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Epileptic encephalopathy with electrical status epilepticus: An electroclinical study of 59 patients

Ebru Arhan *, Ayse Serdaroglu, Kursad Aydin, Tugba Hırfanoglu, A. Sebnem Soysal

Gazi University Faculty of Medicine, Pediatric Neurology, Turkey

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ABSTRACT

Purpose: To evaluate the electroclinical features, treatment effectiveness, and outcome of 59 patients with epileptic encephalopathy with electrical status epilepticus during sleep.
Methods: Medical-files of 59 patients with electrical status epilepticus during sleep were retrospectively evaluated for data concerning: history, physical and neurological examinations, sleep and awake EEG's, psychometric tests and brain MRI.
Results: A total of 31 boys and 28 girls were identified. Patients were evaluated in two groups: symptomatic/structural and idiopathic group. There was no significant difference between the etiological groups in term of mean age at ESES onset, mean interval between the first seizure and the onset of ESES. The mean age at seizure onset was earlier in the symptomatic/structural group than the idiopathic ones. The mean follow-up time after the ESES onset was 4.5 years for all patients. The most effective antiepileptic drugs in our series were clobazam and levetiracetam. In refractory patients, steroid treatment was found effective during the early course of the disease. In the idiopathic group, cognitive decline has improved. However in the symptomatic group, patients did not respond to the treatment and cognitive deterioration did not improve in one third of the group.
Conclusion: The long-term outcome of ESES is highly variable and usually depends on etiology and the duration of ESES. The most efficious antiepileptic drugs in our study are clobazam and levetiracetam.
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1. Introduction

Epileptic encephalopathy with electrical status epilepticus during sleep (ESES) is a condition in which the epileptiform abnormalities themselves contribute to the progressive disturbance in cognitive function. According to the last ILAE proposal, it is defined as an age related, self limited disorder characterized as epilepsy with different seizure types, neurophysiological and motor impairment and typical EEG findings of continuous epileptic activity occupying 85% of non-rapid eye movement (REM) sleep. Although spike-wave activities are offered to occur during at least 85% of non-REM sleep in this classic definition, in patients with a well matched clinical presentation lower cut off rates have been accepted in subsequent studies [1,2].

ESES mostly occur in children with symptomatic or structural epilepsy associated with diffferent types of organic brain lesions. It may, as well, be seen in idiopathic even without epileptic seizures, which is seen Landau-Kleffner syndrome. Benign childhood epilepsy with centrotemporal spikes (BCECTS) sometimes has atypical course, with ESES and cognitive deterioration [1].

Although usually the prognosis of epilepy in ESES is favorable, the main concern is the deterioration of one or more cognitive functions. Knowledge about clinical spectrum has broadened and it is now known that ESES may be responsible not only for acquired aphasia but behavioral and/or psychomotor decline with or without motor symptoms have also been described in patients with ESES [3–7]. However, there is currently limited data on the neurophysiological evaluation of these patients.

In addition to the lack of data on neurophysiological evaluation, there are several unresolved questions regarding the treatment modalities in ESES. Various antiepileptic drugs (AED) such as valproate (VPA), ethosuximide (ESM), levetiracetam (LEV) and benzodiazepines have been tried. Recently classic and new AED's have been switched to benzodiazepines and ethosuximide [3,8,9]. In refractory patients, corticosteroids, gama globulins and the ketogenic diet have also been used as therapuetic alternatives. Despite

* Corresponding author. Tel.: +90 312 2025608.
E-mail address: mehmetarhan@gmail.com (E. Arhan).

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the use of various AED combined with alternative therapuetics, there is not yet a standardized therapy for ESES and treatment strategies have not been reported in a large group of patients.

Yet there is, so far, limited number of studies regarding the long-term neurophysiological outcome and treatment modalities in a large group of patients with the ESES. Therefore, we aimed to describe the clinical features, etiology, the impact of etiology on prognosis, the treatment and prognosis of 59 patients with the ESES syndrome.

1.1. Patients and methods

The present study was a descriptive, retrospective study of 59 consecutive patients with the ESES syndrome followed between 2006 and 2013. Inclusion criteria included:

1. Onset with focal or apparently generalized seizures and focal EEG discharges.
2. Further appearance of atypical absences, and myoclonic, atonic (with or without epileptic falls), and/or generalized seizures.
3. Cognitive impairment and/or behavioral disturbances related to the ESES period.
4. ESES occurring in more than 85% of the non-REM sleep, however, a lower percentage between 85% and 30% was also considered [3,4,10,11].

Myoclonic astatic epilepsy with cognitive deterioration, Lennox Gastaut syndrome not fulfilling the criteria for the ESES syndrome and focal epilepsies with secondary bilateral synchronies not fulfilling the criteria for the ESES syndrome were excluded.

Medical-files were retrospectively evaluated for data concerning: history, physical and neurological examinations, sleep and awake EEG's, psychometric tests and brain MRI. Patients with an underlying etiology were classified as symptomatic/structural while others were classified as idiopathic. Follow up EEG's under different treatment regimens were evaluated along with neuropsychological data.

All patients underwent at least three prolonged sleep EEGs (more than 1 h), and 20 of these 59 patients underwent all-night video-EEG in addition to the routine EEG recordings. The spike-wave index (SWI) on the non-REM sleep EEG during the ESES period was visually calculated based on the total number of spike-waves per unit of time or based on the information provided by the epileptologists in the clinical charts. The ranges of the index considered were: >85%, 50–85%, and 30–50%. Prolonged sleep EEG's were repeated at least two times a year. All 59 patients underwent at least one magnetic resonance imaging (MRI) study.

