

# Predictive Role of Electroencephalography in Regard to Neurological and Cognitive Sequelae After Acute Central Nervous System Infection

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## ABSTRACT

**Introduction:** Electroencephalography can also be used to monitor long-term recovery of the patient after acute phase of the disease. Impaired neurocognitive function after infection, similar to brain injury, may present a transient but also prolonged problem for the functioning of an individual. Some studies have shown that importance of EEG may not be significant in sequel monitoring, because the extensive changes in EEG seen with severe forms of CNS infection do not necessarily imply a longer-term poor outcome. **Aim:** To examine the predictive potential of electroencephalography (EEG) in regard to the emergence of neurological and cognitive sequelae of acute central nervous system (CNS) infection. **Methods:** The study included 62 patients treated at the Clinic for Infectious Diseases, Clinical Center of Sarajevo University, who were diagnosed with acute CNS infection. The EEG record was characterized as: normal, non-specific changes of mild, moderate and severe degree and specific changes. The sequelae (headache, cognitive dysfunction, neurological and neurophysiological disorders, audiological and behavioral disorders) was evaluated by combining neurological, psychiatric, pediatric, otolaryngological, ophthalmic and infectological examination in the Neuroinfective Counseling Department for up to 6 months after discharge. **Results:** After a treatment of an acute CNS infection 25 (40.3%) patients had no sequelae and 37 (59.7%) were with sequelae. The EEG in the initial stage of the disease (Wald's coefficient = 12.8), followed by the age of the patients (Wald = 6.4), had the greatest influence on the prediction of sequela ( $p=0.0001$ ). For each additional degree of verified pathological changes in the EEG, the risk of sequelae was increased by 5 degrees (OR = 5.3), respectively. There was no statistically significant association between changes in cerebrospinal fluid (CSF) findings, meningeal symptoms, and signs with sequelae development. **Conclusion:** Younger age, as well as severe clinical status of a patient, which implies a disorder of consciousness and seizures on admission, are associated with irreversible consequences on a previously mentally healthy individual. Pathological changes (Delta and Theta waves, spike slow complex wave) on the EEG finding significantly predicted presence of sequelae. .

**Keywords:** cognitive manifestation, CNS diseases, EEG.

## 1. INTRODUCTION

Acute central nervous system (CNS) infections are etiologically diverse diseases, characterized by complex pathogenesis, specific clinical symptomatology, and often severe and even life-threatening events. The most common causative agents are viruses and bacteria, and potential, microorganisms known as mycoplasmas, rickettsia, parasites and fungi (1). Infection of CNS is medical emergency, and there is a need of early recognition, effective decision making, and treatment (2). Precise etiologic diagnosis of acute CNS infections is difficult to

determine, because diagnostic capacity of individual hospital centers is rarely sufficiently developed, which, together with lack of standardized clinical protocols, usually leads to imprecise characterization of these infections as "aseptic" or "purulent" (3). The most important etiologic pathogens of purulent meningitis are *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis* (4). With successfully implemented vaccination, economically developed countries have reduced the prevalence of purulent CNS infections, while middle and devel-

oping countries are still having a high rate (5). We know today that aseptic CNS infections can be infectious and non-infectious, but the etiological spectrum of is still unknown. Herpesviruses are the most significant cause of aseptic acute CNS infection (6). Meningeal syndrome involves a variety of neurological symptoms, from fever and headache, to altered quality of consciousness, to lethargy or coma (6). According to the current protocols, diagnosis is established by clinical finding and analysis of CSF, which is the gold standard of diagnosis for these infections. Aseptic infections may have a discretely altered CSF (7).

The persistence of various neurological and cognitive symptoms after CNS infection was first described in 1923 (8). The effects of acute CNS infections on patients' cognitive ability can be eliminated and treated if the etiologic and predisposing factors and extent of brain damage were detected during the infection. Patients with severe impairment on the electroencephalography (EEG), or those with severe cognitive or neurological sequelae on discharge, should be treated by physical therapy or under the supervision of a psychiatrist, speech therapist or neurologist as soon as possible (9). Electroencephalography and various neuroimaging methods, in particular magnetic resonance imaging (MR), can be useful to confirm the diagnosis and to identify focal complications (10).

Electroencephalography can also be used to monitor long-term recovery of the patient after acute phase of the disease. Impaired neurocognitive function after infection, similar to brain injury, may present a transient but also prolonged problem for the functioning of an individual (11). Some studies have shown that importance of EEG may not be significant in sequel monitoring, because the extensive changes in EEG seen with severe forms of CNS infection do not necessarily imply a longer-term poor outcome (12). However, such studies were rarely done in resource-poor settings of developing countries.

