

Use of evoked potentials in preterm neonates

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Premature infants are at high risk of neurological dysfunction, yet clinical neurological evaluation is difficult in this population. Evoked potentials provide objective measures of CNS function, and can be an important adjunct to the clinical examination in preterm infants.

Evoked potentials are averaged electrical responses to sensory stimuli that can be recorded from peripheral and central aspects of the nervous system. Evoked potentials are obtained in response to repetitive stimuli (auditory, visual, or somatosensory), and are a non-invasive means of examining the functional integrity of the sensory pathways within the nervous system. Norms are mandatory as the evoked potentials change rapidly in the neonatal period, reflecting maturation of the nervous system. Abnormalities in latencies and amplitudes of the evoked potential waveforms reflect damage or dysfunction along these pathways. In this paper we review briefly the methodology for preterm evoked potentials, early developmental changes, and some emerging clinical applications.

Methodology and early development

As numerous methodological details differ in recording evoked potentials in preterm neonates and in children or adults, methods for recording the various types of evoked potentials will be reviewed. There are considerable differences among norms from various laboratories as a result of such factors as band-pass and wave identification in the neonates. The difficulty is increased by the very rapid maturational changes in the evoked potentials over the preterm period. Thus it is important to establish norms for each laboratory, or carefully to follow the methods of the laboratory once they have been established. The nomenclature of the component waves of the various evoked potentials differ from laboratory to laboratory. An 'N' denotes a negative wave, followed by a number (for example, N20), occurring at 20 milliseconds (ms) after stimulus presentation. Similarly, 'P200' would denote a positive peak occurring at 200 ms. However, some laboratories only order the successive peaks (N1, P1, N2, etc), while others use the mean latency from the age group with which they are working. The exception is the BAEP, as virtually all laboratories use Roman numerals to denote the positive components.

BRAINSTEM AUDITORY EVOKED POTENTIALS (BAEPs)

The BAEP reflects conduction along the auditory brainstem pathway. Five component waves are routinely measured: waves I and II

arise from the distal and rostral portions of the eighth nerve, respectively; wave III is from the pons and waves IV and V are from the mid-brain. Broad band clicks are the only stimuli for which there are normative data for infants. Click intensity should be calibrated relative to normal hearing thresholds (nHL) for adults in the laboratories. The earphone should be held above the ear, because the weight of the earphone can collapse the ear canal in premature infants. A recognisable BAEP can be recorded in premature infants of 28-30 weeks in gestational age,^{1,2} with stimuli presented at high intensities and slow rates.

The BAEP amplitude is smaller than in full term neonates; the latencies of all the components decrease with increasing conceptional age.^{3,4} Wave V shows greater age related latency decreases than wave I; hence, the I-V interpeak latency (central conduction time) also decreases with age. In neonates wave I can be double peaked, wave II replaced by a prominent negativity after wave I, and waves III, IV, and V usually merged. Despite overall amplitudes being low, the wave I:V amplitude ratio can be high, and the relative amplitudes change during the preterm period.⁵

Latencies decrease rapidly in preterm infants^{6,7} and prematurity itself can affect the latencies. Yamamoto *et al*⁸ found noticeable decreases in the wave I latencies and in I-III interpeak latencies related to extrauterine rather than conceptual age. Collet *et al*⁹ suggested that smaller head size could account for the shorter BAEP interpeak latencies that they also found in preterm infants with longer extrauterine life, although this is unlikely to be the only explanation. The effects of prematurity, even of only a few weeks, can extend for six months.¹⁰

VISUAL EVOKED POTENTIALS (VEPs)

The VEP is a cortical response measured over the occipital lobes to flashing light or patterned visual stimuli. The primary components measured in neonates to flash are P100, P200, and N300, and to pattern the P280. Pattern stimuli are more sensitive measures of visual function and the only way accurately to estimate visual acuity neurophysiologically, however, this role of the pattern VEPs appears reliable only after term.¹¹ Thus in preterm neonates it is the flash VEPs that are widely used.

