Should postanoxic Status epilepticus be treated aggressively?

- No!

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Abstract

Electrographic Status epilepticus (SE) and myoclonus represent frequent findings in patients surviving cardiac arrest; both features have been related to poor clinical outcome. Recent data have outlined that SE appearing during therapeutic hypothermia and sedation is practically invariably related to a fatal issue, as opposed to some patients presenting SE and/or myoclonus after return to normothermic conditions. While it seems reasonable to give a chance of awakening to the latter patients by administering consequent antiepileptic treatment, especially if other favorable prognostic markers are observed, an aggressive treatment of SE arising during hypothermia seems futile in view of the existing evidence.

Background

Despite recent advances in resuscitation and intensive care in the domain of hypoxic-ischemic encephalopathy after cardiac arrest [1], only about 5% of patients survive to hospital discharge [2], and several patients are left with long-term cognitive sequelae [3]. Outcome prediction in this clinical setting represents a daunting task for neurologists and intensivists; therefore, guidelines have been proposed, in which clinical examination and EEG represent paramount tools. As researchers have been particularly successful in refining prognostication for dismal prognosis [4], false-positive rates (FPR) for poor outcome prediction (Cerebral Performance Category of 3 or higher on a scale of 5 [5]) should aim towards 0, with narrow confidence intervals.

In 2006, the American Academy of Neurology published evidence-based practice parameters [6]. Early myoclonus within 24h of cardiac arrest (FPR=0), and an EEG with generalized suppression, burst-suppression, or periodic discharges on a suppressed background (FPR<5%), were reported as reliable markers of unfavorable prognosis (Level C); however, this analysis included almost exclusively subjects treated before the hypothermia era.

Current evidence

More recently, several studies conducted in different cohorts in Europe and North America have addressed the prognostic role of electrographic epileptiform abnormalities and clinical myoclonus in patients treated with controlled temperature management. For the purposes of this controversy, status epilepticus (SE) will be defined broadly as electroencephalographic evidence of repetitive (rhythmic, periodic, evolving) epileptiform transients over more than 5 minutes, and "aggressive" treatment as the use of prolonged pharmacological sedation to induce electrographic burst-suppression or complete suppression.

After therapeutic hypothermia, electrographic seizures or repetitive epileptiform patterns are found in about 1/3 of adult patients [7-9], while early myoclonus (arising after weaning of sedation and hypothermia) has been reported in about 1/6 of patients [10, 11], and thus represent relatively frequent observations in this setting. Several independent investigators have found that the presence of EEG epileptiform alterations suggesting ongoing electrical seizures is incompatible with survival (FPR=0), even if patients were treated with antiepileptic drugs (AED) [9, 12-14].

However, several patients displaying postanoxic SE have in fact been reported to recover with at times a reasonable functional outcome [15, 16]. How is this to understand in view of the previous paragraph? To address this, at first glance, discrepancy, one should target her or his attention towards the early phase of intensive care, in which patients under hypothermia may undergo

EEG. Indeed, the extent of hypothermic EEG abnormalities (particularly, lack of background reactivity and discontinuity) has been shown to correlate with the magnitude of neuronal damage assessed with the neuron-specific enolase (NSE), a marker of neuronal death [17, 18]. A neurophysiologic, non-invasive tool may therefore prove highly informative, especially if recorded just after the first 9-12 hours following the initial insult [19].

During therapeutic hypothermia, recent evidence on 134 consecutive patients highlighted that the presence of epileptiform EEG activity is indeed not compatible with survival, even under continuous infusion of moderate doses of midazolam or propofol, and after additional AED treatment (FPR 0%); this contrasts with a FPR of 7% in patients displaying epileptiform activity only after return to normothermia, or the FPR of 13% for overt myoclonus within the first 48-72 hours [10]. Of note, the lack of EEG background reactivity during hypothermia was also clearly related to a poor prognosis (FPR 2%) [10]. These findings are similar to those reported by another group on 56 subjects investigated with continuous EEG during hypo- and normothermia: epileptiform transients were found in 10% of the 22 patients with good neurological outcome, at 48 hours (thus after hypothermia), but not under hypothermia, and lasted less than 2 hours under AED treatment [20]. A recent study focusing on postanoxic myoclonus highlighted that survival is clearly more frequent in patients without concomitant EEG epileptiform activity [11]Moreover, an earlier Scandinavian study conducted with amplitude-integrated EEG on 95 patients demonstrated that among the 26 subjects with electrographic SE, the 2 who survived presented this condition only after return of normothermia, and out of a continuous background activity, but not burst-suppression [21]. Finally, occurrence of rhythmic, periodic, or ictal epileptiform features induced by stimulations, called “SIRPIDs” was recently assessed in a relatively large patient cohort: these were found in 13% of patients, and their occurrence during hypothermia was not compatible with survival [22].

Conclusions

The aforementioned data seem to converge to the following three points. First, while electrographic epileptiform features, which nearly always present in a rhythmic or repetitive fashion at least for several hours [23], thus fulfilling the SE definition, are general markers of poor prognosis after cardiac arrest, their occurrence during the early resuscitation period, particularly under mild therapeutic hypothermia and sedation, has not been so far reported to be compatible with survival; this is in contrast with some patients who may benefit from AED treatment if their SE declares itself after return to normothermic conditions. It may be speculated that SE arising in hypothermia despite sedation is the hallmark of an agonal cortical activity resulting from a devastating brain insult [10], whereas SE appearing in normothermia may be sometimes amenable to treatment and a reasonable outcome. Second, EEG background reactivity represents a practical additional prognostic marker: its absence during hypothermia seems to

have a smaller FPR for poor outcome, as compared to normothermic conditions (FPR=7-9%) While EEG reactivity in this setting has recently been shown to have reasonable inter-rater agreements among EEG readers, and even with automated algorithms [24], another study found lower agreements [25]. Third, myoclonus, which is also consistently related to poor outcome, is nevertheless not an invariable marker of mortality; of note, sedation and muscle relaxants often prevent its observation during controlled temperature management.

On top of these considerations, risks inherent to aggressive SE treatment, mostly related to potential complications of prolonged ICU treatment, sedation, and mechanical ventilation, have been outlined in recent literature, albeit outside of the setting of post-anoxic encephalopathy [26-28].

It appears therefore reasonable to suggest the following approach in patients with hypoxic ischemic encephalopathy. If EEG features compatible with SE arise only after hypothermia and upon sedation weaning, on a reactive EEG in an otherwise potentially promising clinical context (e.g., return of brainstem reflexes, preserved cortical somatosensory evoked responses), a treatment with non-sedating and at times sedating AED seems warranted, at least for some days. If, conversely, SE appears during sedation and hypothermia on a non-reactive EEG background, aggressive antiepileptic treatment with long-term sedative agents appears futile, as can worsen comorbidities, may divert resources from patients who may better take advantage from intensive treatment, and might unnecessarily induce false expectations in relatives and caregivers.

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