Review Article

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The use of electroencephalography in patients with sepsis: A review of the literature

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ABSTRACT

Sepsis-associated encephalopathy (SAE) is the term used to define brain dysfunction related to infections that are principally located outside the central nervous system (CNS). A number of published studies report that electroencephalography (EEG) has been used in the evaluation of patients with sepsis, alone or usually in combination, to evoked potentials and neuroimaging. This was in an effort to assess if EEG can be a tool in the diagnosis and monitoring of the neurological status in sepsis patients. Although there is no specific test for the diagnosis and prognosis of sepsis related encephalopathy, our literature review suggests that EEG has a role in the assessment of this clinical entity. Due to its low cost and simplicity in its performance, EEG could be a potential aid in the assessment of sepsis neurological complications even in the early, subclinical stages of the syndrome. The aim of this review is to summarize the published literature regarding the application and utility of electroencephalography in adult patients with sepsis.

Key words: sepsis, sepsis associated encephalopathy (SAE), electroencephalography (EEG)

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INTRODUCTION

Sepsis is currently defined as a life-threatening organ-dysfunction caused by a dysregulated host response to an infection.[1] An infection can affect directly the central nervous system (CNS) causing meningitis or encephalitis, however, normal CNS function can be disrupted during an infection affecting any other system. Sepsis-associated encephalopathy (SAE) is the term used to define brain dysfunction related to infections that are principally located outside the CNS. It is estimated to be much more common than all of the intracranial infections put together. SAE is often complicated by acute and long-term brain dysfunction.[2] The major underlying pathophysiological mechanisms involve neuroinflammation, brain and systemic circulatory alterations, and focal abnormalities in specific brain structures like the brainstem, the amygdala, and the hippocampus.[3] SAE could lead to increased mortality, long term psychological disorders, and cognitive impairment. Mortality and morbidity relate directly to the severity of SAE. Even though, no specific tests can diagnose and prognosticate SAE, this entity is associated with abnormal electroencephalogram (EEG) patterns and neuroimaging findings.[4] The early features of SAE are delirium and mild EEG slowing, and prompt recognition of these early features with treatment of the underlying infection can reduce mortality and morbidity.[5]

This type of encephalopathy is mainly diffused and can appear from the early stages of the sepsis syndrome. Clinically, it is consistent with delirium, however, central and peripheral nerves can be affected, and focal neurologic signs like rigidity, asterixis, tremor and multifocal myoclonus can be developed. SAE usually reverses quickly with successful treatment of sepsis. However, a wide range of symptoms can appear during the process of SAE, including alterations of sleep/wake cycle,

disorientation, impaired attention and/or disorganized thinking, as well as agitation and hallucinations in more severe cases.[6,7] Both inflammatory and non-inflammatory mechanisms are involved in the underlying pathophysiology, which is rather multifactorial. All brain cells can be affected, and blood-brain barrier can be damaged. Dysfunction of intracellular metabolism occurs leading to brain injury and cell death.[8–10]

We conducted a PubMed/Medline search on October 2019 using the terms "sepsis AND EEG" as "Title/Abstract" or as "MeSH Terms". The detailed structure of the search in the "Search details" window of the PubMed website was ("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) AND ("electroencephalography"[MeSH Terms] OR "electroencephalography"[All Fields] OR "EEG"[All Fields]). For the purpose of this review, we limited the search only to "Humans" and considered finally only the manuscripts referring to adults. All the references of the identified manuscripts were also searched for additional relevant publications.

