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Electrical Status Epilepticus during Sleep: Risk Factors, Clinical Course, and Treatment Approaches

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Abstract

Background The efforts of clinicians are focused on determining the predictors for electrical status epilepticus in sleep (ESES) manifestation, due to the negative effect of ESES on cognition. Treatment approaches remain a leading problem because of therapeutic resistance.

Objective We looked for potential risk factors for ESES manifestation and summarize the clinical course and therapeutic approaches in patients with idiopathic and symptomatic ESES.

Patients and Methods We retrospectively reviewed the medical data of 51 children with idiopathic ESES and 20 children with symptomatic ESES.

Results We observed an earlier age of seizure onset ($p = 0.0002$) and a higher percentage of cases with multiple seizures ($p < 0.00001$) and with postictal paralysis ($p < 0.00001$) in idiopathic ESES compared with childhood epilepsy with centrotemporal spikes. In the idiopathic ESES, the treatment consisted of corticosteroids in patients with permanent ESES remission and transient remission, levetiracetam (LEV) children with permanent ESES remission and transient, clonazepam (CZP) children with permanent ESES remission and transient, ethosuximide (ESM), and sulthiame. The patients with symptomatic ESES had more unfavorable evolution, as 19 children had persistent or relapsing ESES course.

Conclusion We consider the earlier age of seizure onset (below 5 years) and the presence of multiple seizures and postictal paresis as risk factors for ESES manifestation. ESES is characterized by a significant therapeutic resistance, especially in the group of symptomatic cases. Good results are observed with LEV, ESM, CZP, and steroids.

Keywords
- ESES
- CECTS
- sleep
- corticosteroids
- levetiracetam

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Introduction

After the initial description by Patry et al,[1] electrical status epilepticus in sleep (ESES) was studied in many patients with idiopathic and symptomatic epilepsies.[2–10] Although the prognosis in the idiopathic cases, concerning the seizures and electroencephalogram (EEG), is favorable, a significant proportion of the children remain with cognitive impairment and/or behavioral problems.[5,10–12] Taking into account the negative effect on cognition, the efforts of the clinicians are focused on determining the predictors for ESES manifestation[5,8,13–17] and the factors that have an influence upon the degree of cognitive impact.[5–7,9,11–15,18] A leading problem remains the treatment approaches because of the significant therapeutic resistance of ESES. Generally, the conventional antiepileptic drugs (AEDs) have partial or transient effect[2,9,18,19] and corticosteroids give promising results,[20–22] but polytherapy is often needed.

Aims of this retrospective study were to look for potential red flags in children with childhood epilepsy with centrotemporal spikes (CECTS), which will allow the selection of patients with risk for an ESES manifestation, and to summarize the clinical course and the therapeutic approaches in patients with idiopathic and symptomatic ESES.

Patients and Methods

We have retrospectively studied 71 patients with ESES, treated from 2008 to 2018. Patients with an underlying etiology were classified as symptomatic case ($n = 20$) and those with normal neuroimaging or with findings that are accidental and not connected to the epilepsy as idiopathic ($n = 51$). The idiopathic group consists of patients with idiopathic focal epilepsy (CECTS and Panayiotopoulos syndrome), including two patients with anterior opercular syndrome and one with continuous spikes and waves during sleep. To look for risk factors that can predict ESES manifestation, we compared the clinical course of the patients that later experienced ESES ($n = 51$) with those of children with CECTS without ESES ($n = 277$).

The diagnosis of ESES was mainly based on a sleep video-EEG in nap, made after partial sleep deprivation with a duration that allowed registration of the first nonrapid eye movement (NREM) cycle. We defined ESES as the presence of continuous focal or generalized spike and wave discharges, occupying more than 85% of NREM sleep. EEG was performed at the time of the diagnosis, at 1 month after initiation of a specific treatment, and every 3 to 6 months to evaluate the treatment response or in shorter intervals if a relapse was suspected.

The neuropsychological evaluation was taken into account when considering the treatment approaches, but due to the retrospective character of the study, it was difficult to summarize the cognitive assessment in the patients as different tests were applied and not all of the patients had, initially or as a follow-up, a formal neuropsychological evaluation.

The conclusions about the effect of the treatment were based on the effect of those drugs, used after ESES registration. Corticosteroids were administered in different regimens: (1) intravenous methylprednisolone with an initial dose of 2 to 6 mg/kg, followed by oral administration of the drug for 1 to 3 months; and (2) 6 mg/kg intravenous methylprednisolone in two consecutive courses each lasting 3 days, followed by oral methylprednisolone for 1 to 3 months. Determination of efficacy was based upon combination of EEG and clinical criteria (seizure control) and was classified as follows: (1) permanent or transient remission of the ESES/permanent or transient remission of seizures; (2) transient or permanent seizure reduction, with more than 50% reduction in the seizure frequency; and (3) no effect.

