

Assessing the applications of cortical auditory evoked potentials as a biomarker in children with cochlear implants

Ismail Zohdi Mostafa, Mohamed Ibrahim Shabana, Amira Maged El Shennawy and Hoda Mahmoud Weheiba

ENT Department, Audiology Unit, Cairo University, Cairo, Egypt

Correspondence to Hoda Mahmoud Weheiba, ENT Department, Audiology Unit, Cairo University, 27 Soliman Basha St., Heliopolis, Cairo, Egypt
Tel: +01003455007

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Background

Cortical auditory evoked potentials (CAEPs) are noninvasive measures used to quantify central auditory system function in humans. More specifically, the P1–N1–P2 cortical auditory evoked potential has a unique role in identifying the central auditory system that has benefited from amplification or implantation. P1 reflects the maturation of the auditory system in general as it has developed over time.

Objective

The aims of this study were to assess the CAEP in children with cochlear implants compared with age-matched controls, to study the different variables affecting the results, and to compare the pattern of P1 CAEP in cochlear implant patients compared with that in those with hearing aids.

Methodology

Thirty-five hearing-impaired children (using cochlear implants) were compared with 20 age-matched and sex-matched children with normal hearing. In both groups, P1 CAEP latency and waveform morphology were recorded using free-field auditory stimulation with tone bursts at 500 and 2000 Hz at 100 dB sound pressure level in two sessions that were 6 months apart.

Results

Children using cochlear implants exhibited prolongation of P1 latencies, indicating an overall delay in maturation when compared with that in children who could hear normally. P1 CAEP latency and amplitude improved significantly after 6 months of device use.

Conclusion

Standardized age-appropriate normative data on P1 CAEPs in the pediatric Egyptian population could be used to determine implantation or amplification results.

Keywords:

children, cochlear implant, cortical auditory evoked potentials, free field, P1

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Introduction

Cortical auditory evoked potentials (CAEPs) are non-invasive measures used to quantify central auditory system function in humans. More specifically, the P1–N1–P2 CAEP has a unique role in identifying the central auditory system that has benefited from amplification or implantation. P1 reflects the maturation of the auditory system in general as it has developed over time [1].

CAEPs are not widely used as a clinical biomarker, especially in very young children, because of the difficulty in recording them. Indeed, the use of tone bursts through hearing aids or cochlear implants on using CAEP as a biomarker offers the possibility to evaluate many more frequencies and louder intensities compared with other tests based on a click as a stimulus [2].

On using P1 to assess patients, it may be difficult to make sufficiently audible sounds when testing patients with severe to profound hearing loss, and, therefore, no P1

response to stimuli is observed. Moreover, Nash *et al.* [1] performed P1 testing before cochlear implant or hearing aid fitting in children with severe to profound hearing loss and revealed no response to auditory stimulation.

By measuring the responses of the central auditory system to amplified sound we can learn more about the effects of hearing loss and amplification on the central auditory system and, in turn, improve our understanding of the science underlying auditory rehabilitation [3].

Because P1 latency varies as a function of chronological age, it can be used to infer the maturational status of auditory pathways in children. Of particular interest are children with significant hearing loss. P1 latency is considered as a measure of central auditory development in patients with hearing aids or cochlear implants. Sharma *et al.* [4] have described the use of P1 latency and CAEP waveform morphology as biomarkers for the development of the central auditory pathway in patients with hearing loss with conventional hearing aids or cochlear implants.

P1 latency can provide the clinician with an objective tool to evaluate whether acoustic amplification in hearing-impaired patients provides sufficient stimulation for normal development of the central auditory pathway. This tool when combined with traditional audiological and speech language assessment can provide information on whether to provide the patient with a cochlear implant after an appropriate hearing aid trial [5].

Many researchers worldwide have suggested that there is a need for further research examining the clinical feasibility of the use of P1 latency as an objective tool to evaluate the normal development of functions of the central auditory pathway in children with hearing impairment [6–10]. Thus, there is a great need for objective assessment of central auditory development in children after implantation or fitting of a hearing aid.

