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REVIEW ARTICLE

Neurophysiological investigations of hepatic encephalopathy: ISHEN practice guidelines

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Abstract

By studying neuronal activity through neuronal electrogenesis, neurophysiological investigations provide a functional assessment of the nervous system and, therefore, has been used for quantitative assessment and follow-up of hepatic encephalopathy (HE). The different clinical neurophysiological approaches can be classified depending on the function to explore and their sensitivity to HE. The reliable techniques are those that reflect cortical function, i.e., cognitive-evoked potentials (EPs) (P300 paradigm), electroencephalogram (EEG), visual EPs (latency > 100 ms) and somatosensory EPs (SEPs) (latency between 25 and 100 ms). Short-latency EPs (brainstem acoustic EPs, SEPs of a latency < 25 ms) are in principle insensitive to HE, but can disclose brainstem conduction deficits due to oedema. SEPs and motor EPs can disclose myelopathies. Because of its parallelism to the clinical examination, clinical neurophysiology can complement the neurological examination: (i) to provide evidence of HE in patients who have normal consciousness; (ii) to rule out, at least under some conditions, disturbances of consciousness due to other causes (e.g. drug-induced disturbances, nonconvulsive status epilepticus) with the reservation that the mildest degrees of encephalopathy might be associated with an EEG pattern similar to that induced by drugs; and (iii) to demonstrate the worsening or, conversely improvement, of HE in the follow-up period.

By studying neuronal activity through central or peripheral neuronal electrogenesis, neurophysiological investigations provide a functional assessment of the nervous system. Therefore, their domain is similar to that of the clinical examination and complementary to that of neuroimaging. When compared with the clinical examination, they provide a more quantitative assessment, potentially amenable for follow-up, and may remain interpretable in patients under muscle blockade, in whom clinical examination is not feasible.

Because neuronal electrogenesis depends on neuronal activity that is sensitive to the influence of energy-providing metabolic systems as well as to the influence of those systems that are involved in electrolyte homoeostasis and clearance of toxic substances, clinical neurophysiology has been used for quantitative assessment and follow-up of metabolic encephalopathies (1).

Neurophysiological techniques

Two techniques are available for routine use, both in clinical and in experimental settings: the electroencephalogram (EEG) and evoked potentials (EPs). Recommendations for their execution are reported by Deuschl and Eisen (2). The grading of recommendations in this article was performed according to the EASL criteria (Table 1).

The EEG primarily reflects cortical neuronal activity modulated by both physiological and pathological diencephalic and brainstem influences and by metabolic and toxic factors. Many abnormal EEG patterns are

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Table 1. Grading of evidence and recommendations

	Notes	Symbol
Grading of evidence		
High-quality evidence	Further research is very unlikely to change our confidence in the estimate of effect	**A**
Moderate-quality evidence	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	**B**
Low- or very low-quality evidence	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	**C**
Grading of recommendation		
Strong recommendation	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	**1**
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty; higher cost or resource consumption	**2**

Source: European Association for the Study of the Liver (3).

non-specific and may reflect a wide variety of pathophysiological events, from transient, primary, subcortically or metabolically induced cortical dysfunction to irreversible cortical problems.

Evoked potentials are generated through the passive reception of sensory stimuli ('exogeneous' EPs) or cognitive treatment of sensory stimuli ['endogenous' EPs or 'cognitive' EPs (CEPs]. Exogeneous EPs may be classified according to the type of stimulus used [visual (VEP), auditory (AEP) or somatosensory (SEP)] or their analysis time window (short-latency, middle-latency or long-latency EPs). Contrary to the EEG that only assesses cortical function, EPs may provide assessment of both the brainstem [brainstem auditory EPs (BAEPs), short-latency SEPs (SSEPs)] and the cerebral cortex (long-latency VEP, SEP and AEP). They may also provide a quantitative assessment of some cognitive processes (CEPs). To improve communication with the intensivists and to facilitate patient follow-up, all EP parameters can be summarized into two indices: the index of global cortical function (IGCF) and the index of brainstem conduction (IBSC) (4). The IGCF is derived from flash visual and cortical SSEPs; it is rated from Grade 0 (normal cortical function, never observed in truly comatose patients) to Grade 4 (absence of cortical components). Grades 1–3 correspond to intermediate stages of increasing severity. The IGCF was shown to be correlated with the Glasgow Coma Score (5). The IBSC is derived from subcortical somatosensory and BAEPs: it may reflect medullary, pontine and/or midbrain dysfunction.