Fifty-two patients underwent neuropsychological assessment using the WISC-R test, or the Stanford–Binet scale when the WISC-R test could not be administered. Forty-one patients were evaluated by consecutive neuropsychological tests. Previous neuropsychological tests have been performed in 31 patients. In addition, parents, teachers and caregivers were interwieved regarding deterioration and improvement and with respect to clinical judgment by the authors A.S and E.A, clinical improvement was graded as full, more than 75%, more than 50% and less than 50%.

The estimated onset of the ESES period was defined as the time from the onset of regression; the end of the ESES period was defined as the time of significant functional improvement coinciding with the disappearance of ESES on sleep EEG. Response to drug treatment was evaluated and defined as; seizure freedom and repeated sleep EEG's with complete normalization or disappereance of the ESES, significant reduction in seizure frequency and a more than 75% of improvement of the SWI, 50–74% seizure reduction and a more than 50% improvement of the SWI, 30–49% seizure reduction and a more than 30% improvement of the SWI and no response.

1.2. Statistics

The association between age at seizure onset, age at ESES onset, duration of ESES, SWI and outcome were analyzed by Student's *t*-test. The associations between etiology and epilepsy type and outcome were examined by Fisher's exact test. SPSS for Windows, v.15 (SPSS, Chicago, IL, USA) was used for the analysis. *P*-value <0.05 was considered statistically significant.

2. Results

2.1. General clinical features

There were a total of 59 patients (31 boys and 28 girls) with the ESES syndrome recruited from the Gazi University Department of Pediatric Neurology between 2006 and 2013. Six patients (10.2%) had a family history of epilepsy and two (6.8%) of febrile seizures. Seventeen patients had perinatal insult (10 perinatal asphxia, two intrauterine infections, four neonatal seizures, one prematurity and one neonatal hypoglycemia). Two patients (3.4%) had antedecedents of West syndrome.

ESES evolved from several different probable etiologies. Nineteen (32.2%) patients had benign partial epilepsies of childhood, of whom 14 had benign childhood epilepsy centro-temporal spikes (BCECTS), five had benign childhood epilepsy with occipital paroxsyms. One patient had temporal lobe epilepsy. Eleven patients had cerebral palsy, seven had hemiparesis and four had spastic diplegia.

All patients had magnetic resonance imaging and 20/59 were abnormal. Abnormal imaging findings were; hydrocephalus in three patients, cortical atrophy in three, periventricular leucomalasia in two, encephalomalasia in three, porencephaly in three, polymicrogyria in one, occipital hyperintensity in one, thalamic lesion in three and hypocampal atrophy in one patient.

2.2. Seizures and EEG findings before the onset of ESES

Fifty-three of the 59 patients had experienced seizures before the onset of the ESES. The seizures were complex focal in 29 (49.2%) of these patients. Nine (15.3%) patients had apparently generalized seizures, five (8.5%) patients had secondary generalized focal seizures. Atypical absences were found in three (5.1%) patients. Five (8.5%) patients had myoclonic seizures and one (1.7%) patient had spazm. Six (10.2%) patients had tonic seizures.

There were 31 patients (19 males) in the symptomatic/structural group. The mean age at seizure onset was 3.78 ± 2.08. The current mean age of this group is 11.45 ± 3.66 years. Time between the first seizure and the onset of the ESES is 3.2 ± 2.17 years.

In the idiopathic group, 12 of the 28 patients were male. The mean age at seizure onset was 5.6 ± 2.69. The time lag between the onset of epilepsy and the onset of ESES was 3.1 ± 1.36 years.

There was no significant difference between the etiological groups in term of mean age at ESES onset, mean interval between the first seizure and the onset of ESES. The mean age at seizure onset was earlier in the symptomatic/structural group than the idiopathic ones.

The awake EEG recordings revealed focal epileptiform activity in 37 patients (62.7%), generalized in 7 (11.9%) and multifocal in 15 (25.4%) patients. EEG background activity showed diffuse slowing in 13 (22%) patients in the symptomatic/structural group.

2.3. Characteristics of seizure types and EEG features during ESES

The mean age at ESES onset was 6.4 ± 1.92 years, with no significant difference between the etiological groups. The mean duration of ESES was 21.2 ± 10.03 months (range 3–26 months).

During ESES, 37 (62.7%) patients continue to experience seizures. During follow-up, new seizure types occurred in 30 patients (50.8%). These seizures were absences in 14 (23.7%), atonic seizures in 15 (25.4%) and negative myoclonus in 3 (5%).

During the ESES phase, the SWI was >85% in 44 patients, 50–85% in 13 and 30–50% in 2 patients. No significant clinical difference was seen regarding the percentage of the SWI between the two groups. The characteristics of sleep EEG during the ESES were as follows: focal epileptic activity in 17, secondary generalized epileptic activity in 23, generalized epileptic activity in 19. In the symptomatic group, asymmetric background activity was seen in 2, polyspikes were seen in 3 and diffuse voltage attenuation was seen in 1 patient. In the idiopathic group, there was not any background EEG abnormality. (Fig. 1a and b and Fig. 2a and b).

Before the ESES phase, 21 of 59 (47.5%) patients had normal development, these patients were all in the idiopathic group. In the symptomatic group, 22 patients had mental retardation, one patient has autism.

