Let live or let die after traumatic coma

Scrutinizing somatosensory evoked potentials

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Summary

It is now firmly established that bilateral abolition of somatosensory evoked potentials (SEPs) after a non-traumatic coma has 100% specificity for nonawakening. In traumatic coma, a bilateral absence of the N20 components of SEPs does not implicate nonawareness. Comatose brain-injured patients should be systematically explored with auditory evoked potentials to check the functional integrity of another sensory pathway and the mesencephalic tegmento-tectal region on cerebral MRI should be carefully examined. Repeated evaluations during follow-up are also mandatory.

The development of various neurophysiologic tools over the last decades has made it possible to predict the likelihood of nonawakening of comatose patients with a very high specificity (see ¹ for a review). Indeed, a few meta-analyses have shown that bilateral abolition of

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somatosensory evoked potentials (SEPs) recorded within the first week after a nontraumatic coma had 100% specificity for nonawakening.^{2,3} Accordingly, bilateral abolition of SEPs is the most reliable prognostic indicator available at the early stage of coma after cardiac arrest. Conversely, in case of bilateral absence of SEPs, the rate of awakening of traumatic brain-injured patients ranged from 1% to 5%.^{3,4} As pointed out by Carter and Butt,⁴ the important implications of the prognostic evaluation of comatose patients in terms of neuroethics decision make it mandatory to determine the characteristics of false-positive patients; i.e., those with bilaterally absent SEPs who awake, because a prediction of an adverse outcome may alter patient management. For example, a reduction in the use of some aspects of intensive care (such as intracranial pressure monitoring) was shown in case of severe brain damage and poor prognosis.⁵

The purpose of the present study is to describe and discuss the cases of 3 traumatic comatose patients who awoke despite bilateral abolition of SEPs. These cases emphasize the imperative need for multimodal assessments with repeated measures in saving more lives among patients with very poor prognoses.

METHODS

Between 2007 and 2010, we collected data on all comatose patients admitted to the intensive care unit of our institution with a Glasgow Coma Scale score <8 in order to assess the prognostic values of several clinical and neurophysiologic diagnostic tools.^{6–9} The present retrospective study considered all patients with bilaterally absent SEPs after traumatic brain injury who regained awareness. On the patients included, repeated clinical observations, brain MRI findings, and neurophysiologic assessments are reported over a 1-year follow-up.

Return to consciousness

Clinical awareness was defined by the reproducible presence of one of the following signs: 1) response to simple commands; 2) manipulation of common objects; 3) eye-blink, gestural, or verbal yes/no responses; 4) intelligible verbalization; 5) stereotyped movements not attributable to reflexive activity.¹⁰

Conscious disorders

At 1 year after coma onset, patients in a vegetative state and minimally conscious patients were not included in the present study. Hence, inclusion criteria were restricted to patients alive at 1 year who emerged from a minimally conscious state.

Functional outcome

Disability was assessed using the Functional Independence Measure¹¹ at 1 year.

Brain MRI

The sequences comprised turbo spin echo T2-weighted images (TSE-T2), gradient echo T2 (T2*) images, fluid-attenuated inversion recovery T2 images (FLAIR), and diffusion-weighted imaging (*b* value of 1,000 s/mm²) with generated apparent diffusion coefficient (ADC) maps. The topographic localization of brainstem lesions was determined by 2 clinical neuroanatomists using a 4.7-Tesla atlas coregistered with each patient's MRI set.¹²

Table 1 Gradual categorization of evoked potentials

Grade	SEPs	BAEPs	MLAEPs
1	Normal	Normal	Normal
2	Amplitude reduction (N20 <0.6 μ V) (N20-P24 <0.8 μ V)	Increased I-V interval without amplitude reduction of wave V	Isolated increase of Pa latency (≥ 31.6 ms) without Na-Pa amplitude reduction
3	Absence of cortical response	V/I amplitude ratio <0.5	Na-Pa amplitude <0.3 μ V
4	—	Undetectable IV or V waves	Na present, Pa absent
5	—	Only wave I present	No Na-Pa detected

Abbreviations: BAEP = brainstem auditory evoked potential; MLAEP = middle latency auditory evoked potential; SEP = somatosensory evoked potential.

