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Focal epileptic seizures, electroencephalography and outcome of sepsis associated encephalopathy—A pilot study

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ABSTRACT

Objectives: Sepsis associated encephalopathy (SAE) represents a diffuse and/or multifactorial cerebral dysfunction during response to systemic infection. Study aim was to compare clinical and electroencephalogram (EEG) characteristics and intrahospital survival rate among SAE patients.
Patients and methods: A prospective study, during 42 months' period, included 39 SAE patients assigned in two groups according the outcome (survival: 19, and death: 20 patients). All the patients' features were registered: demography, neurological status, infection type, seizure appearance, brain computerized tomography (CT), EEG, EEG reactivity, Glasgow Coma Score (GCS) and Acute Physiology and Chronic Health Evaluation II (APACHE II) Score. The analysis included EEGs obtained during patients' consciousness change (improvement or deterioration) and the level of consciousness during and at the end of hospitalization.
Results: SAE was detected in 29.5% of patients with encephalopathy (2.8% of all patients hospitalized). Patients with lethal outcome were more likely to be female ($p = 0.0011$), to have focal seizures ($p = 0.034$), lower values of GCS during hospitalization ($p < 0.05$) and longer lasting nosocomial infections ($p = 0.029$). At the time of clinical exacerbation, patients were more likely to have suppression on EEG and less likely theta activity. Delta waves, TW waves and suppression of EEG activity were the most common findings 24 h prior to death ($p = 0.0004$). The lack of EEG reactivity was associated with death ($p = 0.00043$).
Conclusion: Presence of focal seizures, EEG suppression at the time of exacerbation in SAE elderly patients, particularly women, with longer infection duration and lower values of GCS, is associated with intrahospital death.

1. Introduction

Brain dysfunction or encephalopathy may be associated with systemic inflammatory response syndrome [1]. Sepsis associated encephalopathy (SAE) has usually been used for description of diffuse or multifactorial cerebral dysfunction caused by systemic infection, without signs or laboratory confirmation of brain infection [1]. Up to 71% of all critically ill patients with sepsis may develop SAE. The diagnosis is usually clinical, since there were no specific tests [2]. Glasgow Coma Score (GCS) is a common tool for the evaluation of patients' level of consciousness, while Acute Physiology and Chronic Health Evaluation II (APACHE II) Score assesses the morbidity and may estimate mortality in intensive care units (ICU). Electroencephalography (EEG) represents a sensitive, but not a specific diagnostic method, while Computed Tomography of brain (CT) generally shows no particular findings in patients with SAE [2]. Critically ill patients in ICUs develop epileptic seizures in 10–20% of cases, whilst in patients with sepsis this proportion has been even higher [3].

To the best of our knowledge, there are only few clinical studies [2,4–6] that analyzed different aspects of the outcome in patients with SAE during hospitalization. Our study main goal was to contribute to clarification of the link of SAE outcome with clinical and EEG characteristics. Rationale for this study goal was that particular clinical characteristics coupled with specific EEG patterns might be more frequent in particularly vulnerable population of patients with unfavourable SAE prognosis. Therefore, the study aim was to

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compare demography, clinical and EEG characteristics and intrahospital survival rate among SAE patients.

2. Material and methods

2.1. Study design

This is a prospective, observational study performed at Neurological Intensive Care Unit (NICU), Neurology Clinic, Clinical Centre of Serbia during a 42 month period (January 2012–July 2015.) Patients were assigned into two groups according the outcome (group I: survival and group II: death).

Study monitored the following features: demographic data (patients' age and gender), presence of comorbidity: hypertension, diabetes mellitus, cardiovascular diseases, smoking, prior infections (3 weeks' period), as well as the assessment of neurological status (presence of paratonia or gegenhalten, myoclonus, epileptic seizures, hemiparesis and cranial nerve findings). GCS and APACHE II scores were monitored during the entire hospitalization [7]. Epileptic seizures were classified as: focal seizures, generalized seizures or epileptic status (convulsive or non-convulsive). A comparison of outcomes between patients with nosocomial and intrahospital infections was performed [8,9].