Methodology

A total of 35 children with cochlear implants and 20 children with normal hearing of both sexes (33 boys and 22 girls) were included in this study. The study was conducted at the Audiology Unit of Kasr El Aini Hospital, Cairo University. The study group was divided into patients and controls whose ages ranged at the time of testing from 3 to 16 years. The patients (children with cochlear implants) had severe to profound hearing loss and had undergone implantation between the ages of 3 and 7 years with the Nucleus cochlear implant 24 (Bardissi Company, Australia) with speech processors of either Sprint/Espirit or Freedom device types (using the ACE speech processing strategy); seven children were implanted with Medel-Sonatai (Amico Company, Austria) with an Opus 2 speech processor (using the FS4 speech processing strategy). All patients were subjected to full history taking, otological examination, and basic audiological evaluation; aided warble tone response thresholds in sound field were assessed using a two-channel audiometer (GSI model 1761, Amico, Egypt; for patients only), immittance testing was performed using GSI 33 (Grason Stadler middle ear analyzer version II, Amico, Egypt), and the P1 CAEP test was performed using Amplaid model MK12. History focused on age in years, age at onset of deafness, duration of deafness, age at implantation, history of consanguinity, and possible etiology of hearing loss (through prenatal, natal, post-natal, family, and previous history). Personal data included sex, residence, social standard, educational level of mother, and father's occupation.

Participants were seated comfortably in a sound-treated room, and CAEPs were recorded in each participant using a cochlear implant device. Children with cochlear implants were examined in two scheduled sessions after activation. Second session was 6 months after the first session. One channel recordings were obtained using ipsilateral electrode montages. The active (noninverting) electrode was placed on the vertex (Cz), whereas the reference (inverting) electrode (M1/M2) was placed on the right or left mastoid in normal participants and on the

contralateral mastoid to the implanted side in patients with cochlear implants (to minimize stimulus artifacts); the ground electrode was placed on the forehead (Fz). Electrode impedance was kept below 5 Ω .

P1 obligatory cortical auditory responses were recorded in response to tone bursts at 500 and 2000 Hz, applied through a loudspeaker connected to an amplifier to increase its output, placed at an angle of 90° to the side of the patient at a distance of 1 m. The stimuli were presented at a rate of 1/s and at a level of 100 dB sound pressure level. It was confirmed with each child that this was at a loud but comfortable listening level.

Responses were recorded using filter settings of 0.1–50 Hz. The time window was taken as 500 ms. At least two runs of 200 response sweeps were collected for each participant. P1 morphology was evaluated and waveforms were judged replicable on the basis of visual inspection of the recordings. P1 was defined as the first robust positivity in the waveform in the latency range from 40 to 300 ms, with waveform repeatability. Latency and amplitude values were determined for P1. P1 latency is measured at the center of the peak as the time in ms from stimulus onset to the peak. P1 amplitude measures were made from baseline to peak.

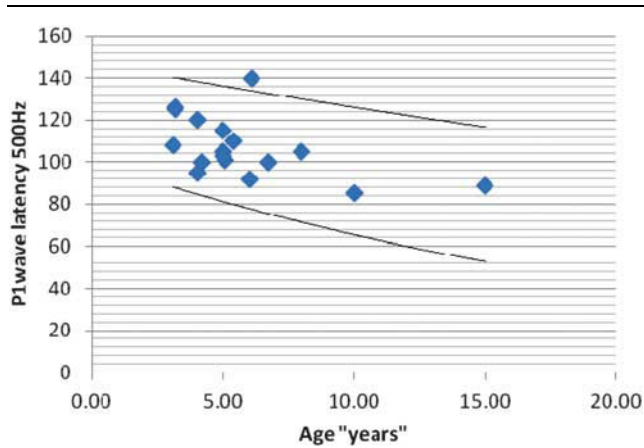
Normative values were estimated, and upper and lower 95% confidence limits were estimated using a linear regression model and were represented by continuous lines. Quantitative (numerical) data were presented as mean and SD values. Student's *t*-test was used to test significance for the comparison between the means of two groups. Analysis of variance was used to compare the means of more than two groups. Paired *t*-tests were used for comparisons after 6 months of follow-up. Qualitative (categorical) data were presented as numbers and percentages. The χ^2 -test was used for comparison of qualitative data. Pearson's correlation coefficient (*r*) was used to determine significant correlations among the different quantitative variables. The significance level was set at *P* less than 0.05, and *P* less than 0.01 was considered highly significant.

