■ Clinical commentary

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Epileptic Disorders

Intracortical focal non-convulsive status epilepticus causing cerebral hypoxia and intracranial hypertension

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ABSTRACT

We describe the pathophysiological consequences and long-term neurological outcome of a patient with acute brain injury (ABI) in whom intracortical electroencephalography (iEEG) captured an episode of prolonged focal non-convulsive status epilepticus (NCSE) that remained undetectable on scalp electroencephalography. A 53-year-old right-handed woman was admitted to hospital due to a large frontal left intraparenchymal hematoma. Over two and a half days, we captured recurrent non-convulsive electrographic and electroclinical seizures compatible with the diagnosis of intracortical focal NCSE. The patient remained sedated and a burst-suppression pattern was obtained. We also performed invasive brain multimodality monitoring including iEEG and measurements of intracranial pressure (ICP), partial brain tissue oxygenation ($PbtO_2$) and brain temperature. During non-convulsive electrographic and electroclinical seizures, the values of $PbtO_2$ decreased and those of ICP increased. Six months later, brain MRI revealed encephalomalacia localized to the left paramedial fronto-basal region. The neuropsychological assessment carried out one year after the injury showed scores below average in verbal learning memory, motor dexterity and executive functions. In summary, iEEG is a feasible innovative invasive technique that may be used to record non-convulsive electrographic and electroclinical seizures which remain invisible on the surface. Intracortical focal NCSE causes metabolic changes such as reduced brain oxygenation and an increase in ICP that can further damage previously compromised brain tissue.

Key words: intracortical electroencephalography, invasive brain multimodality monitoring, intracortical seizures, non-convulsive status epilepticus, acute brain injury

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In recent years, invasive brain multimodality monitoring, including intracortical electroencephalography (iEEG), has emerged as an important strategy in the management of patients with acute brain injury (ABI). An initial study showed that iEEG can provide good quality and safe recordings and may be used to detect electrographic seizures (ESz) that remain invisible on scalp electroencephalography (sEEG) [1-3].

The aim of this case report was to describe a patient with ABI in whom iEEG captured an episode of prolonged intracortical focal non-convulsive status epilepticus (NCSE) for several days that remained undetectable on sEEG, and to report the pathophysiological

consequences and long-term neurological outcome associated with this.

Methods

Patient

The patient was selected from an ongoing prospective research project carried out among comatose adults with ABI in whom we performed invasive brain multimodality monitoring including iEEG. Intracortical electrodes, when possible, were placed next to the damaged tissue. Our study was inspired by studies previously published by the Columbia group [1, 2, 4]. Our protocol excluded any modification of antiseizure drug (ASD) therapy during iEEG.

The patient was a 53-year-old, right-handed woman who was admitted to our emergency unit because of headache, a decreased level of consciousness and a generalized tonic-clonic seizure. Neurological examination showed a score of 4 on the Glasgow Coma Scale, bilateral myotic pupils, decerebrate posturing and bilateral extensor plantar responses. A computed tomography (CT) scan of the brain revealed a large frontal left intraparenchymal haematoma with severe intraventricular haemorrhage, intense hydrocephalus and diffuse cerebral oedema. Signs of subarachnoid haemorrhage over the convexity were also seen (World Federation of Neurosurgical Societies Scale: 5; modified Fisher scale: 4). A CT angiography depicted a saccular aneurysm at the confluence between the right anterior cerebral artery and the anterior communicating artery. Treatment with levetiracetam (1,000 mg/12 hours) was initiated. The rest of the arteries of the Circle of Willis were normal. Informed consent for the insertion of monitoring devices was obtained from the relatives of the patient. Monitoring devices were placed in the left hemisphere. Moreover, a ventricular drainage was inserted in the right side.

EEG

Commercially available eight-contact Spencer minidepth electrodes (AD-Tech, Racine, WI), designed for clinical iEEG recording, were chosen for use, as described by others [1]. An intracortical electrode was placed on the left side. In this case, our neurosurgeon inserted the intracortical electrode by hand, at the bedside in the intensive care unit (ICU). Subsequently, we used electrophysiological recording to place it in its optimal position, and the location of the minidepth multicontact electrode was confirmed by brain CT immediately after the procedure. In addition, 21 subdermal needle electrodes attached with collodion, placed according the international 10-20 system, were included. EEG was recorded using a digital video-EEG monitoring system (Xltek; Natus Medical). The Pz electrode was used as a reference for intracranial recordings. Referential and bipolar montages were used for reviewing. This protocol was approved by the local ethics committee.

