

Clinical Applications of the P1 Cortical Auditory Evoked Potential (CAEP) Biomarker

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Introduction

The P1 cortical auditory evoked potential (CAEP) has been established as a biomarker for assessing the maturation of the central auditory system in children (Sharma et al. 2005; Sharma and Dorman 2006). The P1 is a robust, easily identified positive response occurring at about 100–300 ms post-stimulus, depending on the age of the child. The P1 response is considered an obligatory component of the cortical auditory evoked potential, and generators of early components of the CAEP, such as the P1 and N1, include input from the primary auditory cortex and intracortical and intercortical recurrent activity (Ponton, Eggermont, Kwong and Don 2000; Kral and Eggermont 2007; Sharma, Gilley, Dorman and Baldwin 2007).

Normal Development of the P1 Response

Latency of the P1 wave is thought to reflect the sum of synaptic transmission delays throughout the central auditory pathways (Eggermont, Ponton, Don, Waring and Kwong 1997). Latency changes in the P1, as a function of increasing age, reflect the maturation of the central auditory pathways occurring (at least in part) in response to auditory stimulation. Sharma and colleagues have gathered data describing the developmental trajectory of the P1 response throughout infancy and childhood, and other researchers have further described patterns of development that lead to changes in P1 latency

and morphology (Sharma, Kraus, McGee and Nicol 1997; Ceponiene, Rinne and Näätänen 2002; Sharma, Dorman and Spahr 2002b; Moore and Linthicum 2007). In infants with normal hearing, the average latency of the 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; 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.

Effect of Auditory Deprivation on Central Auditory Development

A sensitive period for stimulation of the auditory system has been described in children who receive cochlear implants; earlier-implanted children tend to have normal P1 latencies (within the first year after implantation) and concomitant success in the acquisition of speech and language (Sharma and Dorman 2006). The latency and morphology of the P1 CAEP 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 about 3.5 years after birth. In general, a child who receives stimulation via a cochlear implant within the first 3.5 years of life will have a P1 latency that enters the normal range within the first 6–8 months after implant activation (Sharma, Dorman and Spahr 2002a, 2002b; Dorman, Sharma, Gilley, Martin and Roland 2007). If the auditory system does not receive adequate stimulation within approximately

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7 years after birth, it is likely that the higher order auditory cortex gets re-organized, CAEP latencies generally remain abnormal, and the overall chances for normal speech and language while using a cochlear implant decrease significantly (Lee et al. 2001; Sharma et al. 2002b; Kral and Eggermont 2007; Sharma et al. 2007). This may be due not only to a lack of activity in the infragranular layers of the cortex in response to sound, but also to a decoupling of communication between the primary and secondary auditory association areas (Kral, Tillein, Heid, Klinke and Hartmann 2006; Kral 2007). There are also morphological changes to the P1 waveform that occur as a result of auditory deprivation. Early deprivation-related waveform negativities, polyphasic waveforms, and low amplitude waveform morphologies have often been observed in children who have not received adequate input to their central auditory pathways (Sharma and Dorman 2006). It is possible that alternative generators may be involved with these waveforms, if the typical auditory pathways have been suppressed (Sharma et al. 2007).

Of course, auditory stimulation does not necessarily need to come in the form of a cochlear implant in order for the central auditory pathways to develop normally. In this chapter, we will describe cases in which hearing aids have provided adequate auditory stimulation and/or maintained sufficient neural plasticity to make later cochlear implantation a success. In general, children who receive early access to sound have better scores in open-set speech discrimination measures than those who are affected by auditory deprivation for longer periods (Geers 2006; Nicholas and Geers 2006). In our own laboratory, we have unpublished data that would indicate that children who do well on speech perception measures tend to have normal P1 latencies. Given this correspondence between measures, and since the P1 CAEP does not require behavioral cooperation, there is potential for clinical implementation of P1 testing. It should be noted that atypical P1 waveforms may sometimes be obtained in those with excellent speech scores, and vice versa; P1 recordings cannot be considered a substitute for behavioral testing. Still, the P1 CAEP provides useful information to supplement other types of audiological evaluation, especially in children who cannot easily be tested behaviorally.