Results and discussion of the P1 cortical

auditory evoked potential test

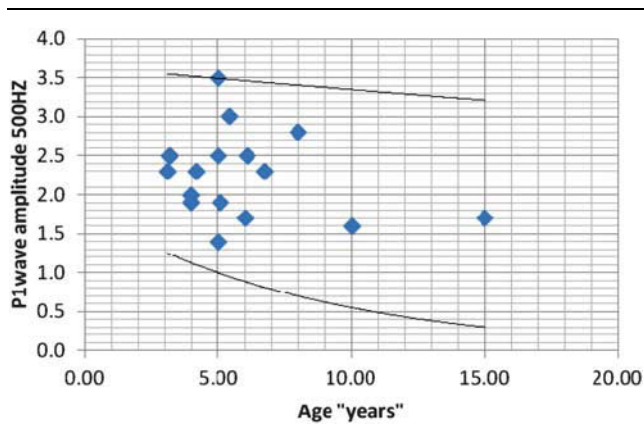
Fifty-five children of both sexes (33 boys and 22 girls) were examined in this study. Their ages ranged from 3 to 16 years, with a mean age of 5.8 ± 2.8 years. The cochlear implant group was divided into two subgroups according to the age at implantation: 20 children received implants above the age of 5 years, and 15 children received implants below 5 years of age, of whom only five received implants below or at 3 years of age. The fathers of most children in the cochlear implant group were employed (40%) and the mothers had middle school education (71.4%). Most children with cochlear implants underwent regular speech therapy sessions (71.4%). The most common cause of hearing loss was a hereditary etiology (48.6%) (Figs 1–3).

Figure 1



P1 latency at 500 Hz in relation to chronological age for the normal hearing group. The solid lines are the 95% confidence limits for the normal development of the P1 response.

Figure 2



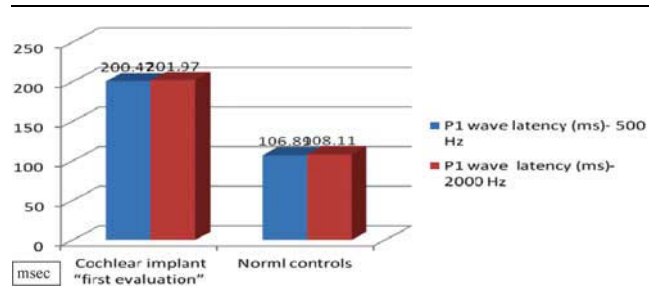
P1 amplitude at 500 Hz in relation to chronological age for the normal hearing group. The solid lines are the 95% confidence limits for the normal development of the P1 response.

Tests results for children who could hear normally

Visual inspection indicates that latencies decrease rapidly in the first decade of life and then decrease more gradually in the second decade of life. These results were consistent with those reported by Ponton and colleagues [11,12]. In addition, Cunningham *et al.* [13] showed that the P1 latency decreased significantly from 13–15 to 19–27 years of age.

Table 1 shows a negative correlation between age and P1 wave latency as well as P1 amplitude at 500 and 2000 Hz in normal hearing controls, which was only of statistical significance as regards P1 latencies (not P1 amplitudes) – that is, the P1 latency was affected by age and showed signs of maturation with increasing age (latencies decreased with increasing age). Such an improvement in scores with age was attributed to the maturation of the auditory system [14]. Similarly, Sharma *et al.* [12] found no age-related changes in the amplitude of N1, although they did identify a correlation between increasing age and an increase in the reliability of N1 elicitation.

Figure 3



P1 wave latency in the cochlear implant 'first evaluation' group versus the normal hearing group.

Table 1 Correlation between age and P1 wave latency and amplitude in the normal control group

	P1 wave latency (ms) (500 Hz)	P1 wave latency (ms) (2000 Hz)	P1 wave amplitude (µV) (500 Hz)	P1 wave amplitude (µV) (2000 Hz)
Age in years				
R	-0.508	-0.500	-0.249	-0.121
P	0.032	0.035	0.318	0.631

Comparison between cochlear implant and normal hearing groups

There was a highly statistically significant difference between the means of the first and second aided audiologic evaluations with the cochlear implant device. There was a highly statistically significant difference between the cochlear implant group and the normal hearing group as regards both P1 latencies and amplitude at the tested frequencies (500 and 2000 Hz) in the first evaluation. In general, the relation between P1 latency in normal children and that in cochlear-implanted children is consistent with that reported in the literature on cochlear implantation in children who were deaf for 4.5 years or more. These children had a delayed latency of the P1 cortical evoked potential, compared with age-matched children who could hear normally [15].

