Original Article

P300 in Individuals with Auditory Neuropathy Spectrum Disorder

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Abstract

Introduction: Typically, individuals with auditory neuropathy spectrum disorder (ANSD) show the presence of otoacoustic emissions and elevated/absent auditory brainstem responses. It has been reported that individuals with ANSD, in spite of absent or abnormal ABRs, show auditory cortical potentials. P300 is an endogenous cortical-evoked potential and reflects the changes in the cortical activity when the attention is paid toward the sound. This can effectively quantify the complex cortical sensory-cognitive processing underlying active auditory perception. Therefore, the present study was taken up to investigate the cortical representation of active auditory discrimination skills in individuals with ANSD using P300 response. **Methods:** Twenty-five individuals with ANSD and 25 individuals with normal hearing sensitivity were the participants. The individuals with ANSD had audiometric thresholds ranging from normal hearing to moderate hearing loss. P300 was recorded using/ba/-/da/stimulus contrast in the oddball paradigm. The latency and the amplitude of P300 response were marked and analyzed using repeated measures ANOVA. Sensitivity and reaction time in identifying the oddball were also measured. **Results:** The result showed poor sensitivity and longer reaction time in individuals with ANSD compared to individuals with normal hearing. P300 responses were prolonged in latency and reduced in amplitude in individuals with ANSD. Both the latency and amplitude of P300 response were related to perceptual measures. **Conclusion:** P300 response was present in individuals with ANSD but with prolonged latency and reduced amplitude.

Keywords: Auditory neuropathy spectrum disorder, event-related potential, P300

Introduction

Individuals with auditory neuropathy spectrum disorder (ANSD) present with the normal cochlear outer hair cell function but lacks synchronous firing of the nerves in the auditory pathway.[1] The audiological profiling of the individuals with ANSD shows the presence of otoacoustic emissions and/or cochlear microphonics indicating normal functioning outer hair cells in the cochlea, abnormal or absent auditory brainstem responses (ABRs) indicating the dyssynchronous firing of the auditory nerve fibers.[2-5] One of the cardinal features of individuals with ANSD is reduced speech perception skills.[3,6-9] The poor speech perception skill in individuals with ANSD is disproportionate to their pure tone hearing loss and appears to be related to the poor temporal processing abilities.[10-13] It has been reported that individuals with ANSD exhibit deficits discrimination speech sound that defer on temporal parameters. Kumar and Jayaram[8,9] showed that individuals with ANSD had significantly longer difference limens while discriminating transition duration or voice onset time in speech sounds. Kraus *et al*.[14] showed remarkably good discrimination skill for the stimuli differing in transition duration but showed poor discrimination for the speech contrast differing in onset frequency of the third formant.

Many individuals with ANSD, in spite of absent or abnormal ABRs, show auditory cortical potentials.[13-16] Rance *et al*.[16] recorded obligatory response from children with ANSD and found no clear relationship between the degree of hearing loss and the P1-N1-P2 response in children with ANSD. They reported a strong positive relationship between presence/absence of response and the aided phoneme scores. The latency, amplitude, and the morphology of response were similar across children with normal hearing, with sensorineural hearing loss, and with ANSD. In another

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study, Narne and Vanaja[15] reported P1-N1-P2 response to be present in nine out of ten individuals with ANSD. The latency of P1, N1, and P2 peaks was significantly prolonged in individuals with ANSD compared to individuals with normal hearing. The mean N1/P2 amplitude was slightly lower with greater variability in individuals with ANSD. In a single case study, Kraus *et al*.[14] recorded P1-N1-P2 and mismatch negativity (MMN) using speech stimuli,/ba/and/pa/ in an individual with ANSD. The P1-N1-P2 potentials were present in the individual with ANSD. However, the latency was within normal range for/ba/and was delayed for/pa/. The individual showed normal MMN for the speech contrast differing in formant transition duration (/ba-wa/continuum) but showed abnormal MMN for speech contrast differing in formant onset frequency (/da-ga/continuum). Kruas *et al*. interpreted these results as individuals with ANSD exhibit deficits in the coding of stimulus onset information because of the dyssynchronous firing of the auditory nerve than the steady state and longer duration timing cues. Kumar and Jayaram[13] also reported the presence of P1-N1-P2 and MMN response for speech stimuli/da/in individuals with ANSD. Gabr (2011) recorded MMN responses in individuals with ANSD using four frequency tonal contrasts using the oddball paradigm.[17] Result revealed a significant delay in latency of MMN in individuals with ANSD, but amplitude did not show any significant difference across groups. There was no correlation between speech discrimination scores and MMN latency for any of the frequencies. However, amplitude of MMN for 4 kHz contrast had a significant correlation with the speech discrimination.

