Submitted: 23 April, 2021 Accepted: 28 June, 2021 Published: 08 September, 2021 DOI:10.22514/sv.2021.132

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REVIEW

Acquired brain injuries: neurophysiology in early prognosis and rehabilitation pathway

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Abstract

Despite advances in intensive care medicine and neurosurgical procedures, the mortality and long-term disability rates for serious traumatic and non-traumatic brain injuries remain high. With improvements in intensive care, the most common proximate cause of death in comatose patients following acquired brain injury is represented by the withdrawal of life-sustaining therapies (ABI). This procedure, however, raises serious ethical concerns, as current approaches in the prediction of consciousness recovery and functional independence lack accuracy. The prediction of neurological outcome after severe ABI at the individual patient level is variable and challenging. Current prognostication models applied in severe traumatic brain injury and the post-cardiac arrest population perform reasonably well in predicting the neurological outcomes in low- and high-severity patients but do not allow for accurate outcome predictions in patients with intermediate severity. The current review highlights new clinical and instrumental prognostication developments, with a particular focus on the prediction of consciousness recovery. In particular, recent research has leveraged neurophysiological techniques (electroencephalogram and somatosensory evoked potentials) to build a strategy for recovery prediction. In addition, we underline the relevance of instrumental motor assessments because motor impairment may affect the reliable evaluation of the effective consciousness level or may hamper patients' complete functional recovery.

Keywords

Severe acquired brain injuries; Coma; Neurological prognosis; Electroencephalography; Somatosensory evoked potentials; Rehabilitation; Disorder of consciousness

1. Introduction

Hypoxic-ischemic encephalopathy (HIE), traumatic brain injury (TBI), intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAH) and brain infarction are common causes of mortality and morbidity [1–11]. Many patients affected by these acquired brain injuries (ABIs) die in the acute stages during their stay in the intensive care unit (ICU). Other patients, after a coma phase, may develop a disorder of consciousness (DOC), characterised by an unresponsive wakefulness syndrome (UWS) or a minimally conscious state (MCS). In some cases, their consciousness level improves, transitioning to emergence from a MCS (E-MCS). However, patients with E-MCS often show a severe neurological disability, mainly characterised by motor disability [12].

Motor disability is usually related to central nervous system (CNS) involvement [13], characterised by signs of upper motor neuron dysfunction, such as spasticity, paresis and increased deep tendon reflexes, but it may also be related to the presence of neuromuscular disorders [14]. Critical illness polyneuromyopathy (CIPNM) is a common and severe neurological complication of patients with a prolonged stay both in the ICU and the intensive rehabilitation unit (IRU) [15, 16]. CIPNM is characterised by muscle wasting and severe weakness with paresis predominantly in the leg and arm limb muscles and sparing of the facial muscles. Furthermore, reduced or absent tendon reflexes are detected. Involvement of the neuromuscular respiratory system, with difficulty weaning from the ventilator, is also a prominent sign. While CNS involvement related to brain lesions is often observed in patients with severe ABIs, CIPNM usually marks patients with sepsis, systemic inflammatory response syndrome and multi-organ failure [17–20]. Moreover, recent evidence [21] has shown that many critically ill patients suffering from cerebral injury can develop CIPNM, resulting in the coexistence of CNS and neuromuscular involvement in the same subject. These patients achieve a poorer outcome than subjects with CIPNM alone [21].

In recent years, improvements in intensive care technology and neurosurgical procedures have reduced the mortality rate of patients with severe ABIs. As a result, many patients were discharged from the acute setting exhibit severe DOCs and/or motor disability [12]. For this reason, early and reliable

prediction of the neurological outcome in a patient with DOC and motor disability has become an increasingly important goal in the acute stages after ABI [22]. Clinical evaluation in a comatose patient is performed according to the Glasgow Coma Scale (GCS) [23], which consists of evaluating three items, eye opening, the verbal response and the motor response. Each component is assessed by a standardised approach that permits objective evaluation and documentation of information about the level of consciousness. Each level of response is assigned a number—the worse the response, the lower the number. The total score ranges from 3 (the worst) to 15.

In the subacute phase, after eye opening, the GCS is no more able to identify the level of consciousness of patient. The Coma Recovery Scale-Revised (CRS-R) is a standardized measure of neurobehavioral function consisting of 23 hierarchically arranged items that comprise 6 subscales designed to assess arousal level, audition and language comprehension, expressive speech, visuoperceptual abilities, motor functions, and communication ability. The lowest item on each subscale represents reflexive behaviour, while the highest item reflects cognitively mediated activity [12].

A reliable prognostication indeed allows better identification of the proper therapeutic management of patients in ICUs, i.e., a reliable prediction of the neurological outcome may help in the choice to pursue aggressive medical or neurosurgical management or in dealing with complex management decisions. In a later stage, a reliable prediction of the neurological outcome allows better identification of patients who need further multidisciplinary rehabilitation treatment compared with those who should be referred to long-term care after hospital discharge [1, 2, 8, 10]. Despite advances in acute care, some patients can still evolve toward Brain death (BD). BD is defined as the presence of all the following clinical signs at the same time: unreactive comatose state (GCS = 3), abolition of brainstem reflex and apnoea test, performed with $PaCO_2$ value >60 mmHg, showing absence of intrinsic respiratory drive. In some countries, instrumental data such as EEG are also required. Having an accurate estimate of this neurological outcome may help in joint decision-making with family members, such as communicating the evolution of patients toward brain death (BD). Early neurological deterioration prediction of BD can also be useful in identifying potential organ donors, in influencing relatives' consent for donation and, in turn, in influencing organ procurement [7, 24].