Motor EPs (MEPs) are recorded from muscles following direct stimulation of the motor cortex, or from transcranial stimulation of the motor cortex, either electrical or magnetic, via transcranial magnetic stimulation (TMS-MEPs). They provide information on motor cortex excitability and cortico-spinal conduction time.

One clear advantage of the EEG is to provide on-line assessment of brain function, in contrast to the EPs, which summate the functional status of the corresponding neural structures over the time needed for averaging. This makes the EEG a unique tool for studying rapidly changing activities (epileptic phenomena, triphasic waves, periodic patterns and cortical reactivity to stimulation).

In addition to providing straightforward brainstem assessment, EPs benefit from their relative resistance to the environmental electrical noise and levels of anaesthesia, which may sometimes completely obscure the EEG in the intensive care unit (ICU) environment (6).

Neurophysiological findings in hepatic encephalopathy

There is widespread evidence that both EEG and cortical EPs worsen in parallel to the increasing severity of HE.

Electroencephalogram

Hepatic encephalopathy of increasing severity is successively associated with a progressive slowing of the EEG, an initial increase, followed by a decrease, in EEG amplitude, a discontinuous pattern and an isoelectric EEG. A remarkable finding is the appearance of triphasic waves. Stupor is often, but not always, associated with triphasic waves; coma is usually associated with δ waves (7). Although triphasic waves are frequent in HE, they are not specific and can also be observed in other types of metabolic encephalopathies (uraemic, hyponatremia) or in drug intoxications (lithium, valproate and baclofen) (8, 9).

There is some debate on the initial changes in EEG, consisting of either a frontal predominance of the α rhythm or an increase in β waves (10–12). This observation is fully in keeping with the hypothesis of an increased GABA-ergic receptor activity. Indeed, benzodiazepine (BZD) administration is known to give rise to the initial appearance of anterior fast (β range) activities, which eventually slows down (and transiently cross the α range) with increasing dosages. Of note, stuporous HE patients may transiently recover following the administration of flumazenil, a BZD antagonist (13). At any rate, research on this issue is still needed to confirm changes in the spatial distribution of rhythms in the first stages of HE, their frequency, pathophysiology and meaning.

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The grading of the severity of EEG alterations in hepatic encephalopathy can be carried out on the basis of visual pattern recognition, but this approach has limited reliability (14). Grading on the basis of the simple semiquantitative evaluation of the frequency of the basic EEG rhythm improves the reliability of EEG evaluation (15). On the basis of the relative power of frequency bands and the mean dominant frequency, an EEG classification can be obtained that has prognostic value both in terms of survival and risk for development of overt HE (16).

Evoked potentials

The IBSC might remain unaltered even in the presence of a cortical dysfunction sufficient as to cause an isoelectric EEG. In fact, IBSC alterations indicate brainstem dysfunction, which either may be the consequence of the same or similar mechanisms as those causing HE, or represent a concurrent pathological disorder. Moreover, SSEPs can detect myelopathy. By contrast, there is widespread evidence that encephalic dysfunction of increasing severity is associated with a progressive worsening in IGCF from Grades 0 to 3 (6). Finally, several studies demonstrated changes in P300 latency and/or amplitudes in patients with the mildest degrees of HE, which are likely to parallel the early neuropsychological changes that can be observed in cirrhotic patients.

