P1 Latency as a Biomarker for Central Auditory Development in Children with Hearing Impairment

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Abstract

We used the latency of the P1 cortical auditory-evoked potential (CAEP) as a biomarker for the development of central auditory pathways in three children who received intervention through hearing aids and/or cochlear implants. Our goal was to examine the clinical feasibility of using the latency of the P1 CAEP as an objective tool to evaluate whether acoustic amplification for hearing-impaired children has provided sufficient stimulation for normal development of central auditory pathways. If clinicians have such a marker, then they can more confidently make a decision about whether to provide a child with a cochlear implant following an appropriate hearing-aid trial. Using the same marker, clinicians will also be able to monitor the maturation of central auditory pathways once electrical stimulation is initiated.

Key Words: Amplification, biomarker, cochlear implant, cortical auditory evoked potential, hearing aid, hearing impairment, objective measure, P1, plasticity

Abbreviations: ABR = auditory brainstem response; CAEP = cortical auditory evoked potential

Sumario

Utilizamos la latencia del potencial evocado auditivo cortical P1 (CAEP) como biomarcador para el desarrollo de las vías auditivas centrales en tres niños que fueron intervenidos con auxiliares auditivos y/o implantes cocleares. Nuestra meta fue examinar la factibilidad clínica de usar la latencia de los CAEP P1 como una herramienta objetiva para evaluar si la amplificación acústica en niños hipoacúsicos ha producido suficiente estimulación para el desarrollo normal de las vías auditivas centrales. Si los clínicos tuvieran tal marcador, podrían tomar decisiones con más confianza sobre si se debe colocar un implante coclear al niño, luego de un período de prueba con auxiliar auditivo. Utilizando el mismo marcador, los clínicos podrán monitorear la maduración de las vías auditivas centrales, una vez que se inicie la estimulación eléctrica.

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With the advent of newborn hearing screening, clinicians must make clinical decisions regarding assessment and management of hearing loss for an infant at a very early age. However, behavioral thresholds for the detection of sound are often difficult to obtain in infants, and thresholds are inadequate to assess the contribution of amplification to central auditory system development. Moreover, there are no clinical measures of speech perception that can be used to evaluate progress or benefit of various habilitative strategies in very young infants (National Institutes of Health, 2002).

We are examining the possibility that the P1 cortical auditory evoked potential (CAEP) may aid in evaluating the benefit of various habilitative strategies in hearing-impaired infants. The P1 response is generated by auditory thalamic and cortical sources (Erwin and Buchwald, 1987; Liegeois-Chauvel et al, 1994; McGee and Kraus, 1996; Ponton and Eggermont, 2001) and systematically decreases in latency with increasing age (Sharma et al, 1997; Cunningham et al, 2000; Ponton et al, 2000). Because P1 latency changes with age, P1 latency can be used as a biomarker for maturation of central auditory pathways. For a discussion of other biomarkers in the central auditory system, see Johnson et al (forthcoming).

P1 response latency has been used to examine the development and plasticity of the central auditory pathways in normal-hearing children and hearing-impaired children fitted with cochlear implants (Ponton, Don, et al, "Auditory," 1996; Ponton, Don, et al, "Maturation," 1996; Ponton and Eggermont, 2001; Sharma, Dorman, and Spahr, 2002a, 2002b; Sharma, Dorman, Spahr, et al, 2002; Eggermont and Ponton, 2003; Sharma et al, 2005). For example, Sharma, Dorman, and Spahr (2002b) have shown that congenitally deaf children who are fitted with cochlear implants late in childhood (after age seven years) show delayed central auditory maturation. On the other hand, children who are fitted with cochlear implants within a sensitive period during early childhood (by age 3.5 years) show normal central auditory maturation within six months of implant use. In general, these age cut offs are consistent with behavioral studies that report children implanted under ages three to four years show significantly better speech perception and language skills than children implanted after age six to seven years (Kirk et al 2002; Manrique, 2002). These data suggest that the poor speech and language skills in late-implanted children may be due to underlying neurophysiologic deficits in central auditory development caused by the absence of early acoustic stimulation during optimum periods of central auditory system plasticity.

Evidence from animal and human studies indicate central auditory pathways do not develop normally in the absence of sound stimulation (Ponton, Don, et al, "Auditory," 1996; Ponton, Don, et al, "Maturation," 1996; Klinke et al, 1999; Kral et al, 2000; Sharma, Dorman, and Spahr, 2002b). Thus, hearing-impaired infants are at risk for abnormal maturation of central auditory pathways if they do not receive adequate sensory stimulation through amplification and, consequently, will be at risk for delayed or abnormal speech and language development. Given that the central auditory pathways are maximally plastic only in the early years of development (Kral et al, 2002; Sharma, Dorman, and Spahr, 2002b), there is a limited time frame for determining whether conventional amplification is providing the stimulation needed for auditory development.