EEG CHANGES IN SEPSIS

The summary of the relevant studies identified, along with their major findings are presented in Table 1. EEG appears to be a fairly sensitive test and can show abnormalities even in cases that the neurological examination of the septic patient is normal. Sepsis can be associated with electroencephalographic seizures (ESZs) or periodic epileptiform discharges (PEDs), increased theta rhythms, predominant delta waves, triphasic waves (TW) and suppression of EEG activity.[11–14]

In one of the earlier studies in 1992, Young *et al.* enrolled 62 patients with sepsis in an effort to define the EEG and associated clinical features of SAE. Three categories of patients were evaluated: non-encephalopathic, mildly encephalopathic, and severely encephalopathic. Also, EEGs were classified into five groups: normal, excessive theta waves, predominant delta waves, triphasic waves, and suppression or burst suppression, in ascending order of severity. This progressively worsening EEG pattern consists of Young's classification. In this study, EEG was proven to be more sensitive than clinical criteria for encephalopathy, and those well-defined categories correlated with mortality.[15] Straver *et al.* also concluded that the decreased fast activity and the increase in slow wave EEG activity amongst the intensive treatment unit (ITU) septic patients were independent of the sedation level.[14]

Similarly, Berisavac *et al.* in 2016, in a small cohort of 39 SAE patients, showed that delta waves, TW waves and suppression of EEG activity were the most common findings 24 hours prior to death ($P = 0.0004$). The lack of EEG reactivity as well as focal seizures were also associated with death ($P = 0.00043$).[13] Semmler *et al.*, in a 2013 study concluded that sepsis and to some extent non-septic ITU patients had more low-frequency EEG activity indicating non-specific brain dysfunction.[16]

Rosengarten *et al.* in 2012 tried to define the neurovascular coupling in patients suffering from community acquired pneumonia (CAP) using simultaneously EEG-Doppler technique. He enrolled two groups of patients, acute pneumonia and recovery phase. Results showed that in both groups, the EEG had a significant drop in the relative peak frequency of the alpha band and an increase in the theta and beta bands indicating an early microcirculatory dysfunction in inflammatory syndromes like pneumonia.[17]

In 2010, Van Den Boogaard *et al.* tried to explain SAE by inducing experimental endotoxemia with Escherichia coli lipopolysaccharide in healthy volunteers. Cytokines (TNF-alpha, IL-6, IL1-RA and IL-10), cortisol, brain specific proteins, EEG and cognitive function tests were measured later. Endotoxemia induced no clinically relevant EEG changes except in one subject. Quantitative analysis detected changes in the central region, and peak frequency in the occipital region indicating a higher state of alertness. Cortisol significantly correlated with this state and the conclusion was that short-term systemic inflammation does not provoke or explain the onset of SAE but leads to an inflammation-mediated increase in cortisol and alertness.[18]

In 2015, Azabou *et al.* in a cohort study with 110 sepsis patients that used early standard short duration EEG concluded that delirium at the time of EEG correlated with the Young and Synek scale scores and seizures in non-sedated patients; mortality correlated with absence of reactivity, delta background and the Young and Synek scores. They also suggested that continuous EEG (cEEG) could have identified more often these abnormalities.[19] In this study, they also found that PEDs were associated with mortality, as also previously shown by Oddo *et al.* in 2009. In their retrospective ITU study, with 201 enrolled patients, they showed that patients with sepsis had a higher rate of ESZs or PEDs than those without sepsis (32% *vs.* 9%, $P < 0.001$) and further analysis revealed that sepsis on ITU admission was the only significant predictor of ESZs or PEDs (odds ratio 4.6, 95% confidence interval 1.9–12.7, $P = 0.002$). Seizures were mainly non-convulsive and along with PEDs, both were related to poor outcome.[12]

Gilmore *et al.*, in 2015, also concluded that non-convulsive spasms and PEDs were common in sepsis patients with altered mental status but did not associate with outcome.

