A Clinical Study of Cortical Auditory Evoked Potentials in Cochlear Implantees

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Abstract Normal maturation of central auditory pathways is a precondition for the optimal development of speech and language skills in children. The temporal cortex gets acoustically tagged due to auditory stimulation and important changes occur in the higher auditory centers due to hearing loss of any type and degree. Cochlear implantation increases auditory sensitivity by direct electrical activation of auditory nerve fibers, enabling phonemic awareness, discrimination and identification ultimately yielding speech understanding. Early implantation stimulates a brain that has not been re-organized and will therefore be more receptive to auditory input and greater auditory capacity. Cortical potentials have enabled us to objectively study this phenomenon. To assess the outcomes of Cochlear implants on the auditory cortex by analyzing cortical auditory evoked potentials (CAEPs) in the habilitation period. This prospective clinical study was performed in 30 pre-lingual candidates with varied etiology of deafness who underwent cochlear implantation at our institute over the last 1 year. The study group had two cohorts (group-1: 0–8 years and group-2: 8–15 years) which included candidates with normal inner ear and no syndromes or handicaps. All implantees in the study group underwent CAEP testing at 6 months and 1 year post-implantation and comparison of the CAEP wave parameters (P1 amplitude, P1 latency and P1 morphology) were done between the two cohorts. In children Implanted early (group-1) there was an early onset rapid increase in P1

amplitude along with a decrease in P1 latency during the follow-up period. Significant change in the CAEP wave morphology was also notable in group-1 unlike in group-2. Candidates who experienced less than 3 years of auditory deprivation before implantation showed P1 latencies, which fell into the range of normal children within 6 months of habilitation. Children with more than 6 years of auditory deprivation, however, generally did not develop normal P1 latencies or morphology even after 1 year of habilitation. The overall outcome with CAEP was much better in group-1 as compared to group-2 and the observations were in comparison with the existing world literature. The advent of CAEP has objectively proved beyond doubt that there is a critical age for stimulating the auditory brain via cochlear implantation. There is considerable evidence for a developmental sensitive period, during which the auditory cortex is highly plastic. If sensory input is deprived to the auditory system during this sensitive period, then the central auditory system is susceptible to large scale reorganization. Restoring input to the auditory system by Cochlear Implant at an early age can provide the stimulation necessary to preserve the auditory pathways. However, if auditory input is not restored until after this developmental period, then the cross-modal reorganized pathways may exhibit abnormal functional characteristics as observed in recorded P1 amplitude, latencies and morphologies of CAEPs.

Keywords Cochlear implants · Central auditory processing · Cortical auditory evoked potentials (CAEPs)

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Introduction

The need for early effective intervention for young children with profound hearing loss involves the use of objective

methods to determine cochlear implant candidacy and for optimizing cochlear implant settings during habilitation. Cortical auditory evoked potentials (CAEPs) can be used to objectively assess hearing sensitivity, central auditory processing, and neural encoding of speech sound [1]. Recent world literature has predicted that CAEPs are essential for objectively predicting Cochlear implant outcomes as well as improving candidacy and implant programming. The P1 cortical evoked potential has been established as a biomarker for assessing the maturation of the central auditory system in children. The gold-standard of this approach is to determine whether speech sound at conversational levels are effectively transduced by the child's hearing apparatus and detected at the level of the auditory cortex [1].

CAEP reflects recurrent cortical activity mediated by cortico-thalamic loops. These recurrent loops mediate subsequent cortico-cortical projections that may be disrupted after auditory deprivation. Restoring function to these modulatory projections may be possible with cochlear implantation, as long as the central auditory system remains maximally plastic and the effects of neural degeneration have not completely taken effect [2]. The P1 is a robust, easily identifiable positive response occurring at around 100–300 ms (milliseconds) post-implantation, depending on the age of the child. The latency of the P1 wave is thought to reflect the sum of synaptic transmission delays through the central auditory pathways. Latency changes in the P1, as a function of increasing age and reflects the maturation of central auditory pathways occurring in response to auditory stimulation [3].