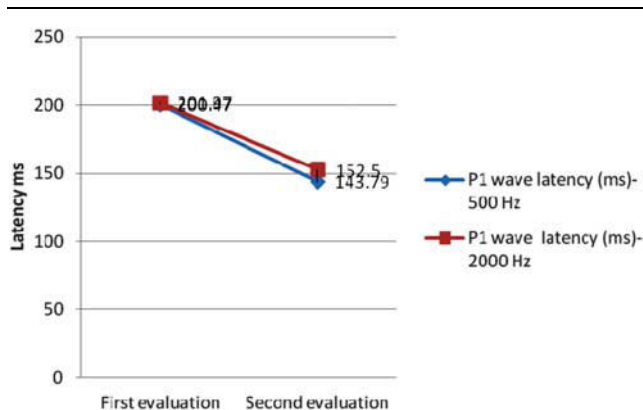
In the present study, P1 showed normal waveform morphology with absent deprivation negativity and polyphasic morphology, yet none of the patients from the study group developed the PI–NI–P2 complex. This is consistent with the results of the study by Ponton *et al.* [15], in which the normal N-1b peak failed to emerge in virtually all of the tested children with cochlear implants. They postulated that the persistent immaturity of the axons of the superficial layer leads to persistent negative effects on the generation of N-1 b and, consequently, on the morphology of the auditory evoked potentials. According to Sharma *et al.* [12], the waveform for the children is dominated by a largely positive P1, followed by broadly negative N1b. Likewise, there was a statistically significant difference between the cochlear implant group and the normal hearing group (6 months after their initial evaluation) as regards both P1 latencies at the tested frequencies (500 and 2000 Hz) and P1 amplitude (2000 Hz only in the second evaluation). Both late-implanted and early-implanted subgroups showed a statistically significant difference compared with controls

during the first evaluation and after 6 months. This is expected in the late-implanted subgroup because of reorganization of the auditory cortex, whereas in the early-implanted subgroup these results reflect limited plasticity, which may be because of inconsistent implant use or because only five of 15 children with early implants were implanted at or below 3 years of age, and according to Sharma *et al.* [14], only children under 3.5 years of age showed age-appropriate P1 latencies by 6 months after implantation.

There was a highly statistically significant difference between P1 wave latency and amplitude during the first and second evaluations of the cochlear implant group (Fig. 4). Improvement in P1 latencies with a cochlear implant depends on the amount of prior auditory deprivation and cochlear implant experience [9]. CAEP latencies reduce with cochlear implant experience in children, particularly in children who underwent early implantation [14,16]. In the present study, as the duration of device use increases the latency of P1 decreases (Fig. 4). From the above results one can conclude that the duration of implant use is obviously critical for the development of the central auditory pathway following implantation.

The present study showed no statistically significant difference between P1 wave latency and amplitude across both frequencies (500 and 2000 Hz) in the first and second

Figure 4



Difference between P1 wave latency during the first and second evaluations in the cochlear implant group.

evaluations of the cochlear implant group – that is, there was no effect of frequency change on P1 test results. There was a statistically significant negative correlation between the age at hearing loss and P1 wave latency and amplitude during the first and second evaluations, and there was a trend toward shorter latencies and decreased amplitudes in the postlingual hearing loss subgroup (acquired deafness), followed by the perilingual and prelingual hearing loss subgroups (congenital deafness), of the cochlear implant group (Table 2). In irregular hearing aid users, P1 latencies before implantation were significantly different during the first and second evaluations, whereas in regular hearing aid users, no significant differences were found in P1 latencies between the two recording sessions (Table 3).

Table 3 shows that in irregular hearing aid users, P1 latencies in the second evaluation are highly significantly different from those in the first evaluation ($P < 0.001$) before implantation, whereas in regular hearing aid users, no significant differences were found in P1 latencies between the two recording sessions ($P = 0.643$). It was observed that latencies at the first evaluation in regular hearing aid users were shorter than those in irregular users. However, at 6 months after implantation, both subgroups showed the same latencies. As a consequence, the latency difference between the first and second recordings was greater for irregular than for regular hearing aid users before implantation. Children with several years of experience with using conventional amplification devices showed rapid progress in auditory skills following cochlear implantation [9].

There was no statistically significant difference in both P1 latencies and amplitude between the early-implanted and late-implanted subgroups as regards the age at implantation during both the first and second evaluations. This could be because of the fact that many of the children in the present study experienced a period without any preimplant stimulation with hearing aids. However, the subgroup receiving implants below 5 years of age had better results (shorter latency and smaller amplitude) than that receiving implants above 5 years of age. A sensitive period was also suggested by Ponton *et al.* [11], which was estimated to be 4.5 years. They indicated that the auditory system does not mature without stimulation. Nonetheless, the auditory system retains its plasticity during the period of deafness, as the

Table 2 Relation between age at onset of deafness and P1 wave in the cochlear implant group