Table 1: Summary of studies

Study Year-1st Author	Study design	Medical setting	Number of patients	Major findings
2019 Nielsen	Prospective Observational	ITU	102 sepsis or septic shock without acute primary CNS disease	The absence of delirium was independently associated with preserved high-frequency beta activity (> 13 Hz) ($P < 10-7$) and cEEG reactivity ($P < 0.001$). Delirium was associated with low-frequency cEEG activity and absence of high-frequency cEEG activity. cEEG was helpful in distinguishing delirious from non-delirious septic patients.
2018 Velissaris-Pantzaris	Prospective, Observational	Internal Medicine Department	17 sepsis, without primary CNS involvement	EEG helped to identify brain alterations at an early stage in sepsis, before clinical signs of encephalopathy were evident. The presence of EEG abnormalities did not correlate with the sepsis severity prognostic scores SOFA, APACHE II or SAPS II.
2016 Berisavac	Prospective		39 SAE patients	At the time of clinical exacerbation, SAE patients were more likely to have suppression on the EEG and less likely theta activity. Delta waves, TW waves and suppression of EEG activity were the most common findings 24 h before death ($P = 0.0004$). The lack of EEG reactivity was also associated with death ($P = 0.00043$).
2015 Azabou	Prospective Observational	ITU	110 Sepsis patients	Absence of EEG reactivity (OR: 4.44; 95% CI [1.37–14.3]), a delta-predominant background (OR: 3.36; 95% CI [1.08–10.4]), periodic discharges (OR: 3.24; 95% CI [1.03–10.2]), Synek grade ≥ 3 (OR: 5.35; 95% CI [1.66–17.2]) and Young grade > 1 (OR: 3.44; 95% CI [1.09– 10.8]) at day 1 to 3 following admission were independent predictors of ITU mortality and were also associated with delirium occurrence.
2015 Gilmore	Prospective Observational	Medical ITU	98 severe sepsis patients	Non-convulsive seizures and periodic discharges are common in patients with severe sepsis and altered mental status. They were less frequent among the most severely ill patients. A lack of EEG reactivity was associated with higher 1-year mortality [mean survival time 3.3 (95% CI 1.8–4.9) *vs.* 7.5 (6.4–8.7) months; $P = 0.002$] but the presence of periodic discharges or non-convulsive seizures was not [mean survival time 3.3 (95% CI 1.8–4.9) *vs.* 7.5 (6.4–8.7) months; $P = 0.592$].
2013 Semmler	Prospective Observational	ITU	25 sepsis vs 19 non-sepsis ITU survivors	Sepsis patients as well as some non-septic ITU patients had more low-frequency EEG activity compared to healthy controls, indicating non-specific brain dysfunction.
2012 Rosengarten	Prospective Observational	Internal Medicine Department	50 CAP patients	EEG showed a significant drop in the relative frequency of the alpha band and increases in the theta and beta bands in pneumonia patients. This was accompanied by a slowing of the peak frequency in the alpha band and fastening of that in the theta band. When compared to the controls, the power in the theta band was significantly higher in the pneumonia groups.
2010 Van den Boogaard	Prospective		15 Experimental induced endotoxemia 10 Healthy controls	Endotoxemia induced no clinically relevant EEG changes except in one subject with a mild encephalopathic episode but without cognitive dysfunction. Quantitative EEG analysis showed a higher state of alertness detected by changes in the central region, and peak frequency in the occipital region witch significantly correlated with cortisol.
2009 Oddo	Retrospective	Medical ITU	201 medical ITU admissions without a primary acute neurological condition	Patients with sepsis had a higher rate of electroencephalographic seizures (ESZs) and periodic epileptiform discharges (PEDs) than those without sepsis (32% *vs.* 9%, $p < 0.001$). Seizures were mainly nonconvulsive. Multivariable analysis, sepsis at ITU admission was the only significant predictor of ESZs or PEDs (OR 4.6, 95%, CI 1.9–12.7, $P = 0.002$) and they were also associated with death or severe disability at hospital discharge (89% with ESZs or PEDs, *vs.* 39%; OR 19.1, 95% CI 6.3–74.6, $P < 0.001$) when controlled for age, coma, and organ dysfunction.
1998 Straver	Prospective		14 SAE patients	All EEGs showed decreased fast activity and an increase in slow wave activity. The abnormalities seen in those patients were independent of the sedation level. Neither the APACHE II score, nor the EEG parameters predicted the outcome.
1992 Young		ITU	62 patients with positive blood cultures	The EEG was more sensitive than clinical criteria for encephalopathy. It also had well-defined categories that correlated with mortality.

ITU: intensive treatment unit; SAE: sepsis-associated encephalopathy; CNS: central nervous system; EEG: electroencephalography.