From the brief review above, it can be seen that the individuals with ANSD show obligatory auditory cortical responses though their ABR is severely abnormal. This provides a unique opportunity to investigate the effect of peripheral dyssynchrony on cortical-evoked potentials. P300 is a cortical event-related sensory-cognitive potential and is consistently related to attention, decision–making, and memory updating.[18] Therefore, it is a valuable tool for investigating these processes in the human brain. Recent studies have provided a strong evidence for an association between the measures of sensory function and cognitive function.[19-21] However, all the studies that have been done so far have investigated the effect of sensory loss on cognitive functioning. Deleterious effects of dyssynchronous auditory nerve firings on cognitive functions are not known. In the present study, we recorded the cortical-evoked potential, P300, using an active oddball paradigm. As P300 potential reflects the changes in EEG activity when the attention is paid toward the deviant sound,[22,23] and it can effectively quantify the complex cortical sensory-cognitive processing underlying active auditory perception, this was used to investigate the cortical representation of active auditory discrimination skills in individuals with ANSD. Specifically, the present study compared the latency and amplitude of P300 at three electrode locations (Fz, Cz, and Pz) between individuals with normal hearing sensitivity and individuals with ANSD. Furthermore, the study also looked the behavioral discrimination scores and reaction time in both the groups of participants.

Methods

A total of 25 individuals (13 males and 12 females) diagnosed as having ANSD, and 25 age-matched individuals with normal hearing sensitivity participated in the study. The participant's age ranged from 17 to 55 years with the mean age of 29.84 years. A certified audiologist diagnosed the individuals with ANSD as per the recommendation of Starr *et al*.[2] All the individuals in the ANSD group had bilateral ANSD. The demographic details and the audiometric thresholds of all ANSD participants are given in Figure 1 and Table 1. Figure 1 shows the mean and one standard deviation of air conduction thresholds for right and the left ear for individuals with ANSD. These participants are chosen from our data pool of ANSD patients and have also participated in other experiments.

None of the participants in both the groups' complained of any other otological or vestibular symptoms. A qualified neurologist ruled out any peripheral neuropathy or any space-occupying lesion in all the participants. Informed consent was taken from the participants using informed consent form which followed the "Ethical guidelines for bio-behavioral research involving human subjects."[24] The study was approved by the Ethical Review Board of All India Institute of Speech and Hearing, Mysore, India.

Stimuli

Stimulus pair /ba/ and /da/ differing in place of articulation was used to record P300 in the oddball paradigm and stimulus /da/ was used to record response in the repetitive paradigm. Primary cue for discrimination of /ba/ from /da/ is the onset of second formant frequency and transition direction. These cues are dynamic, and it has been reported that individuals with ANSD have difficulty in perceiving dynamic spectral cues.[14] Adobe Audition (version 3.0) with MicroBook II sound card (Motu, Cambridge, Massachusetts, USA) interface was used to record stimuli. The sampling frequency was 44100 Hz with 16-bit resolution. The stimuli were recorded in a quiet room. A male speaker with clear articulation uttered the stimuli. The goodness test was done, and the stimuli with clear were considered for the study. The waveform and the spectrogram for the stimuli /ba/ and /da/ are shown in Figure 2. The duration of the syllables was 240 ms and was kept same for both the syllables to minimize the use of durational cues.