In this study, we present three cases where clinical decisions regarding intervention with hearing aids and/or cochlear implants were made using standard audiological and speech-language testing. In each of the cases, P1 latencies were recorded at various times during the intervention process. Our goal was to evaluate the developmental status of the central auditory pathways using P1 latency and to evaluate the extent to which the latency data would

add to the clinical decision-making process.

METHOD

Subjects

We describe data from three hearing-impaired children, two boys and one girl. Research protocols were in accordance with the University of Texas at Dallas Institutional Review Board guidelines. Detailed descriptions for each case are provided below.

Procedures

Standard clinical electrophysiological (ABR [auditory brainstem response]/OAE [otoacoustic emission]) and/or age-appropriate behavioral audiometric techniques were used to evaluate subjects' hearing losses. Hearing aids and cochlear implants were fitted based on the standard candidacy criteria and fitting protocols used at the Callier Center for Communication Disorders. All children underwent formal speech-language assessment.

Cortical Auditory Evoked Potential (CAEP) Recordings

Cortical auditory evoked responses were recorded in response to a synthesized speech syllable /ba/. The duration of the speech sound was 90 msec. This stimulus was identical to the one used in the following studies by Sharma and colleagues: Sharma et al, 1997; Sharma, Dorman, and Spahr, 2002a, 2002b; Sharma, Dorman, Spahr, et al, 2002. The 5 formant CV stimulus was generated using the Klatt speech synthesizer. The starting frequencies of F1 and F2 were 234 Hz and 616 Hz, respectively. The center frequencies for the formants of the vowel /a/ were 769 Hz, 1232 Hz, 2862 Hz, 3600 Hz, and 4500 Hz for F1, F2, F3, F4, and F5 respectively. F3, F4, and F5 were steady-state formants. The amplitude of voicing was constant for 80 msec and fell linearly to 0 in the last 10 msec of the stimuli. The fundamental frequency began at 103 Hz, increased linearly to 125 Hz over 35 msec, and then decreased to 80 Hz over 55 msec. The stimulus was presented at an offset-to-onset interstimulus interval of 610 msec. The stimulus was delivered via a loudspeaker placed at an angle of 45 degrees to the ear with the better audiometric threshold or on the side of the subjects' cochlear implant. Subjects' implant processors and hearing aids were set at their usual settings. Subjects were always tested following their audiological appointments during which the audiologist confirmed that the hearing aids and/or cochlear implant was functioning appropriately.

The stimulus was presented at a comfortable loudness level (approximately 70 dB SPL) for implanted subjects and at least 10–20 dB above threshold for children wearing hearing aids. Our preliminary findings (Buckley et al, 2003; Sharma et al, 2003) suggest that the latency of P1 response is only minimally influenced by variations in sensation level (Thornton et al, 1977), and in all cases we were able to ascertain that the stimulus was clearly audible using behavioral observation.

Subjects were seated in a comfortable reclining chair in a sound booth. Younger children were seated on a parent or caretaker's lap during the recording. Children were able to watch a video movie or cartoon of their choice on a TV monitor that was placed in front of them in the sound booth. Video audio levels were kept to minimum volume. We have found this to be an effective method for engaging young subjects. Evoked potentials were collected using a Compumedics Neuroscan® evoked potentials system. Silver/silver chloride cup electrodes were used for the recordings. The active electrode was placed at Cz. The reference electrode was placed on the mastoid. Eye movements were monitored using a bipolar electrode montage (lateral outer canthus referenced to superior outer canthus). The eye-blink monitoring electrodes and the reference electrode were placed on the nonimplanted side. In the two implanted children, the P1 response was obscured by the presence of a stimulus artifact in the first 100 msec of the recording. In these cases, the reference electrode was moved along the isopotential field of the artifact (typically around the forehead) to a point of null polarity, where the amplitude of the artifact was minimal and the P1 response was easily visualized (Charles Finley, pers. comm., June 2003). Figures 3 and 4 show waveforms where the amplitude of the artifact was minimal, thereby
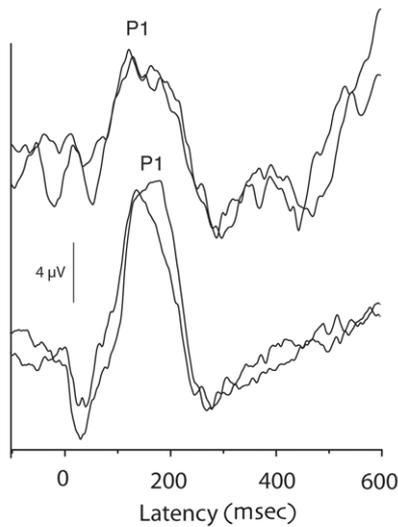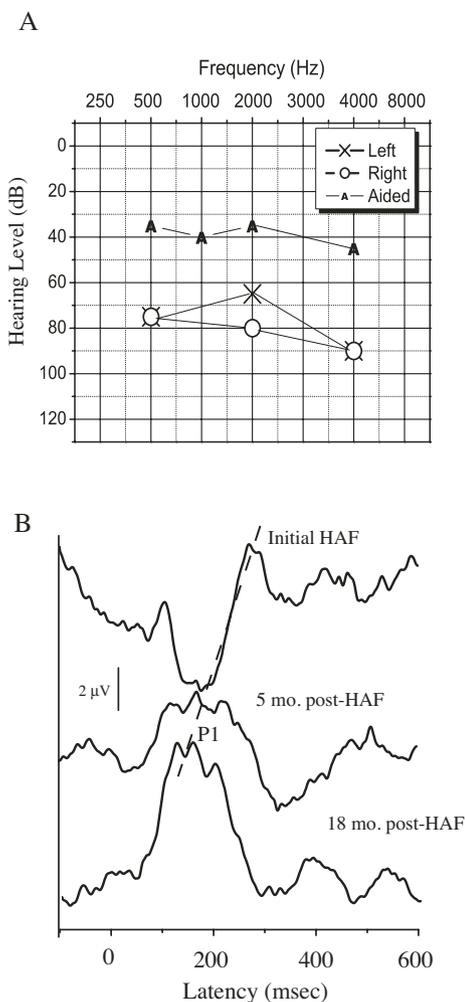
Figure 1. *Top:* Replicable CAEP waveforms from a representative subject who wore hearing aids. *Bottom:* Replicable CAEP waveforms from a representative subject who was fitted with a cochlear implant.