Despite the many advantages it brings, a reliable neurological prognosis in comatose patients after ABI, in particular at an early stage, is still challenging and often calls for a multimodal approach, usually demanding both neuroimaging (brain computed tomography [CT] and brain magnetic resonance imaging [MRI]) and neurophysiological examinations [2, 8–11, 25, 26]. With regard to clinical neurophysiology, this may represent an extension of the clinical examination and an integration of neuroimaging. In fact, clinical neurophysiology plays an important role in the diagnosis, prognosis and monitoring of comatose patients after ABI. We believe that, to date, its potential is not yet sufficiently understood or exploited, particularly where its prognostic use is concerned.

Moreover, neurophysiological tests offer the following advantages: (1) they can be performed at the patient's bedside; (2) they can be performed many times along with clinical examinations; (3) they are inexpensive; and (4) they are independent of the efferent channel of motor behaviour (intentional limb movements, verbalisation, eye movements and emotional facial expressions), on which clinical evidence of consciousness is based.

However, heterogeneity of recordings and interpretation of the neurophysiological studies are potential methodological flaws. Nevertheless, the literature has already gathered data on a clinical consensus on the most useful diagnostic–prognostic neurophysiological tools and procedures, as well as their simplified interpretation [1].

Technicians and neurophysiologists should be specifically trained in the use of these neurophysiological tests and in the knowledge of the most frequent instrumental findings and their prognostic significance in comatose and DOC patients of different aetiologies.

In more detail, some neurophysiological tests, such as the electroencephalogram (EEG) and somatosensory evoked potentials (SEPs), provide more information on the acute phase [1, 26], while others (i.e., long-latency EPs/ERPs) add useful information in the post-acute phase in the cases of patients who are not yet responsive. Thus, the use of neurophysiology in this context of patients in a comatose state or with DOC should indicate not the application of a standard battery of tests but rather the choice of the neurophysiological tests that, on the basis of literature evidence, would be the most informative from the perspective of the given clinical question. For example, concerning the early stage after ABIs, it is important to point out that an EEG, indispensable for diagnostic purposes in comatose patients, whatever the aetiology of coma onset, should be supplemented by SEPs where prognostic purposes are concerned. In fact, SEPs, as well as being reliable indicators of the severity of acquired acute brain injury, show greater stability than an EEG because they are more resistant to sedation and show easily interpretable and comparable waveforms (Table 1).

Lastly, there are also several cases, such as locked-in states, locked-in-like states and diffuse neuromuscular weakness where the lack of a neurophysiological assessment may lead to a delay in observing the real level of consciousness of weeks or even months. We divided the post-coma onset condition into two operational phases: acute/subacute and protracted. The acute phase typically refers to a coma lasting up to 2 weeks; the sub-acute phase usually involves a variety of clinical states and lasts 6–8 weeks after the emergence of the coma, equivalent to the time spent in hospital intensive and sub-intensive care units. The final step, which varies in length depending on the aetiology of ABI, typically refers to time spent in a rehabilitation setting and results in a prolonged DOC. Neurophysiological assessment plays a significant prognostic role in these stages, and it can also help in the diagnosis of an impaired consciousness level in the absence of clinical evidence.

2. Acute phase

TABLE 1. Comparison of EEG and SEP features in comatose patients.

	EEG	SEP
Recordable bedside	++	++
Sensitivity to sedative drugs	++	–
Duration of recording	20–30 minutes	30 minutes
Classification of findings	++	+++
Time dependence of findings	++	–
Poor Prognosis	++	+++
Good Prognosis	++	To be defined
Etiology	HIE	HIE – TBI – ICH

SEP, Somatosensory Evoked Potential; HIE, Hypoxic-Ischemic Encephalopathy; TBI, Traumatic Brain Injury; ICH, Intra-cerebral Haemorrhage. Level of evidence: + ++ +++.

2.1 Somatosensory evoked potentials

SEPs are sensitive to diffuse grey-matter lesions, such as those observed in anoxic brain injury, as well as to a mix of focal and diffuse lesions (cerebral cortex, hemispheric white matter, brainstem) detected in head trauma. Furthermore, at least in the carotid territory, SEPs are sensitive to ischaemic damage [27]. As a result, SEPs are a good indicator of overall cerebral function [28], allowing for functional assessment of neural pathways in addition to neuroimaging. SEPs are important mainly in the prognosis of a poor long-term neurological outcome (Table 1). SEP waveforms can be grouped into several patterns, based on their presence and amplitude in both hemispheres of the main and early cortical complex (N20/P25), regardless of the aetiology of coma onset. SEPs are classified as normal (N) if the N20/P25 amplitude is normal; pathological (P) if the central conduction time (CCT) is abnormally prolonged, and/or the N20/P25 amplitude is less than 1.2 mV or the left-right amplitude asymmetry is greater than 50%; and absent (A) if cortical responses are absent with preserved cervical N13 [7]. Examples of different SEP patterns are reported in Fig. 1.