## 2. AIM

The aim of this study was to examine the predictive potential of electroencephalography (EEG) in regard to the emergence of neurological and cognitive sequelae of acute central nervous system (CNS) infection.

## 3. METHODS

### Patients and study design

This retrospective study included 62 patients treated at the Infectious Diseases Clinic over a four-year period (January 2014 - January 2018). After discharge from the Clinic, for the patients were re-examined 6 months later. Data collection did not interfere with the care and treatment of patients in any way, and statistical analyzes were processed retrospectively and anonymously. Ethical approval was obtained from the Ethics Committee of the Clinical Center of the University of Sarajevo. The reasons for hospitalization were acute CNS infections, which were diagnosed by CSF examination on the day of admission.

Data from case histories, temperature lists, and specialist opinion findings stored in the Hospital Information System (BIS) of the Infectious Diseases Clinic were used. Patients were treated according to current local clinical standards and were included in the study if they had completed: CSF, clinical, laboratory, neuroimaging and neurophysiological diagnostics. The age, gender, length of hospitalization, clinical parameters on the day of admission with special reference to neurological status (fever, headache, and state of consciousness, neck pain, malaise, meningeal signs, tone and muscular motility, reflexes) were analyzed for each patient who matched the sample.

The CSF examination including the number of cells, proteins, and glucose was made immediately after raising suspicion of CNS infection. Electroencephalography was performed at the Pediatric Clinic and the Neurology Clinic using 32 channel techniques for 20 min. Electroencephalography was performed at the Pediatric Clinic and the Neurology Clinic using 32 channel techniques for 20 min.

### Methods

The EEG record was characterized as: physiological, pathological changes of mild grade, medium-severe grade, severe grade and specifically modified. The sequelae were evaluated by combining neurological, psychiatric, pediatric, otolaryngological, ophthalmic and infectological examination in a Neuroinfective Disease Counseling Center. Sequelae included: headache, cognitive dysfunction (loss of concentration and memory), neurological and neurophysiological disorders, audiological and behavioral disorders (disorientation, psychosis, personality disorder, agitation, etc.).

### Statistical analysis

The data were analyzed at the level of descriptive statistics by measuring central tendency (arithmetic mean and median) and variability (standard deviation and standard error). The univariate binary logistic regression examined the individual impact of independent variables on the binary dependent variable survival (presence / absence of sequelae) in patients treated for acute CNS infection. Multivariate binary regression analysis examined the influence of independent predictors (model 1), which showed a significant impact on the dependently variable "presence / absence of sequela". All analyzes were estimated at the level of statistical significance of  $p < 0.05$ .

## 4. RESULTS

The study included 62 patients, of whom 25 (40.3%) had no sequelae and 37 (59.7%) were with sequelae after a treatment of an acute CNS infection. The male patients dominated, 43 (69.4%) with average age of 17 (12-24) years, 19 (30.6%) were female patients with average age of 35 (14-55) years. The average length of illness before hospitalization was 1 (1-4) days. A total of 37 (59.7%) patients had severe clinical status at admission; fever, headache and malaise were dominant symptoms in 58 (93.5%), 52 (83.9%), and 39 (62.9%) patients, respectively. Meningeal signs were positive in 39 (62.9%)

	B	Wald	df	Sig.	Exp(B)	95.0% C.I. for EXP(B)	
						Lower	Upper
Age (years)	.039	5.310	1	.021	1.040	1.009	1.075
Gender (male / female)	.890	2.170	1	.141	2.435		
Length of illness (days)	.114	1.263	1	.261	1.121		
Elevated Body Temperature (yes / no)	-.750	.401	1	.527	.472		
Headache (yes / no)	-.537	.520	1	.471	.584		
Non-contactability (yes / no)	1.496	4.533	1	.033	4.464	1.126	17.692
Back pain (yes / no)	-.303	.232	1	.630	.739		
General weakness (yes / no)	.493	.850	1	.357	1.637		
Confusion (yes / no)	.693	1.723	1	.189	2.000		
Clinical status at admission (moderate / severe)	1.101	4.158	1	.041	3.008	1.044	8.671
Meningeal signs (Negative / positive)	-.079	.022	1	.883	.924		
Consciousness (unconscious / conscious)	.576	1.208	1	.272	1.780		
Muscle tone, Muscle Motor, Reflexes (Present / Absent)	1.609	5.277	1	.022	5.000	1.266	19.741
Organoleptic CSF (clear / blurry)	.022	.002	1	.966	1.023		
Number of cells (cel / mm3)	.000	.013	1	.910	1.000		
Proteinorrhachia (g/L)	.117	1.133	1	.287	1.124		
Glycorrachia (mmol/L)	-.038	.047	1	.828	.963		
MR of the head (physiological / pathological)	1.172	7.328	1	.007	3.227	1.063	6.553
CT of the head (physiological / pathological)	.901	7.196	1	.007	2.461	1.030	4.143
Pyramid and mastoid radiogram (physiological / pathological)	.474	1.264	1	.261	1.607		
*EEG	1.673	13.164	1	.000	5.326	2.158	13.146