Flash VEPs

Flash VEPs are usually recorded in response to red light emitting diodes (LED) set into goggles.^{12,13} The variability of flash VEPs is high, and the range of normal is wide. The recording epoch needs to be long, as the

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components appear at 200–500 ms; a sweep of 1 second is recommended. The waveforms are large, however, and only a few trials (15–30) are needed per average. Pryds *et al*¹⁴ report reliable VEPs in premature infants recording only three trials, using very long interstimulus intervals. With faster rates of presentation, there can be decreases in amplitude and increases in latency.¹⁵

During the premature period the LED VEPs show remarkable developmental changes. Starting at about 24 weeks of gestational age there is only a single, late negative peak at 300 ms (N300). A late positive peak emerges (P450) by 26 weeks and by 37 weeks an earlier positive peak at 200 ms (P200) is seen.^{16 17} Taylor *et al*¹⁷ found no age related changes in latencies of the VEP over the preterm period; Pryds *et al*,¹⁸ studying preterms in the first day of life, found latencies and amplitudes of the N300 to be inversely related to age. The P200 emerges at 200 ms during the late preterm period, and decreases in latency after term.

The morphological changes are thought to index maturational changes in the occipital lobes.^{17 19} There seems to be more rapid maturation of the visual pathway in premature neonates in the extrauterine environment, as components emerge earlier in longitudinal than cross-sectional series.¹⁷ Thus VEP norms need to be established for infants in the premature period, as a function of their gestational age at birth. The effects of preterm birth on the VEPs have been shown to last for several months by some researchers.¹⁰

Flash VEPs can be recorded in sleeping preterm infants, but significant amplitude decrease may be seen with deep sleep.²⁰ The VEPs are otherwise very resistant to various perinatal factors,¹⁸ and are the most readily recorded of the evoked potentials in preterm babies.

Pattern reversal VEPs

In the late preterm period VEPs can be obtained with a small portable television monitor, with large (2°) checks. Due to the large amplitude of the VEPs only about 20 trials per average are required.^{11 21} The waveforms are distinct from those of the flash VEPs, containing only a single late positive wave (P280). Latency decreases correlate with postmenstrual or gestational age,^{11 21} but in preterm infants do not reflect refractive error.

SOMATOSENSORY EVOKED POTENTIALS (SEPs)

SEPs assess the functional integrity of peripheral, spinal, subcortical and cortical aspects of the somatosensory pathway. Median nerve (MN) SEPs are generally very well tolerated in infants; posterior tibial nerve (PTN) SEPs are considerably more difficult and time consuming to record.

Median nerve SEPs

Median nerve SEPs can be recorded in preterm neonates from 25 weeks gestational

age on wards, using a low bandpass (1–100 HZ) and long sweep 200–300 ms, with either unilateral or bilateral stimulation.^{22–24} In preterm neonates under 30 weeks gestational age the N20 has a latency of over 70 ms,²² and decreases very rapidly over the premature period. Most studies, however, have included primarily infants older than 30 weeks gestational age.^{22 25 26} Differences between term and preterm infants tested at the same conceptual age have not been found^{22 27 28} apart from transitory latency increases in the first week of life.²⁹ Birthweight, however, influences the SEPs; more mature waveforms (and shorter latencies) correlate with weight at birth.²⁷ Several other authors have also reported waveform complexity increasing with increasing preterm age.^{25 30} However, Karniski *et al*²⁶ in an extensive study, found that cortical components and scalp topography changed little, except in amplitude, over the preterm period. The component that they described as N2 (equivalent to the N1 or N20 in other studies) was very stable in topography; they also found an early N1, P2, and a later P2 in all the preterm infants (31–40 weeks gestational age) studied. The differences between this study and those that have found morphological changes with age may be due to recording parameters. That study was one of the few that has recorded in response to bilateral stimulation.²⁶ This may well produce a more stable cortical distribution, and as often in clinical practice, information regarding functional asymmetries is sought, unilateral stimulation is likely to be more frequently used. Nevertheless, this is an impressive study, and suggests that by 31 weeks of age, the orientation of the dipoles in the somatosensory cortex is mature; latency and amplitude changes reflect the ongoing myelination process.

