Clinical application of evoked potentials

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Summary

Visual, brainstem and somatosensory evoked potentials have added new dimensions to electrophysiological studies. Signal averaging has made it possible to record low-amplitude electrical potentials in the nervous system in response to external stimuli. Clinical abnormalities are indicated by latency prolongations, furnishing objective evidence for suspected or subclinical disease. The tests are most extensively used for the diagnosis of multiple sclerosis. Other indications include hearing and visual evaluation, especially in neonates, diagnosis of brainstem and cerebellopontine angle tumours, monitoring the integrity of sensory function during surgery for scoliosis or neurosurgical procedures and differentiating toxic or metabolic causes of coma from irreversible structural lesions. The tests are non-invasive and considered in conjunction with the clinical data provide useful electrodiagnostic tools.

An evoked potential (EP) is an electrical response of the nervous system to a brief external stimulus, manifested as a wave or series of waves. The EP originates from various neurogenerators in the pathway being tested. Electrical potentials arising from central and peripheral nervous systems are either spontaneous or evoked. The electro-encephalogram (EEG) is spontaneous whereas K-complexes, photic driving responses and A waves are examples of EPs visualized in the EEG. They are EPs because they occur in response to sensory stimulations with a predictable latency after the stimulus.

An EEG which is used to assess brain activity records spontaneous brain waves with amplitudes reaching 50-100 μV, whereas EP amplitudes are very low and range from 0.5 μV (brainstem auditory evoked potentials) to 20 μV (pattern-shift visual EPs). These EPs are mixed with normal ongoing high-amplitude EEG ‘noise’, which makes reliable visualization of EP waves in the EEG impossible without signal averaging. This may be described as an adverse signal: noise ratio. Indeed, event-related responses may be at least 100 times smaller than the random activity made up of spontaneous cortical rhythms, muscle activity (electromyography), cardiac activity (ECG), eye movements (electro-oculogram), 60 Hz artefacts, slow skin potentials, respiratory artefacts, etc.

Signal averaging

George Dawson introduced EP recording with his first automatic averaging device in the early 1950s. The device was partially mechanical. Computer technology in the 1960s simplified the procedure with the development of averaging devices capable of storing individual traces in memory. The principle in signal averaging is that only the brain response time-locked to the signal is summed by the computer. Unwanted ‘noise’ (random EEG patterns and artefacts) is diminished and the time-locked EP is summed and clarified as the stimulus is repeated. One or more electrical potentials (waves) may appear after a repeated stimulus. If the ‘noise’ is truly random, the signal: noise ratio is improved by the factor \(\sqrt{n}\), where \(n\) is the number of responses averaged. Averaging 100 responses thus improves the signal: noise ratio by a factor of 10. Stimuli are given repetitively and the computer averages the new data with the average results from previous stimuli stored in its memory. The process is continued until the desired waveform becomes sufficiently clarified.

Averaging has made it possible to record somatosensory evoked potentials (SEPs) on electrical stimulation of peripheral nerves, visual evoked potentials (VEPs) on photic flash or pattern-shift checkerboard stimulation and brainstem auditory evoked potentials (BAEPs) in response to sound stimuli (clicks).
Modes of sensory stimulation

Pattern-shift VEPs, BAEPs and short-latency SEPs are the three types of EPs in current clinical use. The post-stimulus latencies may be short (less than 10 milliseconds (ms) for BAEPs, less than 40 ms for SEPs on stimulation of the posterior tibial nerve at the ankle), intermediate (20-120 ms) or long (120-500 ms). Short-latency potentials are subcortical whereas intermediate- and long-latency potentials arise in the cerebral cortex. The subcortical EPs provide no information about cortical function.

Early clinical localization of lesions along the sensory neuritis about 90% have abnormal patterns of compressive lesions of differentiating functional assessment of more central auditory conductions. Wave I arises from the 8th nerve generated distal to the cochlea. Although the anatomical pathways distal to the cochlear nucleus were the first to describe the human BAEPs. Wave I arises from the superior olive, wave IV from the lateral lemniscus in the high pons, and wave V from the inferior colliculus in the midbrain. The clinical localization is ipsilateral to the stimulated ear, and are volume-conducted to the surface. Short-latency components are remarkably stable and unaffected by drowsiness, sleep or light anaesthesia.

Origins, measurement and application of EPs

Origins

The VEP, often called P100, is generated in the striate and parastriate cortex. Activity which originates in the retina travels through the lateral geniculate body to the occipital cortex. It is also thought that some retinal activity passes through the reticular formation and diffuse thalamic projections. This pathway contributes to VEPs recorded at increasing distance from the visual cortex.