According to different aetiologies of brain damage, the same SEP pattern can vary in prognostic meaning. In ICH, a bilaterally absent SEP pattern (AA), in which the cortical responses of both hemispheres are absent, usually predicts death [29]. In TBI, the prediction for the SEP pattern AA may be that of death, a UWS or severe disability [30]. In particular, the prognostic power of the SEP pattern AA reaches 100% specificity only if severe neurological disability (GOS 3 [according to the Glasgow Outcome Scale]) is included in the poor outcome group [30]. Concerning this particular aetiology of brain damage, caution is due in the prognosis of patients with a bilaterally pathological SEP pattern (PP) because of the possibility of diffuse axonal damage. Thus, in TBI, a good recovery is possible despite severe alteration of SEPs.

Concerning HIE, the SEP pattern AA predicts either death or non-recovery of a consciousness state (death or UWS corresponding to CPC 5 or CPC 4 according to the Cerebral Performance Categories) [1–3, 8–10, 26, 31]. In post-anoxic patients, the bilateral absence of cortical SEP is a robust poor prognostic indicator of consciousness recovery independent of the recording time. Recently, Carrai *et al.* [5] showed, even if in a small group of patients, that this SEP pattern also maintained its predictive value for poor neurological prognosis a few hours after cardiac arrest (CA).

Concerning this particular aetiology of brain damage, recent studies have also shown a similarly poor prognosis associated with the SEP pattern absent in one hemisphere and pathologic in the other hemisphere (AP) [2, 8, 9, 26]. Finally, in the last five years, researchers investigated the possible role of cortical SEP amplitude as a poor prognostic indicator of HIE. The authors reported that a cortical SEP present but of bilaterally low amplitude (PP) was also associated with a poor neurological outcome (CPC 5 or CPC 4) [4, 31–34]. What differed across these studies was the amplitude cut-off on the better hemisphere, which varied from 0.6 to 0.3 μV [4, 32–35].

Concerning SAH, the literature data are scant. SEPs seem to be more accurate than both the World Federation of Neurological Societies (WFNS) grades and the modified Fisher scale in the prediction of poor long-term neurological outcomes prior to surgical or interventional treatment, and thus it may be applied as an effective aid in preoperative assessment [36]. Therefore, according to evidence in the literature, the prognostic power of SEPs in predicting a poor neurological outcome, both in terms of consciousness and disability, strictly depends on coma aetiology.

According to the aetiology of coma, some SEP patterns, particularly the bilaterally normal (NN) or the normal-pathologic pattern (NP), can also be useful in predicting a good neurological outcome in the acute stages in a limited number of cases. In more detail, in TBI patients, a NN or NP SEP pattern may predict a good neurological outcome (GOS 4–5) [37]. Concerning HIE instead, a recent study suggested that the bilateral presence of cortical SEPs with an N20-P25 amplitude greater than 3 μV is often associated with a recovery of the consciousness state [35].

Altogether, recent data showed that SEPs could be used not only to predict the long-term neurological prognosis but also to predict an early neurological deterioration evolving toward BD. With the exclusion of HIE, the SEP patterns AA and AP predict evolution toward BD within the first 72 hours of coma with good sensitivity (75%) and specificity (84.9%)