Neurophysiologic assessments

Electroencephalography, brainstem auditory evoked potentials (BAEPs), middle latency auditory evoked potentials (MLAEPs), SEPs, auditory N100, and mismatch negativity (MMN) were recorded at admission and controlled during the follow-up period. The method used for evoked potential recording has been previously described for SEPs¹³ and auditory evoked potentials.^{7,14} To summarize, the global analysis and comparison of results used a gradual categorization (table 1). The late auditory EPs, N100, and MMN were coded as present, probable, or absent. Whenever a difference was observed between right and left BAEPs, both grades were considered. In case of asymmetry of somatosensory or auditory cortical responses, the best response determined the grade.

Ethics

In accordance with the current French legislation, an observational study that does not change the routine management of patients does not need to be declared or submitted to the opinion of a research ethics board.

RESULTS

Between 2007 and 2010, 61 traumatic comatose patients were evaluated with SEPs. Among these, 14 had bilateral abolition of the N20 component of SEPs. At 1 year after coma onset, the outcomes of the 14 patients with bilateral abolition of the N20 component were as follows: 6 have died, 1 was considered in a vegetative state, 4 were minimally conscious, and 3 had severe disabilities.

The characteristics and outcomes of the 3 patients who regained awareness are summarized in table 2.

The initial and the latest neurophysiologic assessments are displayed in figure 1. The most relevant MRI are displayed in figure 2.

Cases

Case 1 is a 20-year-old woman who had a severe closed head injury in a motor vehicle accident which resulted in a comatose state. The bilateral absence of SEPs was explained by mesencephalon lesions involving the medial lemnisci (figure 2A). The auditory pathways were also impaired at the pontomesencephalic level as demonstrated by a bilateral reduction in the amplitude of brainstem responses to auditory stimuli. This was probably due to lesions of the inferior colliculi and paracollicular-related pathways as observed on MRI. A partial resynchronization of the auditory inputs was attested by subcortical Na responses. The follow-up neurophysiologic assessments confirmed the restoration of the auditory track through the presence of the N100 component and, possibly, MMN. A prolonged eye closure, due to a bilateral lesion of the oculomotor nuclei, masked the eye-blink signs of awakening at the

Table 2 Patient characteristics and outcomes

Characteristics	Patient 1	Patient 2	Patient 3
Age, y	20	21	31
Sex	F	F	M
Cause of the injury	Car accident	Fall	Stab wound
GCS on admission to ICU	7 (E1 M4 V2)	4 (E1 M2 V1)	12 (E4 M6 V2)
Secondary intracranial hypertension	No	Day 4	Day 9
Initial cerebral MRI	Week 2	Week 3	Week 7
Lesions	Bilateral tegmento-tectal; splenium of the corpus callosum; bilateral centrum semiovale	Bilateral tegmento-tectal; bilateral superior cerebellar pedunculus; right cerebral pedunculus; right capsulo-lenticular; left splenium of the corpus callosum; right middle temporal lobe; bilateral frontal lobes	Bilateral tegmento-tectal; left temporo-occipital; left diencephalic, hypothalamic, thalamic, and mamillothalamic
Neurophysiologic assessments			
Initial assessment	Week 1	Week 2	Week 2
EEG reactivity	No reactivity	To auditory stimuli	To nociceptive stimuli
SEPs	Grade 3	Grade 3	Grade 3
BAEPs	Grade 3	Grade 2	Grade 3–4
MLAEPs	Grade 4	NA	Grade 4
N100	Absent	NA	Probable
MMN	Absent	NA	Absent
Follow-up assessment	Week 11	Week 3	Week 26
SEPs	Grade 3	Grade 3	Grade 3
BAEPs	Grade 3	Grade 3 left, grade 1 right	Grade 3–4
MLAEPs	Grade 4	Grade 2	Grade 3
N100	Present	Present	Present
MMN	Probable	Present	Absent
Awakening and awareness			
Eyes opening	Week 10	Week 3.5	Week 10
Comprehension of simple commands	Week 11	Week 7	Week 8
Manipulation of objects	Week 12	Week 11	Week 15
Intelligible verbalization	Week 15	Week 18	Week 30
Stereotyped meaningful movement	Week 7	Week 3.5	Week 10
“Yes/no” response	Week 11 (eye-blink and right index)	Week 14 (right hand)	Week 52 (eye-blink and left hand)
Functional outcome			
FIM at 12 months	43	88	24

Abbreviations: BAEP = brainstem auditory evoked potential; FIM = functional independence measure; GCS = Glasgow Coma Scale; ICU = intensive care unit; MLAEP = middle latency auditory evoked potential; MMN = mismatch negativity; SEP = somatosensory evoked potential.

