: decibel

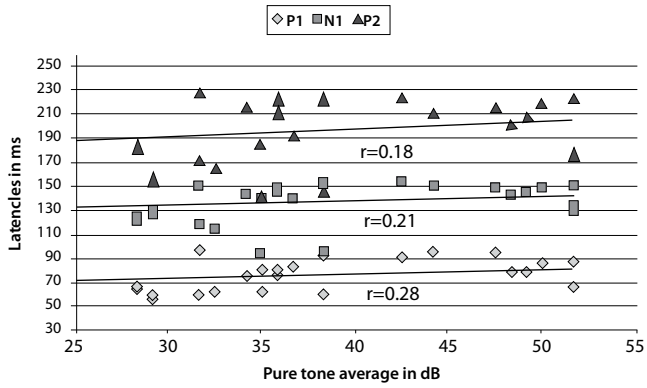

Figure 4. Scatter plot of P1, N1 and P2 latencies as a function of pure tone air-conduction thresholds in octave frequencies in ANSD patients
ms: milliseconds; dB: decibel

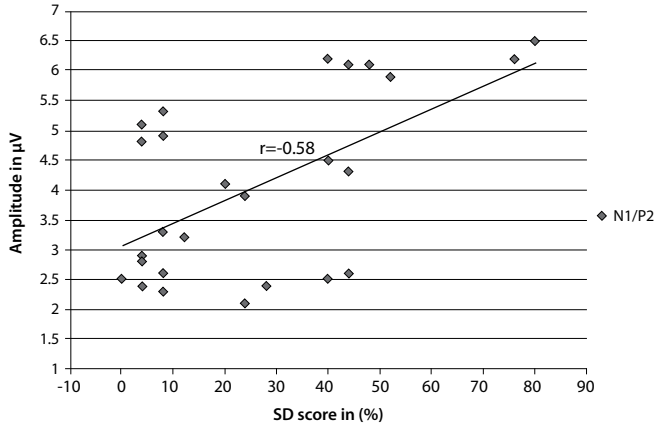

Figure 5. Scatter of N1-P2 amplitudes as a function of speech discrimination scores in ANSD patients
SD: speech discrimination; µV: microvolt

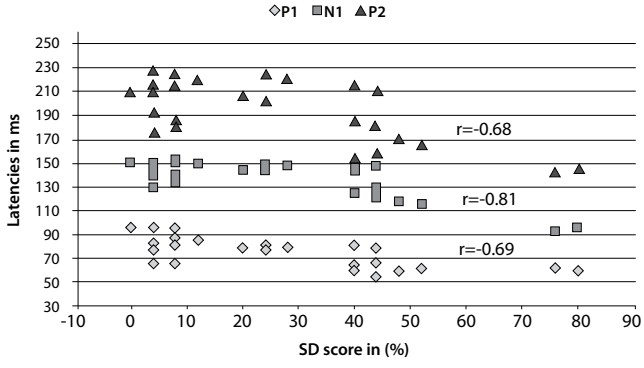

Figure 6. Scatter plot of P1, N1 and P2 latencies as a function of speech discrimination scores in ANSD patients
SD: speech discrimination; ms: milliseconds

The results of this study suggest that ANSD patients do have auditory changes at the level measured by N1-P2. The auditory N1-P2 of those patients revealed reduced amplitude and prolonged latencies than the normal group ($p<0.05$). Hence, arguing a doubt on affection for the origin of these potentials in ANSD patients.

The findings of this study agree with those of Narne and Vanaja, 2008, in which they found that the amplitude of N1-P2 in auditory neuropathy was significantly smaller and that the latencies were significantly longer than those of normal adults. Their findings support the idea of abnormal cortical N1-P2 recordings in ANSD [13]. Rance suggests that the prolonged latencies could be due to dys-synchronous firing rate in those patients [17].

Auditory N1-P2 may be correlated to speech discrimination and not the pure tone average in auditory neuropathy patients [13]. In this

study, no significant correlation was found between the amplitude and latencies versus the pure tone average in ANSD patients, whereas it showed a significant correlation with speech discrimination scores; as the scores got worse, the amplitude of N1-P2 decreased and its latencies were prolonged. This suggests that cortical potentials were affected and hence correlated to speech discrimination scores than to hearing threshold level.

The measurement of auditory N1-P2 in ANSD is useful as an indicator of auditory cortical functions in those patients, but further studies are needed to elicit the responses by various types of stimuli. Also, in addition to evoked potential studies, further research involving simultaneous collection of behavioral and physiological data should also be considered.

CONCLUSION

The neurophysiologic measures of auditory processing that reflect N1-P2 responses to tonal frequency stimuli in ANSD patients are different. The amplitude was reduced or even absent, and the latencies were prolonged. Hence, arguing a doubt on the affection of hypothesized origin of this potential in those patients, which needs further study.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Mansoura University Hospital and KFMMC Hospital.

Informed Consent: Written informed consent were obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

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