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Electrical status epilepticus during sleep (ESES) in benign childhood epilepsy with Centrotemporal spikes (BCECTS): insights into predictive factors, and clinical and EEG outcomes

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Abstract. – OBJECTIVE: Benign childhood epilepsy with centro-temporal spikes (BCECTS), otherwise known as benign rolandic epilepsy, is the most common focal epilepsy in childhood. This study aimed to evaluate the development and resolution of ESES in children with BCECTS and evaluate the clinical and electroencephalography (EEG) parameters associated with prognosis.

PATIENTS AND METHODS: Resolution of ESES was defined as the reduction of the spike-wave index (SWI) to <50%. The SWI short method, measurements from the first 180 s of non-rapid eye movement; and the conventional method, measurements from total NREM stage 2, SW count during the first 60 and 180 s of NREM, SW localization, and ESES type were determined.

RESULTS: Of a total of 126 BCECTS patients, 33, including 13 females, 20 males, who developed ESES during follow-up, were included in the study. ESES remission was observed in 42.4% (n = 14) of the patients. The median time to remission was 10.5 months. The rate of resolution was 87.9 % for the entire population. The mean age at resolution was 9.8 ± 2.05 years and the mean time to resolution was 8.8 months.

CONCLUSIONS: The data demonstrated that age at ESES diagnosis, the time between BCECTS diagnosis and the onset of ESES, time to resolution of ESES, ESES remission, and seizure freedom after ESES were significantly associated with prognosis. The early recognition of ESES evolution in children with BECTS, the better understanding of the relationship between age at ESES diagnosis and remission and prognosis, and timely intervention can prevent long-term sequelae.

Key Words:
Electrical status epilepticus during sleep (ESES), Continuous spikes and waves during sleep (CSWS), Electroencephalography (EEG), Spike-wave index (SWI), Benign childhood epilepsy with centrotemporal spikes (BCECTS), Benign rolandic epilepsy.

Introduction

Benign childhood epilepsy with centro temporal (CT) spikes (BCECTS), otherwise known as idiopathic rolandic epilepsy, is the most frequent focal epilepsy in childhood. The clinical spectrum may vary from benign to disabling, depending on the abnormal background activity, typical spike morphology, amount of inter ictal epileptic discharges and their predominant location, and unusual spike localization[1]. The atypical clinical and electroencephalographic as evolutions have been grouped as "continuum" of different syndromes that constitute the spectrum of rolandic epilepsy.

Although the evolution of BCECTSs to ESES, the terminal end of the spectrum, had been previously described, the predictive electrographical factors are still uncertain. The neurophysiological impairments like reading performance, memory deficits, and language impairments despite normal intelligence have mainly been ascribed to the frequency of paroxysmal discharges, high spike wave index and localization of spike waves[2]. Therefore, electrographical predictors with a reasonably high yield are urgently needed in order to select BECTS patients who may develop ESES during follow-up.

The objective of this study, therefore, was to describe the EEG patterns of long-term follow-up BCECTS patients who developed ESES, and in-

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vestigate electrographically predictive factors for ESES development, resolution, remission, and prognosis.

Patients and Methods

Patient Selection and Protocol Design

The study was conducted in a level 4 Pediatric Epilepsy Center. There were a total of 126 patients who were diagnosed with BCECTS according to the ILAE criteria and were followed up at the Gazi University Pediatric Neurology Department between 2016 and 2019. All of the procedures performed in study involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Of the 126 BCECTS patients, 38 (30%) developed ESES. And of those, 5 patients were excluded due to not being followed-up within 6 months after ESES. The study included BCECTS patients who developed ESES and had regular follow-up for at least 6 months before and after the onset of ESES. Medical records, imaging results, and EEG reports were reviewed. For each patient, demographic characteristics (e.g., age, gender), family history of epilepsy, history of febrile convulsions, clinical signs, and medical history (including age at BCECTS diagnosis, age at ESES diagnosis, frequency of seizures, seizure semiology, antiepileptic drugs (AEDs) used before ESES diagnosis, AEDs used after the onset of ESES, physical and neurological examinations, sleep and waking EEGs, and brain MRIs) were recorded. All of the EEGs were read by board-certified neurophysiologists.

Definitions

Remission was defined as the restoration of normal EEGs at follow-up examinations that were performed at least every 6 months.

ESES resolution was defined as the reduction of the SWI to <50% on follow-up EEGs that were performed at least every 6 months.