making it easy to pick a peak latency for the P1 response. However, as shown in Fig. 3B, some of the waveforms had residual artifact.
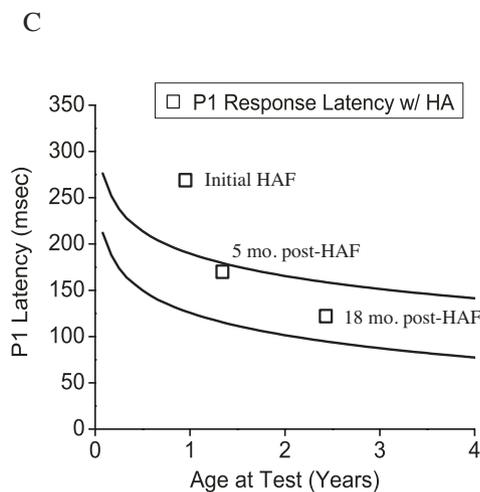
Averaging was automatically suspended by the recording computer when eye blinks were detected. The recording window included a 100 msec prestimulus and 600 msec poststimulus time. Responses were sampled at 1.0 kHz. Incoming evoked responses were analog filtered from 0.1 to 100 Hz. Approximately two runs of 300 response sweeps were collected for each subject.

The typical test session including electrode application, and evoked response recording lasted for about 30 minutes. Waveforms were judged to be replicable based on visual inspection and were averaged together to create a grand average waveform for each subject. Responses were highly replicable, and representative waveforms are
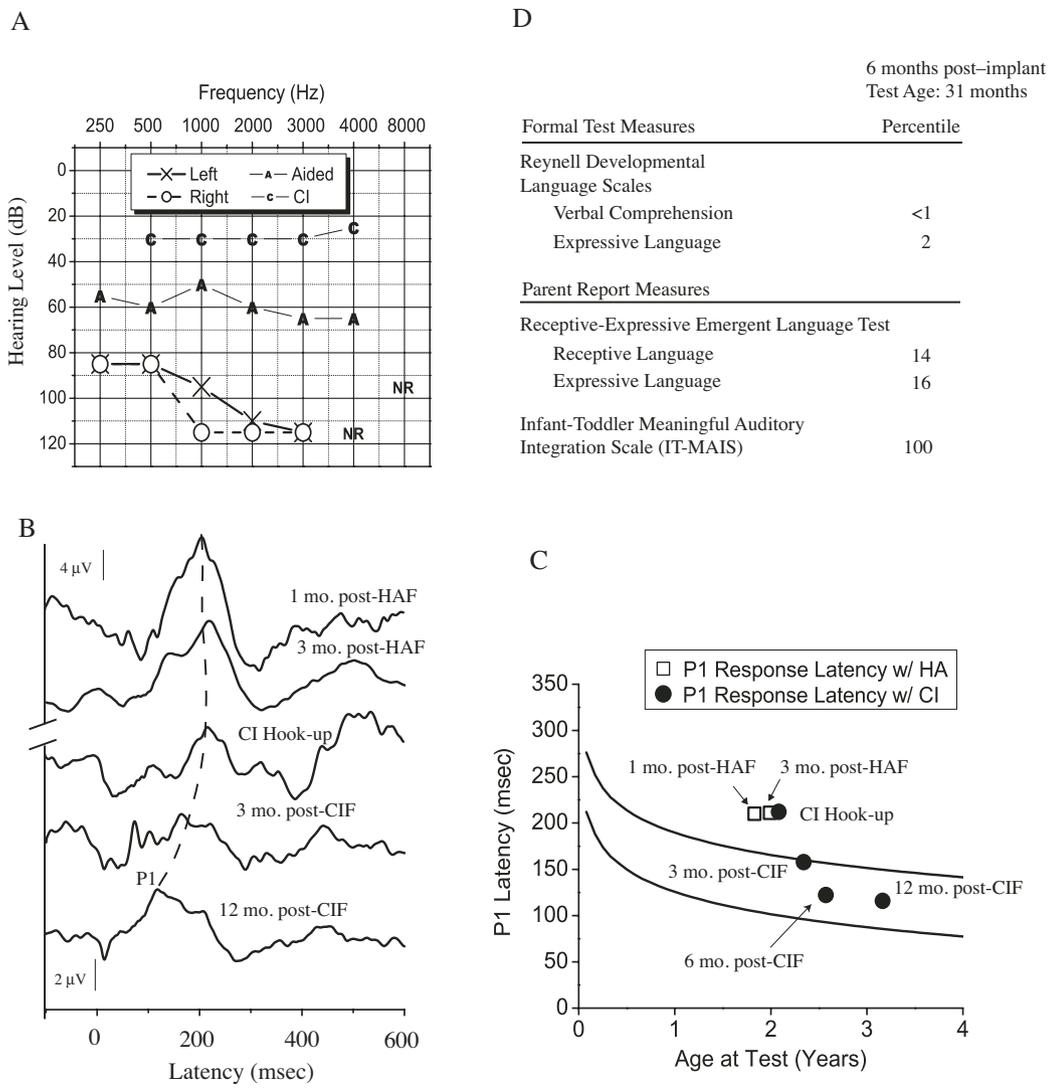

Figure 2. Audiological, electrophysiological, and speech-language evaluation results for Case 1. *A*, audiogram; *B*, cortical auditory evoked potentials; *C*, P1 latency as a function of age plotted against the 95% confidence intervals (solid lines) for normal development of P1 response latency; *D*, speech and language evaluation. HAF = hearing aid fitting.

Figure 3. Audiological, electrophysiological, and speech-language evaluation results for Case 2. *A*, audiogram; *B*, cortical auditory evoked potentials; *C*, P1 latency as a function of age plotted against the 95% confidence intervals (solid lines) for normal development of P1 response latency; *D*, speech and language evaluation. CIF = cochlear implant fitting; HAF = hearing aid fitting.

shown in Figure 1. The P1 response was defined as the first robust positivity in the waveform. The P1 latency was labeled at the peak of the response or, if the peak was broad, at the midpoint. P1 response latencies were plotted against the 95% confidence intervals for normal development of the P1 response (Sharma, Dorman, and Spahr, 2002b).