**Table 1. Univariate regression analysis: The influence of independent predictors on outcome of patients with CNS infection (presence or absence of sequela). B-coefficient; Wald-coefficient; df- number of degrees of freedom, p- probability; EXP (B) - odds ratio; 95.0% CI. for EXP (B) - 95% confidence interval for odds ratio; lower - lower limit; Upper- upper limit. \* EEG (EEG findings are numbered in ascending order, monitoring the severity of: 1. physiological; 2. pathological changes of mild grade; 3. medium-severe grade; 4. severe grade; and 5. specifically modified.**

	B	S.E.	Wald	df	p	Exp(B)	95.0% C.I. for EXP(B)		
							Lower	Upper	
Step 1	Age (years)	.063	.031	4.192	1	.041	1.065	1.003	1.131
	Consciousness (yes / no)	1.788	1.141	2.454	1	.117	5.975	.638	55.940
	Clinical status at admission (moderate / severe)	-.955	.918	1.081	1	.298	.385	.064	2.328
	Muscle tone, Muscle Motor Reflexes (Present / Absent)	-.610	1.261	.234	1	.628	.543	.046	6.430
	MR of the head (physiological / pathological)	.010	.662	.000	1	.988	1.010	.276	3.697
	CT of the head (physiological / pathological)	.632	.510	1.536	1	.215	1.881	.693	5.110
	*EEG	2.154	.686	9.871	1	.002	8.622	2.249	33.056
	Constant	-4.992	2.520	3.923	1	.048	.007		
Step 6	Age (years)	.068	.027	6.475	1	.011	1.070	1.016	1.128
	*EEG	1.975	.550	12.884	1	.0001	7.203	2.451	21.172
	Constant	-6.923	1.896	13.332	1	.000	.001		

**Table 2. Multivariate regression analysis. Impact of independent predictors on the outcome of CNS infection (presence or absence of sequela). \* EEG (EEG findings are numbered in ascending order, monitoring the severity of: 1. physiological; 2. pathological changes of mild grade; 3. medium-severe grade; 4. severe grade; and 5. specifically modified**

patients, while 18 (29%) patients had neurological disturbance of tone, motor and reflex. Organoleptic turbidity was found in 37 (59.7%) CSF samples, while the others had clear CSF. The average number of inflammatory cells was 352 (53-2510) with an average proteinorrhachia of 1.2 (0.5-3.2). Neuroimaging showed that MR was more sensitive method in detecting pathological brain changes than CT and standard radiography. EEG findings with moderate (delta-theta slowdown) changes were dominant, with 7 (11.3%) patients having a specifically modified EEG (spike-slow wave) (Figure 1 and 2).

The following independent parameters did not sig-

nificantly affect development of sequela after acute CNS infection: sex, length of disease before treatment, symptoms (fever, headache, pain in the back of the spine and weakness), meningeal signs and state of consciousness, overall CSF, and standard head radiography (Table 1) However, the age of the subjects proved to be a significant predictor of the presence of sequela (p = 0.021) as the odds (Odds ratio) of having a patient with sequela for each year increased by 4%, with an interval of 1 to 8%. Patients who were unconscious on admission were 4 times (OR = 4.4) more likely to develop sequela, as were patients with severe general admission