Frequent seizure recurrence was defined as having ≥4 seizures within the first 3 months.

Infrequent seizures were defined as having <4 seizures.

Prognosis was graded according to comorbidities, seizures, and EEG abnormalities. Accordingly, a good prognosis was when all 3 parameters were favorable (i.e., seizure freedom, normal EEG, and no comorbidities), a fair prognosis was when any 2 parameters were favorable, and a mild prognosis was when only 1 of the three parameters was favorable. Poor prognosis was defined as the state in which all 3 parameters were unfavorable.

Although there is no consensus on the diagnostic criteria for ESES, generally accepted criteria include a SW index (SWI) between 20% and 90% together with cognitive deficits[3]. ESES treatment should aim to control seizures, prevent encephalopathy, and correct or prevent cognitive impairment[4,5]. Containing ESES early on may prevent residual neuropsychological deficits[6,7]. In this paper, the term ESES was used only to indicate an EEG pattern with a SWI between 50% and 100% in non-rapid eye movement (NREM) sleep (SWI ≥85% indicated typical ESES and SWI between 50% and 85% indicated atypical ESES)[8,9].

Assessment of Interictal EEG Findings

Interictal EEG was recorded while awake and during sleep, without sedation, using an 18-lead digital EEG using the international 10–20 electrode-placement system. One author (AS) reviewed all of the patients who were followed-up with BCECTS between 2016 and 2019, and determined the patients who developed ESES during follow-up. Two electroencephalographers (HKU and EA), who were blinded to the clinical information of the patients, analyzed EEG results from the time of BCECTS diagnosis, the time of ESES diagnosis, and from 6 months before and 6 months after ESES, and the follow-up EEGs obtained every 6 months after ESES diagnosis until January 2019. The dominant region was defined as the localization where spikes were the most frequent and higher in amplitude.

The researchers analyzed the EEG results in terms of the following criteria:

1. The number of spikes and waves occurring in the first 60 and 180 s of NREM sleep.
2. The localization of spikes and waves to unilateral or bilateral CT areas; the ESES pattern was described as anterior if the maximum amplitude was recorded in the frontal, frontocentral, or frontotemporal regions, and as posterior if the maximum amplitude was recorded in the posterotemporal, temporooccipital, or occipital regions on the EEG.

3. The presence of spikes outside of the CT region.
4. The quantification of anomalies during sleep EEG had a central role in the diagnostic criteria of ESES[10,11].

The SWI is a method that quantifies the frequency of spikes in NREM sleep using EEG recordings (of at least 45 min). The literature presents several different SWI assessment methods. Most authors define SWI as the percentage of 1-s bins with at least 1 spike and wave relative to the total number of 1-s bins in NREM sleep[12]. The SWI is higher in the first sleep cycles and progressively decreases throughout the night. In this study, the SWI of NREM sleep during ESES was calculated using 2 different methods: the short and long (conventional) methods. Typical ESES was defined as a SWI ≥85% and atypical ESES as a SWI of 50%–85%[13]. Ebus et al[14] and Filippini et al[15] reported that a conventional SWI represented the first 5 min and 100 s of NREM sleep, respectively, with high sensitivity and specificity. Therefore, the percentage of the first 180 s of NREM sleep occupied by spike waves (defined as SWI-short in the context of this study) and the percentage of total NREM sleep occupied by spike waves (i.e., conventional SWI) were calculated herein[10].

The short method is described as follows: The SWI of each EEG was calculated in an epoch of 180-s duration on NREM2. The number of seconds containing epileptiform discharges was divided by the total number of seconds in the epoch 180 and multiplied by 100 to reflect the SWI as a percentage. The number of spikes was computed for the first 60 and 180 s of NREM2. These evaluations were performed via visual inspection by each reader separately. The interobserver agreement was high ($\kappa = 0.95$). Initial EEG recordings were performed within 7–10 days after the initial seizure for all of the patients. EEG recordings were repeated for all of the patients at the time of BCECTS diagnosis, at the time of ESES diagnosis, 6 months before and 6 months after EEGs diagnosis, and every 6 months after ESES diagnosis (during follow-ups) until January 2019. All of the EEG recordings of all of the patients were analyzed to determine the number of spikes within the first 60 and 180 s of NREM. The obtained data were evaluated on the basis of 2 stages of development, comprising ≤8 years and >8 years.