For the definition of ESz, electroclinical seizure (ECSz) and electrographic status epilepticus (ESE), we used the 2021 version of the American Clinical Neurophysiology Society (ACNS)'s Standardized Critical Care EEG Terminology [5]. Therefore, an ESz was defined as epileptiform discharge averaging >2.5 Hz for 10 seconds (>25 discharges in 10 seconds) or any pattern with definite evolution lasting ≥10 seconds. In addition, the term ECSz was used when there were clinical signs clearly time-locked to the EEG pattern. ESE was defined as an ESz lasting for 10 continuous minutes or for a total duration of 20% of any 60-minute period of recording. All ESz and ESE alone (without clear clinical correlate) were considered non-convulsive. Moreover, any ECSz without prominent motor activity was also considered non-convulsive.

Multimodal monitoring

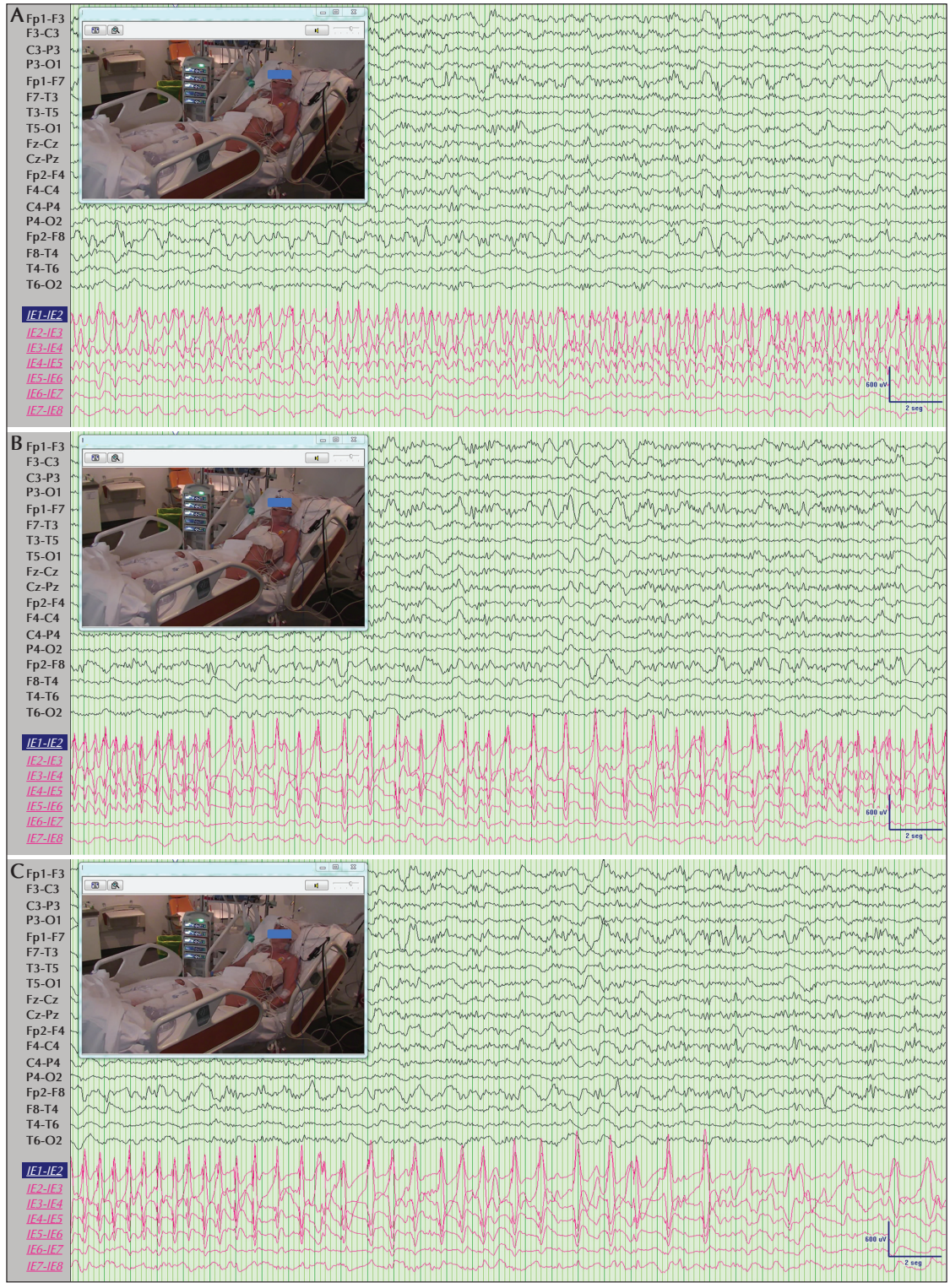
Invasive monitoring included measurements of intracranial pressure (ICP) (Integra Camino 110-4L), partial brain tissue oxygenation ($PbtO_2$) and brain temperature (bTemp) (using a combined oxygen and temperature probe Licox CC1.P1). These devices (ICP, $PbtO_2$ and bTemp) were inserted through a burr hole within a double-lumen bolt.

