EEG ABNORMALITIES AS DIAGNOSTIC AND PROGNOSTIC FACTOR FOR ENCEPHALITIS

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EEG ABNORMALNOSTI KAO DIJAGNOSTIČKI I PROGNOSTIČKI FAKTOR ZA ENCEFALITIS

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ABSTRACT

The aim of the study is to examine whether EEG abnormalities in patients with encephalitis might be prognostic and diagnostic factors for final epilepsy outcome and/or be correlated with the severity of the disability.

The most frequent causes of encephalitis were HSV, WNV, INF V, MTB, St PN, St AU. There was a highly statistically significant positive correlation between the severity of the EEG abnormalities at the beginning of the disease (r = 0.410, p <0.01) and the ultimate outcome.

Electroencephalography in the early stages of encephalitis shows diagnostic and prognostic significance and, in combination with the overall severity of the clinical picture, could contribute to the diagnosis and assessment of outcomes and, ultimately, the correction of treatment and faster recovery of patients. This is particularly true for viral encephalitis.

Keywords: *encephalitis, EEG, consciousness disorder, seizure.*

SAŽETAK

Cilj naseg rada je da se utvrdi da li elektroencefalografi ja (EEG) kod pacijenata sa encefalitisom može biti prognosticki i dijagnosticki faktor u odnosu na krajnji ishod i da li korelira sa težinom bolesti.

Najčešći uzročnici encefalitisa bili su herpes simplex virus, West Nile virus, virus influence, Mycobacterium Tuberculosis, St. Pneumoniae, Staphylococcus aureus. Postoji visoko staatistički značajna pozitivnaa korelacija između težine EEG nalaza na početku bolesti (r=0.410, p<0.01) i kontrolnog EEG nalaza (EEG 2) i ishoda bolesti (r=0.391, p<0.01). Postoji visoko statistički značajna korelacija između EEG1 nalaza (r = 0.391, p<0.01) i EEG2 nalaza i neurološkog deficita (r = 0.477, p<0.01).

EEG u ranim stadijumima encefalitisa ima dijagnostički i prognostički značaj i u kombinaciji sa težinom kliničke slike može doprineti postavljanju dijagnoze i proceni ishoda bolesti i uz to korigovanju terapije i bržem oporavku pacijenata. Ovo se posebno odnosi na virusne encefalitise.

Ključne reči: *encefalitis, EEG, poremećaj svesti, epileptični napad.*

ABBREVIATIONS

AC - alpha coma;
BUE – bacteria of unknown aetiology;
CSF - cerebrospinal fluid;
EEG - electroencephalography;
FSA - focal slow activity;
GSA - generalized slow activity;
HSV - herpes simplex virus;
INF V - virus influence;
MTB - Mycobacterium Tuberculosis;
NF - nonspecific findings;
PCR - polymerase chain reaction;
St PN - St. Pneumoniae;
St AU - Staphylococcus aureus;
VUE - virus of unknown aetiology;
WNV - West Nile virus.

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INTRODUCTION

Encephalitis is defined as inflammation of the brain parenchyma (focal or diffuse) that is associated with signs of focal or diffuse neurological dysfunction (1). Encephalitis affects all ages and genders, although the greatest frequency of presentation is in children and in adults older than 65 years (2, 3).

Encephalitis can arise from infectious, immune-mediated or unknown aetiology. In most cases, the cause of encephalitis is unknown. The most common infectious agents are as follows: Herpes simplex virus (HSV), Mycobacterium tuberculosis (MTB), and the Varicella zoster virus. Less common causes of encephalitis include Streptococcus pneumoniae (ST Pn), Influenza A (INF V), and the Epstein-Barr virus (4). Other less common viruses carried by insects (arboviruses, West Nile virus (WNV)) have also become increasingly common in recent years in our country) (2).

The main clinical features of brain dysfunction in encephalitis are the following: fever, headache, seizures, lethargy, irritability, personality and/or behavioural changes, stiff neck, focal neurological signs, gastrointestinal symptoms, respiratory symptoms, rash, photophobia, or urinary symptoms (2, 4).