Cognitive Function Assessment

According to the protocol of the center, all of the patients underwent psychological and neuropsychological assessments at the time of diagnosis.

Initially, all of the patients were assessed using age-appropriate scales. However, although neuropsychological tests were performed at the time of BCECTS diagnosis, neuropsychological tests were at times not performed during or after the onset of ESES due to the retrospective nature of the study. In these cases, a decision was made based on clinical observations and in consultation with the family and teacher of the patient.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 23.0 (Armonk, NY, USA). The normality of data distribution was analyzed using the Kolmogorov-Smirnov test. Normally distributed numerical variables were presented as mean ± standard deviation, and non-normally distributed numerical data were presented as median (min-max). Categorical variables were presented as numbers and percentages. The Shapiro-Wilk test was used to determine whether the parameters were normally distributed. For the intergroup comparison of continuous variables, the independent samples *t*-test was used for the pairwise comparison of risk groups and the determination of associated factors. The One-way ANOVA test was used for the comparison of more than 2 groups (of normally distributed numerical variables), and the Mann-Whitney U test was used for the comparison of more than 2 groups (of non-normally distributed numerical variables). The chi square and Fisher exact tests were used to compare categorical data. Any correlations between the numerical variables were determined using the Pearson and Spearman correlation analyses. The ROC curve analysis and the Youden index were used to identify cut-off values of numerical variables and analyze diagnostic performance. $p < 0.05$ was accepted as statistically significant.

Results

General Characteristics

Of a total of 126 BCECTS patients, 33, including 13 females (39.4%) and 20 males (60.6%), developed ESES during follow-up and were followed-up for at least 6 months after ESES diagnosis. The mean age of the 38 ESES patients was 10.7 ± 2.49 years. The mean age at ESES diag-

nosis was 8.72 ± 2.02 years. The mean age at the onset of seizures was 6.6 ± 2.24 years. The mean time between BCECTS diagnosis and the onset of ESES was 25.3 months (Table I).

ESES remission was observed in 42.4% (n = 14) of the patients, while the remaining 19 patients (57.6%) did not go into remission. The median time to remission was 10.5 months (range 4–28 months). Remission after ESES was statistically significantly more common in patients under the age of 8 who were diagnosed with ESES ($p < 0.05$) (Table II).

Table I. ESES outcome according to the patient characteristics (n = 33 patients).

	No remission (n = 19) n (%)	Remission (n = 14) n (%)	Total (n = 33) n (%)	*p*-value
Gender				0.727
Female	7 (36.8)	6 (42.9)	13 (39.4)	
Male	12 (63.8)	8 (57.1)	20 (60.6)	
Recurrence				0.496
No	17 (89.5)	14 (100.0)	31 (93.9)	
Yes	2 (10.5)	0 (0.0)	2 (6.1)	
Comorbidity after ESES				0.690
MR	1 (5.3)	0 (0.0)	1 (3.0)	
ADHD	1 (5.3)	0 (0.0)	1 (3.0)	
Learning disabilities	5 (26.3)	6 (42.9)	11 (33.3)	
None	10 (52.6)	7 (50.0)	17 (51.5)	
Regression of bright normal intelligence	2 (10.5)	1 (7.1)	3 (9.1)	
AED was switched for ESES				0.393
No	11 (57.9)	6 (42.9)	17 (51.5)	
Yes	8 (42.1)	8 (57.1)	16 (48.5)	
Age at ESES diagnosis				**0.004**
≤ 8	4 (21.1)	10 (71.4)	14 (42.4)	
> 8	15 (78.9)	4 (28.6)	19 (57.6)	
ESES type				0.195
Typical	13 (68.4)	13 (92.9)	26 (78.8)	
Atypical	6 (31.6)	1 (7.1)	7 (21.2)	
Risk factors				0.148
Infection, FC, hypoxia, etc.	4 (21.1)	0 (0.0)	4 (12.1)	
Family history	1 (5.3)	2 (14.3)	3 (9.1)	
Unknown	14 (73.7)	12 (85.7)	26 (78.8)	
Febrile convulsions				0.744
No	17 (89.5)	12 (85.7)	29 (87.9)	
Yes	2 (10.5)	2 (14.3)	4 (12.1)	
Resolution				**0.067**
No	4 (21.1)	0 (0.0)	4 (12.1)	
Yes	15 (78.9)	14 (100.0)	29 (87.9)	
Seizure status after ESES				0.271
Seizure-free	15 (78.9)	13 (92.9)	28 (84.8)	
Non-seizure-free	4 (21.1)	1 (7.1)	5 (15.2)	
	No remission (n = 19) Mean ± SD	**Remission (n = 14) Mean ± SD**	**Total (n = 33) Mean ± SD**	***p*-value**
Age	11.10 ± 2.46	10.20 ± 2.52	10.71 ± 2.49	0.313
Time to resolution (months)	9.73 ± 8.10	7.92 ± 4.68	8.86 ± 6.62	0.473
Time between BCECTS diagnosis and ESES (months)	30.26 ± 28.61	18.71 ± 16.38	25.36 ± 24.56	0.186
Age of seizure onset	6.77 ± 2.23	6.57 ± 2.34	6.69 ± 2.24	0.808
Age at ESES diagnosis	9.30 ± 2.05	7.93 ± 1.75	8.72 ± 2.02	**0.054**
Spike count per 60 s during ESES	102.52 ± 36.84	90.14 ± 18.37	97.27 ± 30.65	0.258
Spike count per 60 s during RE diagnosis	63.26 ± 51.41	33.0 ± 20.07	49.81 ± 42.76	**0.066**
Spike count per 60 s before ESES	57.80 ± 46.71	40.70 ± 17.39	50.96 ± 38.20	0.282
Spike count per 60 s after ESES	41.05 ± 26.64	19.85 ± 25.59	32.06 ± 27.90	**0.029**