Clinical Methodology

Given the high level of interest in using the P1 in clinical settings, we wish briefly to describe our testing

procedures. The procedures described here are those that have been employed in previous research publications from our laboratory (Sharma et al. 2002a, 2002b; Sharma et al. 2005). The appropriate testing protocol will vary depending on the characteristics of the patient and the information one is attempting to obtain. In normally-hearing children and children with hearing aids, a simple bipolar electrode setup is often used. Typically, we use silver/silver chloride electrodes with Cz serving as the active electrode and a mastoid serving as the reference electrode. In patients with cochlear implants, to minimize electrical artifact, we place reference electrodes along the isopotential contour (Gilley et al. 2006). It is critical to eliminate eye blinks during CAEP recordings. To record eye movements, electrodes are placed on the lateral canthus (active) and superior orbit (reference) of one eye. Eye blinks are rejected first online (during the recordings), and then any remaining eye blinks that may have entered into the collected sweeps are rejected offline using appropriate artifact rejection criteria. A ground electrode is placed on the forehead. Stimuli are presented via insert earphones or in free field, at a comfortable level for the listener. In our lab, stimuli are typically repeating speech sounds such as /ba/. Other types of repeating stimuli may also be used, such as noise bursts or pure tones. The frequency spectrum of the sound being used to elicit the P1 should be kept in mind when using the P1 to assess patients; high frequency sounds in particular may be difficult to make sufficiently audible when testing patients with a severe to profound hearing loss. We play DVD movies without sound to distract the patient during testing; this works very well with our pediatric patients to keep them quiet and relaxed.

Responses that are acquired should be averaged with at least 300 accepted sweeps included, and averaged waveforms should be replicated to assure that the responses are consistent within a subject and across trials. To be able to compare waveforms acquired at different times, from different patients, or from different sites, consistent equipment settings should be used. In our lab, we aim for electrode impedance measures of 5.0 ohms or less, our filter settings are usually 0.1–100 or 500 Hz, we use an A/D rate of at least 2000 Hz, and a time window of 600 ms (with a 100 ms pre-stimulus period). Stimuli are presented at a rate of approximately one or two per second.

Interpretation of the Waveforms

While the P1 CAEP is a robust response that is usually easily identified, care should be taken to ensure that the acquired waveforms are properly interpreted. While filtering may appear to assist in identifying a response, the process of low-pass filtering or “smoothing” may change the appearance of the waveform to the point that peaks are inaccurately picked. Artifact from a cochlear implant may mimic a P1 waveform, especially when recorded using a low pass filter setting of 30 Hz or lower. P1 responses in the CAEP waveform of infants and young children (under the age of 3–4 years) are relatively easy to identify. In older children and adolescents, the CAEP waveform changes to include a P1-N1-P2 complex. Depending on the history of auditory stimulation, it is often difficult to distinguish a P1-N1-P2 complex from a deprivation-related negativity (Sharma + Dorman, 2006). What may look like an N1 waveform in an older child or teenager may actually be a deprivation-related negativity if the patient received late access to audition. A trained eye is a useful asset in identifying and interpreting the CAEP waveform correctly.

Clinical Applications

The morphology of the CAEP typically reflects the maturational status of the central pathways prior to intervention (Sharma and Dorman 2006). After infants and young hearing-impaired children are appropriately stimulated with either acoustic or electrical stimulation, distinct changes in CAEP waveform morphology and latency occur, indicating progress in central auditory development.

Using these distinct and repeatable patterns of the CAEP and the latency of the P1 wave, we have studied the development of the central auditory pathways in over 200 hearing-impaired children who were fitted with hearing aids and/or cochlear implants. In an unpublished data set of 116 children under the age of 2 years, we evaluated the sensitivity and specificity of the P1 response in determining cochlear implant candidacy. In this data set, we found that the P1 biomarker had a sensitivity rate of approximately 89% and a specificity rate of approximately 85%, when compared to the gold standard of the traditional comprehensive audiological battery in making cochlear implant candidacy decisions. Interpretation of this study must be viewed with caution as the clinicians often had access to the P1 data while making candidacy decisions. Nonetheless, these data

provide some indication of the close correspondence of the P1 biomarker with behavioral testing. In the next section, we present four cases to demonstrate the use of the P1 CAEP combined with traditional behavioral measures of audiological assessment in clinical decision-making.

Case Studies

Case 1

Case 1 was a female child who was identified with a profound, congenital hearing loss of unknown etiology. She was fitted with hearing aids at approximately 9 months of age, and wore the aids bilaterally until receiving a cochlear implant at 19 months of age. Her audiogram revealed that she received limited benefit from her hearing aids (figure 1).