During the ESES phase, neurocognitive deficits in the patients were; intellectual deterioration in 24 (40.6%), verbal auditory agnosia in 12 (20.3%), aphasia in 8 (13.5%), behavioral changes in 3 (5.1%), memory deficits in 1 (1.7%), attention deficiency hyperactivity disorder in 16 (%), aggresiveness in 20 (33.8%).

Table 1 shows the general features, seizures and EEG findings before and during the ESES period of all patients.

2.4. Treatment response

Response to treatment was classified as:

(1) Seizure freedom and repeated sleep EEG's with complete normalization or disappereance of the ESES in 18 (30.5%) patients.
(2) Significant reduction in seizure frequency (more than 75%) and a more than 75% of improvement of the SWI in 19 (32.2%) patients.
(3) 50–74% seizure reduction and a more than 50% improvement of the SWI in 13 (22%) patients.
(4) 30–49% seizure reduction and a more than 30% improvement of the SWI in 2 (3.4%) patients.
(5) No response in 7 (11.9%) patients.

Outcome according to the EEG criteria to evaluate response was as follows: normalization of the record (18), improvement of more than 75% of SWI (17), improvement of more than 50% of SWI (12), improvement of more than 30% of SWI (1); transformation of generalized epileptic activity into focal activity (4), and no response (7).

During the ESES phase, the following antiepileptic drugs did not show any efficacy: valproic acid in 17 patients, topiramate in 5 patients, carbamazepine in 7 patients, oxcarbazepine in 9 patients, clobazam in 3 patients, levetiracetam in 7 patients, gabapentin in 2 patients. Three patients were resistant to multidrug treatment.

Positive response was seen with the following antiepileptic drugs, and other treatment options:

Clobazam (14 of 25 patients – 56%): Four received with valproic acid, three received with levetiracetam, two patients with immunoglobulins and one received in combination with steroids. One patient had a temporary response, after 4 years of clinical response seizures recurred.

Levetiracetam (8 of 19 patients – 42%) Three patients had a transient response. Two patients received with clobazam and two received in combination with valproate.

Valproate (6 of 13 patients – 46%) Valproate alone had a transient response only in two patients; both of these two patients were in the idiopathic group. Four patients received with clobazam, two patients received vith levetiracetam.

Steroids (6 of 14 patients – 42%): Steroid was tried if other antiepileptic drugs failed in our patients and patients received steroids in combination with the antiepileptic drugs. Two patients showed a transient response and relapsed after 1 year. One patient became steroid dependent.

Immunoglobulins (1 of 4 patients – 25%): Two patients received immunoglobulins in combination with clobazam. One patient showed a transient response.

Vagal nerve stimulation was performed in two patients. One patient showed a transient response, she has a seizure reduction of 50% after 6 months of VNS but during follow-up her seizures recurred. The other patient however showed a positive response in combination with other antiepileptic drugs. He has a seizure reduction of more than 75% after 4 months of VNS implantation and after 3 years of VNS implantation, his seizure reduction is stil more than 75%:

A transient response was seen in nine patients using; valproic acid and clonazepam (two patients), valproic acid and lamotrigin (one patient), levetiracetam (three patients), valproic acid (two patients) and clobazam (one patient).

Notably, only four patients relapsed during follow-up. Three patients were in the symptomatic group whereas one had atypical centrotemporal epilepsy of childhood. Two of them had response after clobazam was introduced. The other two had a transient response to steroid treatment and relapsed after 1 year and one of them became steroid dependent.

Treatments of the patients are summarized in Table 2.

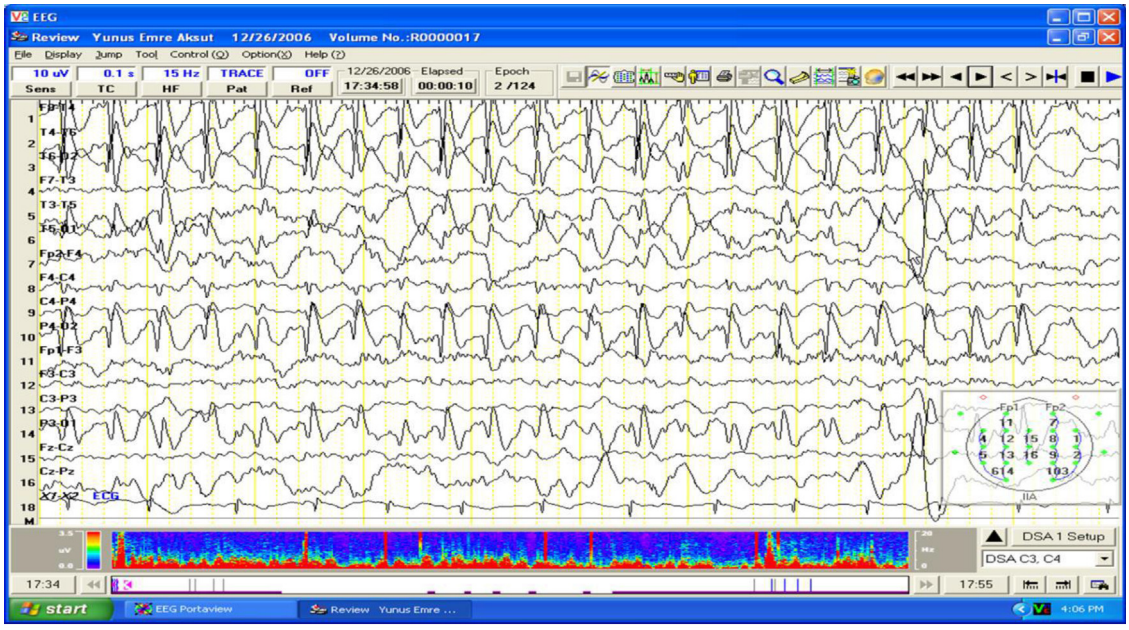
2.5. Outcome

The mean follow-up time after the ESES onset was 4.5 years (range, 1–6 years) for all patients. At the last control, 22 patients in the idiopathic group were seizure free whereas only 8 patients in the symptomatic group have become seizure free. Among 22 patients in the idiopathic group, five patients displayed focal and two patients showed multifocal anomalies in EEG recordings. In the symptomatic group, the EEG showed focal spikes in three, multifocal spikes in five patients.