Table II. Patient characteristics according to age at ESES diagnosis (n = 38 patients).

	Age at ESES diagnosis			
	≤ 8 years n (%)	> 8 years n (%)	Total n (%)	*p*-value
Remission				**0.005**
No	4 (28.6)	15 (78.9)	19 (57.6)	
Yes	10 (7.4)	4 (21.1)	14 (42.4)	
AED was switched for ESES				0.580
No	7 (50.0)	10 (52.6)	17 (51.5)	
Yes	7 (50.0)	9 (47.4)	16 (48.5)	
EEG findings before ESES				0.211
Focal spikes	8 (57.1)	7 (36.8)	15 (45.5)	
Bilateral spikes	6 (42.9)	12 (63.2)	18 (54.5)	
Seizure semiology before ESES				0.381
Focal	6 (42.9)	6 (31.6)	12 (36.4)	
Generalized	8 (57.1)	13 (68.4)	21 (63.6)	
Change in seizure semiology during ESES				1.000
No	14 (100.0)	19 (100.0)	33 (100.0)	
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
EEG dominance				0.510
Anterior (F, FC, or FT)	11 (78.6)	16 (84.2)	27 (81.8)	
Posterior (T, TO, or O)	3 (21.4)	3 (15.8)	6 (18.2)	
Seizure characteristics before ESES				0.333
Sparse	12 (85.7)	16 (84.2)	28 (84.8)	
Frequent	2 (14.3)	1 (5.3)	3 (9.1)	
Initial diagnosis was ESES	0 (0.0)	2 (10.5)	2 (6.1)	
Increased seizure frequency during ESES				0.510
No	11 (78.6)	16 (84.2)	27 (81.8)	
Yes	3 (21.4)	3 (15.8)	6 (18.2)	
Final seizure status after ESES				**0.037**
Seizure-free	14 (100.0)	14 (73.7)	28 (84.8)	
Non-seizure-free	0 (0.0)	5 (26.3)	5 (15.2)	
Risk factors				0.688
Infection, FC, hypoxia, hypothyroidism	1 (7.1)	3 (15.8)	4 (12.1)	
Family history	1 (7.1)	2 (10.5)	3 (9.1)	
Unknown	12 (85.7)	14 (73.7)	26 (78.8)	
Febrile convulsions				0.574
No	12 (85.7)	17 (89.5)	29 (87.9)	
Yes	2 (14.3)	2 (10.5)	3 (12.1)	
Prognosis				**0.031**
Good	4 (28.6)	2 (10.5)	6 (18.2)	
Fair	8 (57.1)	9 (47.4)	17 (51.5)	
Mild	2 (14.3)	5 (26.3)	7 (21.2)	
Poor	0 (0.0)	3 (15.8)	3 (9.1)	
Resolution				0.574
No	2(14.3)	2 (10.5)	4 (12.1)	
Yes	12 (85.7)	17 (89.5)	29 (87.9)	
Comorbidity after ESES				0.412
MR	0 (0.0)	1 (5.3)	1 (3.0)	
ADHD	0 (0.0)	1 (5.3)	1 (3.0)	
Learning disabilities	7 (50.0)	4 (21.1)	11 (33.3)	
No	6 (42.9)	11 (57.9)	17 (51.5)	
Regression of bright normal intelligence	1 (7.1)	2 (10.5)	3 (9.1)	
Age at the time of resolution	7.16 ± 3.63	10.05 ± 7.99	8.86 ± 6.62	0.228