Neuropsychological assessment

We performed a comprehensive neuropsychological evaluation including memory, speech, praxis, visual-motor coordination and executive function. In addition, we used a questionnaire for quality of life. The following tests were employed: 15-word list- Rey Auditory Verbal Learning Test (RAVLT) for verbal memory; Digit Span backward, WAIS III for working memory; Symbol Coding, WAIS III for processing speed; Boston Naming Test for language (naming); Grooved Pegboard for motor dexterity; Trail Making Test- B for executive function; and EuroQoL-5D for quality of life.

Results

iEEG was started on Day 2 after admission and the patient was monitored for 155 hours. There were no complications associated with device insertion. During the next two and a half days of monitoring, we captured frequent spontaneous recurrent, waxing and waning, unequivocal intracortical ESz (*figure 1*). These ESz were unrecognizable on sEEG. All these episodes were non-convulsive. Occasionally, some of these ESz were



■ **Figure 1.** (A-C) A spontaneous unequivocal intracortical ESz involving the deepest and intermediate contacts (E1-E6) of Spencer mini-depth electrode. Ictal electrographic changes are absent on the sEEG. Low filter: 0.53 Hz; High filter: 70 Hz; Notch filter: 50 Hz. Intracortical recording: vertical bar: 600 µV. Distance between solid vertical dark lines: 1 second (speed: 15 mm/second). Note that the intracortical signal is six-fold greater than the scalp signal. Sensitivity for the scalp recoding was 100 µV/cm.

associated with subtle clinical manifestations such as restlessness and erratic movements of the upper left limb (therefore, defined strictly as ECSz following the recommendations of the ASCN) [5]. We also recorded stimulus-induced ESz and ECSz. These reflex seizures occurred in relation to nursing staff manipulation, throughout complementary tests, such as doppler ultrasound, and visits by her relatives.

On Days 5 and 6, the patient remained sedated and a burst-suppression pattern was identified. Interestingly, bursts of high-amplitude rhythmic delta waves involving the deepest contacts were also sometimes seen. On Day 8, 24 hours after withdrawal of sedation, the patient was awake and able to understand simple commands. On Day 17, she was transferred to the neurosurgical ward where she demonstrated progressive improvement. Finally, on Day 39, she was discharged on treatment with levetiracetam (1,500 mg/day) and nimodipine (240 mg/day).

We also qualitatively compared the values of $PbtO_2$, ICP and arterial blood pressure (ABP) between a 24-hour period of continuous recurrent ESz and ECSz and a seizure-free period under profound sedation reaching a burst-suppression pattern (*figure 2*). The values of $PbtO_2$ were notably lower during the period of non-convulsive ESz and ECSz, however, those for ICP were significantly higher with marked variability of ABP.