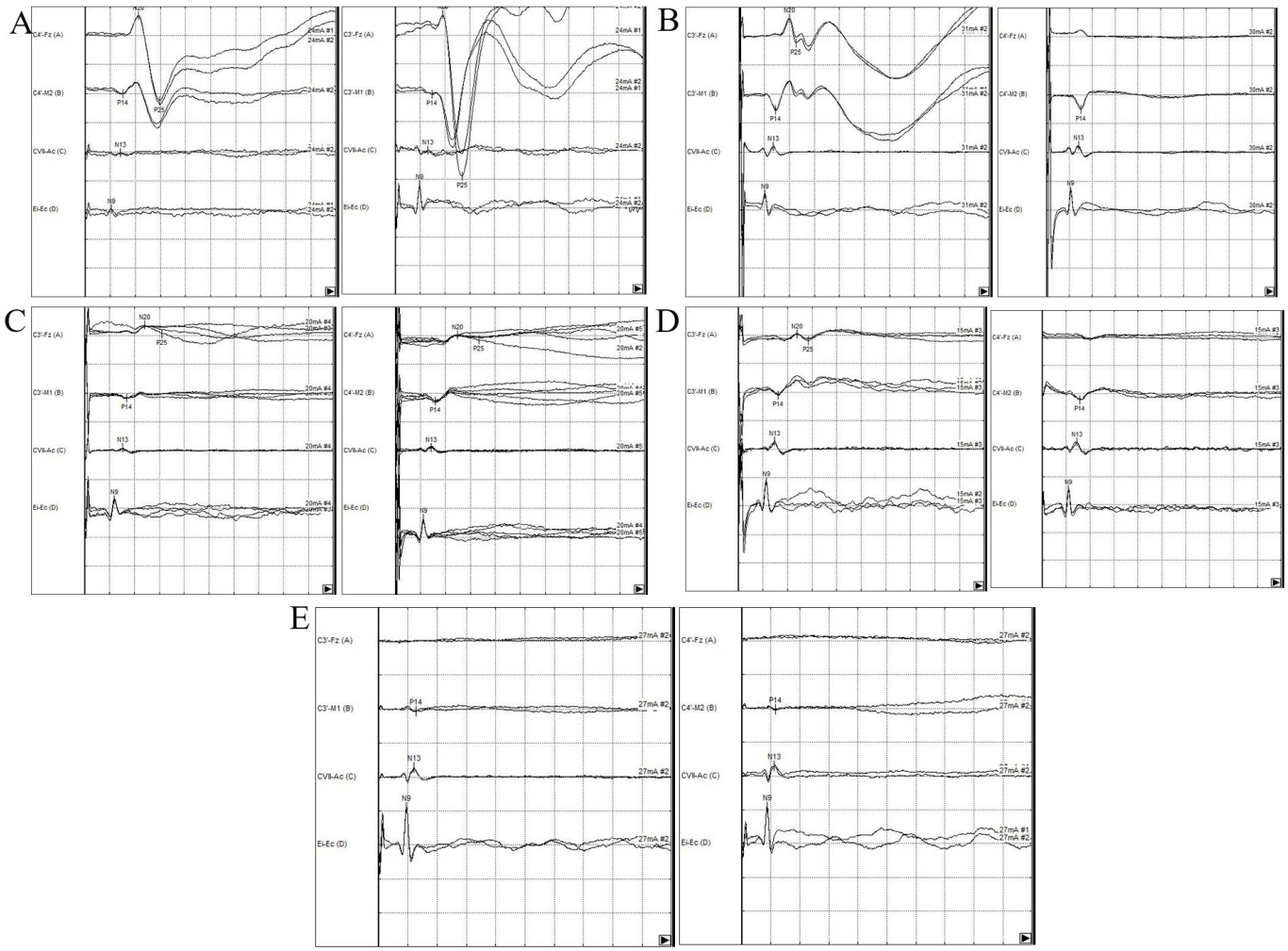

FIGURE 1. Examples of different SEP patterns obtained after median nerve stimulation. (A) Normal on both hemispheres. (B) Normal on left hemisphere and absent on the right hemisphere C. Absent on the right hemisphere and normal on the left hemisphere. (C) Pathological for amplitude ($<$1.2 μV) on both hemispheres. (D) Absent on the right hemisphere and pathological for amplitude ($<$1.2 μV) on the left hemisphere. (E) Absent on both hemispheres. In left columns are showed SEP components after right median nerve stimulation (cortical responses of the left hemisphere). In right columns are showed SEP components after left median nerve stimulation (cortical responses of right hemisphere).

[7]. Concerning HIE patients, however, SEP pattern findings different from AA and AP always excluded BD [24].

It must be pointed out that all data reported above were collected only in adult patients. To date, fewer data are available for comatose children; however, a systematic literature review showed that, even in these subjects, SEPs should be integrated into the process of neurological outcome prediction [38].

2.2 Electroencephalography

EEG has a weaker neurological prognostic value compared with SEPs in all the aetiologies of coma, excluding HIE patients, in which, instead, it may have both a good and poor prognostic meaning (Table 1). A possible explanation is that all coma patients, except for those with CA, are treated with high doses of propofol or midazolam at an early stage after ABIs to control intracranial pressure, creating unreliable EEG findings. In HIE, the EEG instead shows a high prognostic value for both poor and good neurological outcomes, because lower dosages of the interfering anaesthetic drugs are usually used. In this condition, in fact, the EEG usually remains continuous [8, 10].

Concerning the neurological prognosis of HIE, EEG, in contrast to SEPs, is a time-dependent indicator [3]. In fact, when specific EEG patterns are found at a particular time after coma onset, it is possible to predict a neurological outcome with 100% specificity (Fig. 2A). The continuous and nearly-continuous EEG patterns (Fig. 2B–C) [39, 40] found within the first 12 hours after CA are always associated with a good outcome (recovery of consciousness), whereas an isoelectric pattern (amplitude $<$2 μV) after 12 hours, a burst-suppression pattern [39] after 24 hours and a suppression pattern [39] after 48 hours from CA are always associated with a poor outcome (CPC 4–5) [8, 10].

Concerning TBI, evidence in the literature shows that EEG has a predictive value for a good outcome when, approximately one week after coma onset, the reactivity of the background activity is detected (Fig. 3A), whereas its absence usually marks a poor prognosis, above all when it is associated with severe SEP patterns (AP and PP) [30]. In conclusion, to date,