The rate of resolution was 87.9% (n = 29) for the entire population. Of the patients, 4 (12.1%) did not have resolution of ESES. The mean age at resolution was 9.8 ± 2.05 years, while the mean time to resolution was 8.8 months (Table II, Figure 1). The mean time to resolution was 7.9 months for patients ≤8 years of age (at the time of ESES diagnosis), and 22.7 months for patients >8 years of age. This finding was statistically significant ($p < 0.05$) (Figure 1).

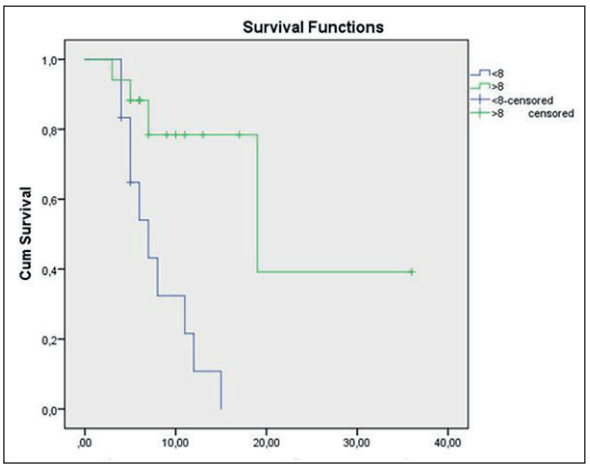

Figure 1. Relationship between age at ESES diagnosis and time of ESES resolution. Time to resolution, defined as the reduction of SWI to <50% (months).

Age at ESES diagnosis was not found to be significantly associated with comorbidity after ESES, switching AEDs for ESES, EEG findings before ESES, seizure semiology before ESES, changes in seizure semiology during ESES, EEG dominance, seizure status before ESES, increased seizure frequency during ESES, risk factors, febrile convulsion, prognosis, or ESES resolution ($p > 0.05$) (Table II).

Moreover, 78.8% of the patients (n = 26) had typical and 21.2% (n = 7) had atypical ESES. The ESES type was not significantly associated with the prognostic factors ($p > 0.05$) (Table III).

Seizures and EEG Findings

Of the patients, 36.4% (n = 12) had focal EEG findings and seizure semiology before ESES, whereas 63.6% (n = 21) had generalized findings. Additionally, 84.8% of the patients had sparse seizures. Furthermore, 2 patients (6.1%) had focal spikes, 29 (87.8%) had bilateral spikes, and 2 (6.1%) had generalized spikes. Of all of the patients, 81.8% (n = 27) had anterior EEG dominance (F, FC, or FT) and 18.2% (n = 6) had posterior dominance (T, TO, or O) (6). As for SW localization, 48.5% (n = 16) of the patients had CT spikes. Only 6 patients (18.2%) developed increased seizure frequency during ESES (n = 6). The EEG findings and seizure semiology and frequency were not significantly different before and after ESES. Seizure freedom after ESES was achieved in 84.8% (n = 28) of the patients. The mean spike count during the first 60 s of NREM was 49.8 at the time of BCECTS diagnosis, 50.9 before ESES, 97 during ESES, and 32 after ESES. The time between BCECTS diagnosis and the onset of ESES was weakly and negatively correlated with spike count per 60 s at the time of BCECTS diagnosis (r = –0.435) and age at onset of the seizures (R = –0.386) ($p < 0.05$) (Table III).

Moreover, age at the time of ESES diagnosis was:

– Weakly and positively correlated with the time between BCECTS diagnosis and the onset of ESES (r = 0.462).
– Moderately and positively correlated with the age at onset of seizures (r = 0.522) ($p < 0.05$) (Table III).

Spike count per 60 s at the time of BCECTS diagnosis was:

– Positively and strongly correlated with spike count per 60 s before ESES (r = 0.886).
– Positively and moderately correlated with spike count per 60 s after ESES (r = 0.501) ($p < 0.05$).

