

Evoked potential tests in clinical diagnosis

BACKGROUND Evoked potentials are used to detect conduction disturbances in the central nervous system. This paper provides an overview of the areas in which evoked potentials are used in clinical neurophysiological diagnostics, with the emphasis on coma and demyelinating disease.

METHOD The article is based on a literature search in PubMed and the authors' long experience of neurological and neurophysiological diagnostics.

RESULTS Somatosensory evoked potential (SEP) can be a reliable predictor of failure to regain consciousness as early as 24 hours after anoxic coma has occurred. If coma is caused by a brain trauma, cerebrovascular episode or other neurological disease, information about which sensory brainstem pathways are damaged can be obtained from somatosensory evoked potentials and brainstem auditory evoked potentials (BAEP), which can also be useful for planning rehabilitation. Normal SEP and BAEP findings in cases of coma caused by trauma are associated with a favourable prognosis. Visually evoked potential (VEP) can often reveal signs of a history of optic neuritis. SEP and BAEP can also reveal subclinical lesions in the central nervous system and be a supplementary diagnostic test for multiple sclerosis.

INTERPRETATION The clinical value of SEP and BAEP is high in coma cases. Evoked potentials are also important in intraoperative monitoring. The clinical value of VEP is high when a history of optic neuritis is a deciding factor for a multiple sclerosis diagnosis. Some selected patients who are being assessed for demyelinating disease will benefit from a full EP study.

Evoked potential (EP) tests are neurophysiological tests that provide diagnostic information about conductivity in important paths in the central nervous system. The principle involves recording electrical potentials from different parts of the nervous system after stimulating appropriate sensory organs or neural pathways, including visual, auditory, somatosensory and motor systems. It has been found to have clinical value for many diseases (1, 2). Event-related potentials (ERP) are used to judge attention and more complex cognitive processes.

Evoked responses are of particular clinical value for determining the prognosis for comatose or severely brain-damaged patients and are also useful in assessing demyelinating diseases. The purpose of this paper is to provide a brief overview of the most usual types of evoked potentials and to describe how the test methods are used in clinical neurophysiological diagnostics, with the emphasis on coma and demyelinating disease.

Method

The article is based on a literature search in PubMed with the search term «evoked potentials» combined with «coma», «multiple sclerosis» and «optic neuritis» and on the authors' long clinical experience of neurological and neurophysiological diagnostics.

The most usual evoked potentials

Somatosensory evoked potentials

Somatosensory evoked potentials (SEP) is a study of the sensory system whereby a peri-

pheral nerve, normally the median or tibial, is stimulated with small electric pulses. The most important evoked response peaks from the median nerve are presented in Fig. 1. The test is normally used to judge conduction velocity and demyelination in the posterior funiculus or to predict the outcome for comatose patients (Fig. 1, left-hand printout).

Brainstem auditory evoked potentials

Brainstem auditory evoked potentials (BAEP) are used to test the auditory system; auditory paths are stimulated by means of clicks delivered through headphones. We record evoked response peaks from the cochlear nerve, superior olive, lateral lemniscus and inferior colliculus (Fig. 2). The test can be used to localise disease to the pontine auditory pathways and to predict outcome in comatose patients. It is used in modified form by audiologists to determine the objective auditory threshold. This modified method is usually called electric response audiometry (ERA).

Visually evoked potentials

Visually evoked potentials (VEP) are used to test the visual pathways by stimulating the eye with an alternating checkerboard pattern. For patients with impaired vision and small children, a lamp with a bright flashing light is used instead (flash VEP). Neural impulses are transmitted from the retina through the optic nerve to the visual cortex. Three of the evoked response peaks are used in clinical practice (Fig. 3). The test is most

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MAIN POINTS

Early testing of somatosensory evoked potentials and brainstem auditory evoked potentials provides sound prognostic information.

Visually evoked potentials can provide information about a history of optic neuritis.

Intraoperative monitoring of motor evoked potentials, optionally combined with somatosensory evoked potentials and brainstem auditory evoked potentials, is used to prevent permanent damage to the nervous system.