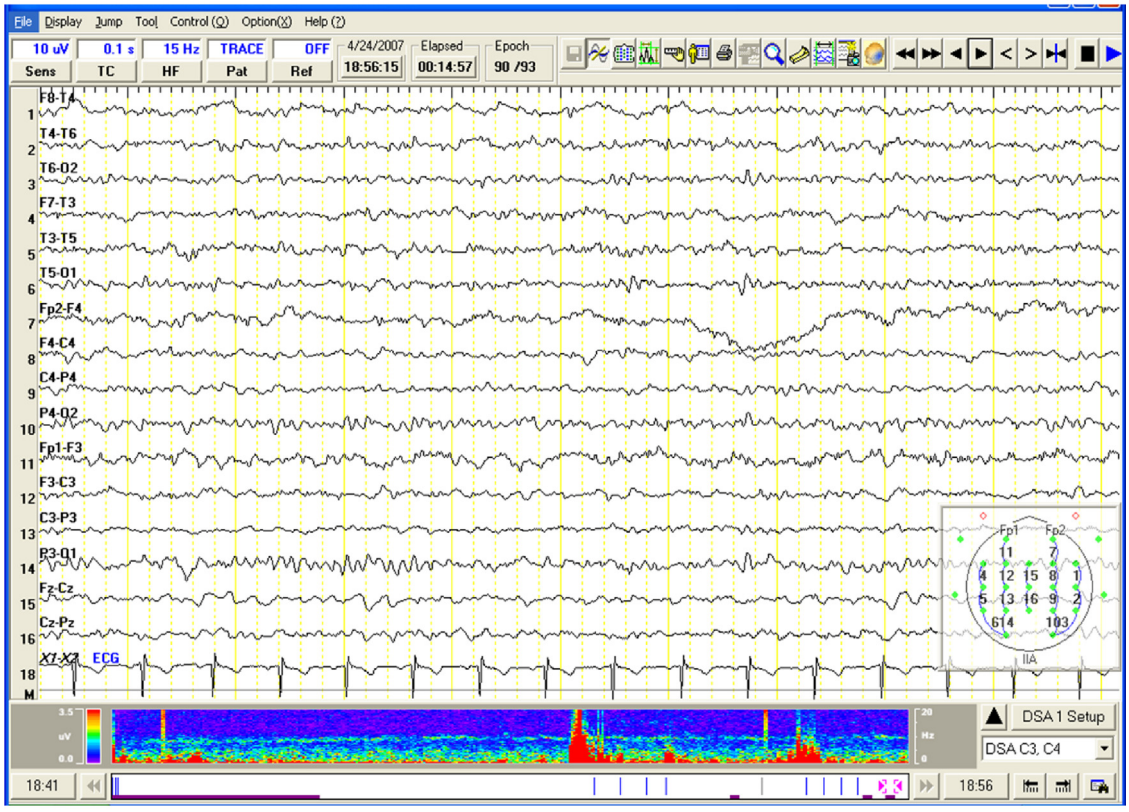
There was a significant correlation between ESES duration and cognitive deficits at the last control. There were 36 patients with ESES duration between 6 and 24 months, of these patients five did not regain baseline cognitive level. Twenty-three patients had ESES duration of more than 2 years, none of these patients regained baseline cognitive levels.

In the idiopathic group, nearly all patients showed definitive control of seizures and normalization of the EEG. The best results were obtained in the rolandic group. Patients with hydrocephalus had better cognitive outcome than the other symptomatic group.

During follow-up, patients with complete seizure control and in patients having a more than 75% seizure reduction, cognitive performance significantly improved. Of the patients in the idiopathic group, cognitive decline has improved outcomes and treatment effectiveness was observed and they returned to normal baseline cognitive levels. However in the symptomatic group, cognitive deterioration did not improve in one third of the group. Table 3 shows the cognitive outcome according to etiology and SWI.