Clinical and EEG evolution

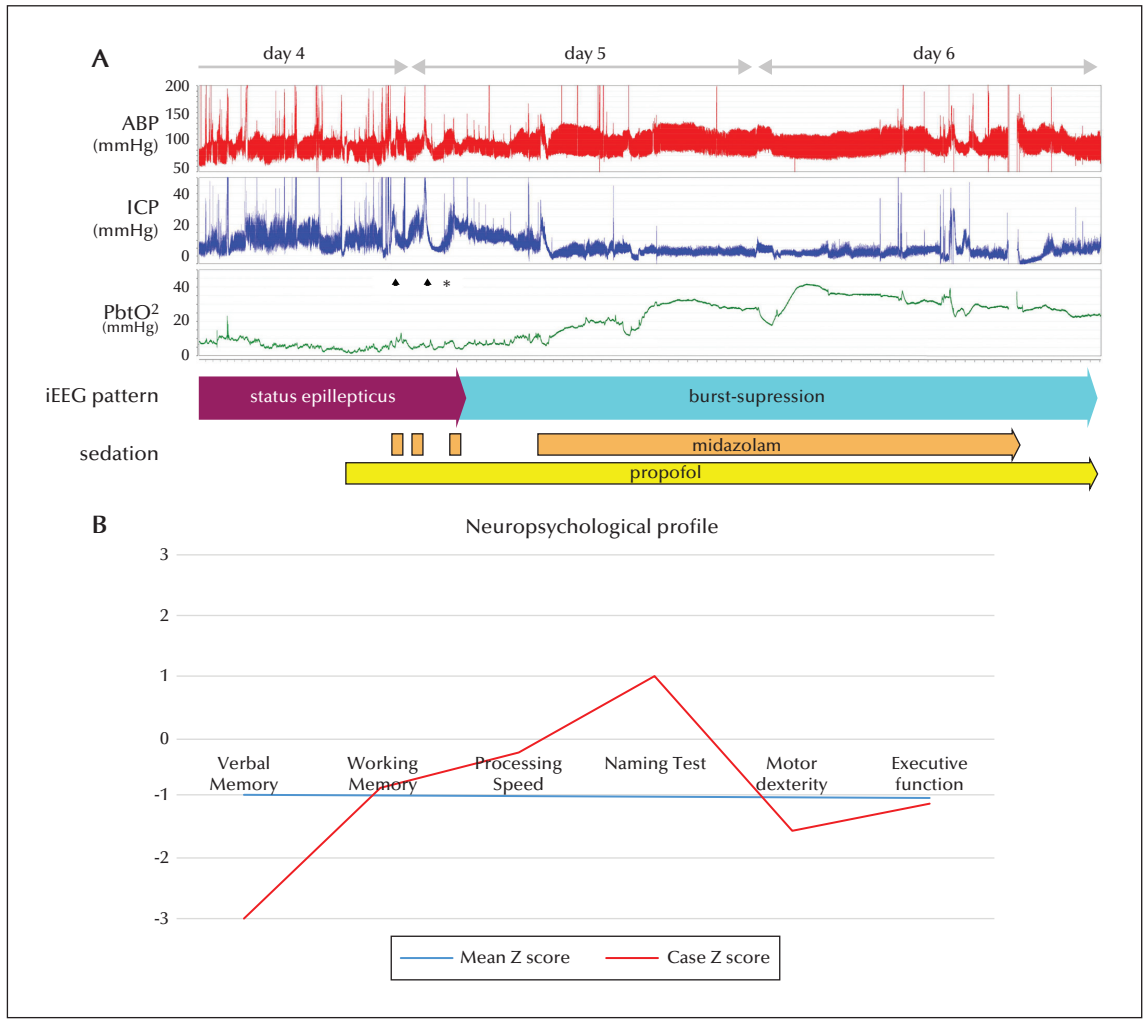
Six months later, control MRI revealed encephalomalacia localized to the left paramedial fronto-basal region and corpus callosum, and a small chronic ischaemic infarction in the right temporal lobe. Hippocampal atrophy or sclerosis was absent. By then, a routine sEEG showed a normal background activity with occasional focal delta waves localized to the right anterior and mid-temporal derivations. Currently, the patient requires partial assistance for activities of daily living and receives occupational therapy to improve memory lapses and episodes of disorientation. The Modified Rankin Scale and Glasgow Outcome Scale-Extended (GOSE) were evaluated, and a peak of 3 and 4 were reached, respectively.

Neuropsychological assessment

The neuropsychological assessment carried out one year after the injury showed above-average scores in processing speed and language (image naming) and average scores in working memory, according to a sex- and age-matched control group. Scores were below average in verbal learning memory, motor dexterity and executive functions, up to two standard deviations below the mean. In addition, emotional alterations such as apathy and lack of motivation were observed according to the questionnaire for quality of life.