There was a weak and positive correlation between the spike counts (per 60 s) during and after ESES ($p < 0.05$). The correlations between other measurements are presented in Table III. A ROC analysis was performed and a ROC curve was plotted to determine the cut-off value for the spike count during the first 60 s of NREM during ESES (Figure 2). The analysis demonstrated that a significant diagnostic model could not be established in terms of final seizure status, prognosis, or the presence of remission or resolution ($p > 0.05$). The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio findings of the established model are presented in Figure 2. The results of the novel SWI-short were determined to be strongly positively and significantly correlated with those of the conventional SWI method (Figure 2).

Other Findings

Of the patients, 33.3% (n = 11) had learning disabilities or other psychiatric disorders, and 9.1% (n = 3) had regression of bright normal intelligence. Among all of the BCECTS patients who developed ESES, there was 1 patient who was followed-up without medication, and 48.5% (n = 16) of the patients switched AEDs. Prognosis was significantly associated with age at the time of ESES diagnosis, time between BCECTS diagno-

Table III. Relationship between age and other clinical parameters

	Age (1)		Time to remission (2)		Time between BCECTS diagnosis and ESES (3)		Age at the time of resolution (4)		Age at ESES diagnosis (5)		Age of seizure onset (6)		Spike count per 60 s during ESES (7)		Spike count per 60 s at the time of BRE diagnosis (9)		Spike count per 60 s before ESES (10)		Spike count per 60 s after ESES (11)	
	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value
1	–	–	0.285	0.323	0.487	**0.004**	0.914	**0.000**	0.877	**0.000**	0.430	**0.014**	-0.096	0.596	-0.081	0.687	-0.105	0.619	-0.130	0.470
2	0.285	0.323	–	–	-0.225	0.440	0.252	0.385	0.181	0.536	0.282	0.328	0.380	0.180	0.326	0.302	0.169	0.640	0.366	0.198
3	0.487	**0.004**	-0.225	0.440	–	–	0.441	**0.017**	0.462	**0.007**	-0.386	**0.029**	0.022	0.902	-0.436	0.023	-0.250	0.229	-0.159	0.377
4	0.914	**0.000**	0.252	0.385	0.441	**0.017**	–	–	0.938	**0.000**	0.555	**0.002**	0.149	0.442	-0.031	0.889	0.129	0.569	0.067	0.732
5	0.877	**0.000**	0.181	0.536	0.462	**0.007**	0.938	**0.000**	–	–	0.522	**0.002**	0.128	0.479	0.099	0.623	0.124	0.555	-0.074	0.682
6	0.430	**0.014**	0.282	0.328	-0.386	**0.029**	0.555	**0.002**	0.522	**0.002**	–	–	-0.092	0.617	0.276	0.173	0.181	0.387	0.147	0.421
7	-0.096	0.596	0.380	0.180	-0.009	0.960	0.149	0.442	-0.083	0.647	-0.092	0.617	–	–	0.313	0.112	0.284	0.0170	0.458	**0.007**
8	-0.088	0.627	0.189	0.518	-0.091	0.613	0.161	0.405	-0.050	0.783	0.007	0.970	0.888	**0.000**	0.255	0.198	0.175	0.402	0.433	**0.012**
9	-0.081	0.687	0.326	0.302	-0.435	**0.023**	-0.031	0.889	-0.101	0.616	0.276	0.173	0.313	0.112	–	–	0.886	**0.000**	0.501	**0.008**
10	-0.105	0.619	0.169	0.640	-0.270	0.192	0.129	0.569	-0.074	0.724	0.181	0.387	0.284	0.170	0.886	**0.000**	–	–	0.209	0.317
11	-0.130	0.470	0.366	0.198	-0.139	0.439	0.067	0.732	-0.076	0.647	0.147	0.421	0.458	**0.007**	0.501	**0.008**	0.209	0.317	–	–

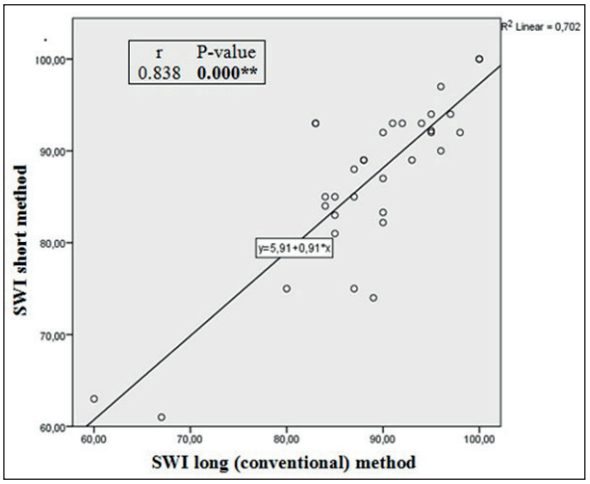

Figure 2. Correlation between the 2 SWI measurement methods.

sis and the onset of ESES, and time to resolution of ESES ($p < 0.05$). Other parameters were not significantly associated with patient prognosis ($p > 0.05$).