Rapid diagnosis and prompt treatment of encephalitis are crucial to the outcome (5). Diagnosis is based upon clinical, laboratory, neuroradiological and electroencephalographic (EEG) characteristics (6). EEG findings in patients with encephalitis have been shown to be correlated with the severity of disease and may have prognostic significance (7). A definitive diagnosis is made by lumbar puncture and the analysis of cerebro-spinal fluid (cytological, biochemical and microbiological). Etiological confirmation is achieved by culturing cerebro-spinal fluid (bacterial) or by the detection of the virus in the cerebrospinal fluid (CSF) of the central nervous system via PCR or specific antibodies. It is of less importance is to prove the presence of the virus outside the central nervous system (throat swabs, stool) or to demonstrate the presence of antibodies in the serum (5).

Encephalitis is a difficult to treat, life-threatening disease characterized by high mortality, and survivors risk multiple complications and consequences (epilepsy, behaviour disorder, disorder of memory and remembering, emotional instability, etc.) (8).

The aim of this study was to determine to what extent EEG recordings of brain function in patients with encephalitis could be used as prognostic tools for the final outcome (lethal or recovery), to what degree they could be prognostic tools for the degree of recovery, and to what degree they are correlated with the severity of disability and possible causal explanations for this disability.

PATIENTS AND METHODS

Our retrospective study included 46 patients with confirmed diagnoses of encephalitis or meningoencephalitis, with or without one or more epileptic seizures. The study was conducted at the Clinic for Infectious Diseases and at the Clinic of Neurology, Clinical Centre in Kragujevac and included all patients treated in the period from March 2012 to January 2015.

At initial patient intake, we evaluated their somatic statuses, neurological statuses and states of consciousness. Blood was drawn for laboratory analysis, and we performed a lumbar puncture and cytological examinations of the CSF. To establish the aetiological diagnosis and disclosure of a causal infection, we also conducted virology, bacteriology, and immune-serology based tests and used PCR.

Standard EEG and video EEG monitoring were performed for all patients in the electroencephalography ward at the Clinic of Neurology. The EEG was recorded on two occasions during hospitalization. The first recording was made within the first three days of hospitalization whenever possible, or as early as possible in critically ill patients, no later than seven days from the start of disease. The recordings were compared with each other and with the general clinical picture of the patient. The second recording was made at the end of hospitalization (at discharge of the patient). Over the next 3-6 months, patients were followed in our infectology and neurology outpatient clinic to determine their somatic, neurological and mental statuses. Over the same period, we also conducted one other control EEG recording.

Disturbed states of consciousness were graded in three levels: low disturbance (somnolence), medium-heavy disturbance (sopor) and heavy disturbance (coma).

Neurological deficits were graded in three levels: low (weakness in the extremities fixation), medium-heavy (manifest weakness) and severe (paralysis of the extremities). A fourth category was composed of patients without neurological deficits.

Pathological EEG findings were classified into 3 categories: Generalized slow activity (GSA), as an indicator of generalized brain damage, focal slow activity (FSA) as an indicator of focal brain damage and Alpha coma (AC) as an indicator of severe brain damage. We also found a group of patients with nonspecific EEG abnormalities (NF) and normal EEGs.

At the final follow-up for disease outcome, we classified patients into 3 categories: partial recovery, full recovery or lethal outcome.

The recordings were compared with previous findings (EEG findings of all three) as well as with the current situation of the patient to determine if the initial EEG correlated to the ultimate severity (EEG time point 1 and EEG time point 2) and whether there were correlations with the final outcome (all three EEG findings).

All data were analysed using descriptive and analytical statistics. Chi-squared tests were used for categorical variables and Student's t-tests were used for continuous variables. We used correlations for EEG findings, outcomes and neurological deficits. SPSS (version 20.0) was used for statistical analyses. Statistical significance was set at $p<0.05$.

RESULTS

We included 46 patients (25 males and 21 females) with a mean age 42.8 years.

The most common encephalitis symptom was a disturbed state of consciousness -97.8% (somnolence 22, sopor 11, coma 12 patients). Other frequent symptoms were fever (95%) and headache (59%).

Twenty-two patients (48%) experienced one or more provoked epileptic attacks during hospitalization (Figure 1), while 5 patients (11%) experienced repeated attacks during the monitoring period and were diagnosed with symptomatic epilepsy.

We observed severe neurologic deficits in 24% of patients, medium-heavy deficits in 11% and no or low-grade disturbances in 65% of patients.

EEG findings during the disease and the control EEG findings are presented in Table 1.

