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Beyond Seizures: The Usefulness of EEG in Septic Patients

The Association Between the Presence and Burden of Periodic Discharges and Outcome in Septic Patients: An Observational Prospective Study

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Background: Sepsis-associated encephalopathy (SAE) is frequent in septic patients. Electroencephalography (EEG) is very sensitive to detect early epileptic abnormalities, such as seizures and periodic discharges (PDs), and to quantify their duration (the so-called burden). However, the prevalence of these EEG abnormalities in septic patients, as well as their effect on morbidity and mortality, are still unclear. The aims of this study were to assess whether the presence of electrographic abnormalities (i.e., the absence of reactivity, the presence and burden of seizures and PDs) was associated with functional outcome and mortality in septic patients and whether these abnormalities were associated with sepsis-associated encephalopathy (SAE). Methods: We prospectively included septic patients, without known chronic or acute intracranial disease or pre-existing acute encephalopathy, requiring ICU admission in a tertiary academic centre. Continuous EEG monitoring was started within 72 h after inclusion and performed for up to 7 days. A comprehensive assessment of consciousness and delirium was performed twice daily by a trained neuropsychologist. Primary endpoints were unfavourable functional outcome (UO, defined as a Glasgow Outcome Scale-Extended-GOSE-score < 5), and mortality collected at hospital discharge and secondary endpoint was the association of PDs with SAE. Mann-Whitney, Fisher's exact, and χ^2 tests were used to assess differences in variables between groups, as appropriate. Multivariable logistic regression analysis with in-hospital mortality, functional outcome, SAE or PDs as the dependent variables were performed. Results: We included 92 patients. No seizures were identified. Nearly 25% of patients had PDs. The presence of PDs and PDs burden was associated with UO in univariate ($n = 15$ [41%], $p = 0.005$ and $p = 0.008$, respectively) and, for PDs presence, also in multivariate analysis after correcting for disease severity (OR 3.82, IC 95% [1.27-11.49], $p = 0.02$). The PDs burden negatively correlated with GOSE (Spearman's coefficient $\rho = -0.2$, $p = 0.047$). The presence of PDs was also independently associated with SAE (OR 8.98 [1.11-72.8], $p = 0.04$). Reactivity was observed in the majority of patients and was associated with outcomes ($p = 0.044$ for both functional outcome and mortality). Conclusion: Our findings suggest that PDs and PDs burden are associated with SAE and might affect outcome in septic patients.

Commentary

The recording and graphical representation of changes in cerebral electric potentials on the scalp—the EEG—is a small miracle. A miracle, first, that the tiny potentials produced by the brain can be detected at all, passing through the cerebrospinal fluid, skull, and scalp, braving interference from noisier sources of electrical activity. But also, a miracle that such rudimentary signals, expressed as squiggly lines of amplitudes on a time axis, can give us any useful information on the function of the brain, as complex as it is, with its 85 billion neurons creating an exponentially larger number of communications to other neurons, each signaling up to a thousand times per second.

What clinical information the EEG can give us about the brain was certainly not immediately obvious upon its discovery, nor fully understood today. After Hans Berger recorded the first EEG nearly a hundred years ago in the hopes that it would shed light on psychiatric disease (and telepathy), he was devastated to find it of limited use for this purpose. The most useful findings were in patients with epilepsy, and this grew to be the new technology's greatest application.[1] Among others uses, the EEG also found a role in the evaluation of critically ill and/or comatose patients, though logistical barriers limited its application until the advent of the digital EEG.

Probably the first description of periodic discharges in sick patients was made in 1955 in a brief report from Paris, where they were described as "paroxysmal slow graphic elements of periodic appearance."[2] The report was based on 5 cases, all acutely ill with brain infection, demyelinating disease, or severe metabolic disturbances. The main conclusions of the

authors were that periodic discharges appeared in acute or subacute contexts, revealed the presence of injury to the underlying brain, and suggested an association with focal seizures, based on similar phenomena observed in patients with epilepsy. Nearly 70 years later, although we are able to describe the discharges with more precise and reproducible labels,[3] these early conclusions remain a reasonable summary of current knowledge.