Procedure

The response was recorded using Neuroscan Scan 4.5 system (Compumedics, Charlotte, NC, USA) with 64 channels QuickCap™. The recording was done in a quiet, well-lit, air-conditioned room. The appropriate size cap was selected for each of the participants based on the measured head circumference. All the 64 channels were active while recording the response and the impedances were <20 kΩ for

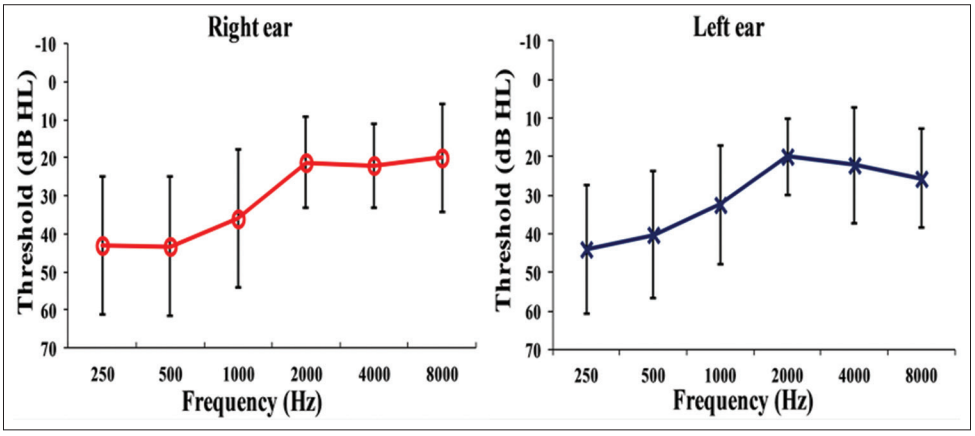

Figure 1: The mean pure tone thresholds and the one standard deviation for the right and the left of individuals with auditory neuropathy spectrum disorder across frequencies from 250 Hz to 8000 Hz

Table 1: The demographic and audiometric details for individuals with auditory neuropathy spectrum disorder

Participants	Age (year)/ gender	Pure-tone average (dB HL)		Speech identification scores (%)	
		Right ear	Left ear	Right ear	Left ear
ANSD1	25/male	35	30	84	86
ANSD2	26/male	28.75	22	48	80
ANSD3	40/female	45	43.75	28	32
ANSD4	19/female	36.25	23.75	76	84
ANSD5	20/female	32.5	36.2	60	40
ANSD6	21/female	10	12.5	68	76
ANSD7	18/male	28.75	25	92	96
ANSD8	17/female	37.5	28.75	76	80
ANSD9	48/male	45	35	76	76
ANSD10	48/male	31.25	30	76	76
ANSD11	20/male	31.25	32.5	68	84
ANSD12	55/male	46.25	47.5	84	80
ANSD13	35/male	30	22.5	40	44
ANSD14	20/female	17.5	15	96	96
ANSD15	21/male	31.25	35	68	44
ANSD16	36/female	47.25	37.25	64	80
ANSD17	41/female	8.75	7.4	72	44
ANSD18	36/male	30	25	64	80
ANSD19	20/male	18.75	25	100	56
ANSD20	18/female	48.75	52.5	36	40
ANSD21	54/male	41.25	36.25	40	35
ANSD22	30/male	22.5	20	30	26
ANSD23	37/female	20	16.25	40	24
ANSD24	24/female	35	45	32	36
ANSD25	17/female	27.5	33.75	28	24

All individuals had absent ABR, stapedial reflexes and present OAE. Pure-tone average: Average of the threshold at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz. OAE: Otoacoustic emission; ABR: Auditory brainstem response; ANSD: Auditory neuropathy spectrum disorder; HL: Hearing level

all the channels. Two sets of extraocular electrodes were placed around the eyes in close proximity to monitor the vertical and horizontal ocular movements.

