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Falsely pessimistic prognosis by EEG in post-anoxic coma after cardiac arrest: the borderland of nonconvulsive status epilepticus

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ABSTRACT – *Background*. Prognostication following anoxic coma relies on clinical assessment and is assisted by neurophysiology. A non-evolving EEG spike burst/isoelectric suppression pattern after the first 24 hours almost invariably indicates poor outcome, while an evolving pattern implies nonconvulsive status epilepticus (NCSE) that may "hide" surviving brain activity and is amenable to treatment. *Case study*. We present the case of a 53-year-old woman who had a witnessed out-of-hospital ventricular fibrillation cardiac arrest, was resuscitated by paramedics, but remained comatose. An EEG, performed 36 hours post-insult, showed an unremitting, non-evolving, unresponsive 2-6 Hz high-voltage spike burst/isoelectric suppression pattern, which remained unchanged at 96 hours post-insult, following therapeutic hypothermia. During this period, she was completely off sedation and taking triple antiepileptic treatment, without systemic confounding disorders. Although the initial pattern was indicative of poor neurological outcome, she eventually made meaningful functional recovery; the last EEG showed satisfactory background rhythms and stimulus-induced epileptiform discharges without seizures. *Conclusion*. In post-anoxic coma, non-evolving >2 Hz spike burst/isoelectric suppression pattern may still reflect NCSE and therefore should be considered in the diagnostic EEG criteria for NCSE. Such borderline patterns should not dissuade physicians from intensifying treatment until more confident prognostication can be made.

Key words: EEG, post-anoxic coma, nonconvulsive status, repetitive epileptiform discharges, false prediction

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Coma after out-of-hospital cardiac arrest (OOHCA) is associated with poor outcome. The rate of survival to hospital discharge is 7-10% with few patients making a satisfactory neurological recovery (Howard *et al.*, 2011). Early prediction of meaningful recovery is important to guide decisions on patient management, particularly given the ethical, social,

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and economic implications of continuing intensive support for patients with severe anoxic brain damage. The assessment of the degree of hypoxic injury remains primarily clinical, assisted by neurophysiological and imaging investigations.

Amid the EEG grades and patterns used for prognostication, repetitive generalised spikes occurring against a completely suppressed background is considered malignant as it is almost invariably associated with a fatal outcome or persistent vegetative state (Zandbergen *et al*., 1998; Koenig *et al*., 2006). Recovery has been sporadically reported only when the pattern is present early and transiently (usually for 24 hours) after resuscitation. On the other hand, repetitive generalised discharges at high or evolving frequency (that can also occur against a completely suppressed background) may reflect nonconvulsive status epilepticus (NCSE), a potentially treatable dynamic state that may hide surviving brain function. There are no agreed EEG criteria for NCSE and interpretation of "intermediate" patterns is subjective and prone to error. Misdiagnosis of NCSE for severe anoxic damage can falsely suggest a poor prognosis and crucially influence decisions on clinical management (Kaplan, 2007).

We describe a patient who suffered an OOHCA and made a meaningful recovery despite a non-evolving, non-reactive, diffuse spike burst/isoelectric suppression EEG pattern, four days after the insult.

Case study

A 52-year-old woman, a smoker with hypertension and hypercholesterolaemia, had an OOHCA. Her husband performed basic life support. Paramedics arrived quickly and identified ventricular fibrillation. She was shocked and resuscitated. Estimated "downtime" was 10 minutes.

On arrival at the hospital, some respiratory effort was noted and her pupils were reactive to light. She was intubated and ventilated. An electrocardiogram demonstrated anterolateral ischaemia and left ventricular hypertrophy and she was started on clopidogrel, enoxaparin, and aspirin. She underwent therapeutic cooling for 24 hours and remained sedated on propofol and remifentanyl. She developed a mild chest infection and was treated with antibiotics.

Upon temporary reduction of sedation, she presented generalised convulsions, controlled with a combination of midazolam, phenytoin, and levetiracetam. A CT brain scan was unremarkable. Initial EEG 36 hours after the cardiac arrest was conducted while still sedated with propofol and remifentanyl. Midazolam had been turned off for 30 minutes. There was an unremitting pattern of diffuse, high-voltage spike discharges with intervals of complete suppression of variable duration that tended to shorten as midazolam was wearing off. There were no associated clinical manifestations and the EEG pattern remained unresponsive to noxious stimuli.