RESULTS

Case 1

The patient was a male child who had been identified with a severe hearing loss in both ears using ABR. The etiology of the

hearing loss was unknown. As shown in Figure 2A, behavioral audiological testing revealed unaided pure-tone averages (PTA) of 78 and 70 dB HL for the right and left ears, respectively. Subject 1 was fitted with hearing aids at the age of 11 months. Soundfield testing using binaural hearing aids revealed a pure-tone average of 37 dB HL (Fig. 2A), suggesting that the child was receiving benefit from his hearing aids. CAEPs were recorded to examine whether the patient was receiving auditory stimulation adequate for development of the central auditory pathways.

CAEP waveforms were recorded at the time of hearing aid fitting (HAF), five months, and 18 months post–hearing aid fitting and

are shown in Figure 2B. Figure 2C shows the changes in P1 latency as a function of chronological age relative to the 95% confidence intervals for the normal development of the P1 response. At the time of initial stimulation with the hearing aids, the CAEP waveform showed an atypical morphology with the presence of a large negativity preceding the P1 response. The P1 latency was significantly delayed. The presence of the early negativity is consistent with our previous results and is indicative of an unstimulated or minimally stimulated auditory system (Sharma, Dorman, Spahr, et al, 2002; Sharma et al, 2004). As auditory experience with the hearing aids increased, the early negativity diminished and P1 response was within normal limits after five months of hearing aid use. This rapid change in P1 morphology and decrease in P1 latency following stimulation is consistent with our previous results (Sharma, Dorman, Spahr, et

al, 2002) and reflects the highly plastic response of a young, deprived central auditory system to new stimulation. At 18 months of hearing aid use, the P1 latency continued to develop in a normal fashion.