In a non-peer-reviewed study, Guérit (17) compared EEG and IGCF, before liver transplantation, in a group of 18 patients with acute liver failure (ALF) who eventually recovered after transplantation. EEG grading was performed according to visual analysis of the dominant EEG frequency (Grade 1: 7–8 Hz; Grade 2: 5–7 Hz; Grade 3: 3–5 Hz and Grade 4: < 3 Hz) and the EP grading using the IGCF. There was a highly significant relationship between EEG and IGCF grades ($P < 0.0001$). However, even the worst EEG alterations (Grade 4) were always associated with preservation of the primary cortical SEP and VEP responses (Grade 3).

Motor-evoked potentials, as well as SSEPs and BAEPs, may reveal signs of brainstem dysfunction or myelopathy, even in patients considered to have minimal HE (18–23), possibly linked to focal oedema occurring in this syndrome, or to concurrent disorders.

Because of its parallelism to the clinical examination, clinical neurophysiology can complement the neurological examination: (i) to provide evidence of HE in patients who have normal consciousness; (ii) to rule out, at least under some conditions, disturbances of consciousness due to other causes (e.g. drug-induced disturbances, non-convulsive status epilepticus) with the reservation that the mildest degrees of encephalopathy might be associated with an EEG pattern similar to that induced by drugs;and (iii) to demonstrate the worsening or, conversely improvement, of HE in the follow-up period. **B**

The usefulness of clinical neurophysiology in evaluating hepatic encephalopathy

Clinical neurophysiology in HE can be considered for:

1. the detection of minimal/subclinical forms of HE,
2. the objective quantification of overt HE,
3. the management of ALF.

Detection of minimal hepatic encephalopathy

Quantitative EEG analysis shows an increase of the relative power of the θ band and a decrease of the mean dominant frequency in the posterior derivations in 15–30% of patients with cirrhosis who do not have clinical evidence of HE (16, 24–27).

In the absence of other causes, the EEG alterations that are observed in this patient population are assumed to reflect the presence of minimal HE. In fact, these alterations (i) roughly correlate with the indices of hepatic dysfunction, (ii) predict the development of overt HE and liver-related death, at least in patients with advanced liver disease (16) and (iii) appear or increase when an amino acid oral challenge causing hyperammonemia is given to patients at risk for HE (28).

The P300 wave, elicited by an active oddball paradigm, was found to be altered in 20–80% of cirrhotic patients with no clinical evidence of HE or with Grade I HE (29). In follow-up studies, changes in P300 latency predicted the occurrence of overt HE (29). However, the changes in the EEG were found to have a higher value than P300 to predict the development of overt HE (30). In fact, P300 reflects a cognitive process, but the initial stage of HE causing changes in the electrogenesis might even precede cognitive dysfunction and more closely represent toxic brain dysfunction (31). At any rate, in the model of minimal HE induced by TIPPS, the delay of P300 latency was found to be more sensitive than those of the late cortical components of SSEPs (32).

Other kinds of CEPs can produce detailed information on the elementary mechanisms underlying cognitive processes in experimental settings (33, 34).

Objective quantification of overt hepatic encephalopathy

In the late 1970s, Conn *et al.* (35) considered the main background frequency of the EEG as one of the dimensions for HE assessment, as well as the mental state, asterixis and ammonia plasma levels. The use of the main background frequency can be biased in case the mixture of more rhythms that is common is overt HE (e.g. δ and θ band), or in case of instability of the tracing. In addition, it is not clear how to evaluate the presence of transients such as *intermittent rhythmic δ activity* or triphasic waves and how to consider the reduction in EEG amplitude occurring in severe coma. Despite these problems and only the rough correspondence of the EEG pattern with the behavioural features of HE on a population basis, the EEG has a unique role in producing

objective data on brain functioning, especially in non-cooperative patients. In the follow-up of single patients the correspondence between the EEG pattern and the clinical findings might be stricter than that on a population basis.