The patients were followed up for at least a year, and the mean period of follow-up was 6 years, ranging between 1 and 10 years.

The associations between disease parameters were examined by Student's *t*-test, Fisher's exact test, and χ^2 test using software package SPSS. Significance was set at a *p*-value of 0.05.

Results

Clinical Data in CECTS Patients and Comparison with Idiopathic ESES

We summarized the data concerning the clinical course in 277 children with CECTS, followed between 2008 and 2018, and compared them with those of the patients that were later diagnosed with ESES ($n = 51$) (►**Table 1**). Patients with ESES experienced seizures at an earlier age (mean age of 5 years compared with 7 years in CECTS), had more generalized tonic–clonic seizure (GTCS), daytime and multiple seizures. The statistical analysis showed a significant difference between the two groups, concerning the age of seizure onset ($p = 0.0002$) (age below 5 years was considered an early age for seizure manifestation), suffering of multiple seizures ($p < 0.00001$), and postictal paresis ($p < 0.00001$). Although more patients with ESES initially experienced daytime seizures and GTCS compared with those with CECTS, there was not a statistical significance.

Imaging and Clinical Data in Idiopathic and Symptomatic ESES

►**Table 1** summarizes the epidemiological data and the clinical course before and at the time of the ESES manifestation. Patients with idiopathic ESES showed a later epilepsy and ESES onset and a more benign disease course compared with symptomatic cases. Symptomatic patients experienced more GTCS, daytime and multiple seizures. The clinical picture at the time of ESES registration was almost similar in both groups except for the higher percentage of the additional motor deficit in symptomatic cases.

All patients underwent imaging study; the results in the symptomatic group are shown in ►**Table 2**.

Treatment of Idiopathic ESES

After the ESES registration, different therapeutic approaches were applied, e.g., treatment with conventional AED or corticosteroids. Corticosteroids were added to the primary treatment "alone" or were "combined" with the introduction

Table 1 Epidemiological data and clinical course of the epilepsy in patients with CECTS and ESES

	CECTS	Idiopathic ESES	Symptomatic ESES		Idiopathic ESES	Symptomatic ESES
Gender (m/f)	175/102	25/26	6/14	Mean age of ESES registration	7 y (3–12 y)	6 y 2 mo (2 y 6 mo to 11 y)
Mean age of seizures' onset	7 y (2 y 5 mo to 10 y 6 mo)	5 y 2 mo (2–11 y)	2 y 8 mo (1 mo to 8 y 10 mo)	Time lag between seizure onset and ESES	2 y	3 y 4 mo
Initial seizures, *n*/%				ESES type, *n*/%		
Focal and GTCS	97/35	31/60.8	15/75	Generalized	27/53	14/70
GTCS	95/34.3	9/17.6	3/15	Focal	14/27.4	2/10
Only focal	85/30.7	9/17.6	1/5	Focal and generalized	8/15.6	4/20
Atypical absences, myoclonic seizures	–	2/4	1/5	Multifocal	2/4	–
Daytime distribution, *n*/%				ESES course ($n=45$), *n*/%		
Nocturnal	184/66.4	28/54.9	6/30	Nonrelapsing	15/33.3	1/5
Nocturnal and diurnal	63/22.7	20/39.2	11/55	Relapsing	19/42.2	15/75
				Persistent	11/24.4	4/20
Daytime only	30/10.8	3/5.9	3/15			
Number of seizures, *n*/%				Clinical course at the time of ESES, *n*/%		
1	32/11.6	2/4				
2–6	156/56.3	6/11.7	3/15			
>6	58/20.9	15/29.4	–	Increase of the seizures' frequency	34/66.7	13/65
Multiple	31/11.2	28/54.9	17/85	New seizures' types	19/37.3	8/40
				Additional behavior changes or cognitive decline	27/52.9	11/55
				(Additional) motor deficit	12/23.5	11/55
				Anterior opercular syndrome	2/4	
Postictal paresis, *n*/%	27/9.8	18/35.3	5/25			
Febrile seizures, *n*/%	26/9.4	4/7.8	2/10			
Family history for epilepsy, *n*/%	27/9.7	6/11.7	2/10			

Abbreviations: CECTS, childhood epilepsy with centrotemporal spikes; ESES, electrical status epilepticus in sleep; GTCS, generalized tonic–clonic seizure.

of another AED. The effect of the corticosteroids and the conventional AED are presented in ►**Table 3** and ►**Table 4**. We did not achieve positive results using oxcarbazepine (OXC) ($n=6$), carbamazepine (CBZ) ($n=2$), and topiramate (TPM) ($n=2$), and even observed worsening of seizures and EEG. Lamotrigine (LTG) was used in five patients and only a temporary response was observed in two of them.