Results of the speech-language evaluation (Figure 2D) conducted after approximately 16 months of hearing aid use showed (1) expressive language skills to be within normal limits and (2) a mild delay in expressive vocabulary and receptive language skills. Articulation skills were age appropriate.

To summarize, patient 1 showed rapid changes in P1 latency following the fitting of his hearing aid. Latencies were within the range of normal following five months of hearing aid use. In this instance, the P1 data indicated that the hearing aid was providing stimulation that was sufficient for normal development of central auditory pathways.
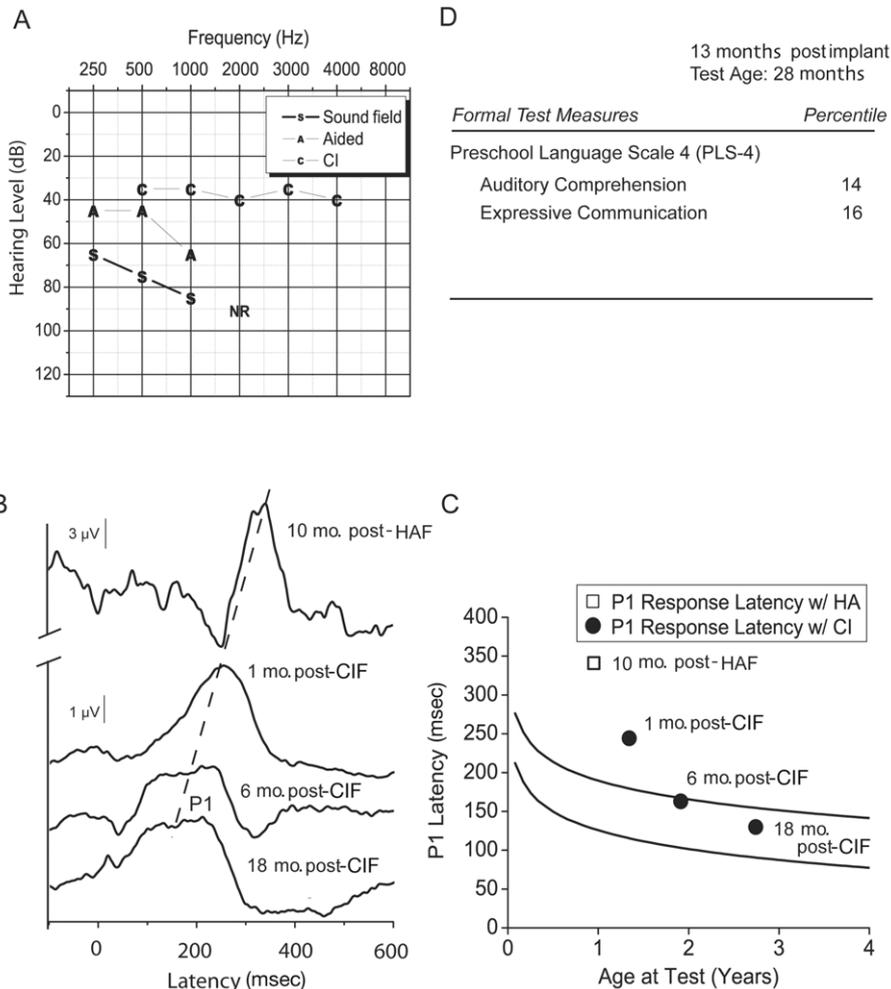
Figure 4. Audiological, electrophysiological, and speech-language evaluation results for Case 3. *A*, audiogram; *B*, cortical auditory evoked potentials; *C*, P1 latency as a function of age plotted against the 95% confidence intervals (solid lines) for normal development of P1 response latency; *D,* speech and language evaluation. CIF = cochlear implant fitting; HAF = hearing aid fitting.

Case 2

This patient was a female child who passed her newborn screening; however, at 18 months, ABR testing revealed a severe hearing loss for the left ear and a profound hearing loss for the right ear. Behavioral testing confirmed a severe-to-profound, bilateral, sensorineural hearing loss (Fig. 3A). MRI testing revealed bilaterally enlarged vestibular aqueducts. Enlarged vestibular aqueducts may be associated with progressive childhood sensorineural hearing loss (Madden et al, 2003). The patient was fitted with hearing aids at 21 months of age. Soundfield testing with hearing aids showed aided pure-tone averages of 55 dB HL (Fig. 3A).

P1 responses were recorded first during the hearing aid trial. As seen in Figure 3C, P1 latencies were delayed when tested at one month after hearing aid fitting. P1 latencies and morphology (Figs. 3B and 3C) suggested that the central auditory system had developed to some extent (albeit not to a normal extent) consistent with the progressive nature of the subject's hearing loss. When tested at three months after hearing aid fitting, the P1 latency continued to show a delay. Critically, the P1 latency did not show any change (decrease) even after three months of hearing aid use. These results suggest that the auditory stimulation provided by the hearing aid was not sufficient to drive normal development of the central auditory pathways. Although the hearing aid trial was a short one, given the rapidly progressing nature of the subject's hearing loss, cochlear implantation was pursued as an option.