On day 3, she was weaned off propofol and some diffuse myoclonus was controlled with clonazepam. She remained comatose but systemically well. Corneal and pupillary reactions were present and her eyes opened to pain. She was hyper-reflexive throughout. There was no obvious clinical evidence of ictal activity. A second video-EEG was performed almost 96 hours post-insult to assess for possible NCSE or anoxic encephalopathy (this time the patient was off propofol for 24 hours and off midazolam and remifentanyl for six hours). The EEG remained unchanged showing quasiperiodic diffuse spike discharges of identical voltage and morphology, interspersed by periods of complete suppression (*figure 1; upper trace*). Discharges occurred at 1.8-6 Hz with frequent clusters of three and four at regular 6-7 Hz frequency, but without evolution in frequency, topography or morphology, or any change in response to noxious stimuli. Four days after the insult, off sedation, on triple antiepileptic treatment, and without confounding systemic disorders, EEG findings were interpreted as indicative of extensive and irreversible cortical damage rather than NCSE.

By day 12, she was transferred to the ward and remained in a minimally conscious state. She responded to deep pain with grimacing and head movements.

A repeat EEG at week four, while on levetiracetam at 1000 mg bd and clonazepam at 2 mg qds, showed some evolution with persistent diffuse spike discharges, brief periods of generalised suppression, but now also clear rhythms present in the intervening periods. Discharges occurred less frequently during resting states, increasing with enhanced vigilance, reminiscent of stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) (Hirsch *et al*., 2004) (*figure 1; lower trace*). A brain MRI scan showed only mild small vessel disease and no evidence of hypoxic brain injury. Around this time, she occasionally opened her eyes and appeared to be tracking people. Over the next four weeks, she gradually became more alert and started to move her arms. An EEG performed in week 7 still demonstrated diffuse spikes, particularly while awake (*figure 2; upper trace*).

By week 10, she was able to sit unsupported and was more awake. At 14 weeks, she was able to walk several metres with the assistance of two people and was answering simple questions. At 17 weeks, she was managing stairs with assistance. She was conversing appropriately, but was disoriented in time and place and had difficulty comprehending questions. Repeat EEG demonstrated generalised bursts of spike/polyspike-and-wave discharges against