Discussion

There are no previous cases of persistent intracortical NCSE in the setting of ABI with a detailed description of the pathophysiological alterations observed in cerebral tissue and its long-term neurological and neuropsychological consequences. Of note, for a number of days, the non-convulsive ESz and ECSz described here were only seen at the intracortical electrode. This is not a new finding, and previous studies have shown that a significant percentage of intracortical ESz in patients with ABI remain undetectable on the scalp [1-3]. We believe that it is important to document the changes of oxygenation of cerebral tissue, ICP and cerebral perfusion accompanying prolonged recurrent intracortical non-convulsive ESz and ECSz (*figure 2*). In addition, although in our case it was not possible to determine which sequelae were secondary to ESz or ABI, we would like to highlight also that the neurological prognosis at one year was relatively good despite intracortical prolonged NCSE. At present, there is growing interest on the cerebral metabolic and systemic consequences of epileptic activity in patients with ABI, in order to optimize sedation and ASD therapy. In a recent study, ESz and periodic discharges (PDs) were shown to be frequently associated with brain trauma with both resulting in metabolic crisis [3]. Metabolic crisis is recognized as a situation of regional metabolic distress characterized by an elevated lactate/pyruvate ratio and decreased extracellular glucose. These features suggest increased glucose consumption, reduced oxidative metabolism, and impaired redox, and have been associated with poor outcome in ABI [3]. Few studies of ABI have shown ESz to be associated with a decrease in PbtO2, elevation of ICP, and a delayed increase in regional cerebral blood flow [2, 3]. Moreover, it seems that high-frequency (> 2 Hz) PDs may be a cause of brain tissue hypoxia [6]. However, data from prolonged intracortical NCSE are lacking. In our case, we have found similar results, and it was possible to stop intracortical ESz by profound sedation based on a combination of propofol and midazolam, decreasing ICP and improving cerebral tissue oxygenation (*figure 2*). Therefore, this case adds further data supporting the importance of continuous iEEG monitoring in subjects with ABI and the beneficial effects of stopping epileptic activity for oxygenation of brain tissue. Conversely, despite the duration and severity of ESz, the neurological outcome was relatively favourable. There is often a significant gap between the severity of the episodes of NCSE in humans and the occurrence of enduring brain damage. Although all animal models of NCSE cause permanent brain sequelae, this has rarely been demonstrated in clinical practice. In the past, enduring cognitive and memory deficits were described in individuals who had experienced focal NCSE [7-9]. Wasterlain *et al.* [10] mentioned, informally, their



■ **Figure 2.** (A) Graphs of values for $PbtO_2$, ICP and ABP throughout a 24-hour period of continuous recurrent non-convulsive ESz and ECSz and a period under profound sedation. During the period of non-convulsive ESz and ECSz, the values for $PbtO_2$ were notably lower and those for ICP were significantly higher, with significant variability of ABP. Arrowheads: intravenous bolus of mannitol; asterisk: the dose of levetiracetam was increased to 1,500 mg/12 h. (B) Graph showing the neuropsychological results of the patient. Note the above-average scores in processing speed and language (image naming) and average score in working memory. Scores were below average in verbal learning memory, motor dexterity and executive functions, up to two standard deviations below the mean.

experience with three patients without prior epilepsy with NCSE whose post-mortem brain examination showed neuronal loss in the hippocampus, amygdala and piriform cortex. Moreover, Fujikawa *et al.* [11] observed widespread neuronal loss and reactive gliosis in three subjects who died after the onset of focal motor and ESE without systemic complications. More recently, Fernández-Torre *et al.* [12] observed neuronal loss, gliosis and neuronal degeneration in an elderly patient with a prolonged episode of localization-related NCSE. Nonetheless, it is impossible to ascertain that cognitive deficits are secondary to epileptic activity in patients with ABI. However, invasive brain multimodality monitoring offers the opportunity to unravel potential metabolic harmful effects.

Some investigators have introduced provocative concepts denominating *microdischarges* and *microseizures* to distinguish between epileptiform activity and ESz based on intracranial EEG using microelectrodes to record electrophysiological disturbances on a millimetre scale [1, 13]. The role of these events in the progression to conventional epileptic seizures is not well known. Nevertheless, it seems that intracortical ESz could contribute to encephalopathy in subjects with ABI

[1, 14] Thus, multifocal *miniseizures* could significantly contribute to diffuse cortical dysfunction, which could lead to altered mental status, coma, or a delay in normalization of the level of consciousness [1, 14]. It remains to be determined whether these *microseizures* are the cause of permanent macroscopical cerebral damage or enduring cognitive deficits.

There are important implications of the findings described here. First, it appears that non-convulsive ESz and ECSz cause metabolic changes, such as reduced brain oxygenation and increased ICP that can further damage previously compromised brain tissue. Therefore, the detection of ESz using video-EEG monitoring could play a relevant role in adjusting sedation and ASD therapy. Second, iEEG in comatose patients allows to correlate closely the alterations observed in the sEEG and their intracerebral source. Therefore, importantly, this may help unravel the significance of ictal-interictal continuum patterns.

Lastly, in this case, we were able to follow the prognosis and long-term neurological and neuropsychological aftermath in a patient with prolonged focal intracortical NCSE in the context of ABI. Further studies are needed to understand the pathophysiology of intracortical ESz and ECSz in ABI and its consequences in order to optimize sedation and ASD treatment. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
None of the authors have any conflicts of interest to disclose.

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TEST YOURSELF

(1) How do you define electrographic seizures (ESz) in critically ill patients?

(2) Define electrographic status epilepticus (ESE) in critically ill patients.

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.