a



b

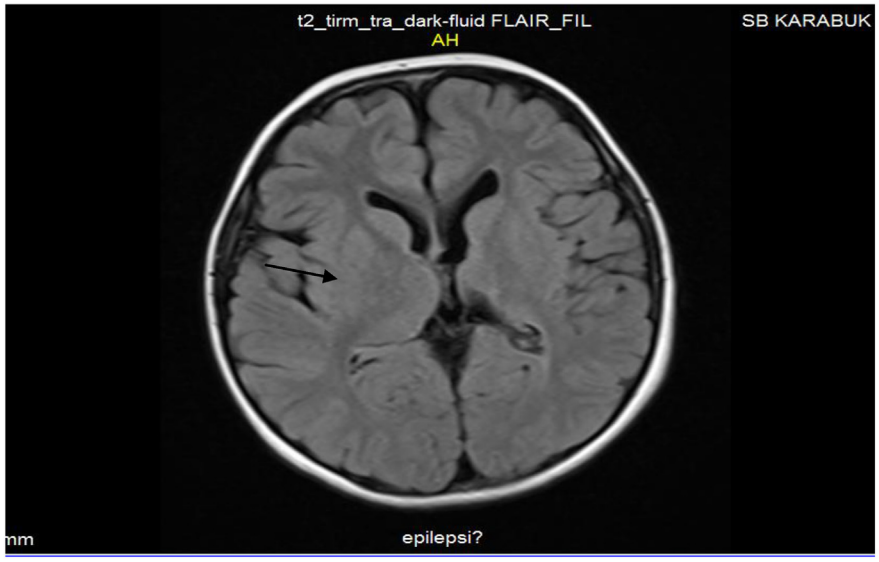
Fig. 1. (a) Ten-year-old boy with atypical centrotemporal epilepsy of childhood. Sleep EEG recording shows asymetric spike and wave discharges in more than 85% of slow wave sleep; (b) EEG recording of the same patient after i.v steroid treatment.

3. Discussion

ESES is an electrographic pattern associated with focal and/or generalized seizures and neurophysiological, cognitive and/or motor impairment [12]. The criterian of ESES is not only a mathematical index but also an EEG criterion. Although the classical definition of ESES suggests SWI occurring between the range of 85–100% of non-REM sleep, later studies have accepted lower threshold values since patients with a SWI < 85% have also demonstrated neuropsychological regression [2–4,10,13–15]. Neuropsychological regression in patients with an SWI of less than 85% has been demonstrated in previous studies [1–3,10]. In their large series, Caraballo reported that psychomotor deterioration was observed even in a modest or not so continuous activation



a



b

Fig. 2. (a) Seven-year-old boy with thalamic lesion. Sleep EEG recording shows asymetric spike and wave discharges in more than 85% of slow wave sleep; (b) Axial FLAIR MRI; lesion in the right thalamus (arrow).

Table 1
Summary of clinical data and electrophysiological findings before and during the ESES period in all patients.

Patient group	No. of patients	Mean age at onset of epilepsy (year)	Seizure types (pre-ESES)	EEG findings (pre-ESES)	Mean age at onset of ESES period (year)	Seizure types (ESES period)	EEG findings (ESES period)
Structrual/ symptomatic	31	3.78 ± 2.08	CFS, SGTCS, AA, myoclonic, Spazm	Focal spıkes, multiffocal focal slowing, generalized spikes	6.4 ± 1.9	Myoclonias spıkes, AA, CFS SGTCS	Diffuse voltage attenuation multifocal spikes polyspikes generalized spikes
İdiopathic	28	5.6 ± 2.69	CFS, SGTCS	Focal spıkes, multifocal spikes generalized spikes	6.4 ± 1.9	AA, myoclonias, CFS, SGTCS	Focal spikes, multifocal spikes generalized spikes

CFS, complex focal seizures; SGTCS, secondarily generalized tonic-clonic seizures; AA, atypical absences.

Table 2
Summary of drug treatment.

Patient group	No. of patients	Drugs used before ESES	Drugs used after diagnosis	Duration of therapy (range)	Successful drugs
Structural/ symptomatic	31	CBZ, VPA, TPM, OXC, PB, LTG and combinations	VPA, LVT, CLB, GB iv steroid, IVIG	3–26 months	CLB, LVT, iv steroid, IVIG
Idıopathic	28	CBZ, VPA, OXC	VPA, LVT, CLB, iv steroid	3–6 months	CLB, LVT, iv steroid, IVIG

CBZ, carbaamzepine; VPA, valproic acid; TPM, topiramate; PB, phenobarbital; OXC, oxcarbazepine; LTG, lamotrigine; LVT, levetiracetam; CLB, clobasam; GB, gabapentin; IVIG, intravenous immunoglobulin.

Table 3
Outcome according to etiology and SWI in our patients with ESES.

Groups	SWI (%) (*n*)	Outcome	
		Favorable	Unfavorable
Symptomatic	>85 (22)	15	7
Symptomatic	50–85 (5)	2	3
Symptomatic	30–50 (4)	2	2
Idıopathic	>85 (16)	All patients	
Idıopathic	50–85 (8)	All patients	
Idıopathic	30–50 (4)	All patients	

of paroxsymal activity during sleep [3]. It is anyway noteworthy that even in patients with a lower SWI, cognitive abilities may be disturbed. It appears thus mandatory to achieve neuropsychological studies in ESES patients with a lower SWI with the assessment of specific cognitive skills, particularly in order to improve rehabilitation strategy. Our study has strenghtened the idea that ESES is an epileptic encephalopathy with a broad range of SWI and confirmed that the electroclinical criteria for the ESES syndrome should be revised.