Treatment of Symptomatic ESES

We found some positive effects using levetiracetam (LEV), clonazepam (CZP), and steroids (►**Table 3**). Only in one child ESES disappeared permanently after initiation of steroids and LEV simultaneously. No effect on EEG and seizure frequency was observed with CBZ ($n=4$), nitrazepam ($n=2$), sultiame (STM) ($n=1$), OXC ($n=2$), and TPM ($n=3$). LTG was used in five patients with transient ESES and seizure remission was observed in two of them.

Overall, ESES was difficult to treat in the symptomatic group as only 1 child was with a permanent ESES remission after initiation of LEV and corticosteroids and the other 19 had a relapsing or persistent course of ESES despite different therapeutic approaches. The response rate of idiopathic ESES was favorable as one-third of the case showed permanent ESES remission, while the other 66.6% ($n=30$) showed relapsing or persistent course of ESES (►**Table 1**).

Table 2 CT/MRI in patients with symptomatic ESES

	n, CT/MRI
Symptomatic ESES	Six: brain malformations (cortical dysplasia, hemimegalencephaly, polymicrogyria, agenesis of corpus callosum)
	Six: lesions due to pre-/perinatal damage (cerebral atrophy, ventricular dilatation, cystic lesions, gliosis)
	One: tuberous sclerosis
	Two: brain atrophy
	One: right temporal hypoplasia with pachygyria, contralateral gray matter ectopia, and calcification due to congenital toxoplasmosis
	One: vascular malformation with focal cortical dysplasia
	One: multicystic leukoencephalopathy without megalencephaly
	One: cerebral stroke due to congenital cardiac malformation
	One: lesions due to meningoencephalitis
	One: microdeletion syndrome (17q21.3), normal MRI

Abbreviations: CT, computed tomography; ESES, electrical status epilepticus in sleep; MRI, magnetic resonance imaging.

Table 3 Effect of corticosteroids and conventional AED on ESES and seizures in idiopathic and symptomatic cases

	Permanent ESES remission, *n*/%	Transient ESES remission, *n*/%	No effect on ESES, *n*/%	Permanent seizure remission, *n*/%	Transient seizure remission, *n*/%	No effect on seizures, *n*/%
AED in idiopathic ESES						
CS ($n=21$)	4/19	13/62 (mean period of 5.2 mo, ranging from 1 to 12 mo)	4/19	5/23.8	14/66.7 (mean period of 5 mo, ranging from 1 to 12 mo)	2/9.5
LEV ($n=20$)	7/35	3/15 (mean period of 5 mo, ranging from 5 to 18 mo)	10/50	8/40	7/35 (mean period of 4.7 mo, ranging from 2 to 13 mo)	5/25
CZP ($n=15$)	5/33.3	4/26.7 (mean period of 7 mo, ranging from 4 to 12 mo)	6/40	6/40	5/33.3 (mean period of 7.6 mo, ranging from 5 to 12 mo)	4/26.7
CLB ($n=5$)	–	2/40 (for 4 and 6 mo, respectively)	3/60	–	3/60 (mean period of 3.5 mo, ranging from 3 to 4 mo)	2/40
ESM ($n=11$)	3/27.3	5/45.4 (mean period of 4.7 mo, ranging from 4 to 6 mo)	3/27.3	5/45.5	6/54.5 (mean period of 4.2 mo, ranging from 1 to 6 mo)	–
STM ($n=10$)	1/10	4/40 (mean period of 4.6 mo, ranging from 3 to 7 mo)	5/50	4/40	2/20 (for 3 and 5 mo, respectively)	4/40
VPA ($n=3$)	1/33.3	2/66.7 (for 2 and 12 mo, respectively)	–	1/33.3	–	2/66.7
AED in symptomatic ESES						
CS ($n=12$)	–	9/75	3/25	1/8.3	3/25	8/66.7
LEV ($n=15$)	–	9/60	6/40	2/13.3	5/33.3	8/53.3
CZP ($n=8$)	–	3/37.5	5/62.5	2/25	1/12.5	5/63.5
ESM ($n=5$)	–	3/60	2/40	–	3/60	2/40

Abbreviations: AED, antiepileptic drug; CLB, clobazam; CS, corticosteroid; CZP, clonazepam; ESES, electrical status epilepticus in sleep; ESM, ethosuximide; LEV, levetiracetam; STM, sultiame; VPA, valproate.