BAEPs are electrical signals occurring as a series of 5 waves of less than 1 μV appearing within 10 ms after an auditory stimulus. Later potentials have been recorded but were less reproducible and have not been found to be clinically useful. Jewett et al. were the first to describe the human BAEPs. Wave I arises from the 8th nerve generated distal to the cochlea. It is a near-field auditory nerve action potential and is therefore not truly a brainstem potential. The retrocochlear yet extra-axial focus of wave I generation allows it to serve as a 'benchmark' for the assessment of more central auditory conductions. Wave II has been thought to be generated by cochlear nuclei and wave III by the superior olive, wave IV from the lateral lemniscus in the high pons, and wave V from the inferior colliculus in the midbrain. The clinical localization is ipsilateral to the stimulated ear, although the anatomical pathways distal to the cochlear nucleus are crossed.

SEPs. In 1947 Dawson recorded the first SEP. It is mediated largely via large-diameter peripheral sensory fibres and dorsal column/lemniscal systems centrally. The cell bodies lie in the dorsal root ganglia; the central processes travel in the dorsal columns of the spinal cord and synapse in the gracile and cuneate nuclei. Second-order fibres cross to the opposite side through the medial lemniscus to the thalamus and third-order fibres to the sensorimotor cortex. On median nerve stimulation EPs from the brachial plexus, dorsal column nuclei and contralateral thalamus are recorded.

Measurements

The EP, like the EEG, is a plot of voltage against time. Latency in ms is the most commonly used measurement. Latency refers to the time interval from the onset of the stimulus to the onset or peak of the EP. The waveform peak is more commonly used. The time interval is called the absolute latency. The time between the two peaks is called the interwave or interpeak latency (IPL).

Amplitude (in μV) is usually measured from baseline to peak or peak-to-peak. Amplitudes are much less useful because of individual variability. They may be useful for comparing the two sides in the same subject.

Applications of EPs

The possible usefulness of EPs in neurological diagnosis can be appreciated by realizing that these studies are, for the most part, central analogies of conduction times in the peripheral nervous system. As a matter of fact, with SEPs the initial latency between the stimulus and Erb's point potential reflects conduction in peripheral nerves. The latency from the wave over Erb's point to later components of the SEP is a measure of central conduction, as is the measure of IPL between wave I and later waves of the BAEPs. With VEPs it is not as easy to separate peripheral from central contributions to the latency because of the lack of far-field markers of activity beginning in the optic nerve. However, in general, the value of all EP studies is related to the fact that they do reflect conduction within central neural pathways; as a result, their usefulness parallels the usefulness of conduction studies in the peripheral neural pathways.

EPs may contribute to clinical diagnosis and patient management. They have many applications in clinical practice: (i) objective evaluation of sensory and neural function; (ii) detection of clinically unsuspected lesions, especially in the diagnosis of multiple sclerosis; (iii) localization of lesions along the sensory pathways; (iv) assessment of neural function in difficult-to-test patients: hearing impairment in neonates, vision in children and retarded subjects; and (v) monitoring of sensory pathway function during anaesthesia.

The tests are non-invasive and provide sensitive, quantitative extensions of clinical neurological examinations but do not provide aetiological information and therefore should be integrated in the clinical context.

Types of EPs and their individual applications

VEPs

Pattern-reversal (shift) checkerboard is the preferred stimulus. These squares reverse without change in the total light output (luminance) from the screen. With strobe-light or pattern-flash there is greater variation in EP measurements. Currently, visual evoked responses are of the most use to the neurologist in: (i) suspected demyelinating disease; (ii) early compressive lesions of the optic nerve and chiasm; and (iii) differentiating functional from organic causes of blindness.

The amplitude of the pattern-reversal response tends to parallel alterations in acuity level. Neuroretinal lesions tend to exert a stronger effect than refractive errors or opacities of the media. The flash-evoked response is rather insensitive to changes in visual acuity and may still be present at near-normal amplitude in cases of severe cataract where acuity is reduced to light perception. Pattern-evoked responses are more sensitive to changes in visual function and therefore the two responses usefully complement each other. The amplitude may be increased in photic-sensitive and progressive myoclonic epilepsy.

Optic neuritis. The widest application of VEPs has been in the clinical diagnosis of multiple sclerosis. In patients with a clear history of optic neuritis about 90% have abnormal pattern-reversal EPs. The P100 latency returns to normal in less than 5% of patients even 10 or 15 years after the visual acuity has returned to normal after an episode of optic neuritis.