In this study, we have analyzed the impact of ESES on long-term neurophysiological outcome and treatment modalities in a large group of patients with the ESES. In our series, two different etiological groups emerged: symptomatic/structural group and idiopathic group. The largest group in our series comprised symptomatic/structural cases. In this group, there were 17 patients with perinatal insults like perinatal asphxia, intrauterine infection, and neonatal hypoglycemia. Presence of pre/perinatal insults have been reported earlier by Scholtes, Liukkonen and Değerliyurt et al. [16–18]. Twenty patients in this group had malformations of cortical development. Polymicrogyria and hydrocephalus are the most commonly reported cortical malformations in the etiology of ESES [3,19]. Thirty-eight percent of the patients were reported to have polymicrogyria in the largest series. Horizontal cortical lamination is preserved in polymicrogyria and this ensures the rapid spread of spike-wave discharges [20]. Only patient with polymicrogyria in our series was due to intrauterine cytomegalovirus infection. There were three patients with hydrocephalus in our series. As distinct from the previous reports, there were three patients with thalamic lesion in our series. The role of the thalamus in the pathophysiology of generalized spike wave discharges, as in ESES, has been shown in animal models [21]. Both cortex and thalamus participate in the generation of spike-wave discharges, although opinions differ on the relative importance and the need for an intact thalamocortical circuit in the generation of these discharges [22]. When normal circuitry is disturbed by a lesion, as seen in the patients reported in our study, electrical firing might be altered. The association of ESES and thalamic lesion has been emphasized in case reports previously [23–25]. This implies that thalamic lesion alone may cause epilepsy and ESES with related disruption of normal neurodevelopment.

It has been postulated that prolonged epileptic activity during sleep as in ESES interferes with spike wave activity generating mechanisms at the site of the epileptic focus and in consequence of this impairs the neural processes and, possibly, the local plastic changes associated with learning and other cognitive functions [26]. In this respect, cognitive involvement may also be prominent, but a less frequent complaint of phenomena than seizures during the stages of pre-ESES and ESES. We found that 40.6% of our patients showed cognitive decline. Along with this decline, major cognitive deficits in our patients were language deterioration, attention deficit and hyperactivity, learning difficulties, aggresiveness and autistic-like behavior. Similar repertoire of cognitive deficits have been commented in previous studies [3,4,13,27]. Besides cognitive dsyfunction, motor disabilities like ataxia, fine motor dsyfunction, dsytonia, clumsiness were also seen in our series. Caraballo et al. described loss of independent gait, worsening of a unilateral deficit, distortion in hand writing in their series [3]. Fejerman and Seegmuller have attributed these motor impairments to negative myoclonus in ESES patients [27,28].

Our study constitutes an attempt to identify the predictors for the long-term cognitive outcomes of patients with ESES. Early onset seizures, appereance of new seizures during ESES period and increase in seizure frequency, resistance to antiepileptic drugs andsymptomatic/structural etiology group, longer duration of ESES are proposed to predict pooroutcome in ESES patients [3,4,29]. In our study, outcome depended on the etiology, duration of ESES and early response to treatment.

Etiology was the main predictive factor in our series. The idiopathic group had the most favorable course, with normal or nearly normal cognitive outcome in 18 of 22 patients and in the idiopathic group, patients with benign partial epilepsy with centrotemporal spikes had an excellent prognosis. This is in contrast with Saltık et al. outcomes [30]. In the symptomatic/structural group, the patients with polymicrogyria had better prognosis than the other structural etiologies. There was only one patient with polymicrogyria. Therefore, we could not make an analysis for this sole patient. Hydrocephalus is the second most common etiology associated with ESES and usually has a good prognosis if recognized early. In children with early-onset hydrocephalus, particularly with behavioral and language disturbances, and/or motor deterioration, ESES should be considered. Periodic EEG recordings during sleep should be done in these children. One other predictive factor for poor long-term neuropsychological outcome is the duration of ESES [17,31]. This may be explained by the hypothesis that markedly abnormal neuronal activity during a critical period of synaptogenesis results in aberrant synapse formation [32]. In a study by Robinson et al. no child with ESES persisting longer than 36 months had normal language outcome [31]. Caraballo et al. found better neurophysiological outcome in patient with a shorter duration of ESES [3]. The duration of ESES in our patients ranged between 3 and 26 months and we found a significant correlation between duration of ESES period and residual cognitive deficits.

Our retrospective study includes patients that were not treated by a standard algorithm, but rather subjected to treatment choices made by the epileptologists on their personal intuition. The response to treatment was not that favorable on the whole. The

most common antiepileptic drugs used for ESES include valproate, ethosuximide, and levetiracetam [12]. Although we did not have an algorithm, we have selected VPA for first line AED for most of the patients, based on previous retrospective reports however, we could not confirm observations of previous studies in which valproic acid played a major role in the treatment of ESES [20,33]. We did somehow saw benefit of valproic acid in some patients but most of them failed. Ethosuximide and sulthiame are not available in our country; therefore we could not try these drugs as the first line therapy for ESES.

We demonstrated a significant effect of levetiracetam and clobazam in treating ESESin our patients. The efficacy of levetiracetam and clobazam is supported by case reports in theliterature [4,31,34–36]. Corticosteroids have shown improvement in selected cases and, in some cases, lead to complete resolution of ESES. Once ESES is recognized, usually during the acute phase, corticosteroid treatment should be considered. In line with previous sturides, steroid therapy was effective for short term in our series [4,20,26]. Of those, two patients showed a transient response and relapsed after 1 year. Liukkonen et al. reported contrary results with steroids, even if given within the 1 year of diagnosis [16]. We tried steroid therapy when other antiepileptic drugs failed and patients received steroids with antiepileptic drugs. Immunoglobulins are considered as a part of the therapuetic protocol in patients with Landau-Kleffner syndrome and not considered as an option in the treatment of ESES. Therefore only a handful of patients treated with intravenous immunoglobulins have been reported in the literature. Intravenous immunoglobulin treatment was associated with improvements in 1 out of 4 patients in our series. In another series, the neurocognitive function of 1 out of 3 patients with ESES improved following the administration of intravenous immunoglobulins [37]. However, there is probably a publication bias of positive results, and the high cost and risk of complications associated with immunoglobulins maketheir role in the treatment of ESES unclear. In previous case reports, carbamazepine, oxcarbazepine, phenobarbital, or phenytoin have been reported to induce the appearance of electrical status epilepticus during slow sleep; therefore these drugs should be avoided during ESES [38,39].

