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Original Article

Epileptic encephalopathy with electrical status epilepticus during slow sleep: evaluation of treatment response from a tertiary center

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ABSTRACT

Background. This study aimed to evaluate the clinical, electrophysiological, etiological features, and treatment response in children with epileptic encephalopathy with electrical status epilepticus during slow sleep (ESES).

Methods. Clinical data, records of electroencephalograms (EEG), and brain magnetic resonance imaging (MRI) findings of 33 patients with ESES who were treated, and followed up for at least one year were retrospectively analyzed.

Results. Of all patients, 57.6% were male, and 42.4% were female. The mean age was 10.45 ± 2.88 years. At first admission, 90% of patients had seizures, and 10% had only school failure. Twelve patients had childhood focal epileptic syndrome. In etiology, asphyxia (n=6), hydrocephalus (n=2), polymicrogyria (n=1), and mesial temporal sclerosis (n=1) were determined. Neurological examination was abnormal in 27.2%, and brain MRI findings were pathological in 36.3% of the patients. During the ESES phase, the spike-wave index (SWI) on the non-rapid eye movement (NREM) sleep EEG was >85% in 16 patients and 50-85% in 17 patients. Only one patient received one, and the others had at least two antiseizure medications. Benzodiazepines were found to be the most effective treatment. In the two-year follow-up, 24 patients (72.7%) were seizure-free, and nineteen patients (57.5%) had complete recovery of SWI on their NREM sleep EEG. There was a significant correlation with reduction of the SWI on the EEG and seizure control ($p < 0.001$). In addition, a significant correlation was found between neurocognitive and behavioral scores scored before and after treatment, seizure control, and EEG recovery.

Conclusions. ESES is an epileptic encephalopathy that can be treated safely with antiseizure medications. Neurocognitive examinations and follow-up of EEG findings are valuable in terms of the treatment response. Benzodiazepines were found to be very effective in additional treatment.

Kew words: electrical status epilepticus during slow sleep, EEG findings, antiseizure treatment.

Epileptic encephalopathy with electrical status epilepticus during slow sleep (ESES) is characterized by an electrographic pattern of encephalopathy, neurocognitive regression, and different behavioral disorders, with typical electroencephalogram (EEG) findings as continuous epileptic slow-spike wave activity in non-rapid eye movement (NREM) sleep.[1-3]

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Tassinari et al.[1] first used the term status epilepticus in sleep in 1977, but the same group termed this phenomenon as ESES in 2000 because it did not always appear with seizures. In the literature, it is used synonymously with continuous spikes and waves during slow sleep (CSWS).[4]

ESES is an age-related epileptic syndrome. Therefore, patients may be in various clinical stages at admission. The average time for the first seizure is 2-4 years, and neurocognitive regression occurs in 5-6 years. Different types of seizures may occur in completely normal

children or may occur following neurocognitive regression.[5-7]

There is no consensus in the literature on ESES diagnostic criteria. Typical EEG findings are 1-3 Hz focal or generalized spike-wave activities (SWI), taking on 85% of NREM sleep.[2,3] However, some authors have accepted lower cut off rates in clinically similar patients with SWI <85%.[8-10]

Clinical seizures tend to resolve spontaneously during adolescence. ESES EEG pattern also disappears in all cases, on average by the age of eleven years.[1] The disappearance of the seizures and the ESES pattern on the EEG may be simultaneous, or the seizures may disappear before or after the disappearance of the ESES pattern on the EEG.[2]

It is currently recommended that ESES syndrome should be treated as soon as possible.[7] Although many antiseizure medications can be used in treatment, different data have been obtained regarding their efficacy, so there is a wide range of treatment strategies and combinations.[10]

Our study aimed to evaluate the clinical, electrophysiological, etiological characteristics and treatment responses of ESES patients.