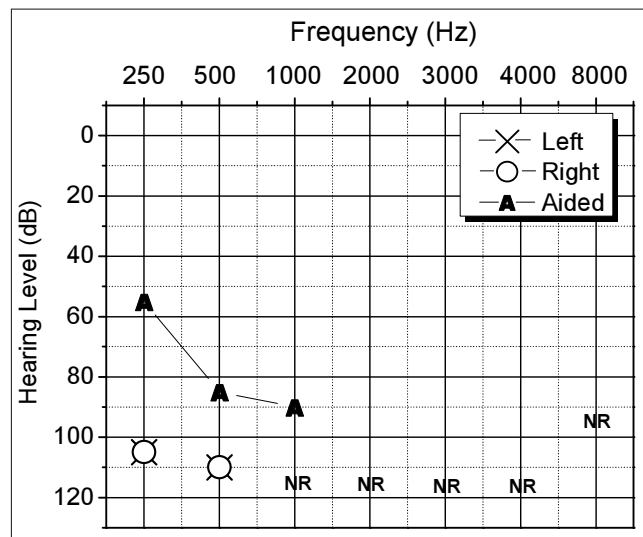


Figure 1: Pure tone audiogram for Case 1

The P1 responses that were acquired prior to implantation (after several months of hearing aid use) had latencies which were well outside of the normal range, peaking at over 300 milliseconds. Hearing aid settings had been manipulated in various ways to attempt a successful fitting for the patient. However, the late P1 response suggested that the patient had not been receiving adequate stimulation from her hearing aids to promote typical development of her central auditory pathways. She met the candidacy criteria for cochlear implantation based on her scores on the traditional audio-

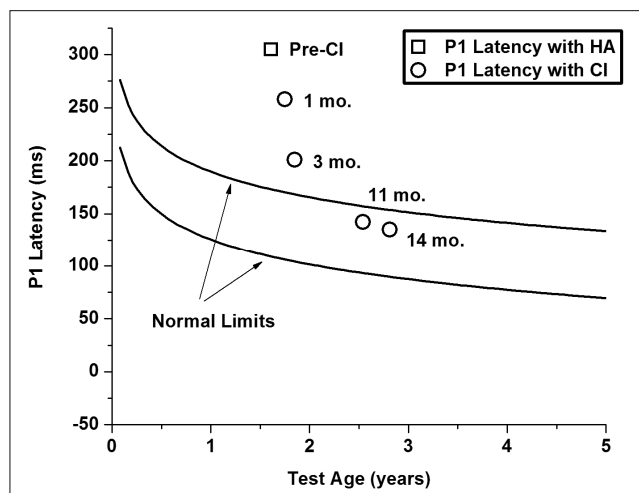


Figure 2: P1 CAEP latencies pre-and post-implantation for Case 1

logical test battery. After receiving her cochlear implant, her P1 latencies decreased rapidly, and data points acquired at 11 and 14 months post-implantation confirmed that she had moved into the normal range (figure 2). In this case, the delayed P1 response after months of hearing aid usage provided clear evidence that the auditory stimulation provided by the hearing aids was not sufficient for central auditory development. After implantation, the responses decreased rapidly to within normal limits, suggesting that the implant was providing stimulation not provided by the hearing aids.

Case 2

Occasionally, observing no P1 response to stimuli is as important as observing the latency of a present response. Case 2 is a good example of this situation. An infant female failed her newborn hearing screening and was tested with ABR at 3 weeks of age; results were consistent with a severe to profound hearing loss. P1 testing performed prior to hearing aid fitting (at 2 months of age) revealed no response to auditory stimulation.

She was fitted with hearing aids at 3 months of age, and P1 testing performed on the fit date again revealed no response (to be expected if auditory stimulation has not been occurring for some period of time).

At 5 months of age (2 months post hearing aid fitting), behavioral observation audiometry (BOA) was attempted; no responses were noted, even in the aided condition. Again, P1 testing performed at that time revealed no response. Finally, at 7 months of age, a behavioral audiogram was completed with visual reinforcement audiometry. Limited benefit from hearing aids was noted for this patient (figure 3).

The P1 recordings that were acquired at this age revealed no response for the fourth sequential test session, which corresponded well with behavioral results (table 1). The supplementary information that the P1 recordings provided to the clinician and to parents in this case was very reassuring, as the audiologist attempted to verify whether hearing aids were providing appropriate benefit and whether the auditory cortex was developing normally. This patient ultimately received a cochlear implant.