The patient met the standard candidacy criteria for cochlear implantation and was fitted with a cochlear implant at 25 months of age. CAEP testing was repeated to assess central auditory maturation after implantation. P1 latencies are shown at hook-up, three months, and six months after implantation (Figs. 3B and 3C). As seen in Figure 3C, there was a rapid decrease in P1 latency following initial stimulation with the implant. P1 latencies reached normal limits after three months of implant use. P1 latency continued to develop normally when tested at 6 and 12 months postimplantation. Results from a formal speech-language evaluation conducted six months postimplantation are shown in Figure 3D. The results indicated some progress in the acquisition of speech and language.

In this case, the hearing aid trial was brief due to the rapidly progressing nature of the hearing loss. The absence of a change (decrease) in P1 latency after three months of hearing aid use provided clear evidence that the auditory stimulation provided by the hearing aid was not sufficient for central auditory development. After implantation, P1 responses decreased rapidly to within normal limits, indicating that the implant was providing stimulation not provided by the hearing aid.

Case 3

Patient 3 failed a newborn hearing screening at birth. ABR testing at one month of age revealed absent ABRs at 100 dB HL bilaterally. ABR traces to rarefaction and condensation clicks were reversed in polarity indicative to us of auditory neuropathy/dys-synchrony (Starr et al, 1996; Berlin et al, 1998), although a formal diagnosis of auditory neuropathy/dys-synchrony was never made in this case. Behavioral testing indicated a moderately severe to severe hearing loss (Fig. 4A). The patient was fit with hearing aids at age one month. Soundfield testing revealed aided thresholds of 45 dB HL and 65 dB HL at 500 Hz and 1 kHz, respectively (Fig. 4A).

P1 latencies were initially obtained at ten months after hearing aid fitting and revealed a significantly delayed P1 response latency (Figs. 4B and 4C). The morphology of the CAEP showed a large negativity preceding the P1 indicative of a minimally stimulated (or unresponsive) central auditory system (Sharma, Dorman, and Spahr, 2002b). The abnormal P1 latency indicated that the use of amplification for 10 months had not provided the stimulation necessary for central auditory development.

The patient met the standard criteria candidacy for cochlear implantation and was fit with a cochlear implant at age 15 months. CAEP testing was repeated after implantation. As seen in Figures 4B and 4C, there were rapid and large decreases in P1 latency resulting in normal values for P1 latency within six months of cochlear implant use. P1 latency continued to develop normally at 18 months postimplantation. Speech and language testing at 13 months postfitting (Fig. 4D) indicated that the patient was

developing speech and language skills.

In this case of suspected auditory neuropathy/dys-synchrony, the P1 results indicated that ten months of hearing aid use had not provided sufficient stimulation for normal development of central auditory pathways. The rapid decrease in latency following implantation indicated (1) that the implant provided stimulation that the hearing aid was unable to provide and (2) that the stimulation provided by the implant was sufficient to drive the development of central auditory pathways.

DISCUSSION

We have described the use of P1 latency as a biomarker for the development of central auditory pathways in three children with hearing loss who received intervention through conventional hearing aids and cochlear implants. P1 latencies for the hearing-impaired children were plotted against the 95% confidence intervals for P1 latency in normal-hearing children (Sharma, Dorman, and Spahr, 2002b). These plots proved clinically useful in that they allowed clinicians to assess whether a hearing-impaired infant's central auditory system was maturing appropriately following intervention.

Both the latency and morphology of the P1 response can serve as biomarkers for the developmental status of central auditory pathways. The CAEP obtained from a minimally stimulated central auditory pathway is usually dominated by a large negativity that precedes the P1 response. This negativity was observed for the patient in Case 1 at the time of initial hearing aid fitting. We have seen this negativity consistently in congenitally deaf children at the time of implantation and in profoundly hearing-impaired children at the time of initial fitting with a hearing aid (Sharma, Dorman, Spahr, et al, 2002; Sharma et al, 2004). This early negativity is strikingly similar to the "long-latency negative potential" reported in studies on preterm infants before 25 weeks postconception (Wietzman and Graziani, 1967). The similarity suggests that certain abnormal CAEP morphology and latency can be interpreted as a sign of an unstimulated auditory system. On the other hand, a cortical response obtained from a partially stimulated pathway is dominated by a P1 component, as observed for the patient in Case 2 at one month post–hearing aid fitting.