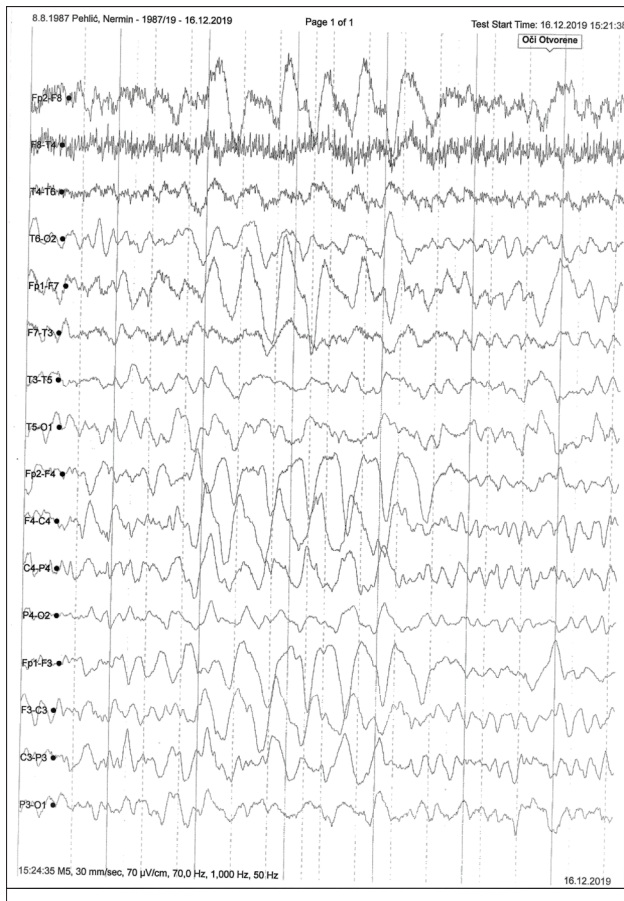


Figure 1. Specific changes (spike-slow wave pattern)

status compared to medium severity, about 3 times (OR = 3, 01).

Absence of muscle motor on admission was significantly influenced the presence of sequela ( $p = 0.021$ ). Absence of a reflex on admission increased the risk of sequelae 5 times (OR = 5.0) (from 1 to 19 times). Pathological changes observed on MR and CT of the head significantly affected presence of sequelae ( $p = 0.007$ ), increasing the risk, MR (OR = 3.2) and CT (OR = 2, 2). Pathological changes (Delta and Theta waves, spike-slow complex wave) on the EEG finding significantly predicted presence of sequelae ( $p = 0.0001$ ).

Using the 6-step Backaer Wald method on all statistically significant variables ( $p < 0.05$ ), the EEG findings from the initial stage of the disease (Wald's coefficient = 12.8), followed by the patients' age (Wald = 6,4) had the greatest impact to the development of sequelae. (Table 2). Model 1 had values (Cox & Snell)  $R^2 = 0.435$  and (Nagelkerke)  $R^2 = 0.0587$ , indicating that the set of sixth step variables explains the deviation between 43.5% and 58.7% of the variance. Furthermore, the results of the Hosmer and Lemeshow test supported the claim that the model was good ( $\chi^2 = 7.5$ ;  $p = 0.479$ ) (Table 2).

## 5. DISCUSSION

The study shows that pathological changes in EEG registration and the patient's younger age are significant predictive factors for various neurological and cognitive sequelae after acute neuroinfectious disease

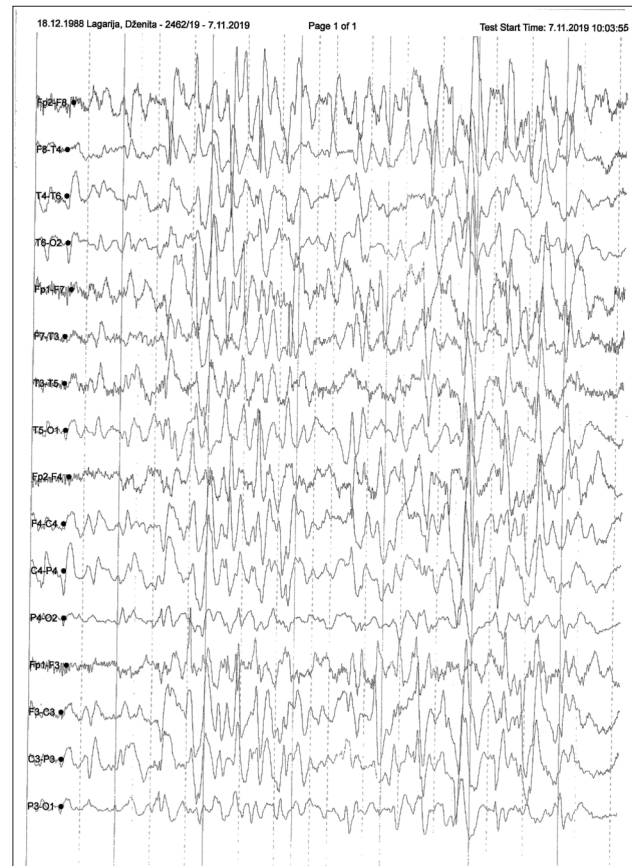


Figure 2. Diffuse Theta-Delta slow waves

such as meningitis and encephalitis.