	Cochlear implant group						
	Prelingual <2 years (N=28)		Perilingual 2–5 years (N=5)		Postlingual >5 years (N=2)		P-value
	Mean	SD	Mean	SD	Mean	SD	
P1 latency (ms) – first evaluation (500 Hz)	209.89	58.00	181.0	33.84	127.0	35.36	0.088
P1 latency (ms) – first evaluation (2000 Hz)	213.57	59.79	173.5	40.23	125.0	35.36	0.054
P1 amplitude (μV) – first evaluation (500 Hz)	4.06	2.12	3.75	1.44	1.75	0.35	0.296
P1 amplitude (μV) – first evaluation (2000 Hz)	4.04	2.26	3.80	1.38	2.05	0.35	0.446
P1 latency (ms) – second evaluation (500 Hz)	150.15	58.27	120.6	45.46	116.0	41.8	0.440
P1 latency (ms) – second evaluation (2000 Hz)	156.41	53.16	144.4	20.42	120.0	36.77	0.567
P1 amplitude (μV) – second evaluation (500 Hz)	2.88	1.71	2.26	1.11	1.15	0.49	0.298
P1 amplitude (μV) – second evaluation (2000 Hz)	3.34	2.54	2.16	0.59	1.25	1.06	0.330

Table 3 Relation between preimplant hearing amplification and P1 wave latency during the first and second assessments in the cochlear implant group

Preimplant hearing amplification	Irregular hearing aid users				Regular hearing aid users			
	First evaluation		Second evaluation		First evaluation		Second evaluation	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
P1 wave latency (ms) (500 Hz)	180	50.81	120	33.47	125	63.56	123	67.85
P1 wave latency (ms) (2000 Hz)	185	48.62	130	29.45	142	68.15	130	61.23
<i>P</i> -value	<0.001				>0.05			

reintroduction of stimulation by the cochlear implant leads to the resumption of the normal maturational sequence. The patients in the study by Ponton *et al.* [11] showed normal latency after 5 years of implantation. In the case of P1 amplitude, all of the patients older than 5 years reached normal amplitude. The results of the study by Ponton *et al.* and our results support the negative correlation found between duration of implantation and P1 latency and amplitude, especially for a duration of hearing loss of more than 5 years [11].

The present study showed that there were factors affecting P1 latency and amplitude other than age at implantation, which was reported by other studies to be the major factor affecting P1 CAEP results. These factors include pre-implant rehabilitation, age at onset of hearing loss, and duration of device use. Although age at implantation in the present study showed no significant effect on P1 wave results, these results could be attributed to the small number of children (only five) implanted at or below 3 years of age in this study. According to Sharma *et al.* [14], children under 3.5 years of age showed age-appropriate P1 latencies by 6 months after implantation. Other factors showed no statistically significant correlation with either P1 latency or amplitude. These factors included etiology of hearing loss, mother's education, father's occupation, regularity of speech sessions, and history of consanguinity. However, there was a tendency, although statistically insignificant, toward shorter P1 latency and smaller amplitude with highly educated mothers, longer duration of device use, and younger age at implantation. Stimulus frequency had no effect on either P1 latency or amplitude. Children with cochlear implants showed prolongation of P1 latencies with overall delayed maturation. Latency and amplitude of P1 CAEPs improved significantly after 6 months of device use.

In conclusion, the P1 CAEP test has been standardized in the pediatric Egyptian population and it can be applied as a tool in the diagnosis of central processing disorders in children with hearing impairment fitted with cochlear implants or hearing aids. The P1 CAEP test can be used to monitor changes in the performance of children in response to sound and auditory training.

Clinical implications of the P1 cortical auditory evoked potential test

The absence of CAEPs while wearing high-powered hearing aids facilitates an early decision on cochlear implant candidacy. Decreases in P1 latency can provide an objective measurement of adequate amplification from

a child's hearing instrument. Therefore, this would assist in the difficult decision making process of whether to implant in difficult to test populations, such as infants. If latency measurements do not decrease to within the age-appropriate range during the hearing aid trial, then this would suggest they are not receiving sufficient stimulation and a cochlear implant should be considered [14,16]. Likewise the presence of robust CAEPs to moderate-level speech sounds (65 dB sound pressure level) can lead to the decision to continue with bilateral hearing aids rather than a referral for cochlear implant candidacy evaluation.

Limitations of the current study

The main limitations of this study are related to the level of noise in the electrophysiological waveforms, especially on using cochlear implant devices. Stimulus artifacts can make it difficult to identify CAEP peaks in a child with a cochlear implant [14,16,17].

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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