Figure 1 Initial (upper panel) and follow-up (lower panel) individual event-related responses

The stimulation side is indicated on the top of each panel. Somatosensory evoked potentials (SEPs): superimposed left and right parietal responses and the difference (contro-ipsi). Brainstem auditory evoked potentials (BAEPs): superimposed left and right ear responses. Middle latency auditory evoked potentials (MLAEPs) = superimposed right and left frontal derivations. N100-MMN = superimposed curves to frequent (bold gray), to rare (fine gray) stimulations, and the difference (bold black).

subacute stage. At 1 year postcoma onset, the patient was alert and well-oriented in time and space but remained severely disabled with a left hemiparesis (right centrum semiovale lesion, figure 2A, right panel), a bilateral static and kinetic cerebellar syndrome (cerebello-rubro-thalamic pathway disruption), and cognitive impairments (diffuse axonal lesions).

Case 2 is a 20-year-old woman who sustained a severe traumatic head injury after a fall of about 2 meters. The bilateral abolition of the N20 components of SEPs was a consequence of a lemniscal tract disruption in the inferior part of the mesencephalon (figure 2B). The auditory pathway was preserved with delayed auditory responses at the brainstem level. This was confirmed on follow-up assessments with delayed auditory cortical responses but preserved N100 component and MMN. The clinical awareness occurred during the third week postcoma onset. At 1-year postcoma onset, the neurologic examination found a left hemiparesis (right capsular and right cerebral pedunculus lesions), a static and kinetic cerebellar syndrome (bilateral lesions of the cerebello-rubro-thalamic pathways), and a cognitive impairment af-

Figure 2 Individual brain lesions on initial MRI and topographic locations on coregistered brain atlas

(A) Patient 1 left: asymmetric and bilateral tegmento-tectal contusion (arrows); middle: corresponding MRI atlas (the delineation of contusion is overlaid in white); right: restricted diffusion (arrows) in corpus callosum, and corticospinal tracts predominantly on the right side. (B) Patient 2 left: bilateral contusion involving the tegmentum and a right cerebral peduncle contusion (arrows); middle: corresponding MRI atlas; right: hematic axonal lesions (arrows) located within the prefrontal lobes (inlay), the corpus callosum and the cingulum. (C) Patient 3 left: asymmetric and bilateral tegmento-tectal contusion (arrows); middle: corresponding MRI atlas; right: restricted diffusion encompassing the ventro-posterior nucleus of the left thalamus (arrow), large hemorrhagic lesion affecting the left temporo-occipital lobes (*). Anatomic structures on 4.7-Tesla MRI atlas: inferior or medial colliculus (1), mamillary body (2), lateral lemniscus (3), brachium collicular inferior (4), medial lemniscus (5), reticular formation (6), central tegmental tract (7), medial longitudinal fascicle (8), brachium conjunctivum (9), red nucleus (10), periaqueductal gray matter (11), substantia nigra (12), optical tract (13), cerebral peduncle (14).

fecting the executive functions and memory (frontal, temporal, and corpus callosum lesions), but no confusion. The patient acquired progressively full independence in most activities of daily living but retained disability in complex tasks.

Case 3 is a 31-year-old man with a stab wound that caused an open head injury. At the first clinical evaluation, only a right hemiparesis and verbal expression disturbances were noticed. The admission CT scan revealed an intracerebral left temporal hemorrhage with peripheral edema as well as a subarachnoid and an intraventricular hemorrhage. At day 9, after a clinical worsening, an elevated intracranial pressure was revealed with coma, bilateral Babinski sign, and partially nonreactive pupils. Hydrocephalus and mesencephalic compression were ob-

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served on a cerebral CT scan performed the same day. A few days later, the left hemisphere and brainstem ischemic lesions were more clearly visible on MRI (figure 2C). At this clinical stage, neurophysiologic testing showed that somatosensory and auditory pathways were functionally interrupted at the brainstem level (figure 1). Identical results were obtained 2 weeks later but clinical awareness occurred 8 weeks later despite a probable right oculomotor nerve paralysis (figure 2C). On neurophysiologic retests, Na-Pa and N100 were present after left ear stimulation without reproducible MMN. After right ear stimulation, the brainstem responses remained altered without further resynchronization. At 1 year postcoma onset, the clinical picture remained fluctuating with reproducible upper limbs motor responses and verbal adapted communication. A major reduction of initiative remained with total dependence for activities of daily living.

