

Are Interictal Discharges Associated with Neuronal Cell Loss in Electrical Status Epilepticus in Sleep?

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What is already known on this topic?

- Encephalopathy with electrical status epilepticus in sleep (ESES) is an electrographic pattern that may be associated with seizures and regressions in language, behavior, or cognitive functions.
- Neuron-specific enolase (NSE) is an established biomarker of neuronal damage.

What this study adds on this topic?

- The lack of difference in serum NSE levels between ESES patients and control subjects may indicate that continuous interictal epileptiform discharges (IEDs) do not result in neuronal cell loss or damage in ESES patients.

ABSTRACT

Objective: Neuron-specific enolase is an established biomarker of neuronal damage. This study aimed to reveal the relationship between serum neuron-specific enolase level and continuous interictal discharges in a group of encephalopathy with electrical status epilepticus in sleep patients for the first time and determine whether there is a neuronal cell loss or damage.

Materials and Methods: We analyzed serum neuron-specific enolase levels in patients with an electrical status epilepticus in sleep pattern on their electroencephalographs with age- and sex-matched control subjects. Patients with a spike-wave index of at least 50% and acquired neuropsychological regression were included in the study. Magnetic resonance imaging of all electrical status epilepticus in sleep patients and control subjects included in the study was within normal limits. Neuron-specific enolase is measured by the enzyme-linked immunosorbent assay kit based on the sandwich technique.

Results: In this study, 14 patients diagnosed with electrical status epilepticus in sleep and 21 healthy controls were included. The median age of electrical status epilepticus in sleep patients was 7.1 years (min-max: 4.5-10.7 years) and 7.7 years (min-max: 3.2-14 years) in the control subjects. According to the results of serum neuron-specific enolase measurements, the mean \pm standard deviation level of neuron-specific enolase was 7.61 ± 3.19 ng/dL for the electrical status epilepticus in sleep group and 6.93 ± 2.55 ng/dL for the control group. Serum neuron-specific enolase levels between electrical status epilepticus in sleep patients and the control group were not statistically significant ($P = .749$).

Conclusion: No significant difference was observed in serum neuron-specific enolase levels between electrical status epilepticus in sleep patients and control subjects. Our results may indicate that frequent interictal discharges do not result in neuronal cell loss or damage in electrical status epilepticus in sleep patients.

Keywords: ESES, CSWS, neuron-specific enolase, interictal discharges, seizure

INTRODUCTION

Encephalopathy with electrical status epilepticus in sleep (ESES) is an electrographic pattern of continuous spikes and waves during non-rapid eye movement sleep that can be associated with regressions in language, behavior, or cognition functioning and with seizures.¹⁻³ Epileptic encephalopathy with continuous spike and wave during sleep (CSWS) and ESES are two separate terms that have been used interchangeably in many studies. The pathophysiological mechanisms and accompanying features underlying ESES are not well known.^{4,5}

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There is no consensus regarding the threshold of epileptiform activity for the diagnosis of ESES. Although a spike-wave index (SWI) of at least 85% of the non-rapid eye movement (REM) sleep is a widely accepted prerequisite for diagnosis, patients with typical clinical manifestations but with lower SWI values were also accepted as ESES in subsequent studies.^{6,7}

Of the many biomarkers associated with epileptic seizures and accompanying brain damage, the most widely studied one is neuron-specific enolase (NSE). Neuron-specific enolase presents in neuroendocrine cells, neuronal cytoplasm, and neuroendocrine tumors. Neuron-specific enolase can initially be detected in cerebrospinal fluid (CSF), then passes into the bloodstream because of disruption of the blood-brain barrier integrity, and increases permeability caused by neuronal damage.^{8,9} Measurement of serum NSE level can be used to predict prognosis after hypoxic and traumatic brain injury, ischemic stroke, and other several disorders associated with cell damage in the central nervous system (CNS).¹⁰⁻¹²

Serum and CSF NSE levels rise in the first 48 hours after seizures, and this increase correlates well with the duration and consequences of epilepsy.^{13,14} As a natural consequence of this, high NSE levels have been shown in status epilepticus (SE). It has been reported to be highest in complex partial and sub-clinical generalized convulsive SE.¹⁵ High NSE levels in status epilepticus could be suggestive that similar levels may also be found in ESES patients. Interictal epileptiform discharges (IEDs) during sleep in ESES have been shown to interfere with learning and memory consolidation mechanisms. However, to date, no markers in serum or CSF have been studied for neuronal damage that IEDs may cause. Our aim in this study is to reveal the relationship between serum NSE level and continuous interictal discharges in a group of ESES patients with normal brain magnetic resonance imaging (MRI) and no epileptic seizure beyond 1 month before the study visit and thus to determine whether neuronal cell loss or damage.