In infants with normal hearing, the average latency of P1 waveform is about 300 ms. A rapid decrease in latency occurs during the first few years of life; a normal P1 latency for a 3 year old is about 125 ms. A smaller decrease in P1 latency is expected from that time on and by the age of 15 years, the average P1 latency decreases to approximately 95 ms. The mean P1 latency in middle-aged adults is approximately 60 ms. This variation of P1 latency according to age can be used to infer the developmental status of the central auditory pathways and can easily be tracked in individuals over time. The latency and morphology of the P1 will vary depending upon the amount of time the central auditory system has been without adequate auditory input. The period during which the central auditory system remains most plastic is for about 3.5 years after birth, after which the plasticity reduces exponentially until it is negligible at 8 years and beyond. In general, a child who receives stimulation via cochlear implant within the first 3.5 years of life will have P1 latency that enters the normal range within the first 6 months after implant activation [3].

If the auditory system does not receive adequate stimulation within 8 years after birth, it is likely that the higher

order auditory cortex gets reorganized due to neural scavenging. CAEP latencies generally remain abnormal and the overall chances for normal speech and language development, while using a cochlear implant decreases significantly. This may be due to a lack of activity in the infra-granular layers of the cortex in response to sound and de-coupling of communication between the primary and secondary auditory areas [4]. Auditory deprivation also causes morphological changes to the P1 waveform. Early-onset auditory deprivation relates to waveform negativities, polyphasic morphology and low amplitude waveforms have often been observed in children who have not received adequate input to their central auditory pathway within the optimal time. Taken together, these results support the conventional wisdom that early electrical stimulation is necessary for normal sensory development of the auditory cortex [2].

Materials and Methods

This prospective clinical study was performed in 30 pre-lingual deaf candidates with varied etiology of deafness, who underwent cochlear implantation at our institute between July 2010 and June 2011. The study group included children with normal inner ear anatomy and no associated syndromes or handicaps. This research was approved by the institutional ethical research review board in July 2010 and an informed written consent from the parents/legal guardians of the study group was taken prior to their inclusion in the study. Candidates were placed into two categories based on their age at implantation.

All chosen candidates were evaluated with CAEP prior to implantation. Comparison of the CAEP parameters were made with respect to a standardized normative value for the CAEP, recorded in children with normal hearing as documented in literature [3]. All children were screened for normal speech, language and neurological development and referrals were made to the audiologist, speech/language pathologist, ophthalmologist, occupational therapist and the child psychologist for assessment of higher mental functions and intelligence quotient. All the participants in the study group were sent to meet the auditory-verbal habilitation therapist at our institute prior to surgery, to make them adapt to the habilitation program. All the children were vaccinated against meningitis 2 weeks prior to surgery.

All these children received Cochlear implants as per standard protocols and they were 'Switched-on' and habilitated at our Cochlear implant clinic for a period of 1 year. CAEPs were tested in all these implantees in sequential intervals of 6 months and 1 year, as an additional research investigation prior to implantation and in conjunction with the usual sequential post-implant mapping

schedules and electrophysiological tests employed by the habilitation team during the habilitation period.