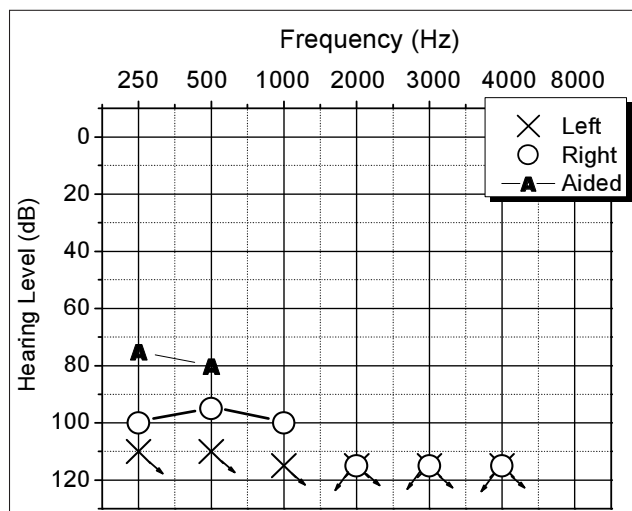


Figure 3: Audiogram for Case 2 at 7 months of age

Table 1: No P1 response could be detected pre- or post hearing aid fitting for Case 2

Age	HA Experience	Audiometric Result	P1
2 months	Pre HA fitting	No behavioral testing attempted	NR
3 months	HA fit date	No behavioral testing attempted	NR
5 months	2 months	Unaided BOA attempted (NR) Aided BOA attempted (NR)	NR
7 months	4 months	VRA/BOA unaided/aided testing completed	NR

Case 3

Case 3 was a 4½ year old female with a history of heart disease (ASD-VSD repair) and speech-language delays. She was seen for an ABR at 2 years of age, and results suggested a moderate hearing loss bilaterally. She was subsequently fitted with hearing aids, and her P1 CAEP was tracked at 2 and 12 months post-fitting. Her audiogram indicated that she was receiving significant aided benefit (figure 4). The P1 latencies we observed corresponded well to the aided pure tone results. In this case we illustrate the effective benefits of bringing auditory stimulation to a plastic auditory cortex.

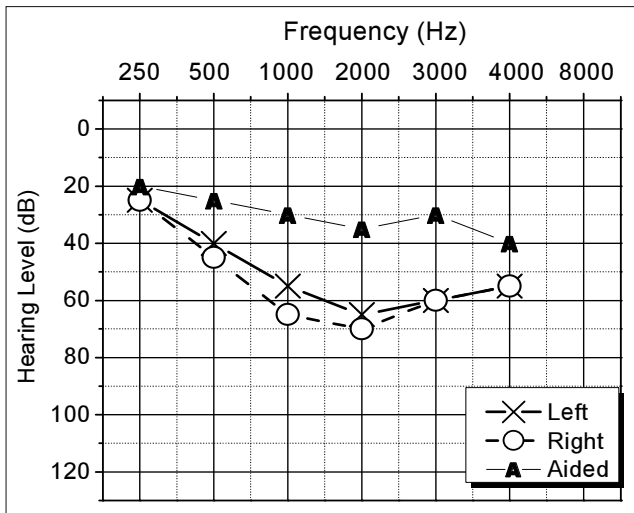


Figure 4: Pure tone audiogram for Case 3

The P1 latencies we measured also indicated that she was receiving significant benefit from her hearing aids. At 12 months post-fitting, her P1 latency moved well into the normal range (figure 5).

The P1 latencies observed for Case 3 were reassuring, in that the cortical potentials we measured corresponded well with the behavioral measures obtained for the pure-tone audiogram. While we do not have a data point for the time period between 2 and 12 months, it is likely, given our previous research, that her P1 latency was normal well before the 12-month marker. Since many young children are difficult to test behaviorally, the P1 CAEP may offer a useful reassurance that the central auditory pathways are indeed receiving adequate auditory stimulation needed for central auditory development. It should be noted that the P1 response is a necessary, but

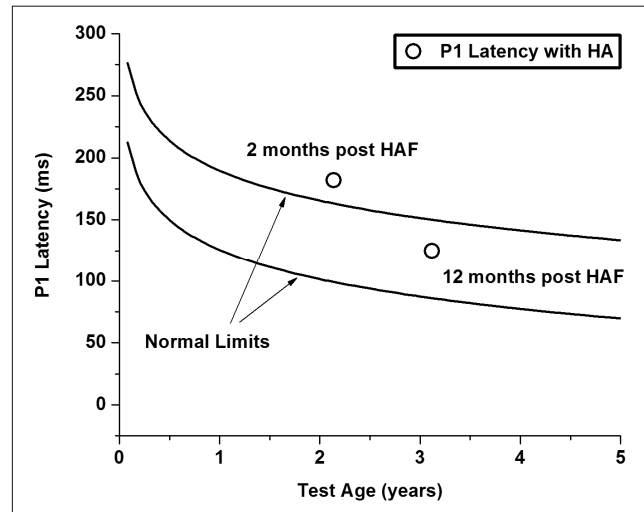


Figure 5: P1 latencies for Case 3 at 2 months and 12 months post hearing aid fitting