In the acute stage of the disease, patients with CNS infection have significant neurophysiological disorders seen with EEG, and a lot of number of these disorders correlate with a decrease in cognitive function. At young age, when congenital cognitive status is still incomplete, the EEG help assessing initial severity of the disease and predicting long-term outcome. Research by other authors pointed to the importance of EEG in recognizing non-convulsive seizures that may ultimately be the cause of cognitive long-term disorders (13).

Neurobehavioral disorders consist of a spectrum of neuropsychiatric and somatic symptoms present after brain inflammation, and may include cognitive and behavioral / psychiatric disorders (14). Comparison of rate of sequelae with other studies is difficult because the settings are different: length of follow-up, outcome of disease designated as "good" or "bad", and different research methodologies. True incidence of acute CNS infections is controversial, due to the low rate of ethologically confirmed cases, but in Western countries it is estimated to be 0.6–4 / 100,000 per year for bacterial meningitis, 5.2–7.6 / 100,000 for viral meningitis, and for encephalitis of 2.73–8.66 / 100,000 (15, 16, 17). Cases suspected of having acute neuroinfection do not tolerate delaying the therapy for more than 48 hours of clinical presentation due to high morbidity and mortality rates in untreated patients, and gold standard of diagnosis during this period is LP (18). According to published studies, if antibiotic therapy is not included

in the first hours after admission of patients with bacterial meningitis, mortality increases from 7% to 26% (19).

In our study, 59.7% of patients had neuropsychological sequelae after treatment of an acute CNS infection, which when compared with the general clinical status at the day of admission, could be characterized as "severe". Sequelae presented in the range from general weakness and headache to severe neurological and cognitive disorders, which persisted in the six-month period after treatment, and were estimated by infectious disease specialists after consulting other specialists (otolaryngologist, ophthalmologist and neuropsychiatrist). In large French study of long-term outcomes of patients with encephalitis of different etiology, the rate of patients who had sequelae was significantly lower (39%), because only general neuropsychological variables, moderate and severe instability, and vegetative status were searched for (20). In the retrospective cohort study by Jouan et al., the incidence of disability after Herpes simplex virus (HSV) encephalitis was high, and only 50% of patients showed complete neurological recovery at one-year follow-up, while the remaining became a burden for their families and society (21). Pillai et al had approximately the same rate of sequelae (49%) in patients after 5.8 years of follow-up, both with HSV as the detected cause, and with cases that were not etiologically differentiated. Epileptic status and changes in MRI at the initial stage of the disease were stressed as predictors of sequelae, which is not in accordance with our study, since status epilepticus is a pathological condition suggesting a difficult clinical status of the patient on admission (22). Studies addressing sequelae after meningitis or encephalitis of different ages have found no prognostic correlation with CSF bio-markers or laboratory parameters, but correlated longer-term poor outcome with severe clinical status of patients who required treatment in an intensive care unit (23, 24). We came to the same conclusions, that there was no correlation between the CSF findings and the development of sequelae, as well as meningeal symptoms and signs at the initial stage of the disease. Clinical and laboratory status upon admission of patients to hospital should be used by physicians to raise suspicion of acute CNS infection and start empirical therapy as early as possible. Studies that had only a pediatric population found a link between severe proteinorrhagia in bacterial meningitis and neurological sequelae, which raised the question of morbidity in the younger population according to the etiology of the infection (25). Structural changes (reduction) of brain gray mass observed by neuroimaging method were correlated with cognitive status of patients suffering from tuberculous meningitis, according to studies of other authors (26). Our study also showed that changes in the observed CT and MR, were significant predictors for the development of sequelae during the six-month follow-up of patients after CNS infection, regardless of etiology. Similar to other authors, MRI proved to be a more significant neuroimaging scan to predict se-

quelae (OR = 3.2) than CT (OR = 2.2). Computed tomography is more used in terms of identifying an alternative diagnosis such as intracranial hemorrhage or hydrocephalus (17, 27, 28).

## 6. CONCLUSION

Younger age, as well as severe clinical status of a patient, which implies a disorder of consciousness and seizures on admission, are associated with irreversible consequences on a previously mentally healthy individual. Studies have also shown the importance of more recent neuroimaging methods, such as functional MR or MR spectroscopy, that can predict impaired cognition based on metabolic or functional changes in the brain. Pathological changes (Delta and Theta waves, spike-slow complex wave) on the EEG finding significantly predicted presence of sequelae.

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- **Conflict of interests:** There are no conflicts of interest.
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