Multiple sclerosis. A prolonged latency is the characteristic finding in demyelinating disease. In optic neuritis the P100 is prolonged in 95% of cases and in 60% with other clinical signs of definite multiple sclerosis but with no history of visual impair-
ment.16 Latencies are also affected in compressive lesions, degenerations (e.g. Friedreich's ataxia), ischaemic optic neuropathy and papillopathy. However, unlike multiple sclerosis the delays are usually shorter. In the diagnostic categories of multiple sclerosis (definite, probable and possible) the incidence of abnormalities in pattern-reversal VEPs has averaged 85%, 66% and 44% respectively.16 In chronic progressive spastic paraparesis without a history of clinical findings to indicate optic neuritis or generalized multiple sclerosis, pattern-reversal EPs are positive in about one-third of cases, the majority of which would otherwise remain undiagnosed.17 Pattern-reversal EPs may be abnormal when results of neuro-ophthalmological examination are normal, but when VEPs are normal no abnormalities are found ophthalmologically.18

BAEPs

The criteria for defining abnormality of central auditory conduction are usually based on relative amplitudes and latencies of waves I, III and V. Absence or marked attenuation of waves III and V relative to wave I and prolongation of IPL between waves I, III and V are the two major types of abnormality. BAEPs are used to test: (i) the peripheral hearing apparatus in conductive and sensorineural hearing disorders; and (ii) the brainstem auditory pathway in central nervous system disorders. The age groups in which BAEPs probably have the greatest clinical utility are newborn babies and infants. Normal development of central auditory pathways requires adequate peripheral input. The use of BAEPs in infants, children and retarded and uncooperative and comatose patients has gained recognition because of the failure of conventional behavioural tests of hearing. Auditory brainstem responses in normal infants appear at around 26 weeks' gestational age and thereafter undergo systematic changes in latency (a shortening), amplitude (an increase) and threshold (a drop). At about 1 year of age the maturation of the cochlear and brainstem pathways has apparently been completed, for the auditory brainstem response at that age closely resembles that of an adult.19 The factors that place neonates at risk for hearing loss include genetic disorders, infections (rubella, toxoplasmosis, syphilis, cytomegalovirus) prematurity (less than 1500 g), hypoxia, drugs and hyperbilirubinaemia. Galambos et al.20 found in their study that at least 10% of babies discharged from the intensive care nursery as healthy hear poorly through one or both ears, and that at least 2% of them suffer irreversible bilateral sensorineural hearing losses so severe as to require correction with hearing aids. They pointed out that the auditory brainstem response test is considered to be the most reliable, sensitive and accurate newborn hearing test available at the present time.

Cerebellopontine angle tumours. BAEPs are the most sensitive means available for the detection of acoustic neurinomas.16 BAEPs are occasionally abnormal when the results of routine audiological tests and computed tomography are normal, whereas the converse has not been found.21 Occasionally the behavioural audiogram has been normal with an abnormal BAEP. In the majority of cases the IPL between I and III, III and V, I and V can be used in interpretation. The I-III separation is the most sensitive measure. Increased absolute latency of waves, inter-ear wave V absolute latency difference, and absence of all waves are less specific signs and may be seen with peripheral hearing loss. There is a small incidence of false positives with normal I-III or I-V separation. The nature of the conduction defects in the latter cases is not known. In most reported series 90-96% of acoustic neurinomas are revealed by abnormal BAEPs.

Intra-axial neoplasms. Most patients with intracranial brainstem tumours have abnormal BAEPs and no patient with a pontine glioma has yet had a normal BAEP.22 All pontine haemorrhages have been associated with abnormal BAEPs. Intra-operatively BAEPs help the surgeon to preserve hearing.

EPs are resistant to the effects of general anaesthesia and do not fatigue on repetition.

Multiple sclerosis. BAEPs are useful in demonstrating a clinically unsuspected lesion and documenting a second lesion. The average abnormality rates in 351 patients classified as definite, probable and possible multiple sclerosis cases were 67%, 41% and 30% respectively. In many studies 20-50% of patients with multiple sclerosis without brainstem symptoms and signs have been found to have abnormal BAEPs.23 The abnormalities in multiple sclerosis consist of loss of amplitude of wave V (55%), prolonged IPLs (13%) or both (33%). In 45% BAEP abnormalities have been detected only in one ear.23

Coma and brain death. BAEPs are normal in cases of coma from toxic or metabolic causes. In brain death only wave I or waves II and III are present. The presence of waves III, IV and V indicates the presence of brainstem function. Interference with blood supply to the 8th nerve and cochlea will abolish wave I.