Continuous EEG was recorded with /ba/ as frequent stimuli and/da/as infrequent stimuli. EEG was recorded using a band-pass filter of 0.1–100 Hz with a sampling frequency of 1000 Hz per channel. A total of 250 trials were presented with frequent stimulus being presented for 80% of the trials, while the infrequent stimulus being presented for 20% of the trials. Thus, the deviant stimulus was presented fifty times in each recording. Interstimulus interval was 2240 ms. It was ensured that none of the two infrequent stimuli occurred one after the other. Following this, EEG was also recorded for /da/ stimulus presented in repetitive paradigm for the equal number of sweeps as that of infrequent in the oddball paradigm. Comparison of the ERPs elicited for /da/ stimuli in oddball and repetitive paradigm eliminates variations in waveform morphology arising purely because of acoustic differences between standard and deviant waveforms and therefore allows examining the effect of memory representations more robustly.[25] The stimulus was presented at 75 dB SPL through loudspeaker kept at a 1 m distance and at 0° azimuth from the participant. In the repetitive paradigm, /da/ stimuli were presented for a total of fifty sweeps. During the recording, participants sat comfortably in a reclining chair and were instructed to press a button with their preferred finger each time they heard the deviant stimulus in the train of standard stimuli. They were asked not to respond for the standard stimuli. The participants were asked to stay as still as possible during the recording and also to reduce the eye movements. Reaction time was calculated as the time taken from the onset of the deviant stimuli to the button press response and was expressed in millisecond. Sensitivity (d') was measured using the inbuilt program in Neuroscan Stim2 system (Compumedics, Charlotte, NC, USA) by calculating the proportions of hit responses with respect to false alarms and misses.

The continuous raw EEG response was epoched from 200 ms prestimulus to 800 ms poststimulus. The response was band-pass filtered from 0.1 to 30 Hz using a finite impulse response filter. The response was baseline corrected, re-reference to the mathematical average of left and right

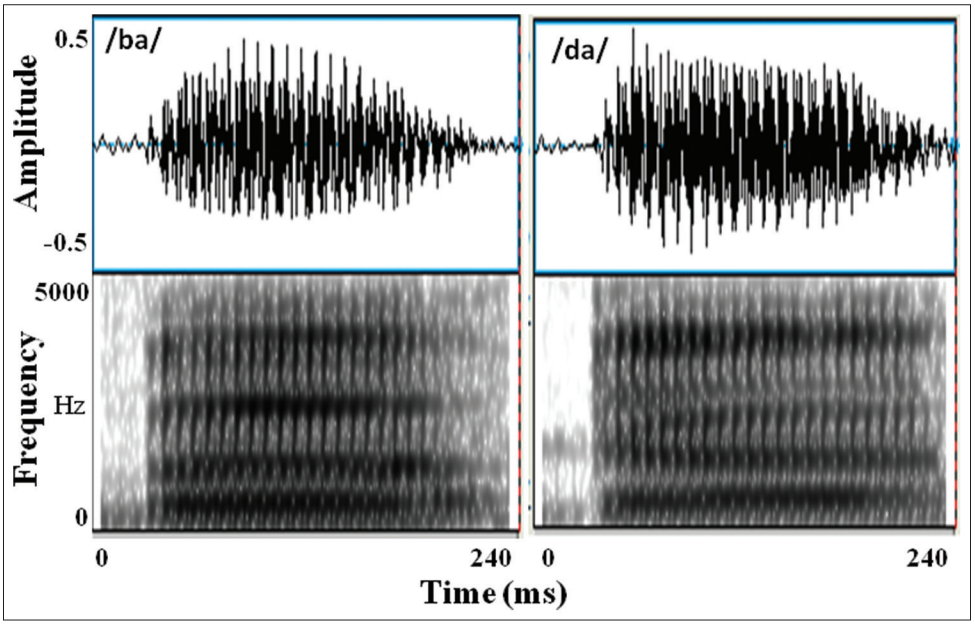

Figure 2: The waveform and the spectrogram of the speech stimuli /ba/ and /da/

mastoid, ocular artifact reduction, and the data from bad electrodes were interpolated using spline interpolation. These processed epochs of /da/ stimuli in oddball and repetitive paradigm were averaged separately. Two experienced audiologists marked the peaks in the waveforms following the criteria given by Polish which suggest any positive peak between 300 to 700 ms, present in oddball paradigm as P300 response.[26] The peak was marked for three electrode locations: Fz, Cz, and Pz. These three electrodes were chosen because of the higher amplitude of P300 at midline electrodes, and a minimum of three electrodes are sufficient to characterize P300.[23] Any discrepancies in the markings were resolved through mutual consensus. Latency and the amplitude were noted and analyzed. Behavioral measures, reaction time, and sensitivity were also noted for further analysis.