Material and Methods

The files of pediatric patients with ESES followed at Istanbul Medipol University Faculty of Medicine Pediatric Neurology Clinic between 2014 and 2017 were reviewed. Demographic data, age at the time of first seizure and ESES diagnosis, consanguineous marriage, family history of febrile convulsion and epilepsy, seizure type, neurological examination, cognitive evaluation, sleep and wakefulness EEG findings, ESES characteristics, antiseizure treatments, comorbid psychiatric findings, brain magnetic resonance imaging (MRI) findings, etiological causes, two-year treatment efficacy, and the follow-up period of the patients were evaluated.

All patients underwent long-term sleep and awake EEG (at least one hour), and 13 patients underwent all-night video EEG in addition to routine EEG recordings. Long-term EEGs were repeated at least twice a year. SWI (%) was obtained as the total number of minutes of all spike- and slow-wave activities divided by the total number of minutes of NREM and multiplied by 100.[11] The diagnosis of ESES was made with calculated SWI, occupying ≥50% of NREM sleep EEG tracing.

Neurological examination and brain MRI were performed for all patients. Neuropsychological evaluation could only be performed in five patients with the WISC-R test. In our study, neurocognitive tests could not be performed to all patients due to inability to reach the examination and presence of intellectually disabled patients. Parents, teachers, and caregivers were interviewed about the patients' neurocognitive status regarding the deterioration and recovery, and they were also evaluated by clinical judgements. Accordingly, neurocognitive abnormalities were graded between 1-5 points according to school success, learning difficulties, intellectual deterioration, memory deficits, behavioral changes (e.g., hyperactivity, aggressiveness, anxiety, lying, nail-biting, shyness, encopresis), and expressive language disturbances. Neurocognitive and behavioral evaluations performed before and after treatment were compared according to seizure outcome and EEG improvement.

The estimated onset of ESES was determined as the regression onset, the end of the ESES period as the time of seizure control, and cognitive improvement time with the disappearance of ESES pattern on the NREM sleep EEG. Response to antiseizure medications was evaluated as the complete disappearance of the ESES pattern, more than 50% reduction of the SWI, less than 50% reduction of the SWI, and unresponsiveness. The clinical response was graded as complete disappearance of the clinical findings observed during the ESES phase, partial recovery, and nonresponsive.

Statistical analysis

Non-measurable values were expressed as mean ± standard deviation. Pearson chi-square and Fisher's exact test were performed for categorical variables. The correlations between cognitive improvement, and SWI change, also seizure reduction were calculated. SPSS for Windows v.17 (SPSS, Chicago, IL, USA) was used for the analysis. A *p*-value <0.05 was considered to indicate significance.

The study was conducted in accordance with the Helsinki Declaration, and the study protocol was approved by the Ethics Committee of Istanbul Medipol University Faculty of Medicine (08.01.2020/09).

Results

General clinical features/seizure and EEG findings before the onset of ESES

A total of the 33 patients (19 boys and 14 girls) diagnosed with ESES syndrome were evaluated in the study. The mean age of the patients was 10.45 ± 2.88 (min. 5, max. 17) years. In all, 12.1% of the patients had a consanguineous marriage of parents, 36.3% had a family history of epilepsy, and 3% had febrile seizures. A total of 90% of patients had seizures at first admission, and 10% had school failure. One of the three patients who presented with school failure had night terrors as an additional complaint, and the other had headaches.

Twelve (36.3%) patients had childhood focal epileptic syndrome, 11 were benign childhood epilepsy with centrotemporal spikes, and one was early-onset childhood occipital epilepsy. Six patients (18%) had a history of asphyxia, two had hydrocephalus, one had polymicrogyria, and one had mesial temporal sclerosis. Before ESES period, nine patients had mental retardation, one had attention deficit hyperactivity disorder, one had bipolar disorder, and one had migraine.

Neurological examination was abnormal in 27.3%, and brain MRI findings were pathological in 36.3% of the patients. Abnormal brain MRI findings of the patients are summarized in Table I.

Thirty of 33 patients had seizures before ESES, and the mean age at first seizure was 5.06 ± 3.01 (1-13 years). The period between the age of seizures onset with ESES onset age was 2.7 ± 2.2 years. The seizure type was generalized in 33.3% (eight patients had tonic-clonic, two had myoclonic seizures), focal in 56.7%, combined generalized, and focal in 10.0%.