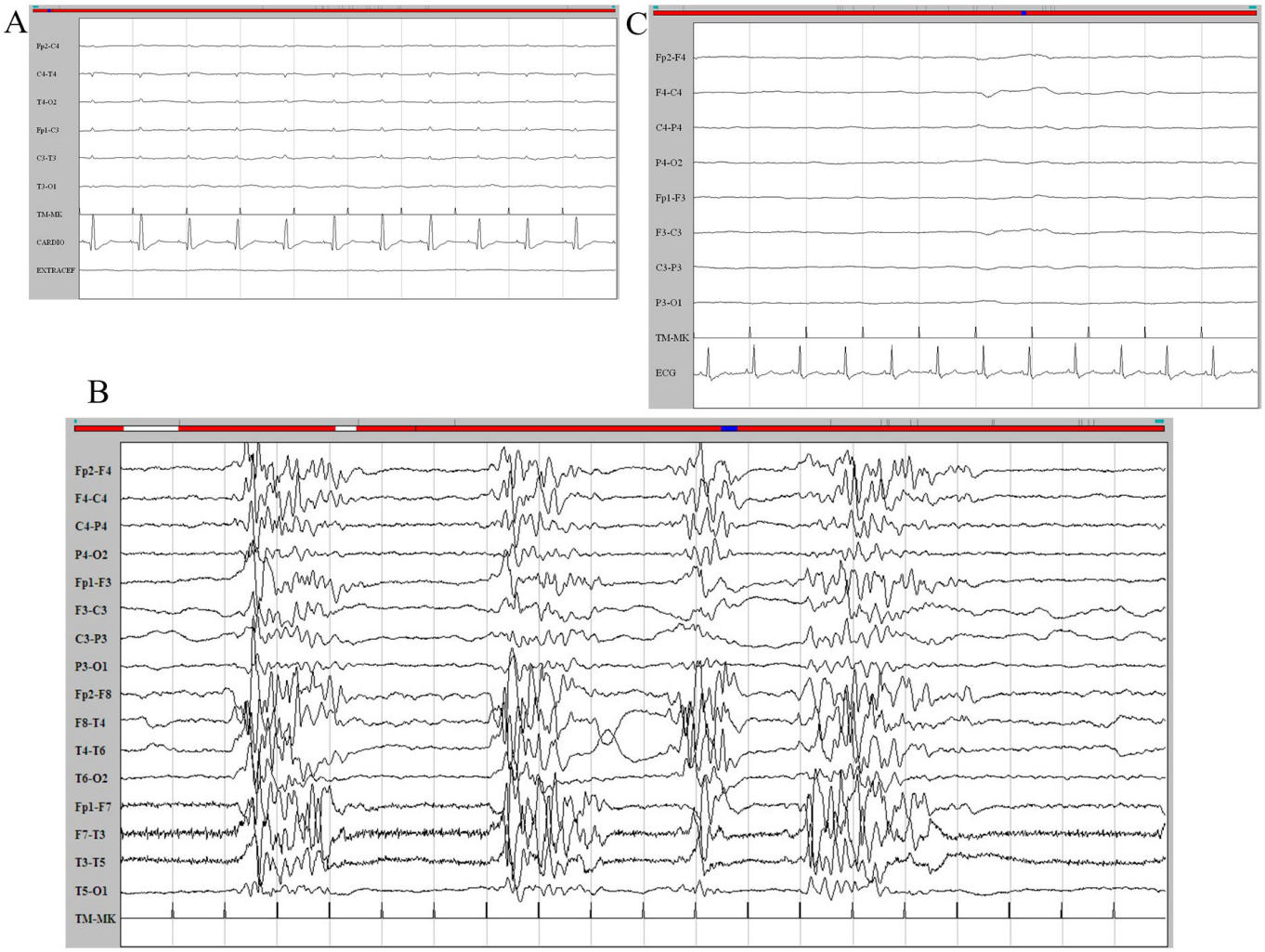

FIGURE 2. Examples of EEG patterns according to Hirsch's: malignant patterns. (A) Isoelectric. (B) Burst-suppression. (C) Suppression. Sweep time: 1 sec/div (A,C) or 2 sec/div (B); sensibility: 7 μV/mm.

when EEG is used at an early stage of coma, except in HIE patients, it is generally employed mainly for its diagnostic value for the detection of a non-convulsive epileptic status, a common consequence of ABIs. Furthermore, EEG has also shown its value as a guide to the treatment of refractory epileptic states or dosing of anaesthetic drugs [41].

2.3 Protracted phase

Establishing the neurological prognosis in post-acute stages, when patients are already admitted to the IRUs, is also important mainly for individualised multidisciplinary rehabilitation planning, given the realistic expectations of the patient's recovery, for assisting physicians in communicating with the patient's family members and caregivers, as well as for research trials focusing on assessment of the intervention effect. However, in contrast to the literature about the acute stages, there are no robust data about the long-term neurological prognosis in patients already admitted to the IRUs. In fact, to date, only a few studies [12, 42–46] have analysed post-acute clinical or instrumental predictors for late neurological prognosis, and they have shown some limitations and conflicting results.

One of the main reasons for the lack of post-acute robust neurological predictors has been the evaluation of only one neurological item at a time in most recent studies. In fact, if on one hand, some authors have focused on the evaluation of clinical or instrumental predictors of the recovery of consciousness [12, 42, 43], other authors have limited their assessment to clinical or instrumental parameters for motor recovery after CNS and/or neuromuscular involvement [13, 21, 47, 48]. Moreover, concerning the prognosis of the recovery of consciousness, another limitation is represented by the evaluation of only one clinical or instrumental parameter at a time in most recent studies.