In summary, the different clinical neurophysiological approaches can be classified depending on the function to explore and their sensitivity to HE. The reliable techniques are CEPs (P300 paradigm), EEG, VEPs (latency > 100 ms) and SSEPs (latency between 25 and 100 ms), which reflect cortical function. Short-latency EPs (BAEPs, SSEPs of a latency < 25 ms) are in principle insensitive to HE, but can disclose brainstem conduction deficits due to oedema. SEPs and MEPs can disclose myelopathies. **B**

Recommendation. The optimal choice of clinical neurophysiological testing, for both research and clinical purposes, could be influenced by the anticipated degree of HE and the dysfunction, which is being sought. The most sensitive techniques (CEPs and quantitative EEG) are the best choices for the mildest degrees of HE, but CEPs rapidly saturate (in terms of change) for increasing degrees of severity. In the case of severe HE, less sensitive techniques can be used (IGCF). In extremely severe HE, the first cortical components of SSEPs are still detectable. The absence of these primary responses should lead to an in-depth assessment of other irreversible causes of brain damage. **2**

Management of acute liver failure

With regard to ALF (i.e. the rapid deterioration of liver function in a subject without previous liver disease, accompanied by encephalopathy), there can be a three-fold potential purpose:

a. Detecting brain dysfunction in patients with rapidly developing hepatic failure and, therefore, contributing to the diagnosis of ALF and the selection for liver transplantation;
b. Gauging the efficacy of ongoing therapy aimed at delaying or reducing brain oedema, or preventing and treating non-convulsive seizures, thereby gaining time if a cadaver graft is not available or *if* the patient is not a candidate for liver transplantation; and
c. Excluding from transplantation those patients who have already developed brain lesions as severe as to compromise any hope of functional recovery and in whom even a graft would not prevent death or unacceptable neurological sequels.

These three goals will be dealt with initially. We then offer some practical recommendations

a. Selecting those patients who need transplant, because of the severity of hepatic encephalopathy

The criteria that are used to select the patients with ALF who need transplantation are clinical. At present, neither EEG nor the EP grading of HE has been used for the selection for transplantation in ALF.

One small non-blinded retrospective study reported the use of SEPs as a tool for OLTs selection (36), showing that the disappearance of middle- to long-latency components (N70) in non-sedated patients (which were still detectable in 24% patients with Grade 4 HE) was superior to the King's College criteria for selection for transplantation (correct classification: 0.96 vs. 0.72 respectively). Such results, however, have been not repeated in a blinded or a larger series of patients. Moreover, it is hard to establish whether the use of sedative drugs would have reduced the diagnostic value of the disappearance of long-latency components of the SSEP.

The choice of a neurophysiological technique should be guided by the severity of HE under investigation. Because of their extreme sensitivity to any cognitive disturbance, CEPs are unlikely to be a valuable tool in the evaluation of ALF. Rather, we recommend using EEG and, if there are significant EEG abnormalities (predominant δ pattern or suppressed low-voltage pattern), to consider the IGCF, which would be analysed according to the presence, abnormality or absence of individual responses and interpeak latencies, or according to Guérit's classification (4).

b. Gauging the efficacy of ongoing therapy aimed at delaying or reducing brain oedema or preventing epilepsy, thereby gaining time in case of cadaver grafts are unavailable or the patient is not suitable for transplantation

The increase in intracranial pressure (ICP) is one of the main problems in patients with ALF. The possibility of substituting (or reducing the use of) invasive ICP monitoring with non-invasive electrophysiological monitoring would be an interesting clinical goal, given the risk of invasive ICP procedures in subjects with ALF. Of note, subclinical epileptic activity can increase ICP (37). The EEG is the only method for the diagnosis of non-convulsive seizures and the only tool available for monitoring its treatment (38–43).