EEG findings before ESES period were focal in 29 (87.9%), multifocal in 9.1%, and generalized in only one patient (3.1%). In 12 (41.4%) of these patients, focal EEG findings were dominant in the left hemisphere and 58.6% (17/29) in the right hemisphere. While 97% of the focal epileptic discharges on the EEG originated from the anterior regions (frontal, frontocentral, or frontotemporal), only 3% were observed on the posterior regions (posterior temporal, temporo-occipital, or occipital).

Seizure and EEG characteristics in ESES

The mean age at initial ESES diagnosis was 7.93 ± 2.65 years (4–12 years), and the mean follow-up period was 29.1 ± 14.2 months (12-36 months). In the ESES phase, there were 16 (48.5%) patients with SWI >85% and 17 patients (51.5%) with 50-85% SWI on the NREM sleep EEG. The cognitive development of our patients was found to be abnormal in 45.5%. There was no significant relationship between SWI on the EEG and neurocognitive status (p = 0.07).

Table I. Magnetic resonance imaging (MRI) findings of ESES patients.

Findings	n (%)
Periventricular leukomalacia	4 (12.1)
Thalamus involvement	4 (12.1)
Hydrocephalus	2 (6.1)
Polymicrogyria	1 (3.0)
Mesial temporal sclerosis	1 (3.0)

Hemi ESES was detected in 30.3% of patients (n = 10/33), and was higher in patients with pathological brain MRI (p=0.02). Neurocognitive abnormalities were detected in 17 patients during ESES phase (51.5%). A statistically significant correlation was found between the difference in neurocognitive and behavioral scores graded before and after treatment with EEG recovery (r=0.53, p=0.001; Fig. 2), but not with seizure control (r=0.1, p=0.54; Fig. 1).

Response to treatment

Among all patients, 97% received polytherapy, and 3% had monotherapy. Initially, 13 patients were treated with valproic acid, 16 patients with carbamazepine, two with clonazepam, and two with phenobarbital. Only one of them continued treatment with monotherapy. The remaining 32 patients used two or more antiseizure medications. In additional therapy, benzodiazepines were found to be the most effective treatment (in 20 patients). Also, additional therapy included sulthiame in six patients, and levetiracetam in one patient was found to be effective (Table II). None of the patients received steroids during the follow-up period. ESES recovery time on the EEG was found to be 9.09 ± 6.9 months. At the end of at least two-year follow-up, a clinically significant response was obtained in 90.9% of patients (24 seizure-free, partial response in 6 patients), and only three patients were clinically unresponsive. Nineteen patients (57.6%) had complete disappearance of the ESES pattern on the EEG, three patients (9.1%) had more than 50% improvement of the SWI, four patients (12.1%) had less than 50% improvement of the SWI, and unresponsiveness was observed in 7 (21.2%) patients. There was a significant relationship between reduction of the SWI on the EEG and a seizure control (p <0.001). Only seven patients with structural lesions in etiology did not have a significant improvement in neurocognitive functions during follow-up. Especially in childhood focal epileptic syndromes, significant improvement in neurocognitive functions was observed before and after treatment.

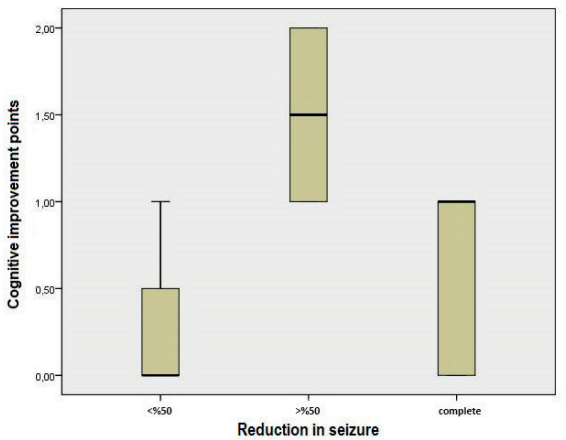

Fig. 1. The relationship between seizure reduction and cognitive improvement.