Table 4 Effect of the "combined" treatment strategies on ESES and seizures in idiopathic ESES cases

Effect on ESES	*n*/%	Effect on seizures	*n*/%
CS + LEV	13	CS + LEV	13
Permanent remission	2/15.4	Permanent remission	2/15.4
Transient remission	4/30.8	Transient remission	8/61.5
Lack of effect	7/53.8	Transient reduction	1/7.7
CS + LEV + ESM	2	Lack of effect	2/15.4
Permanent remission	1/50	CS + LEV + ESM	2
Transient remission	1/50	Permanent remission	1/50
CS + CZP	5	Transient reduction	1/50
Permanent remission	1/20	CS + CZP	5
Transient remission	3/60	Permanent remission	2/40
Lack of effect	1/20	Transient remission	3/60
CS + STM	1	CS + STM	1
Lack of effect	1/100	Permanent remission	1/100
CS + ESM	2	CS + ESM	2
Permanent remission	1/50	Permanent remission	1/50
Transient remission	1/50	Transient remission	1/50
CS + VPA ($n = 1$), CS + LTG ($n = 1$)	2	CS + VPA ($n = 1$), CS + LTG ($n = 1$)	2
Permanent remission	2/100	Transient remission	2/100
CS + LEV + CZP	1	CS + LEV + CZP ($n = 1$)	1
Permanent remission	100	Permanent remission	100
Total	26	*Total*	26

Abbreviations: CS, corticosteroid; CZP, clonazepam; ESES, electrical status epilepticus in sleep; ESM, ethosuximide; LEV, levetiracetam; LTG, lamotrigine; STM, sultiame; VPA, valproate.

Discussion

The current study has summarized the clinical course and therapeutic approaches in patients with idiopathic and symptomatic ESES. The clinical course of the idiopathic ESES showed a typical evolution,[2,6] as the registration of ESES was accompanied by a significant aggravation of the existent seizures in two-thirds of patients, by a manifestation of new seizure types in 37%, and cognitive regression or behavioral changes in half of the cases. The acute phase was followed by a period of recovery, accompanied by clinical improvement with seizure and ESES remission in all long-term followed patients. We reported motor impairment during the acute phase in 23% of the idiopathic cases—ataxia or focal motor deficit. Our observations confirm previous studies, showing that the persistence of the EEG activity can lead to ataxia, dyspraxia, dystonia, or focal motor deficit.[2,10] Kramer et al described oromotor deficit and fine motor clumsiness in one-fifth of their patients.[2] Symptomatic patients had an earlier age of seizure onset (2 years and 8 months) and earlier age of ESES registration (6 years 2 months) compared with idiopathic ESES cases. At the time of ESES onset, the clinical course of the symptomatic patients was similar to that of the idiopathic ones, except for the higher percent of additional motor impairment (55%).

Most of the patients in the idiopathic ESES group experienced initially the same types of seizures compared with the patients with CECTS.[8] However, when comparing their clinical course with those of the typical CECTS,[23] we observed some specific features: (1) the seizures started at an earlier age (mean age: 5 years) compared with CECTS (mean age: 7 years); (2) initially 55% of the patients in the idiopathic ESES group experienced multiple focal and GTCS, compared with only 11% of CECTS; (3) the atypical feature, postictal Todd paresis, was far more common in ESES cases (35 vs 10%). The atypical features were observed by Wirrell et al in 50% of their patients and were defined as factors that necessitate treatment initiation despite the absence of a higher seizure frequency.[24] Although there are no reliable early predictors for the atypical evolution, we considered the earlier age of seizure manifestation (under 5 years) ($p = 0.0002$), the presence of multiple seizures ($p < 0.00001$), and postictal paresis ($p < 0.00001$) as risk factors, similar to the opinion of other authors.[8,25] In a study of Hahn et al, most of the children with atypical evolution were between 2 and 6 years of age at the time of seizure onset.[17] Fejerman[8] described an age of seizure manifestation below 4 in 25 out of 39 patients with atypical evolution of the epilepsy. However, according to Callenbach et al, the age of seizure onset and the presence of multiple seizures are not significant prognostic factors for the disease course and outcome.[26]

Although one-third of the idiopathic patients demonstrated favorable effect with complete ESES remission after the first treatment approach, in the remaining patients ESES demonstrated a significant therapeutic resistance as a whole, an observation reported also by many authors.[5,19,27,28]