Some authors have reported that 10–12% of premature infants may not have consistently recordable SEPs.^{22 23} This has not been our experience. We have recently investigated the maturational patterns of the cortical SEP in the early preterm period (27–31 weeks gestational age).²⁴ At birth, all of the infants (n=20) had normal neurological examinations, no clinical or laboratory evidence of asphyxia, normal cranial ultrasound scans, and on follow up (at periods of 4–18 months corrected age), had normal neurodevelopment. SEPs were seen in all of the infants. Probably the very strict inclusion criteria were critical to our findings of SEPs in all the infants. The waveform consisted of positive, negative, and positive components (at 26 weeks at 80 ms, 110 ms, and 188 ms, respectively). All three of these components (probably the P15, N20, and P22) decreased rapidly in latency over the preterm period, such that by 32 weeks of gestational age they were at 42, 55, and 113 ms, respectively. As with studies in the older preterm infants, there seemed to be no differences in the maturational changes as a function of gestational age at birth.

Posterior tibial nerve SEPs

Many studies on lower limb SEPs in neonates

have had difficulty obtaining responses reliably, with success rates around 55%, lower when preterm babies below 30 weeks were included and higher when post-term babies were included.³¹⁻³³ This may be due to technical reasons. Using a lower bandpass (as is useful for median nerve SEPs in preterm infants), White and Cooke³⁴ reported that successful PTN SEPs were recorded in 93% of infants born between 26 and 41 weeks of gestational age and tested within the first weeks of life; reliable normative data were obtained after 27 weeks of gestational age. Similarly, Pike and Marlow (personal communication, 1993), using a 1-100 bandpass, 25-100 stimuli per average (at a rate of 0.5 Hz), reliably obtained unilateral posterior tibial nerve SEPs in all (n=93) normal preterms from 26 weeks of gestational age. Latencies of the spinal SEP decrease steadily over the preterm period.³¹⁻³⁴ Thus, despite the increasing size of the neonates, the latencies decrease, reflecting the substantial effect of myelination and maturation. The cortical components also decrease in latency over this period.³¹⁻³⁴ The primary cortical component (P1 or P35) occurs at a latency of 75-85 ms in the youngest preterms, but has shortened to about 35 ms by term.³³⁻³⁴ It is also reported that, unlike the median nerve SEPs, prematurity can have substantial, long-lasting effects on the posterior tibial nerve SEPs,³² although this latter study recorded only with high bandpass and a success rate of 57% in the neonates.

Clinical applications

AUDIOLOGY

Even mild hearing impairment early in life can significantly affect the normal development of speech and language, if undetected for more than six months.³⁵ It is therefore very important that premature neonates, who are at risk of hearing impairment, be evaluated during the neonatal period.⁶⁻³⁶ The BAEP is the most widely used and accurate technique for assessing hearing in neonates, but the BAEPs need to be recorded after the infants have reached term and before 3 months corrected age. During the premature period, the BAEPs are not reliable predictors of audiological or neurological sequelae.⁶⁻³⁷ The recording procedures for neonatal screening have been well described.³⁸⁻⁴⁰ Some recent studies have investigated the viability of other techniques as a means of audiological assessment in preterm neonates, and although they look promising, these are not yet established measures.⁴¹⁻⁴³

DIAGNOSTIC AND PROGNOSTIC VALUE IN LESIONS OF PREMATURITY

In order to predict neurodevelopmental outcome in preterm infants, numerous methods have been proposed.⁴⁴ Currently, one of the most widely used is ultrasound imaging, because of its ready applicability and use.⁴⁵ The reliability of techniques such as ultrasound, however, remain imperfect prognostically. The sensitivity, specificity, and positive

predictive value of these findings in determining an adverse outcome in preterm infants ranges from 85%-91% for diffused increased echogenicities on ultrasound; 56%-86% for abnormal resistive index with Doppler; and 56%-96% with abnormal EEG findings.⁴⁵ Prediction of good outcome has been less emphasised in published findings. Evoked potentials have not been thoroughly investigated as prognostic measures in preterm infants, and may prove to be valuable in supplementing the information from other clinical measures.