CAEP waveforms were recorded in response to synthesized speech syllables of /m/, /g/, & /t/. The stimuli were presented via a loudspeaker placed at an angle of 0 (zero) degree in front of the child at a distance of 5 feet. Speech processors were set to the children's usual program settings. Subjects were seated comfortably in a reclining chair placed in a sound booth and they watched a video tape or cartoon on a TV monitor placed in front of them in the sound booth. The video tape audio was on mute. Evoked potentials were collected using Cz as the active electrode. Cz refers to the vertex midline placement. The reference electrodes were placed on the mastoid and a ground electrode on the forehead. Averaging was automatically suspended by the recording computer [5]. The recording window included –200 ms pre-stimulus time to +600 ms post-stimulus time. Incoming evoked responses were analog filtered from 1 to 30 Hz. Approximately 300 response sweeps were collected for each subject. The test session including electrode application and evoked response recording, lasted for about 25 min at each schedule. Sweeps greater than $\pm 30 \mu\text{V}$ were rejected off-line and the remaining sweeps were averaged to compute a final grand-averaged waveform for the individual subject. P1 was defined as the first robust positive cortical auditory evoked potential waveform in the 50–150 ms range [5]. P1 data including amplitudes, latencies and morphology were meticulously collected for all the implantees at 6 months and 12 months after 'Switch On' of the device (Fig. 1).

Observations and Results

All candidates in the study group were evaluated with CAEP prior to implantation during which they were found

to have no significant recognizable waveforms, indicating no auditory cortical activity (Fig. 2). Group-1 had 21 candidates in the age range of 1–8 years (mean age = 3.2 years, male:female = 13:8). These were categorized as 'Early' implanted children. Their mean age of auditory deprivation prior to implantation was 1.5 years. Their mean duration of hearing aid use prior to Cochlear implantation was 1.7 years and their mean average age at implantation was 3.2 years. In group-2, nine pre-lingual candidates were selected. Their age range was 8–15 years (mean age 10.4 years, male:female = 5:4). These were categorized as 'Late' implanted children. Their mean age of auditory deprivation prior to implantation was 8.3 years. Their duration of hearing aid use prior to implantation was 7.7 years. The average age at cochlear implantation in this group was 11.2 years.

CAEPs after cochlear implantation were recorded with the standardized equipment (HEARlab H1000-ACA, 2010, USA) (Fig. 3). All CAEPs were recorded by the same experienced implant audiologist, sequentially at 6 months and 12 months of habilitation respectively. The parameters analyzed were:

- Amplitude of P1 wave (μVs).
- Latency of P1 wave (ms).
- Morphology of P1 wave (good, distorted or polyphasic).

All the above measurements were recorded by giving a speech stimuli /g/, /t/, /m/ via a constant acoustic stimulation through the implant. Among them, the /g/ stimuli was found to provide the most robust P1 wave forms and hence this stimulus was taken as the constant for comparison of the P1 wave morphology among both the groups in our study. Data was collected for the various parameters and was analyzed using the paired student 't' test with SPSS 17.0 software by our bio-statistician.

Group I (age 1–8 years, $n = 21$)

The mean average amplitude of P1 wave was $7.17 \mu\text{V}$ at 6 months post-implant and $9.49 \mu\text{V}$ at 12 months post-implant. The above improvement in the amplitude by $2.32 \mu\text{V}$ over a period of 6 months in group-1 was statistically significant (P value < 0.050). The mean average latency of P1 wave was 156.2 ms at 6 months post-implant and 119.7 ms at 12 months post-implant. The above reduction in the latency of the P1 wave with time by 35.5 ms was also statistically significant (P value < 0.031). This reduction in latency shows that electrical stimulation via the cochlear implant is more conducive with the habilitation process and with progress of time. The above findings also support the world literature, which suggests that CAEPs are best elicited from 1 year of Cochlear implant use onwards

Fig. 1 Test set-up for CAEP in a Cochlear implantee

Fig. 2 Pre-implant CAEP **Fig. 3** Post-implant CAEP at 1 year

and generally are recorded robustly in implantees with long duration of implant use [6].

Visual analysis of P1 wave morphology at 6 months and 12 months recorded the following observations. Six candidates had good morphology at 6 months and continued to do so at 12 months. Nine candidates had distorted wave morphology at 6 months and two of them had improved to obtain good morphology at 12 months. Six candidates had polyphasic (poor) waveforms at 6 months and two of them improved to have good morphology at 12 months. The above results showed that wave morphology significantly improves with time. This was in conjunction with the relevant literature which suggests that further improvement of wave morphology happens, even after 12 months of implantation [6].