In principle, an increase in ICP can give rise to both cortical (EEG, IGCF) and IBSC alterations. Despite the fact that the EEG changes reflect the severity of ALF in experimental animal models (44) and that a good relationship between EEG changes and ICP/cerebral perfusion pressure was also proven in humans (45), there is no proof that EEG monitoring is superior to clinical evaluation for non-sedated patients. With regard to EPs, the latencies of the late components of flicker vision EPs (fVEPs) (latency range > 100 ms) were found to reflect changes of ICP, but the time course of their changes was slower than that of ICP in an open non-blinded study (45). The P1 component of fVEP proved to be an index of HE in an open, non-blinded study comparing 10 patients with ALF and 10 patients with acute hepatitis who did not develop ALF, despite the absence of formal comparisons with other classifications (46). In the same setting, BAEPs were found to detect mainly prolongation of the III–V interpeak and, to a lesser extent, of the I–V

interpeak that did not correlate with HE or with its outcome. Of note, an imperfect correlation between ICP and clinical neurophysiological parameters should not automatically be interpreted as a failure of clinical neurophysiology, because it may also reflect the fact that some increase in ICP may be neurologically irrelevant.

It may be difficult to differentiate those EEG and IGCF alterations that are due to metabolic disturbances from those that are due to increased ICP. Additional problems occur by the concurrent use of sedative drugs in these patients, or by hypothermia (47), which also influence brain electric activity (48).

By contrast, because the relationships between body temperature and subcortical conduction times are known, any IBSC change, in conjunction with ICP monitoring, can provide some help to detect the brainstem consequences of increased ICP. This is the basis of systems designed for continuous monitoring of EEG spectrum, BAEPs and SSEPs (49) or for continuous monitoring of EEG and SSEP (50).

In summary, the use of EEG monitoring in patients with ALF admitted in ICU is worth investigating, as EEG is the only tool to monitor seizure activity. EEG, BAEPs and SEPs can theoretically complement ICP monitoring by establishing the neurological relevance of an increase in ICP. The issue of whether the installation of an invasive ICP monitoring system might be avoided or reduced based on EEG, IGCF or IBSC findings, thereby avoiding an increased risk of intracerebral bleeding, deserves further clarification. **B**

c. Excluding from transplantation those patients who have developed brain lesions as severe as to compromise any hope of functional recovery and in whom even a graft cannot prevent death or unacceptable neurological sequel

The EEG may not provide useful information to exclude patients from transplantation, because full EEG recovery has been described in patients with ALF even without transplant and flat EEG (51). In fact, the absence of EEG activity does not prove the existence of severe brain oedema and brainstem deficits (4, 6). Moreover, at least in experimental settings, EEG activity was proved to be absent in ALF even when fVEP still showed the existence of cortical activity (44).

The issue of whether absent cortical EP components (IGCF Grade 4) or BAEP changes consistent with major pontine involvement constitutes a sufficient criterion to exclude an individual patient from transplantation deserves further discussion.

Few uncontrolled studies have evaluated the applicability of SSEPs in the detection of patients with ALF who have excessively severe brain damage. Madl *et al.* (36) found that all the three patients out of 25 with ALF in which N20 disappeared died in a few hours. Similar results were obtained by Yang *et al.* (52, 53), who observed that all patients in whom N20 and P25 disappeared had died within 24 h after SSEP recording. By contrast, data on children with ALF due to Reye's syndrome also indicated possible recovery in subjects with absence of scalp SSEPs components (54). However, this study was performed in children and its applicability in adults is uncertain. Moreover, major signs of pontine involvement can also reflect a pre-existing, pontine damage (multiple sclerosis, posterior fossa tumour, etc.) which is prognostically irrelevant.