The retrospective nature of this study was a major limitation to our ability to precisely determine the results. Therefore, most of the information obtained was based on the medical files of the patients. Another issue was that the treatments are not readily comparable because of the lack of a standard treatment algorithm. Additional study design modifications can enhance the merit of our study. Beyond these limitations, our study has several advantages over previous studies, such as large number, a homogenous group of patients with ESES, and long-term follow-up, covering different aspects of clinical and electrophysiological outcome parameters.

Summary

This study confirms that ESES is an epileptic encephalopathy with a broad SWI. Patients with an SWI of >50% should be followed up frequently along with neuropsychological assessments at regular intervals. The impact of ESES on the development and functional ability of children is significant. Etiology seems to have the major impact on long-term prognosis, as severe permanent cognitive deterioration is rare in idiopathic cases, whereas patients with symptomatic/structural epilepsy have considerably worse long–term cognitive outcome. Children with hydrocephalus and thalamic injury should be monitored cautiously for the evolution of ESES. Duration of ESES also have a strong impact on the outcome. According to our study, clobazam, levetiracetam and early steroid treatment seem to be valuable switching options, in combination with other antiepileptic drugs or alone, until more prospective data on treatment modalities for ESES are available. For effective management, it is crucial to have a standard algorithm for the treatment of ESES. It is hoped that this information can provide a model for further study and add to the existing data.

Conflict of interest

The authors declare that they have no conflict of interest.

References

[1] Brazzo D, Pera MC, Fasce M, Papalia G, Balottin U, Veggiotti P. Epileptic encephalopathies with status epilepticus during sleep: new techniques for understanding pathophysiology and therapeuticoptions. Epilepsy Res Treat 2012;2012:642725.

[2] Van Hirtum Das M, Licht EA, Koh S, Wu JY, Shields WD, Sankar R. Children with ESES: variability in the syndrome. Epilepsy Res 2006;70:248–58.

[3] Caraballo RH, Veggiotti P, Kaltenmeier MC, Piazza E, Gamboni B, Lopez Avaria MF, et al. Encephalopathy with status epilepticus during sleep or continuous spikes and waves during slow sleep syndrome: a multicenter, long-term follow-up study of 117 patients. Epilepsy Res 2013;105:164–73.

[4] Kramer U, Sagi L, Goldberg-Stern H, Zelnik N, Nissenkorn A, Ben-Zeev B. Clinical spectrum and medical treatment of children with electrical status epilepticus in sleep (ESES). Epilepsia 2009;50:1517–24.

[5] Boel M, Casaer P. Continuous spikes and waves during slow sleep: a 30 months follow-up study of neuropsychological recovery and EEG findings. Neuropediatrics 1989;20:176–80.

[6] Veggiotti P, Termine C, Granocchio E, Bova S, Papalia G, Lanzi G. Long-term neuropsychological follow-up and nosological considerations in five patients with continuous spikesand waves during slow sleep. Epileptic Disor 2002;4:243–9.

[7] Kevelam SH, Jansen FE, Binsbergen Ev, Braun KP, Verbeek NE, Lindhout D, et al. Copy number variations in patients with electrical status epilepticus in sleep. J Child Neurol 2012;27:178–82.

[8] Larrieu JL, Lagueny A, Ferrer X, Julien J. Epilepsy with continuous discharges during slow-wave sleep. Treatment with clobazam. Rev Electroencephalogr Neurophysiol Clin 1986;16:383–934.

[9] Larsson PG, Bakke KA, Bjornaes H, Heminghyt E, Rytter E, Brager-Larsen L, et al. The effect of levetiracetam on focal nocturnal epileptiform activity during sleep–a placebo-controlled double-blind cross-over study. Epilepsy Behav 2012;24:44–8.

[10] Scheltens-de Boer M. Guidelines for EEG in encephalopathy related toESES/CSWS in children. Epilepsia 2009;50:13–7. 2009.

[11] Tassinari CA, Cantalupo G, Rios-Pohl L, Giustina ED, Rubboli G. Encephalopathy with status epilepticus during slow sleep: "the Penelope syndrome". Epilepsia 2009;50:4–8. 2009.

[12] Veggiotti P, Pera MC, Teutonico F, Brazzo D, Balottin U, Tassinari CA. Therapy of encephalopathy with status epilepticus during sleep. (ESES/CSWS syndrome): an update. Epileptic Disord 2012;14:1–11.

[13] Yasuhara A, Yoshida H, Hatanaka T, Sugimoto T, Kobashi Y, Dyken E. Epilepsy with continuous spike-wave during slow sleep and its treatment. Epilepsia 1991;32:59–62.

[14] Fortini S, Corredera L, Pastrana AL, Reyes G, Fasulo L, Caraballo RH. Encephalopathy with hemi-status epilepticus during sleep or hemi-continuous spikes and waves during slow sleep syndrome: a study of 21 patients. Seizure 2013;22:565–71.

[15] Caraballo RH, Cejas N, Chamorro N, Kaltenmeier MC, Fortini S, Soprano AM. Landau-Kleffner syndrome: a study of 29 patients. Seizure 2014;23:98–104.