MATERIALS AND METHODS

Study Population and Study Design

We performed a case-control study at a tertiary pediatric neurology center in Istanbul. Patients who were followed up with idiopathic ESES in our pediatric neurology outpatient clinic were re-evaluated, and 14 patients who met the following criteria were included in the study:

1. Presence of the ESES pattern, defined as spike-wave index at least 50% of the non-REM sleep tracking,^{16,17}
2. patients who had their last seizure at least 1 month ago,
3. ESES development based on early brain damage was not included in the study group, so all patients had normal cranial MRIs,
4. ESES patients with a neuropsychologic regression in cognitive, behavioral, or language.

In the same week, serum samples for NSE measurement were obtained, and sleep-wake Electroencephalogram (EEG) and developmental evaluations were performed. Clinical data were obtained by the retrospective chart analyses, including age at onset of ESES, sex, number of seizures in the last year, and antiepileptic drugs used. Patients with metabolic

disease, neuroendocrine tumor, cerebral stroke, or a history of traumatic brain injury were excluded from the study. A control group was formed from 21 children with a headache duration of less than 3 months, who underwent cranial MRI to exclude secondary causes, and without any underlying neurological (including migraine and similar) or chronic systemic etiology. Medical histories, physical examinations, and all MRIs of control subjects were within normal limits for age.

The 10/20 international electrode placement system¹⁸ was used for all EEGs and was recorded without sedation. Spike-wave index was defined as a percentage of non-REM sleep occupied by spikes and waves at a minimum of 1 sleep-wake cycle.¹⁹ EEG patterns were evaluated and classified as follows: generalized: all cerebral regions; diffuse: significant parts of both hemispheres; hemispheric: a major part of one hemisphere; focal: limited part of one hemisphere.²⁰

Measurement of Serum Neuron-Specific Enolase concentration

Three milliliters of blood were drawn from the patient and centrifuged at 3000 rpm for 10 minutes. After centrifugation, serum samples were frozen within the first 4 hours and then stored at -80°C until analysis. Serum NSE is measured by the enzyme-linked immunosorbent assay kit from DRG-International, Inc., based on the sandwich technique.

Evaluation of Cognitive Functions

The Turkish version of the Wechsler Intelligence Scale for Children-Revised (WISC-R) ($n = 13$) and Stanford-Binet scale ($n = 1$) were performed to evaluate intellectual abilities. Assessment of behavior, language, or cognition regression was built on qualitative reports and/or quantitative assessments of psychological, neuropsychological, and speech therapists, along with the statements from the non-standardized parent and teacher reports about behavior, school performance, and communication during clinical visits. Additionally, interviews were conducted with parents, caregivers, and teachers regarding deterioration, recovery, and clinical evaluation by the authors H.K and S.S.

Statistical Analysis

Data obtained from this study were analyzed by International Business Machines Statistical Package for the Statistical Package for Social Sciences version 20.0 software (IBM Corp.; Armonk, NY, USA). Frequencies, percentages, mean (\pm standard deviation), median, minimum, and maximum values were used to provide definitive statistics. The distribution of the continuous variables was evaluated by using Shapiro-Wilk and/or Kolmogorov-Smirnov tests. Categorical variables were compared by the chi-square test. For the comparison of 2 groups that show abnormal distributions, Mann-Whitney *U* test was used. A *P*-value less than .05 ($P < .05$) was accepted as an index of statistical significance. Written informed consent was obtained from the legal guardians, and the study protocol was approved by the institutional review board of the Cerrahpasa Medical School (2018-2617).

RESULTS

In this study, 14 patients with ESES and 21 healthy controls were included. The median age (min-max) was 7.1 (4.5-10.7), and the sex ratio (female/male) was 1.3 : 1 in ESES patients. The

Table 1. Comparison of Demographic Features and NSE Levels Between Groups

	Patient Group (n = 14)	Control Group (n = 21)	P
Age (years)			
Median (min-max)	7.1 (4.5-10.7)	7.7 (3.2-14)	.801 ^a
Mean (±SD)	7.6 (±1.7)	7.7 (±3.3)	
NSE (ng/mL)			
Median (min-max)	7.27 (3.56-17.24)	6.95 (1.39-13.29)	.749 ^a
Mean (±SD)	7.61 (±3.19)	6.93 (±2.55)	
Sex, n (%)			
Female	8 (57.1)	13 (61.9)	.778 ^b
Male	6 (42.9)	8 (38.1)	