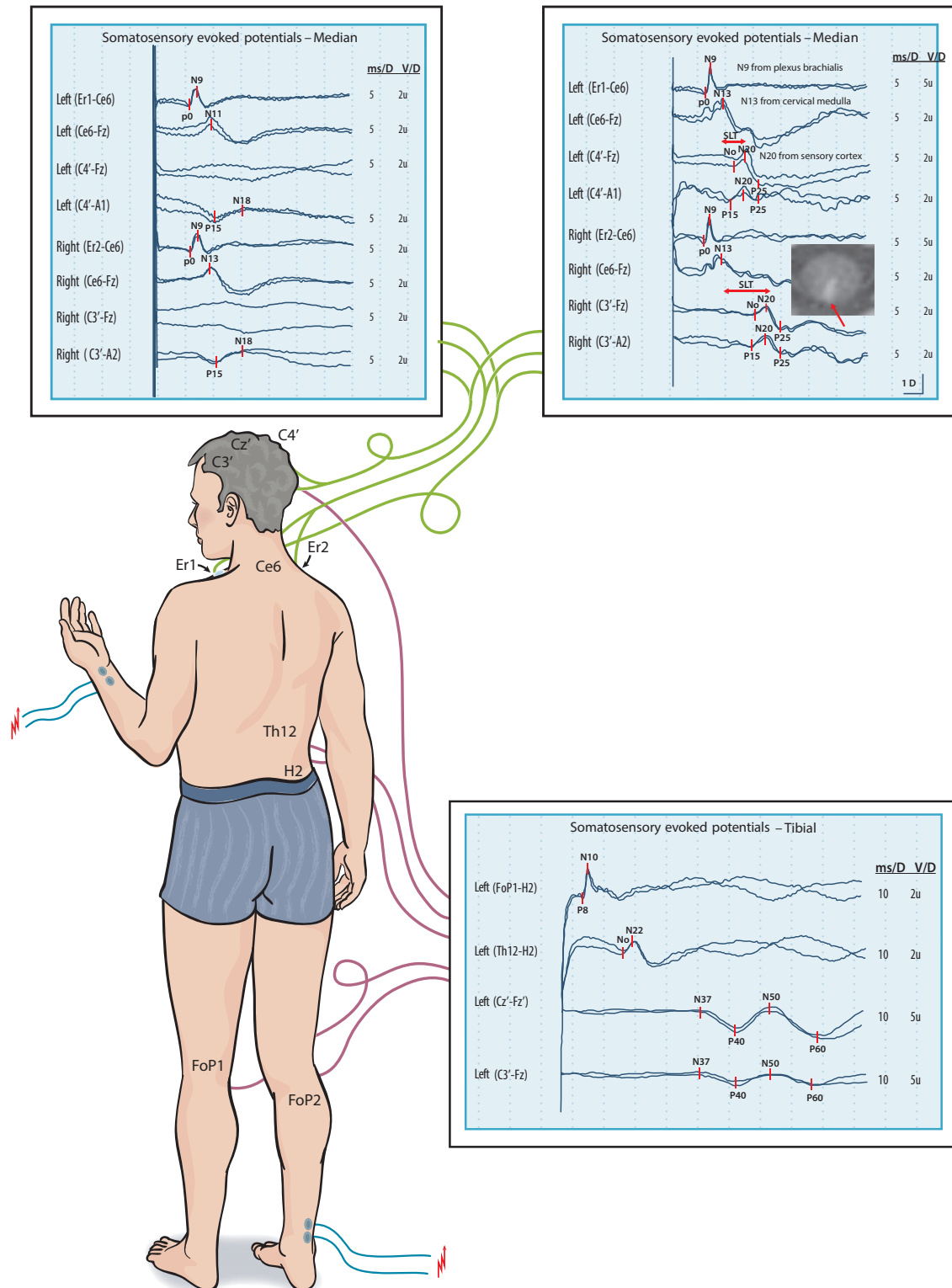


Figure 1 Test of somatosensory evoked potentials (SEP). This is a test of the sensory system whereby a peripheral nerve, normally the median or tibial, is stimulated with small electric shocks. The most important evoked response peaks are marked on the patient. The printout on the upper left is from an examination of a patient with cerebral anoxia damage. In SEP tests there was no response from cortical N20 bilaterally in channels 3 and 4. There was a normal response from the plexus brachialis (N9, channel 1) and cervical medulla (N13, channel 2). Note that intact P15 and N18 in channel 4 (reference electrode on the earlobe) indicate that the brainstem function in the medial lemniscus is intact. Such findings indicate that there is a poor prognosis for regaining consciousness. The printout to the right is from a patient with paresthesia and a sense of heaviness in the right arm and leg. It shows normal left-side median SEP peaks from the brachial plexus (N9), cervical medulla (N13) and sensory cortex (N20). However, N20 latency is significantly increased after stimulation of the right side (24 ms) compared to the left (18.7 ms). Double arrows: Central conduction time (CCT = N20-N13, upper normal limit 7.2 ms) is longer in the medial lemniscus system on the right side (11.4 ms) than the left (5.4 ms). A cross-section from T2-weighted MRI at level C2 with a wedge-shaped signal increase dorsally which affects the right cuneate fasciculus (see single arrow) is also shown. The findings indicated a clinically isolated syndrome, and not a definite multiple sclerosis. The printout to the bottom right is from a patient with intermittent blurred vision in the one eye for the last couple of years. The printout shows tibial SEP with prolonged latency for the evoked potential P40 from the sensory cortex. Central conduction time is also considerably prolonged (P40-N22 = 34.1 ms, upper normal limit 22 ms). Prolonged P40 latency was also found on the right side, and both the median nerve SEP and VEPs showed bilateral latency prolongation, while BAEPs were slightly abnormal on the right side. Note normal peripheral potential from the left fossa poplitea (FoP1) and normal lumbar potential from the electrode over Th12 in the midline (N22). These findings, coupled with inter alia MRI findings and spinal fluid tests, were consistent with multiple sclerosis. Illustrasjon © J. Engqvist/Illumedic