SEPs

The SEP screens the central sensory pathways,24 and can also evaluate proximal parts of the peripheral sensory nervous system.25 SEPs are valuable for evaluating sensory and neurological function in individuals unable to co-operate in clinical assessment, especially in infants, comatose or anaesthetized patients. Absolute latencies are affected by limb temperature and peripheral neuropathies, so clinical interpretation is based on IPLs. Interside latency differences are very reliable and sensitive measurements. Side-to-side amplitude differences may be useful if technical errors are excluded. Peripheral nerve values reach adult levels by about 3 years whereas spinal cord values do not reach adult level until about 5 years.26

The diphasic positive-negative waveform recorded at Erb's point is generated by impulses passing through motor and sensory fibres through the brachial plexus. Most of the negativity is generated in the sensory fibres with a latency of 9 ms (N 9). In the lower limb, potentials are generated in the cauda equina and root entry zones of the spinal cord.27

The potential at 13 ms (labelled P/N 13) is composed of positivity at FZ (G1) and negativity at C2 (G2). The P/N 13 may be ranked by minor lobulations which are too inconsistent for clinical interpretation.8 Most human clinical-pathological correlations suggest that C2 negativity (12-14 ms) and scalp positivity at 13 ms are generated in the dorsal column and dorsal column nuclei. On upper limb stimulation N 19/P 22 is recorded from contralateral somatosensory cortex. Evidence from intrahalamic recordings and human clinical pathological data22 suggests that N 19 is generated in the thalamus. Epileptogenic lesions (epilepsia partialis continua, myoclonic epilepsy) produce augmentation of P 22 but not N 19 and it is thought that P 22 is generated in the parietal sensory cortex.

Multiple sclerosis. The most useful role of EPs in multiple sclerosis is documenting a clinically silent second lesion in suspects. The best yield is given by SEPs using leg stimulation, presumably reflecting the large extent of neuraxis screened.28 The addition of arm and cervical SEPs may increase the diagnostic yield. Upper limb SEPs are abnormal in about 60% of all patients with multiple sclerosis and in 40% with no sensory symptoms or signs. The yield on lower limb stimulation is about 75% in all multiple sclerosis patients. Many abnormalities are unilateral, especially on upper limb testing.

Other degenerative diseases. Abnormal SEPs have been recorded in hereditary spastic paraplegia, Friedreich's and other hereditary cerebellar ataxias and subacute combined degeneration due to vitamin B12 deficiency. In these diseases degeneration of the centrally directed axon from the first sensory neuron is the primary pathological process.29
Coma and brain death. Thalamocortical potentials are involved early in lesions of cerebral hemispheres and will therefore be affected earlier than brainstem auditory evoked responses. Lower medullary components (N/P 13) are preserved in the majority of patients who are brain-dead whereas BAEPs, including wave I, are present. The integrity of the peripheral mechanisms confirms that the stimulus has been adequate and that a volley has reached the central nervous system.

Intra-operative monitoring. SEPs are resistant to anesthetic agents. They can be used to monitor spinal cord function during surgical procedures involving manipulation of the cord such as corrective procedures in scoliosis, operations for cord tumours and intramedullary arteriovenous malformations, lami­nectomies and other procedures. There have been no reports of significant postoperative neurological deficits where SEPs have remained normal and this despite the fact that only sensory function is being monitored.

Radiouleopathies andplexopathies. Recording SEPs in the presence of attenuated or absent sensory nerve action potentials with plexus injuries suggests continuity between peripheral and central structures. This finding can aid in microsurgical repair. Comparison of SEPs from median, ulnar or segmental cutaneous nerve stimulation is helpful in anatomical localization of the part of the plexus affected. 3,31

Conclusion

EPs provide accurate, objective and completely reproducible data. The information does not yield a specific diagnosis but points to abnormal function in that particular sensory pathway. They have multidisciplinary uses and are valuable in such disorders as multiple sclerosis, intrinsic and extrinsic posterior fossa tumours, trauma, coma, brain death, stroke, conversion symptoms, operative procedures and intensive-care monitoring as well as in infants for the purpose of examining hearing and visual symptoms which cannot otherwise be accurately assessed.

The most extensive use of EPs has been in the diagnosis of multiple sclerosis, which in the past has been essentially clinical, based on a course of relapses and remissions and the demonstration of multiple lesions. EPs may uncover unsuspected lesions. Two recent reports 32,33 have recommended reclassification of multiple sclerosis to account EPs. Therefore the introduction of "laboratory-supported", 'probable', and 'definite' multiple sclerosis would extend the limits of diagnostic criteria. EPs have added an exciting new theoretical and practical dimension to electrophysiological studies in various states of normality and abnormality. They have become a clearly established diagnostic tool supplementing the more classic EEG studies of non-evoked potentials.

EPs are being overserved in many clinical laboratories. Clinical enthusiasm must take into consideration the value and cost effectiveness and clinicians must refrain from requesting laboratory procedures unnecessarily. The test should be considered only when there is a reasonable possibility that new and relevant information will be provided to affect the management of the patient.

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REFERENCES