not sufficient, precursor to speech and language acquisition and success. We have seen cases in which children had a normal P1 response to the sound /ba/ and were clearly receiving some benefit from a hearing aid, but received a cochlear implant later on because of high frequency inaudibility or other complicating factors.

Case 4

Case 4 was a 16 year old female who was diagnosed with a hearing loss at 18 months of age. The loss was presumed to be congenital, and there was a history of hearing loss in the patient's family. The patient wore hearing aids bilaterally until at least the age of 5½ years, when she received her first cochlear implant on the left side. Her speech recognition score on the LNT-W for the first-implanted side was 84%. She received a cochlear implant on the right side at the age of 14 years, and had a speech recognition score of 52% on the LNT-W for the second-implanted side (more than twice the average score of about 20% we usually see for children who receive a second implant over the age of 7 years; Peters, Litovsky, Parkinson and Lake 2007).

A replicable P1 response was recorded for the right and left sides, with cochlear implants set to their usual settings. An N1 and P2 waveform were also visually recognizable in each condition. P1 latencies were very similar between ears, and were found to be well within normal limits for her age (figure 6). A possible conclusion when interpreting these results is that the patient's consistent use of

hearing aids prior to cochlear implantation contributed to the maturation of her auditory pathways on the unimplanted side and prepared the system for her later success.

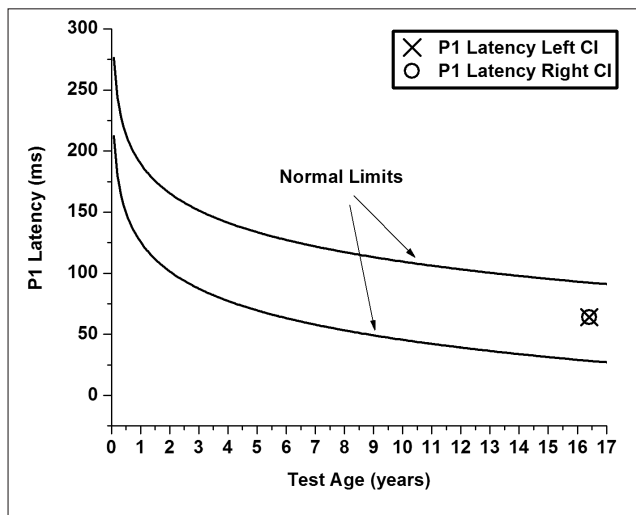


Figure 6: Case 4 P1 latencies within normal limits

Discussion

The P1 has a unique role in identifying central auditory systems that have benefited from amplification or implantation. While many audiometric tests create a snapshot in time that reflects threshold sensitivity, the P1 reflects the maturation of the auditory system in general as it has developed over time. The cases we have presented here are examples of the benefit that children receive when they are provided with appropriate intervention early in life. The access to audition for these patients maintains neural plasticity and allows for development of the central auditory pathways. It is likely that the development of early communication behaviors following early intervention may be promoted by normal development of the central auditory pathways (Sharma et al. 2004). While the P1 is useful as a marker of a plastic neural system, it cannot encompass the complex influences that lead to expert use of oral speech and language.

While there is some potential clinical value of the P1 CAEP, there are often serious issues to consider. The age, hearing history, absence of device artifact, and cooperation of the patient is vital to the success of waveform acquisition and interpretation, and cannot be taken lightly. Of course, it is vital that clinicians attempting to perform the P1 are well-trained and able to test and in-

terpret their results accurately. With these caveats acknowledged, the P1 evoked potential may hold promise as an addition to a clinical testing repertoire for hearing impaired infants.

In conclusion, the P1 biomarker may have a role to play within the battery of audiological test procedures. When recorded appropriately and interpreted properly, P1 biomarkers results may provide useful information regarding maturation of the central auditory pathways in children with hearing impairment. This information, when used cautiously in conjunction with other test results, may provide clinicians with better direction as they make decisions about appropriate intervention for hearing impaired infants and children.

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