The most frequent causes of encephalitis were HSV (PCR from CSF to HSV-1) WNV (serology from serum and CSF), INF V and viral encephalitis of unknown origin (Table 2).

We found isolated bacteria in 35% of patients: MTB (PCR from CSF and Lowenstain +), St PN (CSF culture and haemocultures), and St AU (CSF culture and haemocultures). Five patients were diagnosed with bacterial meningitis of unknown origin, with the initial lumbar puncture after the start of antibiotic therapy.

We isolated a Candida species (Candida IgM and IgG + in CSF) in one patient.

Lethal outcomes were observed in 13.8% of patients with viral encephalitis, partial recovery in 34.5% and complete recovery in 51.8% of patients. Lethal outcomes were observed in 37.5% of patients, with all others making a full recovery (62.5%).

There was a highly statistically significant positive correlation between the severity of the EEG findings at beginning of the disease (EEG 1) and the disease outcome or degree of recovery (r = 0.410, p<0.01). There was also a highly statistically significant positive correlation between the control EEG reading (EEG 2) and the disease outcome (r = 0.391, p <0.01), but there was no statistically significant correlation between the findings from EEG 3 and disease outcome (r = + 0.131, p = 0.446).

There was a highly significant correlation between the EEG time point 1 findings and the degrees of neurological deficit (r = 0.391, p <0.01) and between EEG time point 2 findings and the degrees of neurological deficits (r = 0.477, p <0.01). There were no statistically significant correlations between EEG 3 readings and neurological deficits (r = 0.224, p = 0.189).

There was a highly statistically significant positive correlation between the degree of neurological deficit and the disease outcome (r = 0.736, p <0.01).

A total of 69% of patients (20 patients) with viral encephalitis showed abnormal findings on their EEG. That there was a highly statistically significant positive correlation between the severity of abnormalities at EEG time point 1 and the disease outcome (r = + 0.515. p<0.01) and between EEG time point 2 and disease outcome (r = 0.562, p<0.01), indicating the potential value of EEG monitoring for prognosis. There was no statistically significant correlation between the abnormalities observed at EEG 3 and the disease outcome (r = 0.204, p=0.328). There was a highly statistically significant positive correlation between the severity of the neurological deficits and the disease outcome (r = 0.597, p<0.01). Other patients (31%) showed nonspecific or normal findings at EEG 1 and EEG 2.

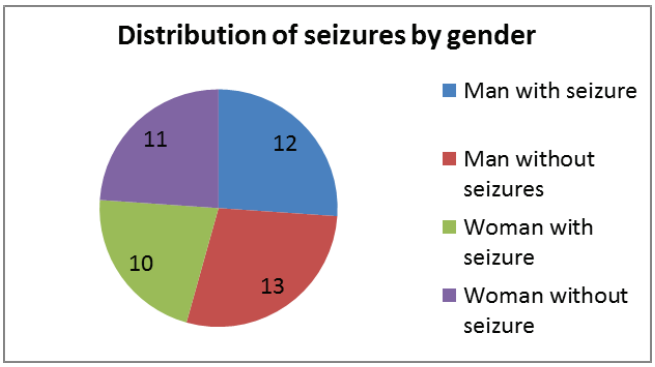

Figure 1. Distribution of seizures by gender

For patients with bacterial encephalitis, EEG 1 and EEG 2 findings were abnormal in 43.8% of patients, and there were no correlations with the severity or with recovery. There were no statistically significant correlations among the severity of abnormalities at EEG 1, EEG 2 or EEG 3 and disease outcome. (r = + 0.375, p=0.153; r =

Table 1. Number of patients with EEG findings during disease

EEG findings	EEG 1	EEG 2	EEG 3
AC	2	1	0
GSA	16	10	0
FSA	12	9	0
NF	12	20	8
Normal EEG	4	5	29
Without EEG	0	1	9

Table 2. Causes of encephalitis.

Causes		male	female	Number of patients	%
Viruse	HSV	7	11	18	39.1
	WNV	2	1	3	6.5
	INF V	2	2	4	8.7
	VUE	3	1	4	8.7
Bacteria	MTB	3	1	4	8.7
	St PN	2	2	4	8.7
	St AU	2	1	3	6.5
	BUE	4	1	5	10.9
Fungus	Candida.	0	1	1	2.2

0.253, p=0.362; r = -0.167, p=0.645). There was a highly statistically significant positive correlation between the severity of neurological deficits and the disease outcome (r = 0.946, p<0.01).