In the absence of any pre-existing pathology, a bilateral absence of N20 or BAEPs indicating structural pontine involvement provides firm evidence that the current neurological status of the patient is not just due to HE but that some secondary complication occurred (brainstem haemorrhage or brainstem lesions due to an increase in ICP). Although absent cortical SEPs indicate a particularly severe neuronal dysfunction, usually of an ominous prognosis, there is still some theoretical possibility that this situation may be reversible. Indeed, while there is now universal agreement that, in post-anoxic coma, a bilateral loss of N20 heralds death or vegetative state (54, 55), in head trauma a bilateral N20 loss after midbrain dysfunction has been associated with recovery in up to 15% of patients (56). An increase in ICP may cause bilateral loss of the N20 because of midbrain compression, thus interfering with subcortical conduction. Thus, even if unlikely, the possible reversibility should be investigated with imaging (computerized tomography scan or, if negative, magnetic resonance imaging or single photon emission computed tomography to recognize whether blood flow is still detectable). Noteworthy, such extreme alterations have never been described as a mere consequence of sedative drugs.

That is to say that the actual prognosis in this situation depends on its aetiology and pathophysiology, which must be sought before taking any positive or negative decision regarding transplantation.

Neurophysiological tools cannot be used in isolation to exclude consideration for liver transplantation. Even the bilateral absence of the N20 component of SSEPs is, in itself, not sufficient to exclude transplantation. However, it would be ethically unacceptable to offer transplantation to such a patient without further examination aimed at determining the irreversibility of the central nervous system compromise. **B**

Statements

- The EEG, although unspecific, provides information on the severity of HE (minimal to severe), independent of patient cooperation. It is influenced by drugs, electric noise and, when suppressed in severe coma, cannot reliably provide information on residual cortical or subcortical activity. **A**
- The EEG can occasionally indicate the occurrence of other kinds of brain damage alternative to HE, or provide patterns highly suggestive of HE in confused/stuporous patients (triphasic waves). **A**
- The EEG classification based on visual pattern recognition, although informative, does not allow reliable

grading. An estimate of the basic background frequency should always be provided. Quantitative EEG analysis may improve the reliability of EEG assessment. **B**

- Through the IGCF, sensory EPs can provide information on cortical function in severe HE. **C**
- Sensory EPs through the IBSC and MEPs, through the study of the cortico-spinal conduction time, may reflect conduction defects due to brainstem dysfunction or myelopathy. These can share same or similar causal mechanisms with HE or reflect other concurrent conditions. **B**
- Cognitive EPs require accurate methodological procedures both regarding the stimulus paradigms, recording and interpretation. Widespread clinical use may be problematic. These tests may provide an insight into the cognitive processes in research settings. **1**
- The use of neurophysiological monitoring tools for acute HE due to ALF is reasonable and research in this area is worthwhile. The EEG can detect non-convulsive and/or subclinical epileptic activity that can occur in these patients. **2**

Practical issues

Electroencephalogram

For diagnostic purpose, the 19 electrodes of the 10–20 International System are suggested. For monitoring purposes, four electrodes (for instance, P3, P4, F3 and F4) may be sufficient. No real agreement was found on the duration of EEG recordings: from 20–30 min – in order to display possible variations in the vigilance levels – to 5–10 min, which are considered enough by some members of the Commission. Eyes closed and eyes open recording was suggested whenever possible; photic stimulation was not considered necessary. Whenever possible, a polygraphic recording was considered preferable to understand unusual EEG patterns. The recording of the EEG at the same time of the day (e.g. morning vs. morning) and feeding conditions (e.g. fasting vs. fasting) was considered to be an ideal, but sometimes impossible, practice. In the case of EEG quantified by spectral analysis, no real consensus was found on the best measure to be considered: mean dominant frequency or spectral bands. No real consensus was found concerning the evaluation of fluctuating EEG: some members of the Commission prefer to consider the best segment, others the worst one and others both. **2**

Evoked potential

Consensus for the usefulness of median SSEPs and the uselessness of BAEPs were expressed, with variable answers for VEPs. A modification according to the problem to be addressed (minor degrees of encephalopathy and for research purpose: CEPs; minor degrees for clinical purpose: VEPs; more severe degrees: SEPs). At any rate, EPs should be elicited, recorded and interpreted according to standard guidelines. Both latencies and amplitudes should be considered. The patient's temperature should be considered in EPs interpretation. **2**

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