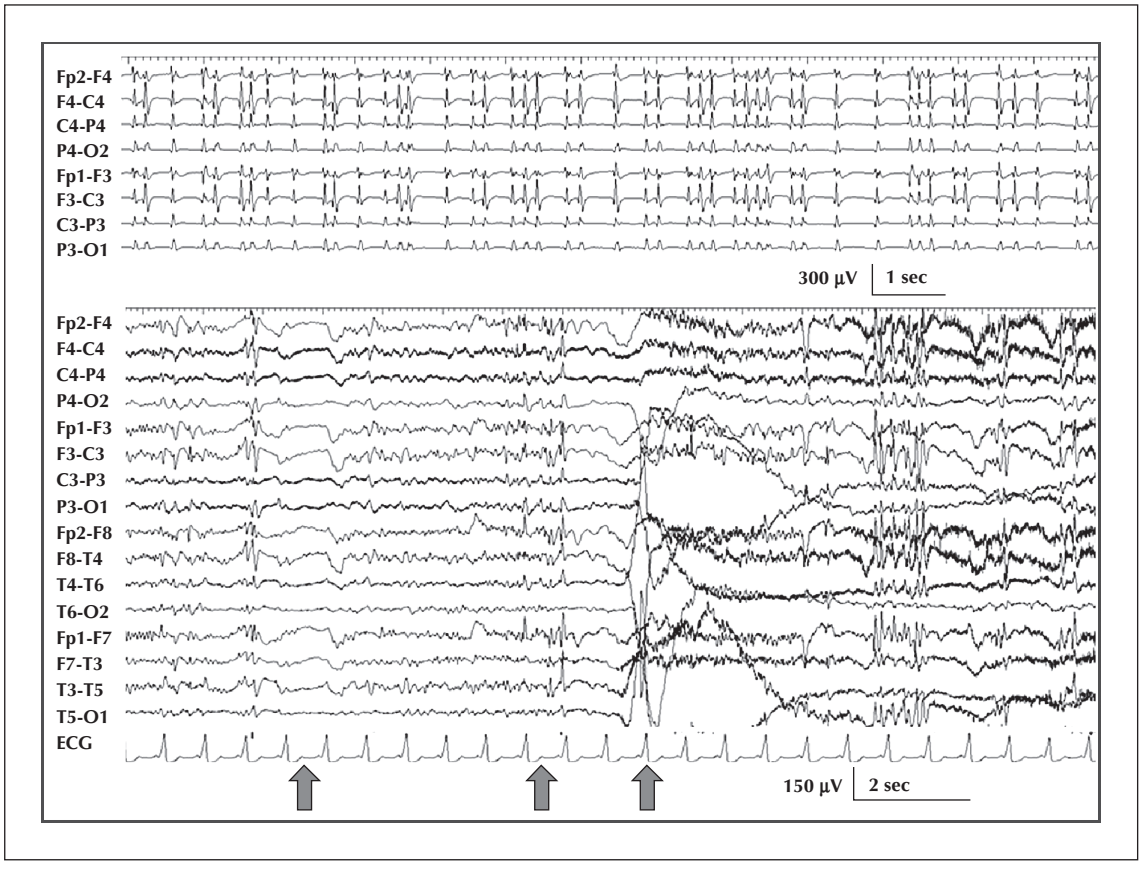

Figure 1. Upper trace: four days after cardiac arrest, the patient was comatose, off sedation, and receiving triple antiepileptic treatment. The EEG showed an unremitting burst suppression pattern, unresponsive to stimulation and without associated clinical manifestations, apart from very subtle eyelid twitching every 4-5 seconds. Lower trace: four weeks after the insult, there were still generalised bursts of spikes and brief periods of suppression (left arrow), but biological activity returned. Discharges appeared to depend on the level of vigilance; the patient was resting (first third of trace), her name was called (middle arrow) and she opened her eyes (right arrow).

a moderately, diffusely slow background, without periods of generalised suppression (*figure 2; lower trace*).

The patient was discharged to a rehabilitation centre. At 9 months after insult, she was feeding herself and was independently mobile. She needed only supervision for stairs. She continued to demonstrate cognitive deficits, including severe memory impairment and was only able to follow one-step commands. She could not hold a prolonged conversation. However, she responded appropriately to simple questions, was socially engaged with others, and increasingly demonstrated initiating behaviour in some tasks. She recognised individuals she was familiar with and appeared happy.

Discussion

Our patient had an OOHCA but made meaningful functional recovery, regaining good social rapport, speech, and useful motility. While she will continue to need 24-hour supervision, she will be able to live at home. Early favourable predictors included a relatively short downtime and reactive pupils, and therapeutic hypothermia may have significantly contributed to the positive neurological outcome (Rossetti *et al*., 2010; Rittenberger *et al*., 2012). However, the EEG on day 4 was recorded after therapeutic hypothermia and had demonstrated unreactive, non-evolving, generalised spike burst/isoelectric suppression, a pattern that carries an almost 100% prediction of brain death (Zandbergen *et al*., 1998; Koenig *et al*., 2006), including patients who have therapeutic hypothermia (Thenayan *et al*., 2010). There are only two reported patients who have had burst suppression patterns on days 2 and 3, respectively (the second without epileptiform activity), with good recovery. However, no information on sedation or concurrent systemic disorders that could impact the EEG was available (Chen *et al*., 1996).

Persistent burst suppression is regarded as a marker for severe injury to the thalamus, cortex, and interconnecting circuits (Koenig *et al*., 2006) and prognosis is even worse when bursts consist of high-voltage