Results

The sensitivity and the reaction time in the identification of oddball stimuli are shown in Table 2. Independent sample *t*-test showed a significant difference between the groups in reaction time ($t(48) = -5.50$, $P < 0.001$) and sensitivity ($t(48) = 4.34$, $P < 0.001$). The individuals with ANSD had longer reaction time and poorer sensitivity in identifying the deviant stimuli compared to individuals with normal hearing sensitivity.

The presence of P300 was confirmed by comparing response in oddball and repetitive paradigm. P300 peak was present in all individuals with normal hearing sensitivity, whereas it was present in only twenty individuals (80%) with ANSD. The grand averaged waveforms of stimuli /da/ in oddball and repetitive paradigm in individuals with normal hearing sensitivity and with ANSD across three midline electrodes Fz, Cz, and Pz are shown in Figure 3. Comparison between the repetitive and deviant waveform of /da/ stimuli showed that

Table 2: The reaction time and the sensitivity measure for individuals with normal hearing and with auditory neuropathy spectrum disorder

	Reaction time (ms)		Sensitivity	
	Mean	SD	Mean	SD
Individuals with normal hearing	434.91	104.32	0.99	0.001
Individuals with ANSD	598.41	105.71	0.91	0.09

ANSD: Auditory neuropathy spectrum disorder; SD: Standard deviation

reliable P300 could be elicited with its typical morphology in both the groups. On visual inspection, it is evident from Figure 3 that P300 peak was present only in oddball paradigm and not in repetitive paradigm across channels and groups. The presence of P300 was ascertained by a carrying out a randomized boot strapping test between waveforms of oddball and repetitive paradigms for both the groups separately. The rectangular boxes in Figure 3 represent the region where two waveforms differed from each other significantly ($P < 0.05$) on this test. It can be noted that there are significant differences between two waveforms from 290 ms (in normal hearing individuals) and from 332 ms (in ANSD) poststimulus time regions indicating the presence of significant P300 in both the groups.

The mean latency and the amplitude of P300 across groups and channels are shown in Table 3. From Figure 3 and Table 3, it can be seen that individuals with ANSD had prolonged P300 latency and reduced amplitude compared to individuals with normal hearing sensitivity. The variance in the response was also more in individuals with ANSD as reflected by the higher standard deviation for both latency and amplitude parameters. Repeated measures ANOVA was performed with electrodes

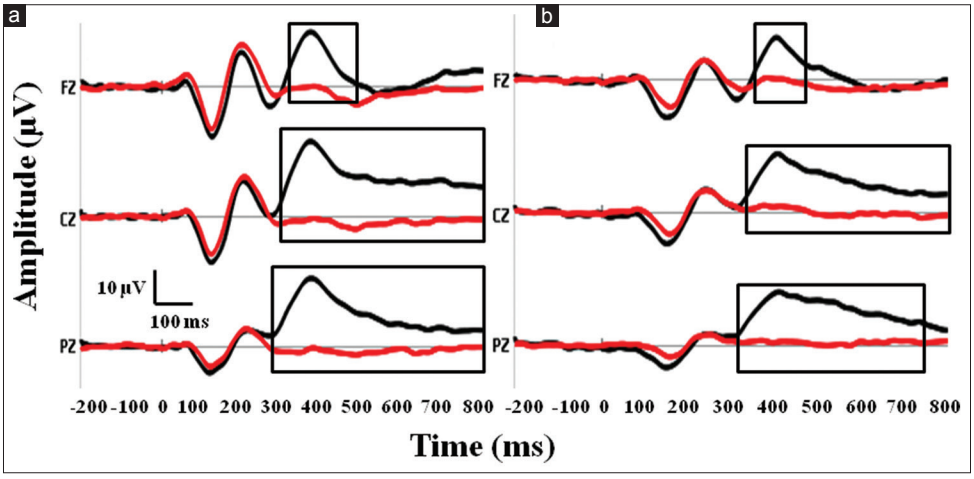

Figure 3: Grand mean response obtained from individuals with normal hearing (a) and with auditory neuropathy spectrum disorder (b) in oddball (black waveform) and repetitive paradigm (red waveform). The black boxes show the region of significant difference across oddball and repetitive paradigm

Table 3: The mean and the standard deviation of latency and amplitude of P300 response across three electrodes as obtained from individuals with normal hearing and with auditory neuropathy spectrum disorder