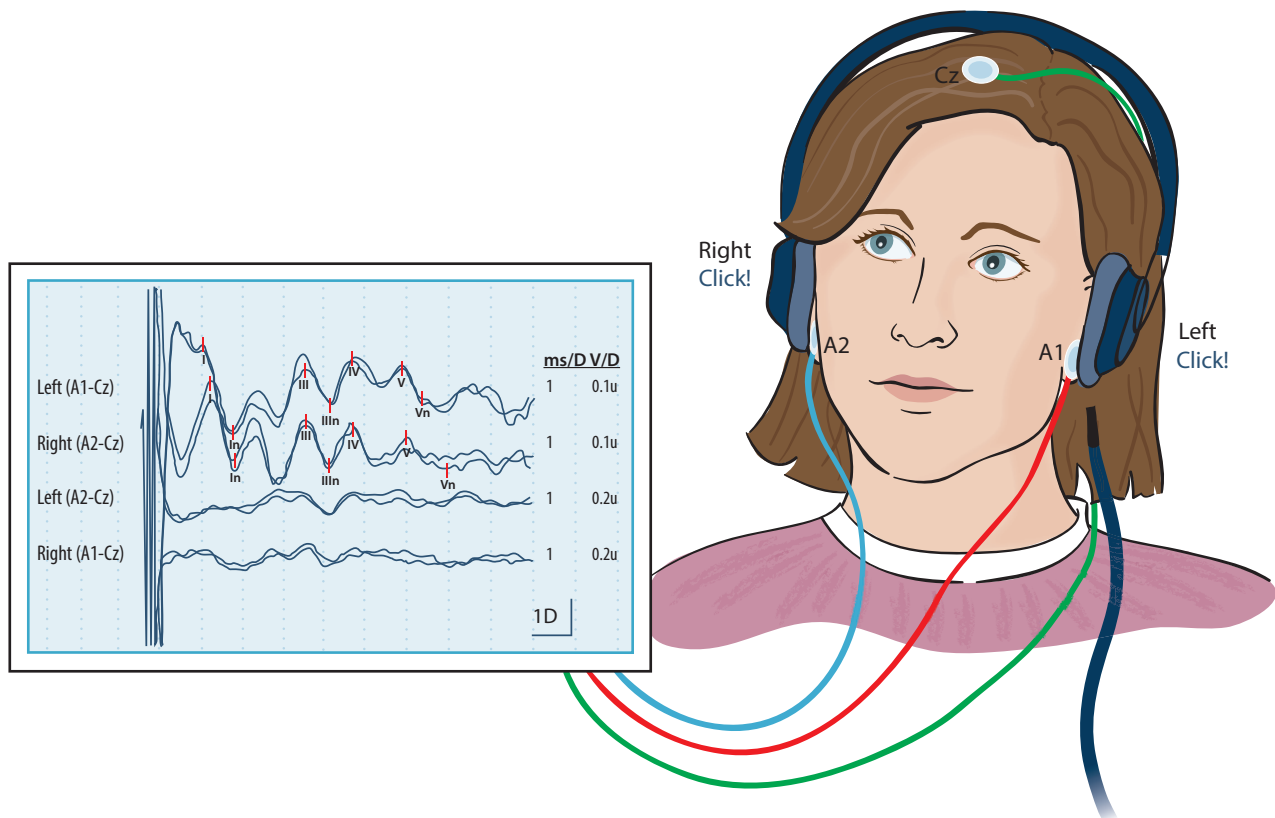


Figure 2 Brainstem auditory evoked potentials [BAEP]. This is a study of the auditory system where the auditory paths are stimulated by means of clicks delivered through headphones. The printout is from a patient with acute coma caused by thrombosis in the basilar artery. Somatosensory evoked potential N20 was extinguished bilaterally. Brainstem auditory evoked potentials showed normal wave I, III and IV from the left ear (channel 1, with electrode on the left earlobe – A1) and right ear (channel 2 with electrode on the right earlobe – A2). From the right ear, the V wave from the superior colliculus has reduced amplitude and is not very replicable. Moreover, the difference between waves I and V is clearly prolonged (5.3 ms). The findings indicate a structural affection in the upper pons near the superior colliculus. A few days later, waves III and IV on the right side became extinguished. Channels 3 and 4 show earlobe-vertex recordings from the contralateral ear on the unstimulated side. Wave 1 (from cochlea and auditory nerve) is not shown here, but the contralateral channels can help to identify waves IV and V. The combination of extinguished N20 and abnormal BAEPs indicate a low probability of the patient regaining consciousness. Illustration © J. Engqvist/Illumedic

frequently used to document a history of optic neuritis, for example in cases of suspected multiple sclerosis. It is also useful for monitoring disease progression in multiple sclerosis.

Electroretinography

Electroretinography (ERG) is carried out with the aid of a corneal electrode in some clinical neurophysiology laboratories and ophthalmology departments (3). It can reveal whether a retinopathic condition is affecting the dark-adapted vision (rods) and/or light-adapted vision (cones). The test is used, for example for cases of suspected retinitis pigmentosa, achromatopsia, congenital stationary night-blindness, juvenile retinoschisis, Stargardt Disease, acute zonal occult outer retinopathy (AZOOR) and Usher's syndrome.

Motor evoked potentials

Motor evoked potentials (MEP) are used to test conductivity in corticospinal pathways by stimulating the cortex from the outside of the head by means of a transcranial magnetic stimulator or electrical pulses. This is a sort of «reversed evoked potential», because the

evoked potentials are recorded from muscles. The test can be used to identify motor cortex in order to prevent paralysis in connection with neurosurgical interventions and as trial therapy for some pain conditions and depressions (4). According to an extensive literature review, it can also be used as a supplementary test for reduced conductivity or conduction block in the pyramidal tract in selected patients on suspicion of motor neuron disease, multiple sclerosis and cervical myelopathy and for psychogenic paralysis (5).