A number of authors have demonstrated the value of VEPs and SEPs for assessing cortical damage and predicting outcome in the asphyxiated term newborn.³⁰⁻⁴⁶⁻⁴⁸ In term asphyxia evoked potentials can predict both poor and good outcome. Abnormal VEPs predict poor outcome,⁴⁷ while normal SEPs can predict good outcome.⁴⁶⁻⁴⁸ These studies do not seem to be generally applicable, however, to preterm infants.⁷

A recent study investigated the accuracy of VEPs in predicting neurodevelopmental outcome in preterm infants (Ekert P G, abstract presented at IEPS V, Milan, September 1994). VEPs were recorded in the first and second weeks of life, in 45 followed up to a mean age of 21 (4) months. Abnormal outcome (death or cerebral palsy (CP) and/or corrected mental developmental index (CMDI) <84) occurred in 17 infants (30%). Multiple regression analyses showed that periventricular leucomalacia (PVL) (P=0.002) and birthweight (P=0.014) were predictive of adverse outcome. VEPs did not predict adverse outcome (with a sensitivity and accuracy of 33% and 63%, respectively). Abnormal VEPs in infants with head ultrasound abnormalities were also not predictive of adverse outcome, with sensitivity and accuracy of 18% and 65%, respectively. Mean CMDI in infants with and without VEP abnormalities were not significantly different (P=0.57). Thus, in contrast to the term asphyxiated infant, VEPs were poor predictors of neurodevelopmental outcome in preterm infants. An exception is the study by Placzek *et al.*¹⁶ who found that VEPs correlated with visual acuity measures in preterm infants, as well as neurological development, although the follow up period was very short. Pike *et al.*⁴⁹ also reported that the VEP recorded at term in infants born prematurely could contribute to the prediction of visual impairment; this was an extensive study on visual outcome, and not on general neurological sequelae. De Vries *et al.*⁵⁰ had previously shown that abnormal or absent VEPs in preterm infants with PVL predicted abnormal visual outcome.

The prognostic role of SEPs in preterm infants has also been investigated. Due to the pathophysiology of brain damage in preterm infants it is expected that the SEPs would be a better measure of the damage and more sensitive to long term sequelae than VEPs. The somatosensory afferent pathways pass through the periventricular region, which is most at risk of injury in the preterm brain - intraventricular

haemorrhage (IVH) and periventricular leucomalacia (PVL). PVL is strongly associated with adverse neurological outcome in preterm infants. PVL is often heralded by early head ultrasound scan changes (periventricular echoes (PVE) which may or may not resolve, hence delaying the definitive diagnosis of PVL. Abnormal SEPs may be associated with developed PVL, or may predict the development of PVL.

Klimach and Cooke⁵¹ found a close relation between SEPs recorded close to term and outcome at 6–16 months: the head ultrasound scans and clinical picture were much less reliable prognostically. Infants with asymmetrical SEPs developed hemiplegia, which was not necessarily the case with infants with unilateral lesions. Bilateral SEP abnormalities always predicted neurological sequelae. However, in a larger series, de Vries *et al*⁵² studied primarily preterm infants with cystic PVL and found the SEPs recorded close to term were no more reliable than ultrasonography.

Consistently abnormal SEPs did not always predict sequelae, nor did normal SEPs guarantee normal outcome, although the specificity of SEPs was still 92%. This research also included repeat studies within the preterm period in a proportion of infants, and in the 19 with persistently abnormal SEPs only two were normal on outcome. Pierrat *et al*⁵³ recorded SEPs in preterm infants with extensive cystic leucomalacia. They also found that the SEPs recorded at term were not useful measures, whereas those cases in whom they had recorded SEPs during the earlier preterm period were all abnormal, consistent with the outcomes. De Vries *et al*⁵² suggested that there may be a role for SEPs in the assessment of preterm infants at risk of neurological sequelae, but that the studies would need to be repeated during the preterm period. This was the protocol of a recent study (Ekert PG, *et al*, paper submitted).