Group-2 (age 8–15 years, $n = 9$)

The mean average amplitude of P1 wave was $3.75 \mu\text{V}$ at 6 months post-implant and $5.78 \mu\text{V}$ at 12 months post-implant. The above improvement in the amplitude by

$2.03 \mu\text{V}$ over a period of 6 months in group 2 had moderate statistical significance (P value = 0.034). The mean average latency of P1 wave was 267.7 ms at 6 months post-implant and 232.6 ms at 12 months post-implant. The above reduction in the latency of the P1 wave over time, by 35.1 ms (P value < 0.046), shows that impulse transmission via the Cochlear implant is more conducive with implant usage and progress of time.

Visual analysis of P1 wave morphology at 6 months and 12 months in group-2 showed the following observations. Four candidates had good morphology at 6 months and continued to do so at 12 months. Two candidates had distorted wave morphology at 6 months and no further change after 12 months. Three candidates had polyphasic (poor) waveforms at 6 months and none of them improved at 12 months. The above results showed that, as the age of the implantee progresses, no significant improvement in wave morphology was found over time, even after 12 months of implantation. This reflects upon the guarded outcomes which may be encountered in late implanted

candidates in whom the eventual performance with cochlear implantation may be sub-optimal to their anticipated results.

On further analysis of the latencies and amplitudes between the groups-1 and -2, the following observations were made and inferences derived. The mean average difference in the P1 wave amplitude between the two groups at 6 months was 3.42 μ V and at 12 months was 3.71 μ V. Thus early implanted children (group-1) had maintained a better amplitude of the P1 wave at both schedules of testing, which was statistically significant ($P < 0.05$). This helps us to infer that age can inversely influence the amplitude of the P1 wave (higher the age at implantation poorer the amplitude). We also observed that, in both groups-1 and -2, the P1 wave amplitudes were higher (mean average increase by $2.18 \pm 0.25 \mu$ V, $n = 30$) at the final 12 month schedule than at the previous 6 month schedule. This helps us to conclude that after cochlear implantation, auditory stimulation via the implant influences the amplitude of the P1 wave over time (more the duration of implant use better the amplitude), possibly due to the neural re-organization which takes place over time at the higher auditory centers. In summary P1 wave amplitudes were found to be more robust in group-1 as compared to group-2 and this trend persisted till the end of the follow-up period of 1 year and further-on.

On analyzing the P1 wave latencies between the groups-1 and -2, the following observations were noted. The mean average difference in the latency between the two groups at 6 months was 111.5 ms and at 12 months was 112.9 ms. Early implanted children (group-1) had maintained a shorter latency for the P1 wave at both schedules of testing, which was statistically significant ($P < 0.017$). This observation suggests that age is the critical factor which influences the P1 waveform latency (older the age at implantation, longer is the latency period for P1 wave). We also observed that, in both groups-1 and -2, the P1 wave latencies reduced (mean average fall by 37.2 ± 0.7 ms, $n = 30$) at the final 12 month schedule than at the previous 6 month schedule. This result highlights the fact that implant driven electrical stimulation of the auditory cortex, helps in faster impulse transmission, which improves with implant use and habilitation over time. We infer a vital point from this result that, even though the latencies in older age groups may reduce over time with implant usage, but they may still not fall within the normative range, as noted in the early implanted individuals.

A positive non-parametric correlation over time was recorded overall in both the groups ($n = 30$) on comparison of the P1 wave amplitude versus latency over time ($r = 0.34$ at 6 months and $r = 0.67$ at 12 months), which helps us to infer that the amplitude and latency show improved correlation with time and hence longer the period

of implant usage, better is the auditory cortical neural activity.