There were no statistically significant differences in the outcome of the disease depending upon the cause (viral vs. bacterial) (p=0.546). There were no statistically significant differences in neurological deficits depending upon the cause (viral vs. bacterial) (p=0.728). None of the three EEG recording showed statistically significant correlations with the cause (viral vs. bacterial) (p1=0.203, p2=0.342, p3 =0.346).

DISCUSSION

HSV encephalitis is the most common type of sporadic encephalitis in the world and in our country (39% of patients) (4). In our sample of patients, three patients showed evidence of WNV, which is a relatively rare and new agent in the region. In 2013, the first published cases of encephalitis caused by the virus in our country were reported; 44 patients with WNV encephalitis were admitted during the summer of 2012 (2). There are no precise data on the incidence of encephalitis caused by INF in Serbia except in the form of case reports from patients who had neurological complications in the form of encephalopathy caused by this virus (9). Mycobacterium tuberculosis is a relatively rare cause of encephalitis (1-5% worldwide) (4, 10); however, in our study, the frequency of this bacterium was 8.7%, which was as common as other bacterial pathogens (St Pn, St Au). The cause of encephalitis in more than one-third of cases is typically unknown (4), whereas in our study it was 19.6%.

In our total population of patients with encephalitis, abnormal EEG findings were predictive of a severe clinical picture and poorer prognosis as early as the first and as late as the control EEG findings. There was a significant correlation between the severity of the EEG findings and the degree of recovery. It has previously been suggested in HSV encephalitis that the weight of the initial EEG findings may be a useful prognostic factor for disease outcome (11).

All patients with viral encephalitis and a lethal outcome showed EEG abnormalities that correlated with the severity and could serve as a diagnostic, as well as prognostic tool, as seen in other studies (11). Survivors of viral encephalitis usually emerge with cognitive changes and damage to their executive functions (12). In most patients with partial recovery, we observed EEG abnormalities that reflected the seriousness of their clinical picture as early as the EEG 1 and EEG 2 time points (recorded during the early stages of the disease). Abnormalities at EEG 1 and EEG 2 in patients with a viral infection correlated with the severity and the final outcome. EEG 3 was typically normal or showed nonspecific abnormalities, and it did not correlate with recovery or severity. In our study, it showed little practical significance.

Patients with bacterial encephalitis with lethal outcomes consistently showed abnormal, pathological findings on their EEG, but none of the three EEG recordings were specific for the severity or prognosis of the disease. One possible explanation is that the time interval over which we worked was inadequate to capture these effects. The window between the first EEG, which was recorded very early, and the second EEG, may have been too long given that the full clinical picture develops more slowly in bacterial infection compared to viral infection, and there is a prompt and favourable response to causal therapy. The third EEG in most cases was nonspecific and corresponded to recovery, with no statistically significant correlations and with no significance as a prognostic tool.

Of the total 46 patients, death occurred in 10 patients (22%). Other studies have shown differing rates of mortality of 10-18% (13, 14). Mortality in bacterial and viral encephalitis is typically similar, but in our study, a higher mortality rate was observed in bacterial encephalitis, which was not unexpected because these were patients of older age, had more comorbidities, and developed more severe complications, all of which are common in other studies (14). The frequency of provoked epileptic seizures and symptomatic epilepsy correlated with the severity of disability (11).

In 36 patients, there was a favourable outcome. The majority made a full recovery (56%), and 22% made a partial recovery. One study demonstrated an inverse relationship between patients with complete and partial recovery (36% vs. 56%). There was a significant positive correlation between the severity of the complete clinical picture and the final outcome of both viral and bacterial encephalitis. A more severe clinical picture was associated with a worse prognosis, which was expected (14).

CONCLUSION

Electroencephalography in the early stages of encephalitis shows diagnostic and prognostic significance, and, in combination with severity of the clinical picture, could contribute to the diagnosis and assessment of outcomes and therefore the earlier correction of treatment and faster recovery of patients. This is particularly true for viral encephalitis, as electroencephalography was not specific in bacterial encephalitis. The diagnostic usefulness of EEG in bacterial encephalitis requires further verification in a larger sample. In most retrospective studies, the sample size are small, and our research should be extended to a larger sample.

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