Intraoperative monitoring

In intraoperative monitoring, MEP, SEP and BAEP can be used to prevent permanent damage to the spinal medulla and other parts of the nervous system (6). Motor evoked potentials are often used to monitor the function of the corticospinal pathways in some spine operations.

Event-related potentials

Event-related potentials (ERP) are evoked when a subject performs a task which involves responding rapidly and correctly to a stimulus. The change in the electrical activity of the brain is measured simultaneously for

about one second. The P300 is the most common event-related potential (7). P300 is reported to correlate with the degree of consciousness of patients who have survived cardiac arrest (8), but the method is not sufficiently reliable for use as a diagnostic instrument on individual patients. As a result, event-related potentials are most used in neuropsychological research. Method guidelines were recently published in an international consensus report (9).

Somatosensory evoked potentials with pain

Cortical responses to brief impulses of heat pain are mostly used in pain research (10). A group of experts appointed by the European Neurological Society recommends that laser-evoked potentials (LEP) should also be used routinely in cases of neuropathic pain and other thin-fibre neuropathy because the response peaks will be severely weakened if the A-delta fibres do not function (11). The method has not yet become widely used in clinical settings.

Coma

SEPs and BAEPs are extensively and increasingly used in intensive care units to

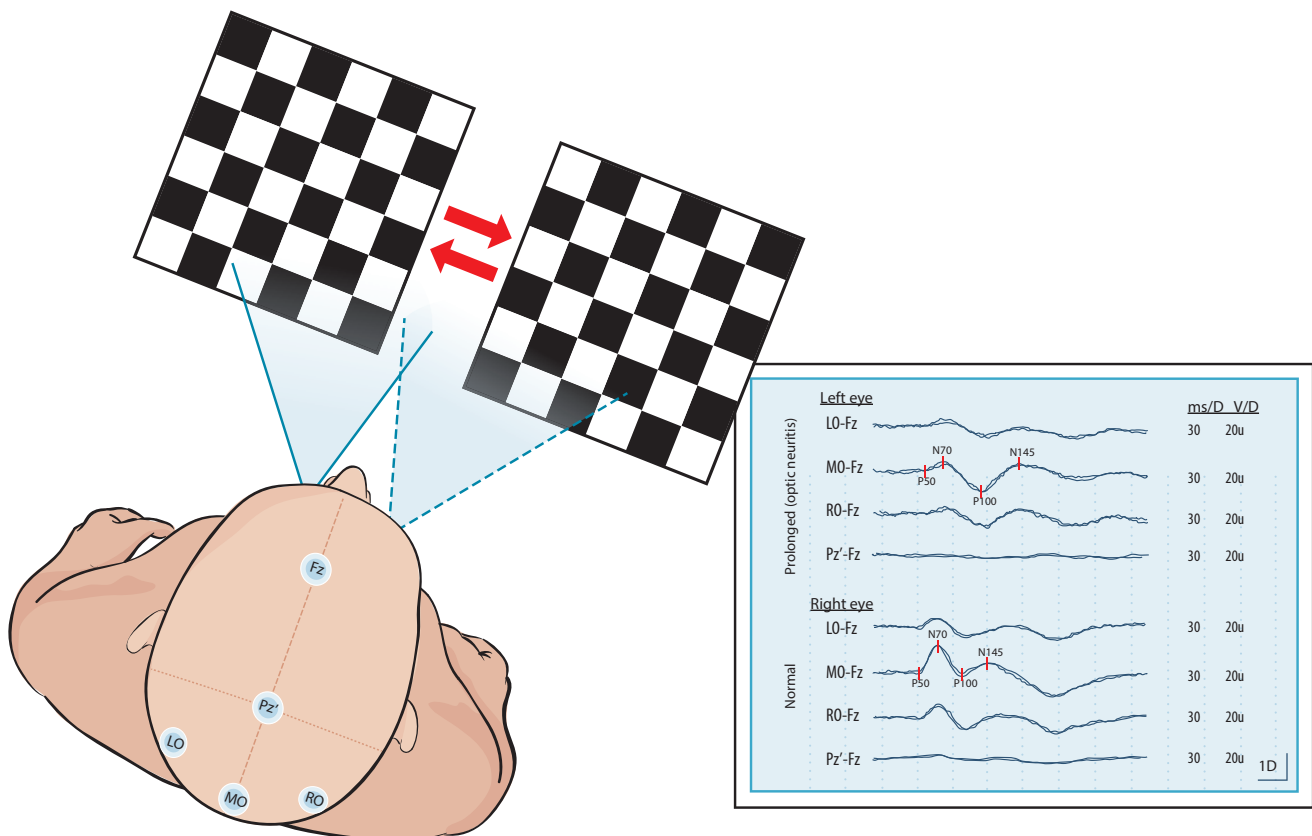


Figure 3 Study of visually evoked potentials (VEP) where the visual pathways are examined by stimulating each eye with an alternating checkerboard pattern. The print-out is from a patient who was suspected of having a history of optic neuritis. There are normal VEP amplitudes with a symmetrical response from the right (RO) and left (LO) lateral occipital region. VEP latency of P100 recorded over the midline occipitally (MO, channel 2) is prolonged from the left eye (118 ms) compared with normal latency on the right side (98 ms). The finding confirmed the clinical suspicion of previous optic neuritis. Illustration © J. Engqvist/Illumedic

assess the extent of injury and predict the outcome for comatose patients. This makes it essential to be able to take relatively noise-free measurements and document the response peaks by making at least two successive replications of the measurements.