[16] Liukkonen E, Kantola-Sorsa E, Paetau R, Gaily E, Peltola M, Granstrom ML. Longterm outcome of 32 children with encephalopathy with status epilepticus during sleep, or ESES syndrome. Epilepsia 2010;51:2023–32.

[17] Scholtes FB, Hendriks MP, Renier WO. Cognitive deterioration and electrical status epilepticus during slow sleep. Epilepsy Behav 2005;6:167–73.

[18] Değerliyurt A, Yalnizoğlu D, Bakar EE, Topçu M, Turanli G. Electrical status epilepticus during sleep: a study of 22 patients. Brain Dev 2014. http://dx.doi.org/10.1016/j.braindev.2014.04.007. S0387-7604(14)00114-4. [Epub ahead of print].

[19] Caraballo R, Cersósimo R, Fejerman N. A particular type of epilepsy in children with congenital hemiparesis associated with unilateral polymicrogyria. Epilepsia 1999;40:865–71.

[20] Guerrini R, Genton P, Bureau M, Parmeggiani A, Salas-Puig X, Santucci M, et al. Multilobar polymicrogyria, intractable dropattack seizures, and sleep-related electrical status epilepticus. Neurology 1998;51:504–12.

[21] Steriade M, Contreras D. Spike-wave complexesand fast components of cortically generated seizures. I. Role of neocortex and thalamus. J Neurophysiol 1998;80:1439–55.

[22] Blumenfeld H. From molecules to networks: cortical/subcortical interactions in the pathophysiology of idiopathic generalized epilepsy. Epilepsia 2003;44:7–15.

[23] Monteiro JP, Roulet-Perez E, Davidoff V, Deonna T. Primary neonatal thalamichaemorrhage and epilepsy with continuous spikewave during sleep: a longitudinal follow-up of a possible significant relation. Eur J Paediatr Neurol 2001;5:41–7.

[24] Guzzetta F, Battaglia D, Veredice C, Donvito V, Pane M, Lettori D, et al. Earlythalamic injury associated with epilepsy and continuous spike-waveduring slow sleep. Epilepsia 2005;46:889–900.
[25] Kelemen A, Barsi P, Gyorsok Z, Sarac J, Szucs A, Halasz P. Thalamic lesion andepilepsy with generalized seizures, ESES andspike-wave paroxysms – report of threecases. Seizure 2006;15:454–8.
[26] Tassinari CA, Rubboli G. Cognition and paroxysmal EEG activities: from a single spike to electrical status epilepticus during sleep. Epilepsia 2006;47:40–3. 2006.
[27] Seegmuller C, Deonna T, Dubois CM, Valenti-Hirsch MP, Hirsch E, Metz-Luts MN, et al. Long-term outcome after cognitive and behavioral regressionin nonlesional epilepsy with continuous spike-waves duringslow-wave sleep. Epilepsia 2012;53:1067–76.
[28] Fejerman N, Caraballo R, Cersosimo R, Ferraro SM, Galicchio S, Amartino H. Sulthiame add-on therapy in children with focal epilepsies associated with encephalopathy related to electrical status epilepticus during slow sleep (ESES). Epilepsia 2012;53:1156–61.
[29] Seri S, Thai JN, Brazzo D, Pisani F, Cerquiglini A. Neurophysiology of CSWSassociated cognitive dysfunction. Epilepsia 2009;50:33–6.
[30] Saltık S, Uluduz D, Cokar O, Demirbilek V, Dervent A. A clinical and EEG study on idiopathic partial epilepsies with evolution into ESES spectrum disorders. Epilepsia 2005;46:524–33.
[31] Robinson RO, Baird G, Robinson G, Simonoff E. Landau-Kleffner syndrome: course and correlates with outcome. Dev Med Child Neurol 2001;43:243–7.
[32] Kevelam SH, Jansen FE, van Binsbergen E, Braun KP, Verbeek NE, Lindhout D, et al. Copy number variations in patients with electrical status epilepticus in sleep. J Child Neurol 2012;27:178–82.
[33] Inutsuka M, Kobayashi K, Oka M, Hattori J, Ohtsuka Y. Treatment of epilepsy with electrical status epilepticus during slow sleep and its related disorders. Brain Dev 2006;28:281–6.
[34] Aeby A, Poznanski N, Verheulpen D, Wetzburger C, Van Bogaert P. Levetiracetam efficacy in epileptic syndromes with continuous spikes and waves during slow sleep: experience in 12 cases. Epilepsia 2005;46:1937–42.
[35] Atkins M, Nikanorova M. A prospective study of levetiracetam efficacy in epileptic syndromes with continuous spikes waves during slow sleep. Seizure 2011;20:635–9.
[36] Raha S, Shah U, Udani V. Neurocognitive and neurobehavioral disabilities in Epilepsy with Electrical Status Epilepticus in slow sleep (ESES) and related syndromes. Epilepsy Behav 2012;25:381–5.
[37] Arts WF, Aarsen FK, Scheltens-de Boer M, Catsman-Berrevoets CE. Landau-Kleffner syndrome and CSWS syndrome: treatment with intravenous immunoglobulins. Epilepsia 2009;50:55–8.
[38] Fejerman N, Caraballo R, Tenembaum SN. Atypical evolutions of benign localization-related epilepsies in children: are they predictable. Epilepsia 2000;41:380–90.
[39] Caraballo R, Fontana E. Michelizza CBZ inducing atypical absences, drop-spells and continuous spike and waves during slow sleep (CSWS). Boll Lega It Epil 1989;66/67:379–81.