In fact, only Scarpino *et al.* [43] accounted for the association of post-acute clinical and instrumental parameters for neurological outcome prediction, as suggested by Kotchoubey and Pavlov [49]. Until then, regarding clinical variables, only the total score on the Coma Recovery Scale–Revised (CRS–R) at patient admission to the IRUs and the improvement in the score during the first 4 weeks after admission had been investigated as post-acute neurological predictors [12]. Concerning instrumental parameters, EEG is the most investigated test for both diagnostic and prognostic purposes.

In contrast to neuroimaging (brain CT and MRI), as already underlined, EEG is a simple, risk-free, and inexpensive test

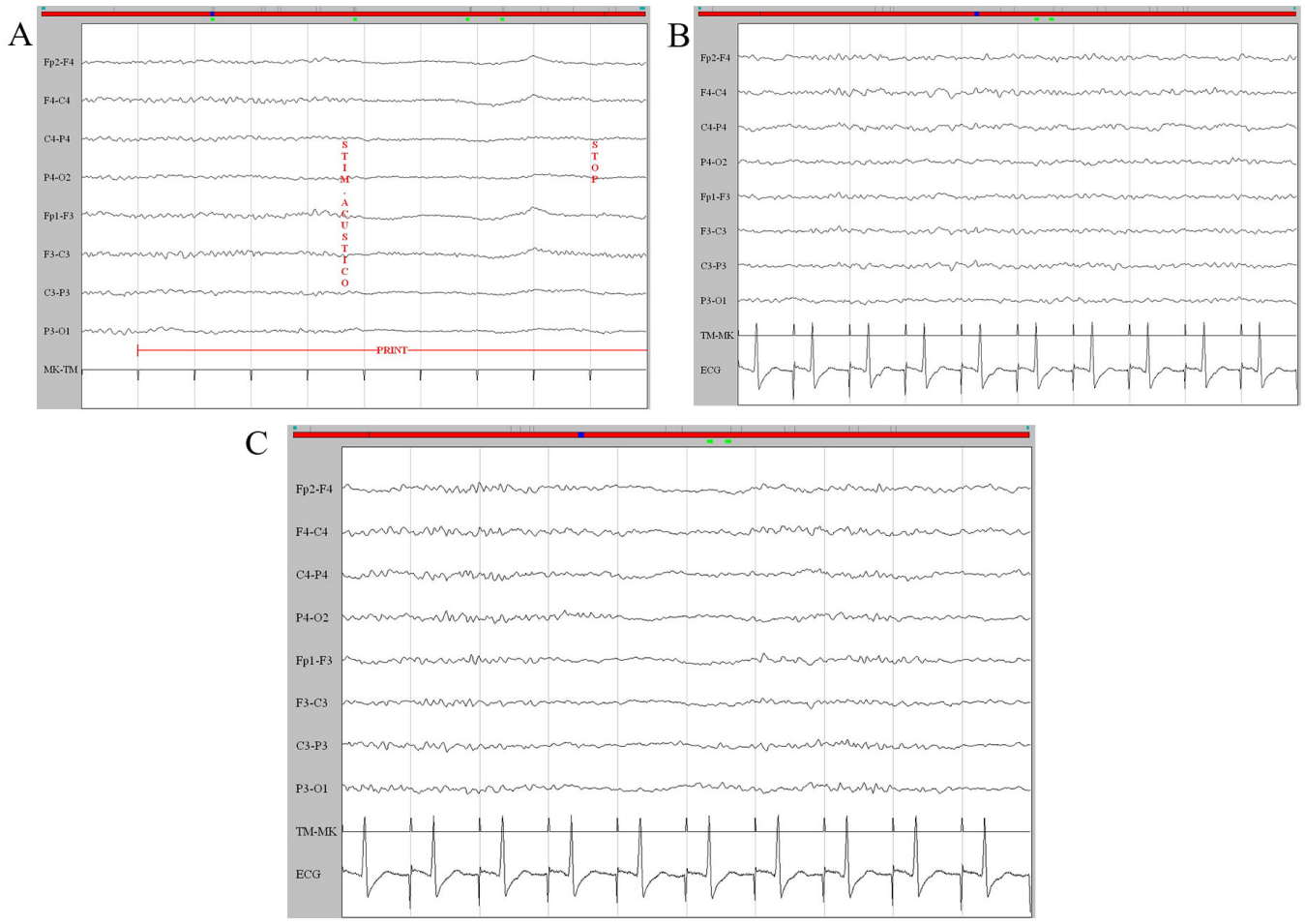

FIGURE 3. Examples of EEG patterns according to Hirsch's classification: benign patterns: (A) reactive background; (B) continuous; (C) nearly-continuous. Sweep time: 1 sec/div; sensibility: 7 μV/mm.

that can be performed at the patient's bedside. For these reasons, EEG findings represent the neurological predictor most investigated, also in the post-acute phases in patients with severe ABIs [1, 44]. However, while the 2012 American Clinical Neurophysiology Society (ACNS) terminology for EEG in the critical care setting [39] was accepted by researchers as standards for identifying specific EEG patterns as indicative of poor and good prognosis in the acute stages; data for the post-acute stages are still conflicting. This knowledge gap exists mainly because researchers have not yet agreed on specific terminology and classification of post-acute EEG findings in patients with DOC and because there is still no consensus on which EEG features are the most useful for prognostic purposes.