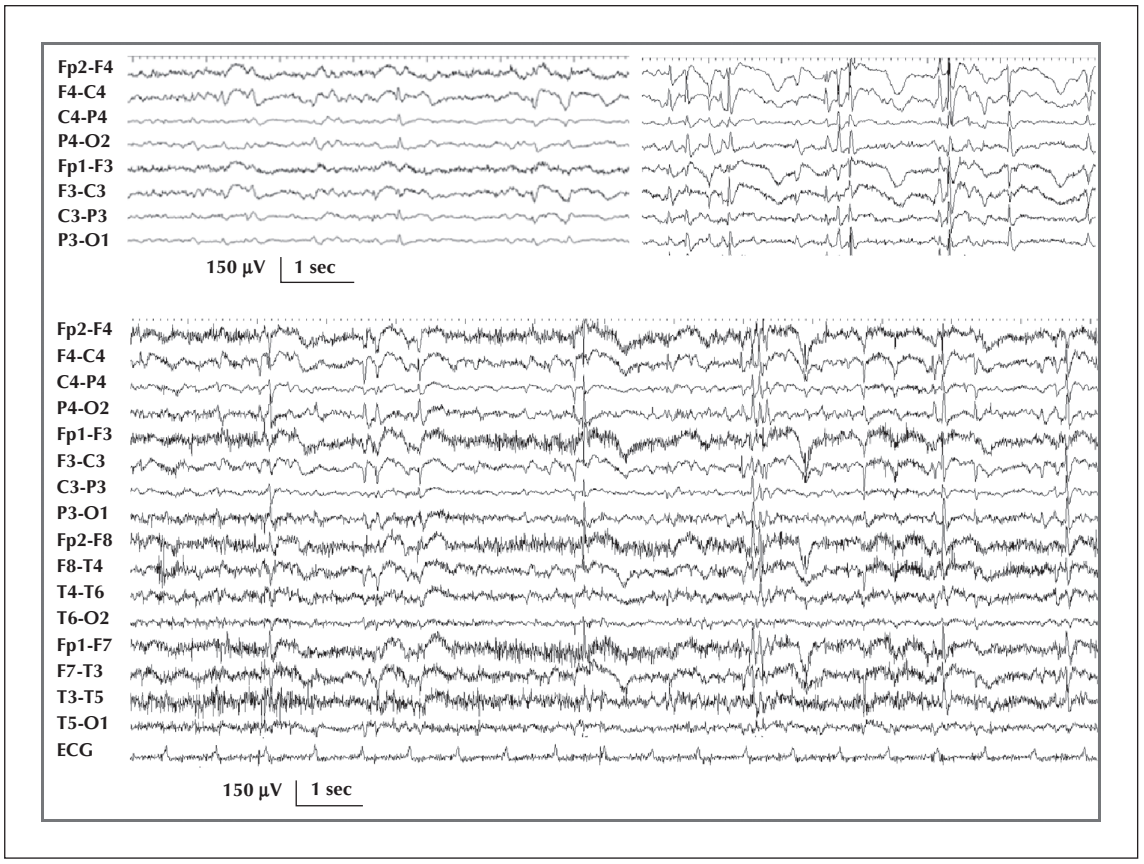

Figure 2. Upper trace: seven weeks after the cardiac arrest. Left: resting with eyes closed; right: alert, eyes open, but still not following comments. Lower trace: 15 weeks after initial insult; fully alert, communicating with relatives and singing.

spikes. However, some of these patterns may reflect NCSE, necessitating intense antiepileptic treatment. Differentiation between NCSE and irreversible anoxic thalamic-cortical damage is typically based on the frequency and temporal evolution of bursts. Proposed diagnostic EEG criteria for NCSE include fast repetitive generalised or focal epileptiform discharges (>3.5 Hz [Jirsch and Hirsch, 2008], >3 Hz [Young *et al*., 1996], ≥2.5 Hz [Kaplan, 2007]), or rhythmic, periodic or quasiperiodic waves at >1 Hz with evolution in frequency (by at least 1 Hz), location or morphology. Clinical improvement or appearance of normal EEG patterns following intravenous administration of lorazepam is diagnostic but is variably obtainable because of concurrent metabolic or systemic derangements.

Our patient's EEG, four days after coma onset, after therapeutic hypothermia, and off sedation, did not exactly fulfil the NCSE criteria specified above. Diffuse spike bursts on a flat background were repetitive from <2-6 Hz, showed irregular rhythmicity (rhythmic clusters of 3-4 for half a second, interrupted by single bursts at 2 Hz or even less), and lacked evolution (*figure 1; upper trace*). No trial with lorazepam was attempted in view of the concurrent triple antiepileptic medication that included clonazepam, and somatosensory evoked potentials (SSEP) that could have provided early evidence of some functional integrity at the thalamocortical level (van Putten, 2012) were not performed. Although an ictal component was impossible to rule out, it was then felt that the EEG pattern reflected severe anoxic cortical damage and a false prediction of poor prognosis was given.

During her four months in hospital, our patient did not suffer severe systemic complications. She received meticulous care and made gradual motor and cognitive recovery. Brain MRI, performed in week 4, was favourable. In tandem, serial EEGs recorded the reappearance of brain activity. The periods of suppression became less frequent (*figure 1; lower trace, left arrow*) and finally disappeared. Diffuse spike discharges persisted, behaving like SIRPIDs (Hirsch *et al*., 2004); discharges were infrequent and of low voltage during rest and sleep, but were promptly activated with enhanced vigilance, remaining frequent and of high voltage when awake. They retained the morphology and field of the spike bursts recorded on days 2 and 4 after the insult, suggesting that they are the same

phenomenon, but became less dense after the resolution of her coma. SIRPIDs may remain clinically silent (Hirsch *et al*., 2004), but there is good evidence that they can also be ictal, either when focal (Hirsch *et al*., 2008) or bilaterally diffuse (Koutroumanidis *et al*., 2008). It is therefore likely that the dense spike bursts of the fourth day of coma indicated NCSE, despite the lack of seizure-like evolution. Her comatose state was probably mainly due to the abnormal "ictal" electrical activity rather than severe anoxic damage, the degree of which became clear over time.

In post-anoxic coma, high-voltage diffuse repetitive spikes over a completely suppressed background may reflect NCSE even when they are irregular or transiently regular, but non-evolving at the slower range of 2 Hz. Fernández-Torre *et al*. (2012) also noted epileptiform discharge frequencies at less than 3 Hz in several of their patients with unequivocal NCSE and suggested caution when relying on strict frequency limits. Concurrent antiepileptic medication may be deceptively ineffective and should not deter physicians from intensifying treatment and optimising management for these patients until confident prognostication can be made. The latter must be based on the combination of neurological examination, EEG, SSEP, MRI, and biochemical markers (Tiainen *et al*., 2003), the prognostic values of which should be prospectively updated in the era of therapeutic hypothermia. □

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