On comparison of P1 wave morphology in the two groups, it was found that 40 % had good morphology in group-1 ($n = 21$) at 6 months, which improved to 49 % by 12 months, while in group-2 ($n = 9$), 44 % had good morphology at 6 months and there was no further improvement noted at 12 months in this group. This supports the world literature that cortical potentials evolve slowly over time and improve over years of implant use. This phenomenon is more vivid in early implantees, while a few late implantees may never develop good morphology even after many years of implant use.

Thus CAEPs objectively reiterate the significance of the “Critical age” for implantation and emphasize the phenomenon of neural plasticity, neural scavenging and cerebral re-organization in auditory deprived children beyond this critical age [6].

Discussion

Congenital deafness leads to atypical organization of the auditory nervous system. However, the extent to which auditory pathways reorganize during deafness is not yet fully understood. In humans, the CAEP provides information about maturation of auditory pathways terminating in auditory cortex, and reflects recurrent cortical activity mediated by cortico-thalamic loops. These recurrent loops mediate subsequent cortico-cortical projections and may be disrupted after auditory deprivation. Restoring function to these modulatory projections may be possible with cochlear implantation, as long as the CAS remains maximally plastic and the effects of degeneration have not completely taken effect [7].

The latency of the P1 CAEP has been used to examine cortical maturation in children with cochlear implants. Sharma et al., examined P1 latencies in children with Cochlear implants and revealed prolonged latencies as compared to normal-hearing children. Further analysis revealed that P1 latency appears to continue a developmental progression after implantation over few years. In normal-hearing children the latency of the P1 component of the cortical evoked response to sound varies as a function of age and thus, can be used as a biomarker for maturation of central auditory pathways. In normal-hearing newborns the mean P1 latency is approximately 300 ms. Over the first 2–3 years of life there is a rapid decrease in latency (to approximately 125 ms at age 3 years) and then a more gradual decrease into the second decade of life. The mean P1 latency in normal-hearing adults (aged 22–25 years) is approximately 60 ms. Since, P1 latency varies as a function of chronological age, it can be used as a biomarker to infer

Table 1 Descriptive analysis of CAEP waveforms ($n = 30$)

Groups	Duration (months)	Mean average amplitude (μ V)	Mean average latency (ms)	Good morphology	Distorted morphology	Poly phasic morphology
Group-1 ($n = 21$)	6	7.17	156.2	6	9	6
	12	9.49	119.7	10	7	4
Group-2 ($n = 9$)	6	3.75	267.7	4	2	3
	12	5.78	232.6	4	2	3

the maturational status of auditory pathways in infants and children [8].

Children who are implanted after the age of 7 years almost always showed evidence of abnormal central auditory maturation when examining the latency of the P1 response. However, if implantation occurs very early in childhood, then the P1 latency typically followed a normal developmental trajectory. These results support the conventional wisdom that early stimulation is necessary to support normal sensory development. Understanding the physiological mechanisms associated with both normal and abnormal sensory development may help us better understand and plan for successful rehabilitation in children with Cochlear implants [9].

Dorman et al. assessed the P1 latency in 245 congenitally deaf children fit with Cochlear implants following various periods of auditory deprivation. They concluded that if children experienced lesser than 3.5 years of auditory deprivation before implantation, their P1 latencies fall into the range of normal children following 3–6 months of electrical stimulation. Children who had experienced greater than 7 years of auditory deprivation, however, generally did not develop normal P1 latencies, even after years of stimulation via the implant and their waveforms were markedly abnormal. The results of our study are in conjunction with this study by Dorman et al. [3].

The P1 latency of the cortical evoked potential could be a useful diagnostic tool for determining the development of the auditory system. Amy Nash et al. used the latency of the P1 wave of CAEP, to study the development of the central auditory pathways in over 200 hearing-impaired children who were fitted with hearing aids and/or cochlear implants. Their observations have been very similar to the inferences we have derived from our study [10].