Another limitation is that most of the previous studies focused on one EEG descriptor at a time as the neurological indicator. Background reactivity was the most studied EEG descriptor [42, 43, 46, 50], and, despite being tested in a variety of ways, it was strongly associated with a better long-term neurological outcome when observed in a typical 30-min EEG recording. Another EEG descriptor that has been studied extensively is represented by the detectable transient patterns of stage II sleep (Fig. 4), which are used as a diagnostic method for assessing the extent of DOC as well as a late neurological predictor [43, 50, 51]. In most of the studies, this EEG feature was investigated through prolonged recordings. However, when this descriptor is examined through a standard 30-min EEG recording, its presence is also related to an improvement in the neurological outcome, albeit with reduced sensitivity, because of the lower probability of occurrence in a short EEG recording.

Epileptic discharges have also been investigated as a neurological predictor, albeit with conflicting results. Some authors have shown that, when present, epileptic discharges hamper the recovery of consciousness [43, 52], whereas Bagnato *et al.* [53] reported that the occurrence of structural epilepsy does not affect the recovery of consciousness.

Some classifications for the post-acute EEG of patients with DOC have been proposed in order to standardize EEG interpretation and therefore to identify particular EEG descriptors associated with a poor or good neurological prognostic meaning. In more detail, Bagnato *et al.* [42] randomly assigned a specific score to each pattern of specific EEG descriptors considered as strong neurological predictors (reactivity, voltage and frequency), resulting in a total score ranging from 3 to 7. Higher scores were associated with a higher likelihood of raising one's level of consciousness. Scarpino *et al.* [43] instead used the 2012 ACNS EEG terminology [38], which previously had only been used in the acute setting, to interpret the post-acute EEG. The authors observed that the presence of higher fre-

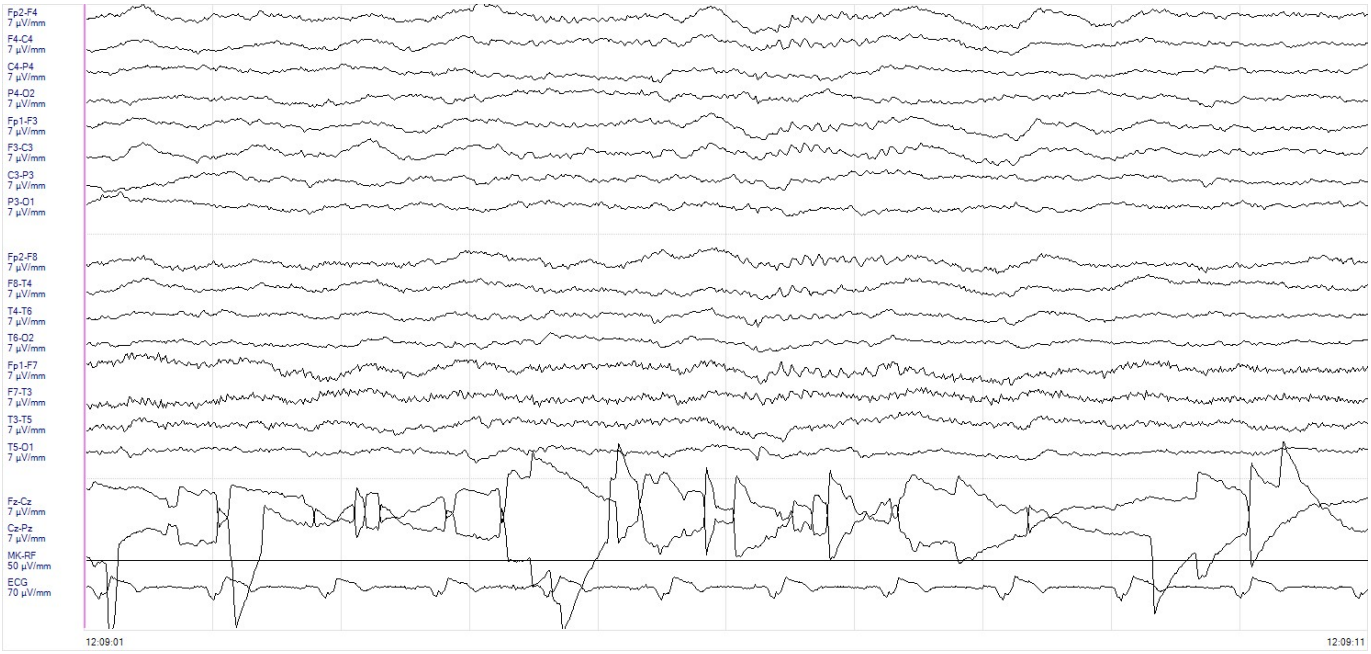

FIGURE 4. Example of spindle activity. Sweep time: 1 sec/div; sensibility: 7 μV/mm.

quencies (alpha waves), detectable transient patterns of stage II sleep, reactivity and variability in background EEG activity (a descriptor never considered previously) were associated with an improvement in the consciousness level. In contrast, the presence of epileptic discharges and lower frequencies (delta waves) and the absence of reactivity and variability in the background activity were associated with a poor prognostic meaning [43]. Estraneo *et al*. [45] also proposed a post-acute EEG classification even though the authors showed that its reliability was greater when used as a diagnostic tool to better assess a patient's consciousness level, rather than when used as a prognostic tool. This classification was based mainly on the assessment of the EEG reactivity associated with the evaluation of specific parameters of the background activity, such as frequency, voltage or the presence of an anterior–posterior gradient.