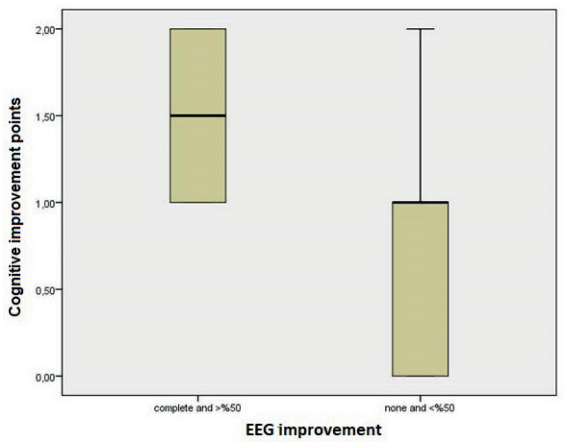

Fig. 2. The relationship between reduction of the SWI on NREM EEG and cognitive improvement.

Gender, age, consanguinity, family history of epilepsy and febrile convulsion, age at the time of ESES, ESES duration, and SWI on the EEG at the diagnosis did not significantly differ in treatment response. In follow-up with treatment, there was a significant difference in seizure control only according to etiology. Family history of epilepsy, pre-ESES seizure type, abnormal brain MRI, abnormal neurological examination, neurocognitive retardation, etiology, and the type of additional therapy were statistically significant in the reduction of SWI on the NREM sleep EEG. Despite the lack of significant difference in treatment of seizure control, benzodiazepines were found to be the most statistically significant treatment in terms

Table II. Demographic and clinical characteristics of patients and response to treatment of seizure.

Characteristics		Seizure response to treatment, n (%)			p
		Seizure free	>50% reduction	<50% reduction	
Gender	Female	13 (92.9)	1 (7.1)	0 (0)	0.059
	Male	11 (57.9)	5 (26.3)	3 (15.8)	
Abnormal neurological examination	Yes	4 (44.4)	4 (44.4)	1 (11.1)	0.056
	No	20 (83.3)	2 (8.3)	2 (8.3)	
Neurocognitive retardation	Yes	10 (58.8)	4 (23.5)	3 (17.6)	0.139
	No	14 (87.5)	2 (12.5)	0 (0.0)	
Abnormal brain MRI	Yes	10 (83.3)	1 (8.3)	1 (8.3)	0.49
	No	16 (76.2)	4 (19.0)	1 (4.8)	
Etiology					0.02
Childhood focal epileptic syndrome		11 (91.7)	0 (0.0)	1 (8.3)	
Structural		4 (40.0)	4 (40.0)	2 (20)	
Unknown		9 (81.8)	2 (18.2)	0 (0)	
SWI on the EEG at the diagnosis					0.162
>85%		14 (87.5)	1 (6.3)	1 (6.3)	
50-85%		10 (58.8)	5 (29.4)	2 (11.8)	
Additional treatment					0.14
Benzodiazepines		16 (80.0)	3 (15.0)	1 (5.0)	
Sulthiame		5 (83.3)	1(16.7)	0 (0)	
Levetiracetam		1 (100)	0 (0.0)	0 (0)	

SWI: spike-wave index ,EEG: electroencephalogram, MRI: magnetic resonance imaging

of reduction of the SWI on the NREM sleep EEG (p = 0.009; Table III, Fig. 3).

Discussion

In our study, age, gender, age at the first seizure, and age at ESES were found to be consistent with the literature. It has been reported in the literature that the age of onset of seizures in patients with ESES is younger than in other epileptic patients.[12,13] In our cases, while no patient was diagnosed before the age of 4, only one patient was diagnosed at the age of 16. The time between the age of first seizure and the diagnosis of ESES was approximately two years.

Although the classical ESES definition suggests that the SWI occurs between 85 to 100% of NREM sleep, in later studies, lower threshold values were accepted in the ESES definition since patients with an SWI <85% also showed neuropsychological regression.[6,8,10,14-18] In our study, no correlation was found between SWI and psychomotor evaluation (p = 0.07). Also, we did not find a significant statistical relationship between SWI on the EEG at the diagnosis and treatment response.