The child with a suspected auditory neuropathy/dys-synchrony (Case 3) also showed delayed P1 latency and a negativity preceding the P1 after 10 months of hearing aid use. This outcome suggests an unresponsive or unstimulated central auditory system in some cases of auditory neuropathy/dys-synchrony. However, we have seen great variation in P1 latency in our sample of children with a diagnosis of auditory neuropathy/dys-synchrony suggesting different degrees of central auditory pathway development within this population (Martin et al, 2005; see also Rance et al, 2002; Michalewski et al, forthcoming). Preliminary data suggest that in some children with auditory neuropathy/dys-synchrony, long-term development of the P1 cortical response may be abnormal (Martin et al, 2005).

When the auditory pathway is stimulated within the sensitive period (via a cochlear implant or a hearing aid), the plasticity of the central auditory pathways is signaled by rapid and large decreases in P1 latency. This was observed following appropriate intervention for all the cases reviewed here. In all the cases, P1 latencies reached normal limits within a few months. This outcome is consistent with our previous results (Sharma, Dorman, and Spahr, 2002a) and with animal studies (Kral et al, 2002).

We have used a speech sound /ba/ to elicit the P1 response. The advantage of using this CV stimulus is that energy is spread over a relatively wide range of low and midfrequencies. However, there is very little energy at high frequencies, for example, 4 kHz and a normal P1 response can be elicited in the presence of very poor audiometric thresholds at 4 kHz. Thus, even in the circumstance of a normal P1 latency, thorough audiologic/speech evaluation needs to be done to ensure that a child is receiving the range of frequencies necessary for speech recognition.

Children described in this study made advances in speech and language acquisition when measured at 16 months (Case 1), 6 months (Case 2), and 13 months (Case 3) after intervention with a hearing aid or cochlear implant. The advantage of having P1 data was that clinicians were able to

document immediate changes in central auditory pathways that convey speech signals for cortical processing. A normal pathway is likely to be a necessary, but not sufficient, condition for development of speech and language skills.

The cases in this study highlight the clinical use of the P1 response latency as a biomarker for central auditory development in hearing-impaired children. When combined with a standard test battery, P1 latency can play a useful role in determining the effectiveness of intervention strategies for hearing-impaired children.

Problems to Be Solved

As indicated in the present study, our initial clinical results are promising with respect to the use of P1 latency as a measure of central auditory development in children who receive intervention with a hearing aid or a cochlear implant. However, there are factors we need to consider before the measurement of P1 latencies can gain widespread clinical use. These include the effects of audibility, reduced spectral information, frequency response of the hearing aid, and implant mapping parameters on P1 latencies. We are in the process of evaluating these and other factors that may affect the measurement of P1 latencies in the hearing-impaired population. Finally, we are developing techniques to minimize the occurrence of an artifact in scalp recordings from cochlear implant patients.

CONCLUSION

Our results suggest that the P1 latency can provide clinicians with an objective tool to evaluate whether acoustic amplification for hearing-impaired children has provided sufficient stimulation for normal development of central auditory pathways. This tool, when combined with traditional behavioral measures of audiological and speech-language assessment, can provide information relevant to the issue of whether to provide a child with a cochlear implant following an appropriate hearing aid trial. Using the same measure, clinicians can also monitor the development of central auditory pathways after the child has been fitted with a hearing aid or a cochlear implant.

REFERENCES

Berlin C, Bordelon J, St. John P, Wilensky D, Hurley A, Kluka E, Hood L. (1998) Reversing click polarity may uncover auditory neuropathy/dys-synchrony in infants. *Ear Hear* 19:37–47.

Buckley K, Sharma A, Tobey E. (2003) Effect of Hearing Impairment on P1, N1, P2 Auditory Evoked Potentials. Paper presented at the American Academy of Audiology Convention, San Antonio, TX.

Eggermont JJ, Ponton CW. (2003) Auditory-evoked potential studies of cortical maturation in normal hearing and implanted children: correlations with changes in structure and speech perception. *Acta Otolaryngol* 123:249–252.

Erwin RJ, Buchwald JS. (1987) Midlatency auditory evoked responses in the human and the cat model. *Electroencephalogr Clin Neurophysiol Suppl* 40:461–467.

Johnson K, Nicol T, Kraus N. (Forthcoming) The brain-stem response to speech: a biological marker of auditory processing. *Ear Hear.*

Kirk KI, Miyamoto RT, Lento CL, Ying E, O'Neill T, Fears B. (2002) Effects of age at implantation in young children. *Ann Otol Rhinol Laryngol Suppl* 189:69–73.

Klinke R, Kral A, Heid S, Tillein J, Hartmann R. (1999) Recruitment of the auditory cortex in congenitally deaf cats by long-term cochlear electrostimulation. *Science* 285:1729–1733.