We recorded SEPs in the first and second weeks of life in 88 preterm infants (<32 weeks gestation) at a mean age of 6.5 days for the first study and 13.4 days for the second study (Ekert P G, submitted for publication). The mean (SD) weight was 948 (27) g and the mean gestational age was 27.5 weeks. Abnormal SEPs recorded early in life are influenced not only by maturational factors, such as gestational age and postnatal age, but also by periventricular haemorrhage or PVE. Intraventricular haemorrhage was associated with changes in the SEP. Grades I and II haemorrhages are associated with either normal SEPs or the loss of some late components. More clinically important haemorrhages, including those involving the periventricular white matter (grades III and IV) may be associated with the loss of early components as well. The association between abnormal SEPs and subsequent cystic PVL was significant ($P < 0.014$). Abnormal SEPs were also associated with PVE ($P < 0.012$); absent components were associated with PVE ($P < 0.004$) but not with subsequent PVL

($P < 0.123$). However, abnormal SEPs in the second week of life were strong independent predictors of cerebral palsy on follow up ($P < 0.025$). The fact that the SEPs in the second week of life are more reliable predictors is consistent with the findings of Pierrat *et al*.²⁹

These data suggest that the SEPs are sensitive measures of perturbations in cerebral function in preterm infants, but probably because of the resilience of preterm brain, very early abnormalities may not necessarily predict longer term outcome; the SEPs recorded close to term are also not highly predictive. Thus, there may be only a relatively narrow window, definitely during the second week of life as seen in the above study (Ekert P G, submitted for publication), in which the SEPs should be recorded for predictive purposes in this population.

As sequelae more often affect the lower than upper limbs, the posterior tibial nerve (PTN) SEPs may prove more valuable predictors of outcome in premature infants. In a very recent study White and Cooke⁵⁴ have shown that in fact PTN SEPs were accurate predictors of outcome at 3 years of age. The study included primarily preterm infants (median gestational age of 30 weeks), with the SEPs being recorded at the end of their hospital stay (at a mean of 37.5 weeks). There was a significant correlation between abnormal PTN SEPs and the subsequent presence of cerebral palsy. All infants but one with bilaterally normal SEPs had normal outcomes (24/25), and of those ($n = 14$) with bilaterally abnormal PTN SEPs, 12 had cerebral palsy and one global delay of infants with unilateral abnormalities ($n = 9$), five were normal on outcome. Thus, these data suggest that, in fact, PTN SEPs will be more valuable than any of the other evoked potentials in predicting neurological sequelae in preterm infants; the drawback is the tremendous time investment that is needed to perform these studies in this population.

APNOEA

A few studies have examined BAEPs in preterm infants, including some with apnoeic episodes.^{55–56} Henderson-Smart *et al*⁵⁷ studied exclusively apnoeic infants and found abnormal BAEPs in preterm infants with apnoea, and that when the apnoeas ceased, the BAEPs returned to within normal limits. They suggested that apnoea in preterm infants is related to neural function of the brainstem. However, the suggestion that the BAEPs can reflect immaturity of the brainstem pathways needs to be tempered with the result of other studies that have found the BAEPs to be too variable in the preterm period to be considered accurate measures of CNS maturity.^{7–58} Chen *et al*⁵⁹ found that BAEP interpeak latencies decreased with aminophylline treatment in apnoeic infants, but that these decreases did not predict which preterm infants with apnoea responded to the treatment. Further study is needed on this question, given the number of these infants that suffer apnoeic episodes, and the lack of clear understanding as to the aetiology of preterm apnoea.

HYPERBILIRUBINAEMIA

Neonatal hyperbilirubinaemia can lead to serious neurological sequelae and auditory impairment,⁶⁰⁻⁶¹ but the toxicity of bilirubin on the neonatal CNS depends on many factors, and outcome cannot be accurately predicted. Thus, investigators have examined evoked potentials particularly BAEPs, in hopes that they may indicate whether the infant would benefit from exchange transfusion or if the infant was likely to suffer neurological or audiological impairment. A concern, particularly in preterm infants, is to determine what bilirubin concentrations are safe. Prolonged BAEP interpeak latencies while infants are hyperbilirubinaemic, and improvement following exchange transfusions, have been widely reported.⁶²⁻⁶⁴ In these studies, however, BAEP abnormalities were not always correlated with bilirubin concentrations, and follow up data were not obtained to determine if these transient abnormalities were significant (transient BAEP abnormalities are frequently seen in the preterm population).⁶ A few recent reports found no relation between bilirubin and BAEPs.⁶⁵⁻⁶⁶ The latter study suggested that the otoneurological toxicity of bilirubin is related to the bilirubin binding properties of serum albumin. A replication of these data with a larger series would be important to confirm the role of BAEPs in hyperbilirubinaemia.