The certain cause of ESES is unknown. However, in most patients, structural lesions of the brain that begin at an early stage are shown, and genetic factors have been described. There is a notable group of patients whose etiology remains unknown.[4,5,13,19,20]

Abnormal brain MRI findings were found in 36.3% of our cases. The most common abnormal findings were thalamic involvement in four patients (33.3%) and periventricular leukomalacia in four patients (33.3%). In the literature, the incidence of structural brain abnormalities has been reported as 20- 50%, thalamic involvement in 29%, and periventricular leukomalacia in approximately

Table III. Demographic and clinical characteristics of the patients and their SWI on the EEG after treatment.

Characteristics		EEG: reduction in spike–wave index, n (%)		p
		Complete disappearance + >50%reduction	<50% reduction + no response	
Gender	Female	11 (78.6)	3 (21.4)	0.21
	Male	11 (57.9)	8 (42.1)	
Focal seizures	Yes	16 (76.2)	5 (23.8)	0.04
	No	4 (40.0)	6 (60.0)	
Abnormal neurological examination	Yes	3 (33.3)	6 (66.7)	0.01
	No	19 (79.2)	5 (20.8)	
Neurocognitive retardation	Yes	8 (47.1)	9 (52.9)	0.01
	No	14 (87.5)	2 (12.5)	
Abnormal brain MRI	Yes	6 (50.0)	6 (50.0)	0.04
	No	16 (76.2)	5 (23.8)	
Hemi ESES	Yes	8 (80.0)	2 (20.0)	0.28
	No	14 (60.9)	9 (39.1)	
SWI on the EEG at the diagnosis				0.085
>85%		13 (81.3)	3 (18.8)	
50-85%		9 (52.9)	8 (47.1)	
Etiology				0.001
Childhood focal epileptic syndrome		10 (83.3)	2 (16.7)	
Structural		2 (20.0)	8 (80.0)	
Unknown		10 (90.9)	1 (9.1)	
Additional treatment				0.009
Benzodiazepines		15 (75.0)	5 (25.0)	
Sulthiame		5 (83.3)	1 (16.7)	
Levetiracetam		1 (100.0)	0 (0.0)	

ESES: electrical status epilepticus during slow sleep SWI: spike-wave index ,EEG: electroencephalogram, MRI: magnetic resonance imaging

25% of patients.[3,13,17,21-23] The presence of thalamic lesion alone can lead to epilepsy and ESES, with impaired neurodevelopment. An impaired thalamocortical circuit leads to the propagation of sudden wave discharges.[24] Polymicrogyria and hydrocephalus are the most commonly reported cortical malformations in the etiology of ESES.[6,25] The presence of polymicrogyria allows rapid propagation of sudden wave discharges.[26] In our series, only one patient had polymicrogyria, and two patients had hydrocephalus.

Family history of epilepsy and consanguineous marriage were significantly higher in our patients. These results suggest that the possible genetic causes of ESES may be higher in our patients. However, genetic studies could not be performed on our patients due to economical problems.

In previous studies, it was reported that the rate of moderate-to-severe neurocognitive impairment was 53% in ESES, and neurocognitive decline was observed in two-thirds of the patients.[3,6,27] Arhan et al.[10] reported that cognitive impairment was 40.6%. The present study determined neurocognitive impairment in 51.5% of our patients. In addition, the first complaint of 10% of our patients was school failure without seizures. Attention deficit hyperactivity disorder, hyperkinetic behavior, expressive language disorders, and learning disability have also been reported in the ESES period.[6]