Kral A, Hartmann R, Tillein J, Heid S, Klinke R. (2000) Congenital auditory deprivation reduces synaptic activity within the auditory cortex in a layer-specific manner. *Cereb Cortex* 10:714–726.

Kral A, Hartmann R, Tillein J, Heid S, Klinke R. (2002) Hearing after congenital deafness: central auditory plasticity and sensory deprivation. *Cereb Cortex* 12:797–807.

Liegeois-Chauvel C, Musolino A, Badier JM, Marquis P, Chauvel P. (1994) Evoked potentials recorded from the auditory cortex in man: evaluation and topography of the middle latency components. *Electroencephalogr Clin Neurophysiol* 92:204–214.

Madden C, Halsted M, Benton C, Greinwald J, Choo D. (2003) Enlarged vestibular aqueduct syndrome in pediatric population. *Otol Neurotol* 2494:625–632

Manrique M. (2002) Long term results with cochlear implants in children. Paper presented at the 6th European Symposium on Paediatric Cochlear Implantation, Canary Islands, Spain.

Martin K, Sharma A, Dorman, M, Roland P, Bauer P, Sweeney M. (2005) Cortical maturation in children with auditory neuropathy/dys-synchrony after cochlear implantation. Paper presented at the 10th Symposium on Cochlear Implants in Children, Dallas, TX.

McGee T, Kraus N. (1996) Auditory development reflected by middle latency response. *Ear Hear* 17:419–429.

Michalewski H, Starr A, Nyugen T, Kong Y, Zeng F. (Forthcoming) Auditory temporal processes in normal-hearing individuals and in patients with auditory neuropathy/dys-synchrony. *Clin Neurophysiol* 116(3):669–680.

National Institutes of Health. (2002) *Auditory/Perceptual Processing by Infants with Hearing Loss: Issues in Clinical Assessment and Management.* NIDCD RFA. Bethesda, MD: National Institutes of Health.

Ponton CW, Don M, Eggermont JJ, Waring MD, Kwong B, Masuda A. (1996) Auditory system plasticity in children after long periods of complete deafness. *Neuroreport* 8:61–65.

Ponton CW, Don M, Eggermont JJ, Waring MD, Masuda A. (1996). Maturation of human cortical auditory function: differences between normal-hearing children and children with cochlear implants. *Ear Hear* 17:430–437

Ponton CW, Eggermont JJ. (2001) Of kittens and kids: altered cortical maturation following profound deafness and cochlear implant use. *Audiol Neurotol* 6:363–380.

Ponton CW, Eggermont JJ, Kwong B, Don M. (2000) Maturation of human central auditory system activity: evidence from multichannel evoked potentials. *Clin Neurophysiol* 111(2):220–236.

Rance G, Cone-Wesson B, Wunderlich J, Dowell R. (2002) Speech perception and cortical event related potentials in children with auditory neuropathy/dys-synchrony. *Ear Hear* 23(3):239–253.

Sharma A, Dorman MF, Kral A. (2005) The influence of a sensitive period on central auditory development in children with bilateral and unilateral cochlear implants. *Hear Res* 203:134–143.

Sharma A, Dorman MF, Spahr AJ. (2002a) Rapid development of cortical auditory evoked potentials after early cochlear implantation. *Neuroreport* 13:1365–1368.

Sharma A, Dorman MF, Spahr AJ. (2002b) A sensitive period for the development of the central auditory system in children with cochlear implants. *Ear Hear* 23:532–539.

Sharma A, Dorman MF, Spahr AJ, Todd NW. (2002) Early cochlear implantation in children allows normal development of central auditory pathways. *Ann Otol Rhinol Laryngol Suppl* 189:38–41.

Sharma A, Dorman MF, Todd NW, Gilley P, Fainberg J, Martin K. (2003) Central auditory system development in children with hearing impairment. Paper presented at the Association for Research in Otolaryngology, Fort Lauderdale, FL.

Sharma A, Kraus N, McGee T, Nicol T. (1997) Developmental changes in P1 and N1 auditory responses elicited by consonant-vowel syllables. *Clin Neurophysiol* 104:540–545.

Sharma A, Tobey E, Dorman M, Martin K, Gilley P, Kunkel F. (2004) Central auditory maturation and babbling development in infants with cochlear implants. *Arch Otolaryngol Head Neck Surg* 130:511–516.

Starr A, Picton T, Sininger Y, Hood L, Berlin C. (1996) Auditory neuropathy/dys-synchrony. *Brain* 114:1157–1184.

Thornton AR, Mendel MI, Anderson CV. (1977) Effects of stimulus frequency and intensity on the middle components of the averaged auditory eletroencephalic response. *J Speech Hear Res* 20:81–94.

Weitzman L, Graziani L, Duhamel L. (1967) Maturation and topography of the auditory evoked response of the prematurely born infant. *Clin Neurophysiol* 23:82–83.