Lack of EEG reactivity was more frequent in those who were on continuous sedation during cEEG and this was associated with higher mortality up to 1 year following discharge.[20]

In a small prospective study by Velissaris *et al.* in 2019, we assessed patients with sepsis in the early stages without clinical sings of neurological involvement. Abnormal EEG findings were detected in six out of seventeen patients (mild slowing in the theta range, intermittent delta activity on a mildly slow background).[21] In the 2019 study by Nielsen *et al.* assessing the use of cEEG, the absence of delirium in septic patients was independently associated with a preserved high-frequency beta activity and cEEG reactivity ($P < 0.001$). Delirium was associated mainly with low frequency cEEG.[22]

ECG AS A TOOL FOR THE DIAGNOSIS AND PROGNOSIS OF SAE

The diagnosis of SAE relies on detailed clinical examination (including evaluation using Glasgow Coma Scale, and central and peripheral nerves evaluation), cognitive assessment tests, serum specific biomarkers of brain injury (*i.e.*, neuron-specific enolase, S-100 beta-protein),[23] and abnormal findings in the EEG, somatosensory-evoked potentials and neuroimaging.[24] The detailed clinical examination can be accompanied by the performance of a lumbar puncture in the case where a CNS infection suspicion is raised. The measurements of specific neurologic indexes such as plasma S-100b protein and neuron-specific enolase are valuable but these are not affordable nor broadly available to all medical settings.[25] Neuroimaging with brain CT and MRI can be performed with various specificity as they do not reveal specific abnormalities in most sepsis cases but combined with EEG may provide helpful patterns for diagnosis.[26] Somatosensitive Evoked Potentials have also been used as they could be sensitive markers of sepsis-associated cerebral dysfunction.[4,8,10]

Electroencephalography has been trialed for many years as a diagnostic and monitoring tool in SAE. It is a sensitive test for detecting brain abnormalities in many clinical entities; however, it is generally used in combination with other tests to assess CNS alterations. Regarding its use, the raw EEG can be assessed visually or analyzed by quantitative methods extracting descriptive features like frequency, power, linearity and amplitude. EEC tracing and power is correlated with the cerebral and the systemic blood flow, a fact that reveals its possible utility in conditions with altered brain perfusion like sepsis.[27]

EEG can also identify early abnormalities even in cases that the neurological examination of the sepsis patient is normal.[21] Mild ECG slowing seems to be the earliest feature of SAE. Analyzing and assessing data from the existing literature, sepsis can be associated with increased theta rhythms, predominant delta waves, triphasic waves, burst suppression patterns, decreased reactivity as well as ESZs and PEDs. Young's classification provides a structured approach and defines how these data should be interpreted.[15,28] These early features that can be captured before any clinical signs develop alongside with the simplicity and the low cost of the method (*e.g.*, compared to expensive unvalidated and broadly unavailable biomarkers) consist the main advantages regarding the use of EEG in the diagnosis of SAE.

Nevertheless, inter-observer variability may prove to be a serious limitation in the use of this modality. Ronner *et al.* in 2009 showed that Kappa values for the individual Young's criteria were highly variable, indicating discrepancies in the interpretation of specific phenomena thus making EEG diagnosis of non-convulsive seizures in ITU patients not very reliable.[29]

CONCLUSIONS

This overview highlights the clinical use of EEG in the non-CNS sepsis patients. We found a body of references in the literature, but most of the studies were evaluating the combination of EEG with other modalities resulting in variations in the specificity and sensitivity in the diagnosis of SAE. Clinicians are very often faced with difficult cases of neurological complications of unknown origin and sepsis can be triggering these abnormalities even in the very early stages of the disease.

Applying EEG is a simple, cost effective approach in the differential diagnosis of encephalopathy especially in the lower income medical settings. There is a growing body of evidence suggesting that EEG could be helpful in the initial assessment of sepsis and aid in the recognition of SAE and its complications, when CNS infections have been excluded. Larger studies are needed in order to establish solid EEG interpretation criteria and standardize its use as well as confirming or discarding any prognostication potential in this rather complex and multifactorial entity of brain dysfunction.

Conflict of Interest

None declared.

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