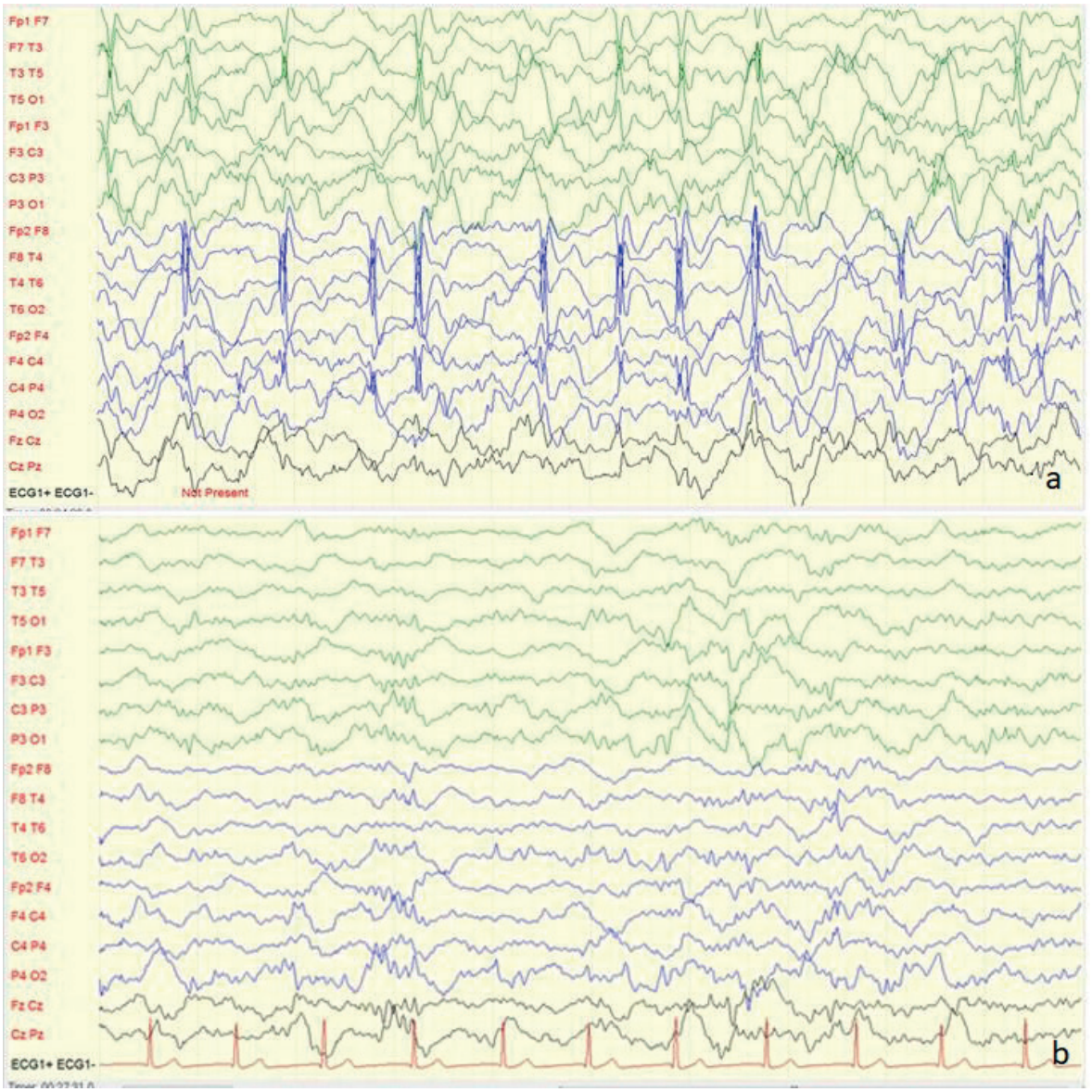

Fig. 3 . (a) ESES pattern (SWI> 85%) is seen in NREM sleep of an 8-year-old female patient with atypical benign rolandic epilepsy treated with valproic acid; **(b)** after the addition of benzodiazepine to the treatment of the same patient, the ESES pattern on the EEG shows complete disappearance.

Therefore, it can be considered that patients with various neurocognitive psychiatric symptoms should be evaluated in terms of ESES. van den Munckhof et al.[22] showed that in children with ESES, cognitive improvement after treatment was strongly associated with reduction of the SWI, but there was no significant increase in intelligence quotient (IQ). Previous studies have found that cognitive performance and prognosis are related to the location, severity, and duration of EEG abnormalities.[6,7,10,22] In our study, improvement in EEG abnormality and reduction of the SWI showed a significant correlation with cognitive improvement. However, it was found that decrease of seizures and cognitive recovery did not correlate (Figs. 1-2).