Recent investigations [44] have attempted to compare these previously proposed EEG classifications in order to identify which of them had the best predictive power for long-term neurological outcomes and thus the potential to be used in routine clinical practice among IRUs. Scarpino *et al*. [44] showed that the classification based on ACNS EEG terminology [39] had better predictive power than those of Bagnato *et al*. [42] and Estraneo *et al*. [45]. However, these data were retrospective and monocentric [44]. Thus, further prospective, multicentre studies are needed to obtain more solid and reliable data.

Concerning neuromuscular disorders, some neurophysiological parameters, such as nerve conduction (electroneurography-ENG) and electromyography (EMG), for the evaluation of spontaneous activity, have been used for CIPNM detection in critically ill patients [13, 21, 47]. The authors showed that the presence of CIPNM may prolong recovery time in IRUs, worsen the final outcome and increase the cost of hospitalisation [54, 55].

Intiso *et al*. [21] observed that despite a full motor recovery (40%–50% of CIPNM survivors [56, 57]), most of the patients reverted to a lower health status, including a problematic return to active daily living, resocialisation and participation. Patients perceived reduced endurance and poor physical stress tolerance as particularly debilitating.

Concerning CNS involvement, motor evoked potentials (MEPs), in association with clinical evaluation performed with the Medical Research Council scale (MRC), have been evaluated as predictors of motor function recovery. In a previous study [48], the authors showed that MEPs could be a supportive tool to increase the prognostic accuracy of upper limb motor and functional outcomes in hemiparetic patients, especially in those with severe initial paresis (MRC <2) and/or with motor evoked potentials absent in the post-stroke acute phase.

Most of these previous studies [13, 21, 42–44, 48, 54] evaluating instrumental parameters for prognostic purposes, focused only on motor recovery or consciousness recovery. Despite this limitation, the evaluation of an instrumental parameter for prognostic purposes is an important strength of these studies because it is well known that, in patients with DOC, clinical evaluation alone may not always be reliable, given the presence of several confounding factors. For example, in some cases, patients might show a lower CRS-R score because of motor impairment; on the other hand, clinical evaluation of motor disorders might also be questionable and inconclusive, especially in non-cooperative or severely cognitively impaired patients.

However, in contrast to the acute phase, in which in recent years, authors have proposed a multimodal approach for patients with severe ABIs, there is still no evidence about a multimodal clinical and instrumental evaluation of critically ill patients in the sub-acute stages, keeping account of both potential consciousness and motor recovery. This is an important topic because most rehabilitation treatments focusing on motor and functional recovery require the patient's cooperation. For this reason, in recent years, many studies have pointed out the

need to implement strategies for treating neuromuscular and CNS disorders in non-cooperative patients as well. On the other hand, knowing the expected level of motor and functional recovery after CNS damage or neuromuscular complications may help in early decision-making on medical and rehabilitation treatment, especially in patients who do not show a severe DOC and who can immediately cooperate during the rehabilitation treatment.

3. Conclusions

Prognosticating neurological outcomes is an important goal in both the acute and post-acute stages in patients with DOC after severe ABIs. Kotchoubey and Pavlov [49] suggested the need for a combination of clinical data and auxiliary variables for neurological prognosis, including neurophysiological examinations that are simple, inexpensive and recordable at the bedside. These instrumental tests offer an extra advantage over clinical examination, not only at an early stage, when neurophysiological tests can be employed in sedated and/or curarised patients, but also in post-acute stages, in order to better identify individualised medical and rehabilitation treatments according to the patients' real clinical condition. Finally, neurophysiological tests provide a functional evaluation of the nervous system, complementing and integrating neuroradiological techniques. For all these reasons, a neurophysiological evaluation should be included in multivariate models both for early prognostication of evolution toward BD and for long-term neurological outcome prognostication in all coma aetiologies.

AUTHOR CONTRIBUTIONS

MS: Literature search, Manuscript writing. GL: Literature search, Data collection. BH: Literature search, Manuscript revision. RS: Data collection, Figures and Tables. AM: Data collection, Figures. FC: Manuscript revision, Language editing. FL: Literature search, Manuscript revision. AG: Manuscript design, Manuscript revision.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Thanks to all the peer reviewers for their opinions and suggestions.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Francesco Lolli is the member of Guest editor of the journal.

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How to cite this article: Maenia Scarpino, Giovanni Lanzo, Bahia Hakiki, Raisa Sterpu, Antonio Maiorelli, Francesca Cecchi, *et al*. Acquired brain injuries: neurophysiology in early prognosis and rehabilitation pathway. Signa Vitae. 2021;17(5):1-10. doi:10.22514/sv.2021.132.