An important limitation of the work done in the interim is that most studies of EEG in critical-care settings are based on retrospective databases of EEG records that were requested based on perceived clinical need (typically suspicion of seizures or status epilepticus), often in highly heterogenous patient populations. Although this approach has allowed us to discover and characterize the rich variety of EEG abnormalities found in these contexts, the biased nature of the samples limits our ability to extrapolate their significance. For example, a landmark retrospective study in critical-care EEG showed a high rate of nonconvulsive seizures among EEG-monitored hospital patients, with strong associations between periodic discharges and seizures, and helped to expand the scope of critical-care EEG.[4] It is important to keep in mind, however, that the patients who underwent EEGs in the study were mostly selected because their clinicians believed them at risk of subclinical seizures. It therefore remains difficult to know what clinical contexts justify the need for continuous EEGs and how aggressively to treat or monitor findings such as rhythmic and periodic patterns.

Thankfully, prospective studies examining the EEGs of sick patients that focus on specific populations based on prespecified criteria are now helping to clarify the picture. A recent randomized control trial examined the EEGs of patients who remained comatose after surviving cardiac arrest, and compared aggressive treatment of rhythmic and periodic pattern to standard care.[5] The present observational prospective study by Ferlini et al[6] looks specifically at the EEGs of patients suffering from sepsis and reports the associations between periodic discharges and clinical findings.

The great value of this study comes from its method of patient selection. Patients were recruited for continuous EEG for up to 7 days if they met simple, prespecified criteria: adults with a diagnosis of sepsis of less than 48 hours old, expected to be in ICU for more than 24 hours. There were several exclusion criteria, the most important being that patients must not have had acute or chronic comorbid intracranial disease. The study therefore provides us with a relatively "pure" sample of septic patients, allowing us to draw more general conclusions on EEG findings in this population. In addition to extensive bloodwork and chart data, the investigators systematically assessed the patients' level of consciousness and delirium status twice daily.

The most pertinent EEG findings of the 92 analyzed patients were as follows: 96% had an abnormal background, rhythmic delta activity was present in 52%, and periodic discharges, mostly generalized, were present in 25%. Strikingly, in this population without previous brain disease, not a single patient suffered from an EEG seizure, despite the high burden of rhythmic and periodic patterns. But if they were not associated with seizures, periodic patterns were associated with an unfavorable functional outcome as well as higher mortality. Furthermore, they were independently associated with sepsis-associated encephalopathy, based on scores obtained on consciousness and delirium scales tested at bedside.

These findings suggest a future shift in the role of EEG in critical care, and perhaps a new vista for its use. In general, the EEG has been used to sniff out the risk of seizures, yet the absence of seizure in this population, even when rhythmic and periodic patterns are present, is surprising. There has been a trend in considering that these patterns signaled a high risk of seizures, but perhaps the risk is lower than believed, at least in patients without brain injury. In this population, such patterns seem to now signal worse encephalopathy and a poorer prognosis.

As the authors note, prior research has suggested that patients with sepsis may be at particularly low risk of seizure, so this group of critically ill patients may be on the low end of a seizure-risk spectrum, where one can imagine that, for example, patients with subarachnoid hemorrhage might be at the other. We must also recognize also that septic patients with no history of brain disease make up only a small part of critically ill patients who might benefit from an EEG, and indeed undergo them less frequently. A task of future research will be to systematically examine other homogenous critically ill populations, both with and without brain disease, and see what their EEGs look like and what they are associated with. Surely, certain groups will have strong associations with seizures and others will not. Mapping out associations with clinical variables and prognosis could expand the use of EEG greatly within certain populations, even where seizure frequency is low.

An immediate implication for hospital EEG readers is that the clinical context matters and that reports will need to be tailored to the clinical scenario. Just as Berger discovered that his new technology took him outside his chosen field of psychiatry, epileptologists may increasingly be asked to go further beyond the question of seizure-risk assessment and into a more global clinical evaluation of critically ill patients. The useful boundaries of an old technology continue to expand.

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