Central auditory pathways are maximally plastic in response to auditory stimulation for a period of about 3.5 years in early childhood. If stimulation is delivered within that period, then P1 latency and morphology reach age-normal values within 3–6 months following the onset of stimulation. However, if stimulation is withheld for more than 7 years, then most children exhibit a delayed P1 latency and abnormal P1 morphology, even after years of implant use. The different morphology of the response, suggests that the P1 measured in normal hearing children

and early implanted children has a different generator than the response labeled as ‘P1’ in late implanted children. This outcome suggests reorganization of auditory cortex in the face of long-term auditory deprivation [3, 11].

In our study, overall group-2 implantees have shown poorer measurements of CAEPs than in group-1. The mean average amplitude was found to be lesser in group-2 than in group-1 and the mean average latency was found to be more than in group-1. The total number of good morphologies recorded in group-2, were significantly lesser than in group-1. These results objectively prove that the critical age and neural plasticity are important factors influencing central auditory processing. Earlier the age at implantation, better the central auditory processing and hence, the better are CAEPs waveforms. Longer the duration of deafness, poorer the outcome of Cochlear Implantation as reflected by the CAEP measurements (Table 1). Those candidates having an early onset good morphology persist to have good morphology later also during their habilitation period. Sharma et al. in 2002, observed that pre-implanted P1 latencies reduced significantly after implantation. Hence, the improvement in P1 latencies with a CI depends on the amount of prior auditory deprivation and CI experience [10].

In our study, the correlations of amplitude with latency was more statistically significant in group-1 ($r = 0.68$) and than in group-2 ($r = 0.37$). Better amplitudes correlated with good morphology. Correlations improved with time and habilitation. Those candidates with early onset good CAEP morphology have better auditory verbal outcomes with habilitation, reflecting optimal activity in the central auditory pathways (Graph 1). Hence, CAEP is an ideal objective prognostic tool for assessment of long term outcomes of Cochlear implantation and it is a ‘window’ to the auditory brain for objectively assessing the influence of Cochlear implantation on central auditory system. It is imperative to note that, the N1-P2 CAEP is not without imperfections and limitations (most important is its inapplicability to infants), but it is a valuable component of the audiologist’s toolbox. Its success in hearing threshold estimation lies in the use of appropriate test parameters, efficient procedure, and rigorous interpretation [12]. Hence, a judicious application of this advanced technological research tool is necessary for optimal evaluation of suspected cases of central auditory processing disorder and

Graph 1 P1 latency as a function of age at implantation

for objective evaluation of Cochlear implant candidacy and long term outcomes with cochlear implantation.

Conclusion

There is considerable evidence for a developmental sensitive period, during which the auditory cortex is highly plastic. If sensory input is deprived to the auditory system during this sensitive period, then the central auditory system is susceptible to large scale reorganization. Restoring input to the auditory system by Cochlear implant at an early age can provide the stimulation necessary to preserve the auditory pathways. However, if auditory input is not restored until after this development period, then the cross-modal reorganized pathways may exhibit abnormal functional characteristics as observed in recorded P1 latencies, amplitudes and morphologies of CAEP. The optimal time to implant a congenitally deaf child is within the first 3 years of life, when central auditory pathways are maximally plastic. If auditory stimulation is withheld for a period for 8 years or longer, the plasticity of the central auditory pathway is greatly reduced. The loss of central auditory plasticity in congenitally deaf children aged 8 years and above is correlated with relatively poor development of oral speech and language skills. The primary auditory cortex may be functionally de-coupled from higher order auditory cortices, which may result in recruitment of higher order auditory cortex by other

modalities like vision and consistent with the lack of auditory-visual integration seen in late implanted children as noted in group-2 of our study. CAEP has opened a new window for implant teams to study the central auditory responses after cochlear implantation. It is an ideal biomarker for the performance of the central auditory pathways and is a good prognosticator for the objective assessment of optimal functioning of the cochlear implant, providing an easy and efficient way to assess long term outcomes of Cochlear implantation.

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