Both the general outcome and the interpretation of the responses are influenced by the cause of the coma. There are four main clinical groups of coma conditions: anoxic ischaemic brain damage following cardiac arrest or respiratory arrest, traumatic brain damage, cerebrovascular disease or space-occupying lesions in the central nervous system and metabolic or toxic coma. In most cases, the cause of the coma will be known after hospital-based investigations during the first 24 hours. In contrast to electroencephalography (EEG), EP studies do not provide essential aetiological information, but they may often provide good prognostic information. With metabolic/toxic coma, normal SEP findings will strengthen clinical suspicion of a reversible condition. Patients with traumatic head injuries, cerebral haemorrhage or infarction will more often have complications such as oedema, herniation or hydrocephalus, and repeated EP testing is often indicated. Anoxia

primarily has a diffuse effect on grey matter, and the outcome depends on the duration of the anoxia.

Somatosensory evoked potentials are very valuable for early prediction of the outcome of post-anoxic brain damage. Bilateral absence of response from the sensory cortex (N20) is the best predictor of failure to regain consciousness, i.e. death, a persistent vegetative state or minimal consciousness, with a specificity of 100 % (12, 13) (Fig. 1). The same applies if anoxia patients receive hypothermia therapy, at least down to 33°C (14). On the other hand, the presence of a N20 response peak from the sensory cortex (on one or both sides) can *not* be interpreted as a definite favourable predictor, because about half of these patients will not regain consciousness.

In contrast to EEG, somatosensory evoked potentials are not substantially affected by general anaesthesia or sedatives, and N20 is measurable even in cases of sedation to isoelectric EEG. According to the most recently published international recommendations (15), somatosensory evoked potentials can be conducted 24 hours or earlier after cardiac arrest, but we often recommend, particularly

with children (16), monitoring the course with repeated tests over several days.

SEPs are also a useful predictor with children, but in contrast to the situation with adults, a good prognosis has been reported for a few children even in the bilateral absence of N20 (17). Few articles about SEP in children have been published (17) and the findings must therefore be interpreted more cautiously than for adults.

Normal BAEP findings have no predictive value for anoxic brain injuries, because cortical neurons are more sensitive to hypoxic-ischaemic damage than neurons in the brainstem. Preserved brainstem activity, on the other hand, has far greater predictive value for traumatic brain damage. Normal BAEPs will be a good sign in this situation, and given normal SEPs in addition, the predictive value for waking up is 90 % and the probability of a favourable outcome 75–80 % (13). Pathological BAEP tests (particularly the absence of wave V) indicate pontine dysfunction and are associated with death or a persistent vegetative state in over 90 % (15). Bilateral absence of somatosensory evoked potentials from the sensory cortex is not associated with death or a vegetative state in all brain dam-

aged patients, but is a good predictor for this group as well (18).