Seizures in our patients were mostly focal. While seizures were initially uniform and less frequent, it was reported that seizures varied,

and the incidence and duration of seizures increased in resistant cases. In a retrospective study, 98% of 117 patients, and in another study 77% of 21 cases had focal seizures.[8,9] It has been reported that seizures are generally focal in ESES syndrome, and seizures mostly start as focal during sleep in patients with generalized seizures.[8,9,13]

Most of our patients had focal EEG discharges before the ESES period. The epileptic focus in the EEG was mostly on anterior regions of the hemisphere (97%). Other ESES studies have also reported that epileptic activities are more common on anterior regions of the brain.[9,13]

The electrographic activity in ESES may occur diffusely in both hemispheres or predominantly asymmetric in one hemisphere or limited hemispheric in only one hemisphere. Caraballo et al.[9] reported that there was no significant relationship between the asymmetric electroencephalographic findings of ESES, and the clinical presentation of the patients regarding the percentage of the SWI. All patients with asymmetric ESES were found with symptomatic/structural etiology. In our study, 30.3% of the patients (n = 10/33) had limited EEG findings in the form of hemi-ESES in only one hemisphere, and there was a significant relationship between hemi-ESES and brain MRI abnormalities (p = 0.02). It was observed that the presence of hemi-ESES did not make a significant difference in terms of the reduction of the SWI after treatment.

Although many antiseizure medications can be used in the treatment of seizures, different data have been obtained regarding their efficacy. Therefore, a wide range of treatment priorities and combinations are proposed, and there is still no consensus on the treatment of ESES. It is also reported that immunomodulatory treatments, ketogenic diet, and surgical treatment are effective in selected cases.[18]

In a study that analyzed 112 articles and 950 treatments administered to 575 patients, antiseizure medications were found to be effective in 49% of patients (n=495), benzodiazepines in 68% (n=171), and steroids in 81% (n=166), as cognitive or EEG improvements. Surgical treatment resulted in improvement in 90% of patients (n=62). In a subgroup analysis of sequentially reported patients (585 treatments in 282 patients), antiseizure medications improved 34% of the patients, benzodiazepines 59%, and steroids 75%. The postoperative recovery rate was 93% in selected cases. Before the onset of ESES, normal development and the absence of structural abnormalities have been observed to affect the treatment rate positively.[18]

The efficacy of antiseizure medications (including benzodiazepines) that we used in our study was quite high (90.9%) without steroid use. Benzodiazepines were the most effective treatment in additional therapy. Although it was not statistically significant in patients receiving sulthiame for additional treatment, it was observed to have a clinically and electrographically significant effect. In a study, it was reported that sulthiame (5-30 mg/kg/day) given in additional treatment had a significant effect on seizure control and EEG abnormalities in children with ESES syndrome.[28]

The limitations of our study were the small number of patients, the retrospective nature of the study, and the lack of neurocognitive tests due to inability to reach the examination. A larger number of more comprehensive studies are needed in terms of etiology determination and treatment efficacy.

This study confirms that ESES is an epileptic encephalopathy over a wide SWI range. Patients with SWI >50% on the NREM EEG should be followed up regularly with neuropsychological evaluations. The etiology and duration of ESES can be considered to significantly affect long-term prognosis. In our study, benzodiazepines, and sulthiame were found to be effective in combination with other antiepileptic drugs or alone.

Ethical approval

The study was conducted in accordance with the Helsinki Declaration, and the study protocol was approved by the Ethics Committee of Istanbul Medipol University Faculty of Medicine (08.01.2020/09).

Author contribution

Study conception and design: GT, YT, BK; data collection: BK, MA; analysis and interpretation of results: BK, MA, YT, GT; draft manuscript preparation: BK, YT, GT. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare the study received no funding.

Conflicts of interest

The authors declare that there is no conflict of inretest.

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