^aMann-Whitney U test, ^bChi-square test.
SD, standard deviation; NSE, neuron-specific enolase.

median age (min-max) was 7.7 (3.2-14), and the sex ratio was (female/male) 1.6 : 1 in the control group. The mean (min-max) serum level of NSE was 7.61 ± 3.19 ng/dL (3.56-17.24) in the ESES group and 6.93 ± 2.55 ng/dL (1.39-13.29) in the control group. Serum NSE levels between ESES patients and the control group were not statistically significant (P=.749). A correlation was not found between spike-wave index in EEG and serum NSE levels (r = 0.453; P=.012) in ESES patient group. Comparison of demographic features and NSE levels between ESES patients and control subjects is summarized in Table 1. Patient data, WISC-R, and EEG features are summarized individually in Table 2.

DISCUSSION

The most significant finding of this study is the similar serum NSE levels in the healthy control group and ESES patients with active bioelectrical status findings at least one month after their last seizures. Increasing evidence from various studies suggests that NSE can be a sensitive and reliable indicator of brain damage, and serum levels rise with the increased permeability of the blood-brain barrier after seizures. It has been reported that serum NSE levels increase after complex partial and generalized tonic-clonic seizures and may also be

a sensitive marker in determining neuronal damage associated with non-convulsive status epilepticus.^{21,22} Even though the increase in NSE secondary to seizure-related neuronal cell damage is a well-known entity, the relationship of this increase with the ESES and the effect of IEDs on the neuronal cell was evaluated for the first time in this study. The normal serum NSE level in our study group suggests that IEDs in ESES patients are not associated with neuronal damage or loss.

Markedly high NSE levels are associated with higher neuronal damage.^{23,24} Increased serum NSE concentrations have also been reported in status epilepticus. The mean NSE level was lower in patients with rare and short-term seizures than in patients with status epilepticus.²⁵ It has been shown that there is no increase in NSE gene expression after status epilepticus. The absence of any changes in mRNA levels after the seizure indicates that the NSE increase is a direct outcome of nerve cell damage and change in blood-brain barrier permeability.^{26,27} Therefore, the elevation in serum NSE indicates the extent of the seizure-related neuronal damage.

In ESES patients, toward the adolescence period, seizures may gradually decrease or even completely recover. In neuropsychologic regression, although partial impairments remain, there is a tendency for stabilization in regression and even improvement.^{3,28,29} Similarly, the EEG pattern of ESES improves with the reappearance of physiological elements of sleep. Even without improvement in EEG, improvement in cognitive functions can be seen in ESES patients.³⁰ The improvement of continuous interictal discharges and neurocognitive impairment with antiepileptic drugs or in the adolescence period suggest the possibility of an irreversible underlying pathogenetic mechanism such as neuronal cell loss. The presence of similar serum NSE levels in patients with ESES and the control group in this study may support that the neurocognitive decline seen in ESES is at least not associated with neuronal damage.

Our study excluded the patients with a seizure in the last month prior to the study visit to eliminate the patients with neuroinflammation and neuronal cell loss secondary to seizure. The

Table 2. Patient Data Including Demographic, WISC-R, and EEG Features

Patient	Age at Study, Months/Sex	Age at ESES Onset (Months)	IQ ^a (WISC-R)	EEG Pattern	EEG SWI	Seizure ^b Frequency	AED
#1	80m/m	56	55	Diffuse	100	Monthly	Polytherapy
#2	125m/f	90	50	Generalized	90	None	Dual therapy
#3	83m/m	65	86	Generalized	93	None	Polytherapy
#4	72m/f	56	64	Focal	83	Yearly	Polytherapy
#5	105m/m	60	50	Hemispheric	95	None	Dual therapy
#6	102m/f	78	78	Generalized	60	Yearly	Polytherapy
#7	128m/f	77	40	Generalized	61	Yearly	Polytherapy
#8	82m/m	36	58	Hemispheric	95	Monthly	Dual therapy
#9	54m/f	40	65*	Generalized	80	Yearly	Polytherapy
#10	87m/f	68	63	Generalized	95	Yearly	Polytherapy
#11	82m/m	45	68	Generalized	80	None	Polytherapy
#12	75m/m	48	79	Diffuse	85	Yearly	Polytherapy
#13	100m/m	76	82	Bilat. Focal	50	Yearly	Polytherapy
#14	108m/f	60	40	Generalized	70	None	Dual therapy

^aIntelligence quotient; ^bSeizure frequency: monthly: every few months; yearly: at least once per year; none: no seizures in 12 months; *Stanford-Binet scale m, male; f, female; AED, antiepileptic drug.

absence of difference in serum NSE levels between ESES patients and healthy controls indicates that IEDs alone are not associated with neuroinflammation and neuronal cell loss. It is known that there is no correlation between the frequency of IEDs and seizures in ESES patients. Neuroinflammation, by itself, also causes seizures over time.^{31,32} The lack of a positive correlation between frequency of IEDs and seizures in ESES patients is suggestive of an absence of a causal relationship between IEDs and neurogenic inflammation.