EPs can have similar predictive value for patients with coma due to cerebrovascular causes (Fig. 2). In the event of substantial supratentorial bleeding or infarction, the absence of SEPs and BAEPs predicts a poor outcome, while normal findings are equally uncertain predictors as in cases of anoxic damage (19). Repeated EP testing beyond the first week elicits little supplementary information in this group (20).

Optic neuritis and other demyelinating disease

Evoked potentials are used less than previously in the diagnosis of multiple sclerosis because the most recent international diagnostic criteria for multiple sclerosis, which previously included SEPs, BAEPs and VEPs (21), now mention only the last of these (22). It is stressed that at least one multiple sclerosis attack must be documented by a neurological examination, visually evoked potentials in patients with earlier visual disturbances, or MRI findings in areas that are consistent with clinical symptoms (22).

Optic neuritis occurs with multiple sclerosis, as an isolated syndrome and with other conditions. The diagnosis is primarily clinical. Visually evoked potentials may be useful for revealing subclinical neuritis, but are not regarded as mandatory in the acute phase (23). Most patients (> 90 %) who have suffered optic neuritis have quite substantially extended VEP latency for several years even if their vision becomes normalised (1, 2) (Fig. 3).

Neuromyelitis optica (Devic's disease) is a demyelinating disease with optic neuritis and pronounced myelitis (22) where most patients have antibodies for a membrane-binding water channel protein (aquaporin 4). The patients have reduced VEP amplitude and normal latency (24). Delayed and/or reduced amplitude VEPs may also be due to other conditions that affect the optic nerve, such as tumour, sarcoidosis, vitamin B₁₂ deficiency, neurosyphilis or spinocerebellar ataxia (2).

Somatosensory evoked potentials can still provide important supplementary information in selected patients with suspected multiple sclerosis and uncertain MRI findings. SEPs are also useful if MRI cannot be used because of patient claustrophobia. The test is more sensitive when applied to the lower extremities (Fig. 1, lowermost panel) than to the median nerve (2). Despite the fact that the American Neurological Association considered that somatosensory evoked potentials could also be useful (25), visually evoked potentials were the only EPs that were included in the first McDonald criteria (26). In the most recent revisions of 2005 and 2010 (22), even more emphasis has been placed on MRI and on practical simplification of the multiple sclerosis diagnosis. We

would like to stress that there is still no single certain diagnostic laboratory marker for this disease. MRI is a sensitive, but relatively unspecific examination where some patients may receive a false positive diagnosis (27). Evoked potentials are also aetiologically non-specific, but MRI, spinal fluid examinations and neurophysiological examinations are all recommended for use in differential diagnosis (28).

VEPs, SEPs and BAEPs can all reveal lesions that cannot be detected with MRI (29). Evoked potentials correlate with disease duration, functional status, morbidity (30) and disease progression (31). Even compared with modern MRI technology, multimodal evoked potentials will provide supplementary information for a number of patients with isolated clinical symptoms (32). Evoked potentials may therefore be valuable as objective markers of disease in therapy studies (33).

Conclusion

Evoked potential studies may often be an important supplement to information from EEGs, imaging methods and other laboratory tests. This applies especially to comatose patients, but the methods are also useful for evaluating optic neuritis and other demyelinating diseases. In intensive care departments, different types of evoked potentials (SEP, BAEP) are largely used for comatose patients, and because these tests are affected to only a limited degree by sedatives and general anaesthetics, they can provide early and useful clinical information about the extent of damage to the central nervous system and give an indication of outcomes for very many patients.

Although the tests are relatively simple and non-invasive, thorough and specialised training of practising neurophysiology technicians and clinical neurophysiologists is required, as well as adequate experience of using standardised methods in order to obtain technically good readings in clinical surroundings (34, 35). In the future, more efficient data processing may make evoked potential tests even more sensitive and specific and hence even more appropriate for diagnostics and for intraoperative and other neurointensive monitoring.

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