DISCUSSION

In critical care, SEPs are routinely used for the prognostic evaluation of comatose patients. In the present study, a bilateral absence of the N20 components of the SEPs in a case of traumatic coma, contrary to anoxic coma, does not implicate nonawakening. As previously stated, given the potentially negative consequences on care management, it is mandatory to recognize false-positive (nonawakening) prognostic markers.⁵ This point is of particular interest in traumatic brain-injured patients because, for an equivalent clinical state, such as the vegetative state and the minimally conscious state, the prognosis is generally better after traumatic causes.¹⁵ Moreover, whereas the progression toward a chronic vegetative state is scarce after a traumatic coma, many patients go through the minimally conscious state during follow-up and late emergence from minimally conscious state is not rare, especially in young traumatic brain-injured patients.¹⁶

In posttraumatic coma, the presence of focal brain lesions may abolish specific sensory pathways; thus, recording another sensory modality with evoked potentials becomes of utmost importance. AEP recordings have progressively increased in comatose patients because they explore the functional condition of the auditory path from the peripheral nerve to the associative areas with event-related potentials (MMN and P300). Abolition of cortical MLAEPs has shown the same specificity as SEPs (100%) in the prognosis of nonawakening of postanoxic comatose patients.¹³ In all 3 cases presented above, MLAEPs were bilaterally abnormal at initial evaluation but a Na component was still present in patients 1 and 3. In patient 2, the MLAEPs were not recorded at the initial assessment but were present with an isolated delayed Pa latency at 3 weeks postcoma onset. Remarkably, the functional activity in the auditory pathways improved because, in all 3 cases, late N100 AEPs were noted during follow-up. A previous study has shown that a partial resynchronization of the signal above the lesion is sometimes possible.¹⁷ In that study, BAEPs, MLAEPs, N100, MMN, and the novelty P300 to the patient's own name were recorded in 50 patients who remained comatose for more than 24 hours. Among these, 11 patients had a novelty P300 (but no MMN) and 1 case had a novelty P300 but no Pa component of the MLAEPs. This highlights the role of late auditory EPs, N100, and, whenever possible, that of event-related potentials in predicting the outcome of posttraumatic coma, especially when the SEPs are bilaterally abolished. The neurophysio-

logic follow-up has also proved useful in monitoring functional recovery of dedicated sensory pathways.

Another way to restrain the risk of erroneous prognosis of nonawakening based on abolished SEPs is to look for focal lesions of sensory paths with MRI. It has been proposed to exclude from SEP exploration all patients with focal lesions, subdural effusions, and decompressive craniotomies.⁴ Regrettably, the majority of severe traumatic patients have focal lesions. Indeed, in a series of 448 consecutive severely head-injured patients, only 10% had normal cerebral CT scans during the immediate posttraumatic period (1 to 7 days after trauma).¹⁸ Hence, instead of excluding 90% of traumatic comatose patients, we propose to offer patients with absent SEPs systematic examinations with appropriate brain MRI sequences that explore the anatomy of the traumatic lesions, coupled with a careful examination and a proper interpretation of the images.

Anatomically, a mesencephalic lesion that involves the tegmentum should receive particular attention because of the potential involvements of the medial lemnisci, the oculomotor nuclei, and the inferior colliculi, which all play key roles in prognostic evaluation.

From a methodologic perspective, evoked potentials are difficult to perform in posttraumatic coma (risks of scalp edema and skin lesions). In addition, experimented teams are necessary to avoid false-positive results due to recordings of insufficient quality. In the present study, no methodologic problem could explain the bilateral obliteration of the parietal contralateral response. Actually, the functional disruptions of the somatosensory pathways were clearly explained on MRI by pontomesencephalic lesions involving the medial lemnisci.

From a functional point of view, in our 3 patients, the quality of the functional recovery seemed related to the importance of the BAEPs abnormalities because the clinical outcome was rapidly satisfactory in patient 2 (mild bilateral amplitude decrease of brainstem responses), slowly satisfactory in patient 1 (significant bilateral amplitude reduction of pontomesencephalic responses), and poor in patient 3 (auditory pathways were functionally interrupted at the brainstem level). Thus, the extent of the brainstem mesencephalic lesion may be crucial because the specific pathways or regions may be totally destroyed, partially disrupted, or only siderated.

Altogether, the present study confirms that bilateral abolition of the N20 components of the SEPs does not implicate nonawakening in traumatic coma and highlights the place of a wider approach of prognostic evaluation that combines repeated clinical assessments, multimodal evoked potentials, and cerebral MRI with a special attention to the midbrain level. The results lead us to recommend that patients who remain in a comatose state at least 1 week after a traumatic brain injury should be systematically explored with SEPs, BAEPs, MLAEPs, and MRI before making any decision of care limitation.

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DISCLOSURES

The authors report no disclosures.

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