Poor neuropsychologic outcomes are associated with a long duration in the pattern of ESES.^{3,33} If neuropsychologic regression was caused by neuronal cell loss caused by IEDs, it would be unlikely to expect a relationship between the duration of the ESES pattern and the neuropsychologic outcome because neuronal cell loss is an irreversible process. The absence of a relationship between IEDs and serum NSE elevation and thus neuronal cell destruction, which was found in our study, indicates the possibility of reversible causes at the forefront of neuropsychologic regression, and this is in a sense consistent with the duration of the ESES and the neuropsychologic outcome.

A framework is proposed with the synaptic homeostasis hypothesis for the effect of slow-wave sleep on cognitive functions. Sleep recovery function is closely related to a decrease in overnight slope and is required for optimal cognitive performance during wakefulness.^{34,35} It has been shown in various studies that spike-wave density interferes with learning and memory consolidation by disrupting physiological slow-wave activity.^{5,36} As evidence of impaired slow-wave homeostasis, there was no reduction in slow-wave amplitude and slope across the night in ESES patients, while a significant decrease was observed in healthy controls.³⁷ Slow-wave homeostasis normalizes during remission of ESES, and cognitive sequelae are pronounced larger in patients with the most impaired slow-wave homeostasis during the active ESES phase.³⁸ The cognitive regression, which reverses after the antiepileptic treatment that suppresses the interictal spikes during sleep, is in line with this prediction in patients with ESES. It is also compatible as it reduces the likelihood of an irreversible process such as neuronal cell damage and associated serum NSE increase.

There are few studies examining epileptic encephalopathies using serum NSE values methodology. In young male children, mutations in WDR45 should be considered as a cause of epileptic encephalopathies, with severe developmental delay and brain atrophy. In such cases, serum NSE was found to be elevated, although, generally, no neuroendocrine tumor was present. It has been suggested that high NSE may indicate that it can be induced by neuronal damage that is the cause of chronic neurological disorder. It has even been also suggested that scanning for NSE in serum and cerebrospinal fluid in early childhood will help diagnosis in early childhood.^{39,40}

The tendency of improvement in neuropsychologic deficit in the pubertal period suggests that the underlying cause in the pathogenesis of cognitive decline is a reversible process. With puberty, decrease in interictal discharges and accompanying improvement in cognitive functions support this idea. Interictal epileptiform discharges possibly cause the cognitive deficit without neuronal cell loss, which is an irreversible process. There is also a group of patients with no or slight

improvement in cognitive functions during puberty. Possibly, these patients may have experienced more frequent seizures during the active disease process, and these frequent seizures have caused irreversible neuronal cell damage, which in turn prevented the anticipated recovery of the neuropsychologic deficit in puberty. However, this theory needs to be confirmed with prospective studies.

It is known that antiepileptic drugs other than carbamazepine or oxcarbazepine do not affect serum NSE levels.^{41,42} The aforementioned study has limitations such as short follow-up period (1 month) and serum NSE level in healthy control patients only at baseline. In this sense, none of the patients in our study group were receiving carbamazepine or oxcarbazepine treatment. In our study, the effect of antiepileptic drugs on NSE could not be evaluated. This subject, which can be considered as the subject of a separate study, can be considered a study limitation for our cross-sectional study. Several other potential limitations should be addressed. The number of patients participated in the study was limited and it might be useful to have a positive control. In addition, patients who had a seizure within the first 24 hours could be included in the study as a positive control. Studies in which much larger numbers of patients were also evaluated for serum NSE over several interim periods and positive controls were included will certainly provide us with more information in the future.

The serum NSE levels did not differ between ESES patients with normal brain MRI and age- and sex-matched healthy controls. Although these normal serum NSE levels in ESES patients show that the frequent IEDs that characterize ESES do not cause neuronal cell loss, confirmation of this result in prospective studies will increase the level of evidence.

Ethics Committee Approval: This study was approved by Ethics committee of Istanbul University-Cerrahpasa, (Approval No: 03.01.2018-2617).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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