We confirm previous observations that steroids have a favorable effect.[2,6,20–22,29–31] Using steroids, we achieved a positive initial response with ESES remission in 81% of our patients (17/21), but later 76% (13/17) of the responders relapsed. Our short-term efficacy of steroid treatment was higher than that reported by Kramer et al[2] but, like them, we observed a very high relapse rate that was discussed by the authors as a factor that could not justify the long-lasting treatment. In contrast to these results, in another study of 44 patients treated with steroids for 21 months, the treatment led to improvement in 77% of patients with normalization of EEG in 50%, but a long-lasting effect was reported in a higher percent of the children (45%).[20] Unlike other reports, Liukkonen et al did not describe improvement with corticosteroid even though the therapy was initiated within the first year of ESES registration.[5]

We used steroids alone or combined with an introduction of another AED. These two approaches had the same initial effect on seizures (91% in the first vs 92% in the second group) but the first approach was more successful concerning the initial effect on ESES (81% in the first vs 65% in the second group). The relapse rate, concerning seizures, was almost the same (74% of the responders of the first group vs 67% of the second group). Although a smaller percentage of the second group experienced another ESES relapse (53% of the responders of the second group vs 76% of the first group), we think that this fact alone cannot justify simultaneous administration of several drugs. The risk of adverse reaction should always be taken into consideration when introducing several drugs simultaneously.

From the new AEDs, promising results were obtained with LEV.[18,32–34] Our results are comparable to those of Aeby et al.[32] In half of our patients, ESES responded to LEV and, unlike the results of Aeby et al, only 30% of the initial responders relapsed.

Like other authors,[35–37] we also achieved some good results with STM—initial ESES remission in half of the patients, which was, unfortunately, transient in almost all cases. Fejerman et al reported better results—improvement in 19 out of 28 patients with symptomatic and 21 out of 25 patients with idiopathic epilepsy.[35] According to Gross-Selbeck, the combination of STM and CLB was effective.[37]

Benzodiazepines should also be considered in the treatment options.[2,19,31,38,39] Like previous reports,[40] we observed a positive effect on ESES in almost two-thirds of our patients treated with CZP, but 45% of the responders relapsed after several months. Inutsuka et al observed a positive effect in 50% of their patients after a short 1-week treatment course with diazepam.[19] Kramer et al did not confirm previous observations as only three out of eight patients had an initial favorable response, but all relapsed soon after.[2] The effect of benzodiazepines was also disappointing in the series of Liukkonen et al.[5] Unlike previous studies showing a favorable response to CLB,[2,10,37] we observed only a transient ESES remission in two cases. However, the number of our patients was too small to draw definite conclusions. We used it rarely as the drug is not available in our country.

The response to the drug treatment in the symptomatic group was disappointing as a whole. Permanent remission of ESES was observed in only one patient after introduction of steroids and LEV. Transient effect was achieved with steroids, LEV, ethosuximide (ESM), and CZP, but the effect rapidly disappeared after a few months.

The etiology seems to have a major impact on the treatment responses and on the outcome. Almost all (19/20) symptomatic patients had persistent or relapsing ESES versus 67% (30/45) of the idiopathic patients. When comparing the EEG response after initiation of different AEDs in the idiopathic and symptomatic group, we found no statistically significant difference regarding the initial effect on ESES. However, no patient in the symptomatic group had a long-lasting ESES remission with LEV, CZP, corticosteroid, STM, and ESM and the difference in the long-term efficacy reached statistical significance when using LEV. When comparing the effects of AEDs on seizure frequency, we did not report a statistical difference regarding the initial effects, but in a significantly smaller percentage of our symptomatic cases there was a persistent remission of seizures when using LEV, ESM, and corticosteroid, although this difference is not statistically significant.

Conclusion

The earlier age of seizure manifestation and the presence of multiple seizures and postictal paresis are potential risk factors for ESES manifestation in CECTS. ESES is characterized by a significant therapeutic resistance, especially in symptomatic cases. Good results are observed with LEV, ESM, and CZP, but often a polytherapy is needed. A favorable response is achieved with steroids. The etiology seems to have a major impact on the treatment responses and the outcome.

The study has some weaknesses due to the retrospective design—e.g., variable time of follow-up, different treatment regimens. Not all patients were, initially and as a follow-up, studied with specific neuropsychological test. Nevertheless, cognitive problems and behavioral changes were taken into account when monitoring the patients.

Note

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Conflict of Interest

None declared.

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