SMALL FOR GESTATIONAL AGE (SGA)

Evoked potentials have been used to assess the effects of intrauterine growth retardation on neurological development. Watanabe *et al*⁶⁷ recorded VEPs and suggested that neurological development in SGA infants progressed relatively normally and independently of the intrauterine conditions which caused the slower physical growth. In contrast, Hrbek *et al*⁶⁸ found that although the VEPs of SGA infants generally corresponded to that of age matched normal neonates, there was a tendency towards longer latencies in the SGA infants, as well as the presence of late slow waves, which the authors felt were a sign of neurological immaturity. Both of these features, however, were transient. Pryds *et al*¹⁸ examined VEPs in eight SGA infants and found no abnormalities. However, Pettigrew *et al*⁶⁹ and Soares *et al*⁷⁰ found that the BAEP interpeak latencies were shorter in SGA infants than age matched controls, although Soares *et al*⁷⁰ suggested that this was not due to precocious development of auditory brainstem pathway, but to immaturity of the cochlea. This was because the shorter I-V interval was due to a longer latency wave I, and not to a shorter than usual latency of wave V. Sarda *et al*⁷¹ found that the BAEPs in SGA infants were closely associated with the presence or absence of maternal hypertension, suggesting that aetiology of the growth retardation affects the evoked potentials. As other studies have not correlated aetiological factors with the evoked potentials, this may explain the reported variability.

Gallai *et al*²⁵ found no differences in SEPs

between SGA and normal babies, both in preterm and term populations, although a more recent study found a proportion of SGA infants to have abnormal SEPs (de Vries L S, 1993; personal communication). These abnormalities were not associated with neurological sequelae in infants with normal head ultrasound scans, but in a smaller number with both abnormal head ultrasound and abnormal SEPs, cerebral palsy was seen. In the SGA babies growth retardation does not seem to affect the CNS routinely or uniformly, according to the evoked potentials, but as some authors have found abnormalities in the evoked potentials, not always associated with nervous system disorders, some caution needs to be exercised in interpreting studies in this population.

Conclusions

This paper has reviewed the techniques used for recording evoked potentials in the premature infant and the early developmental changes. The maturational changes in the evoked potentials, including morphological changes, and the very rapid latency changes within the first months of life, provide an invaluable means for assessing and monitoring development within the central nervous system. The maturational changes are such that normative values are requisite, and the norms must take into account both the infant's gestational age at birth as well as the postnatal age. These norms can then be used to aid in the assessment of gestational age, and whether there has or has not been normal maturational development, either in utero or during the postnatal preterm period.

Evoked potentials are of increasing value clinically in preterm neonates, primarily because of the difficulty in obtaining reliable neurological evaluation of these infants. Median nerve SEPs may provide reliable information in preterm infants at risk of PVL, and when recorded in the second week of life, predict cerebral palsy. PTN SEPs seem to be even more reliable indicators of outcome, but the difficulty in obtaining them in preterm infants needs to be taken into consideration. Further study is needed in some areas, such as in apnoeic preterm babies clearly to establish the role that evoked potentials (in this case BAEPs) may have in understanding both the aetiology and the clinical course of this dysfunction. In other conditions, such as delayed intrauterine growth, that may lead to neurological sequelae, evoked potentials can provide objective CNS assessment. Evoked potentials may also prove useful in the monitoring of treatment modalities for preterm infants.⁷²⁻⁷⁴ The evoked potentials are a valuable adjunct in the assessment of preterm neonates and, as their value is recognised, we expect their use to increase.

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