Inclusion criteria were as follows: older than 18 years patient hospitalized in NICU, diagnosis of sepsis (presence of Systemic Inflammatory Response Syndrome with microbiology confirmation of the positive blood culture) and SAE confirmed by EEG examination [10,11], neuroinfection excluded by meningeal signs examination and lumbar puncture, and CT scan without radiology signs of exclusion criteria (see below). Exclusion criteria were: patients younger than 18 years, primary brain injury (cerebral trauma, cerebral infarcts and haemorrhage, intracerebral tumours, intracranial infections and abscesses) or secondary brain injury (acute primary metabolic disorders – renal and hepatic encephalopathy, electrolyte dysbalance, cardiopulmonary reanimation with resuscitation, endocrine disorders, hypertensive encephalopathy, hypo/hyperthermia, alcohol intoxication), as well as acute psychiatric illness (psychosis).

2.2. EEG recording

EEG was recorded within the first 24 h after sepsis was verified, and was repeated each time when change in patients' consciousness level was observed (improvement or deterioration) during the entire hospitalization. EEG was also recorded at discharge, and 90 days after discharge in survivors, or during the last day of hospitalization in patients who died. According to Young et al. [6] the classification of encephalopathy's severity consists of five categories: 1. normal EEG; 2. excessive theta (low-voltage, generalized waves >4 Hz but <8 Hz), 3. predominant delta (medium to high voltage waves of 4 Hz or less), 4. triphasic waves (either typical or atypical triphasic waves as the principal abnormality) 5. suppression (no activity exceeding 20 μV on bipolar or referential montage, showed non- electrocerebral silence) or burst suppression pattern (BSP). Patients who had intermittent rhythmic delta activity (IRDA), usually frontal (FIRDA) or any other intermittent delta activity were classified as III category (predominant delta). Those who had periodic lateralized epileptiform discharge (PLEDs), general periodic epileptiform discharge (GPEDs) or bilateral independent periodic lateralized epileptiform discharge (BiPEDs), were classified in specific patterns, while those with epileptic changes (spikes waves, sharp waves, spike wave complexes etc) were categorized in the interictal patterns. Epileptic status was classified as ictal EEG, convulsive (CSE) and non-convulsive (NCSE). EEG (Valor T 40, Natus, Middleton, WI, USA) was recorded over 30 min with silver-silver chloride disc scalp electrodes placed according to the International 10–20 system. Patients were stimulated by verbal command (e.g. opening of the eyes) while in case of no response, sternal rub and/or nail bed compression were used.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional – Ethics committee of Medical Faculty, University of Belgrade and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients or their next of a kin relative.

Table 1
Demography.

Variable	Group I No	Group II No	P
All patients	19 (48.7%)	20 (52.3%)	1.00
Male gender, no(%)	16 (84.2%)	8 (40%)	
Female gender, no(%)	3 (15.8%)	12 (60%)	**<0.0001**
Age	62.74 ± 15.31	70.4 ± 15.69	0.124
Age male	66.19 ± 13.86[a]	60.86 ± 14.03[b]	0.386
Age female	44.33 ± 8.02	76.75 ± 12.5	**0.0011**
Comorbidity			
Hypertension	11	2	**0.002**
Diabetes mellitus	5	6	1.00
Cardiovascular disease	4	10	0.096
Infection 3 weeks before admission	3	4	1.00
Smoking	3	4	1.00
Other chronic diseases	7	7	1.00

[a] p = 0.018 vs. female Group I.
[b] p = 0.016 vs. female group II.

2.3. Statistical analysis

Numerical continuous variables with normal distribution were presented as mean and standard deviation. To assess the statistical significance of numerical data parametric T test was used, while categorical variables and those without a normal distribution were analyzed by Mann-Whitney and Kruskal–Wallis test. Nominal data are presented as absolute numbers and percentages. For the assessment of statistical significance Chi-square test and Fisher exact probability test were used. The difference was considered as statistically significant if $p < 0.05$. Package SPSS version 15.0 for Windows (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

3. Results

A total of 1413 patients were hospitalized at NICU during the observed period. From this number, 132 (9.34%) had encephalopathy. Finally, the study included a total of 39 patients with SAE (2.76% of total number of hospitalized patients or 29.55% of patients with encephalopathy), assigned by outcome to group I – survivors (19 patients) and group II – lethal outcome (20 patients).

3.1. Demographics

From 39 patients, 24 (62%) were men and 15 (38%) were women. The average age of patients by gender is shown in Table 1a.

Gender comparison between groups demonstrated statistically significant difference in age between genders, as well as a significant difference in mortality, reporting a higher frequency of death in women. Comorbidities were similarly distributed among groups and there was no statistically significant difference (Table 1).

3.2. Clinical presentation

At the admission a CT scan was done in all the patients, as an inclusion criterion. There was no statistically significant difference in the description of CT findings between two groups. Values of