	Latency (ms)			Amplitude (μV)		
	Fz	Cz	Pz	Fz	Cz	Pz
Individuals with normal hearing						
Mean	372.88	372.80	375.52	7.50	9.80	8.81
SD	25.48	27.44	29.97	6.04	5.38	3.84
Individuals with ANSD						
Mean	412	413.08	422.64	4.32	6.40	6.04
SD	33.25	28.94	42.70	5.92	5.77	4.68

ANSD: Auditory neuropathy spectrum disorder; SD: Standard deviation

locations (Fz, Cz, and Pz) as within-subject factor and groups (normal and ANSD) as between subject factor on latency and amplitude of P300. The result showed a significant main effect of electrode location on latency ($F[96, 2] = 4.12$, $P < 0.05$) and amplitude ($F[96, 2] = 10.18$, $P < 0.001$) of P300. The main effect of group was also significant for both latency ($F[48, 1] = 24.78$, $P < 0.001$) and amplitude ($F[48, 1] = 4.99$, $P < 0.001$) measures. However, none of the two-way interactions were significant. Pair-wise comparisons with Bonferroni's corrections revealed the following: the amplitude of P300 was significantly more for Pz and Cz electrode locations when compared to Fz. There were no significant differences in the amplitude between Cz and Pz electrodes. None of the electrode pairs (Fz-Cz, Fz-Pz, and Cz-Pz) showed a significant difference for the latency of P300. Independent sample *t*-test showed a significant difference between the groups for all the electrode location (Fz, Cz, and Pz) for latency ($P < 0.001$) and amplitude ($P < 0.05$) except for the amplitude at Fz electrode site ($P > 0.05$).

To investigate the relationship between behavioral and neural measures, Pearson's product-moment correlation analyses were performed separately for both the group of individuals. There was a significant correlation between reaction time and the amplitude of the P300 peak at Cz electrode site ($r = -0.414$, $P < 0.05$) for individuals with normal hearing. None of the other correlations were significant.

Discussion

The study was conducted with an aim to investigate the neural processing of speech contrast in individuals with normal hearing and with ANSD. P300 for speech contrast /ba/-/da/ were recorded in an oddball paradigm. The RT and sensitivity were analyzed from the behavioral responses. Individuals with ANSD showed significantly longer reaction time and poorer sensitivity compared to individuals with normal hearing sensitivity. However, sensitivity was more than 80% in all individuals with ANSD. Moreover, robust P300 responses were present in 80% of individuals with ANSD.

In general, P300 waveform morphology of individuals with ANSD was similar to that of normal hearing participants but with some noticeable differences. Specifically, P300 amplitude was reduced, and latencies were prolonged in individuals with ANSD compared to the normal hearing group. P300 latency has been considered as the time taken to reach the perceptual decision that an informative event has occurred.[27,28] Kutas and Dale[29] observed that whenever P300 latency is unchanged and the reaction time is prolonged, then the prolongation of the reaction time is attributed to some aspect of response selection or execution rather than before it. On the other hand, when P300 latency and reaction time are both prolonged, then the effect is thought to reflect the difficulty encountered in stimulus evaluation. In the present study, both reaction time, as well as the latency of P300, is significantly prolonged in individuals with ANSD, indicating that the prolonged latency and reaction time are because of the difficulty in discriminating the speech sounds. P300 amplitude reflects the amount of information transmitted during the presentation of a stimulus.[30-36] The amount of information is assumed to have an inverse relationship with the participants' degree of uncertainty about having correctly perceived an event. In

the present study, the amplitude of P300 was significantly reduced in ANSD group, indicating increased uncertainty in evaluation and classification of the stimulus due to distorted peripheral input. In addition, correlational analyses revealed no significant correlation between latency and amplitude of P300 peak and behavioral reaction time. This indicates that there is no relationship between the behavioral response and the neural response.

Conclusion and Clinical Implication

To our knowledge, this is the first study to systematically report the auditory P300 results in individuals with ANSD. Results of the present study demonstrated that auditory P300 could be reliably recorded in the majority of individuals with ANSD, however, with the reduced amplitude and prolonged latency. The individuals with ANSD had poorer discrimination ability and longer reaction time compared to individuals with normal hearing sensitivity.

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Conflicts of interest

There are no conflicts of interest.

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