Discussion

BCECTS is the most common focal epilepsy of childhood. Although most patients have a good prognosis, atypical evolution is possible, the most common being ESES. This was a retrospective study that used EEG, cognitive impairment, and seizures as criteria for ESES diagnosis, ESES resolution, and prognosis. To apprehend the severe extreme of the EEG spectrum, a SWI of ≥ 85% was used for typical ESES and a SWI of 50%–85% was used for atypical ESES in NREM sleep as diagnostic criteria. The literature comprises 3 previous studies that reported the incidence of ESES as 0.2%–0.6% of all childhood epilepsies[10,16]. ESES usually occurs between the ages of 4 and 14, and 1 and 2 years after the onset of seizures. The literature has reported the mean age of diagnosis as 7.8 years for BCECTS and 5.4 years for ESES[17]. In the current study, the mean age of ESES diagnosis was 8.7 ± 2.02 years.

Consistent with the literature, it was found herein that ESES resolution was associated with seizures. It is known that, regardless of the severity of epilepsy, seizures disappear with the termination of ESES. Epilepsy remission means that there is at least 1 year of seizure freedom. The relationship between epilepsy and ESES resolution has been demonstrated in previous studies[8,18]. It is possible that the relationship between seizure control and ESES resolution is a result of the natural course of the epileptic syndrome. The resolution of ESES was reported as significantly associated with seizure freedom and older age (N10 years) at the last follow-up [19]. It was observed that ESES remission was more common among children ≤8 years of age, but that ESES resolution rates were similar for the 2 age groups. Particularly among patients ≤8 years of age, time to resolution, presence of remission, and seizure freedom were associated with a good prognosis.

All of the patients who were non-seizure-free after ESES were >8 years of age. BCECTS represents the milder end of a spectrum that includes syndromes like CSWS and LKS. ESES can occur in all diseases within this spectrum. Furthermore, the evolution of ESES differs between individuals and also depends on etiology; therefore, it is possible that this condition is a reflection of the natural course of the syndrome. Disruption of normal brain development in a critical period due to genetic predisposition or environmental factors (such as an early developmental lesion) may be responsible for a change in neurotransmission that causes hyper-excitability. Most researchers agree that the plastic changes that occur in the brain, which result in the transfer of SW activity, are the critical point in both adults and children (5–6 years of age) with focal epilepsy[20]. This has been supported by studies that have shown that a static lesion that develops in the early stages of life (before the critical period) can rearrange cortical networks in adjacent brain regions due to active network reorganization processes, and that impaired function can be restored[11].

Studies on neuropsychological disorders, which are primarily responsible for the need for treatment in children with CSWS and BCECTS, have revealed that interictal epileptiform discharges observed on EEGs may be responsible for disrupted brain function[16,21]. Children with BCECTS do not have neurological or intellectual deficits, but behavioral and neuropsychological problems have been reported. These problems were associated with the presence of intermittent slow-wave focus during wakefulness and multiple asynchronous bilateral SW foci[2,13]. Continuous psychological tests during SW discharges indicated short-term impairment of cognitive function. However, the prognosis is good, and these deficits tend to go back to normal over the long-term follow-ups[14,15].

Another follow-up study of patients with BCECTS revealed that learning and behavioral deficits were more common in patients with atypical features[22]. The major underlying cause behind cognitive deficits in BCECTS is the increased evolution and duration of ESES. The majority of patients with a long duration of ESES have residual deficits. An ESES duration of ≥2 years is a poor prognostic factor for cognitive deficits[18]. The remission or resolution of ESES, as observed on EEGs, is generally associated with positive cognitive outcomes[8,15]. In children with cognitive, language, behavioral, or motor deficits, achieving ESES control over a shorter period of time (less than 12–18 months) may improve the developmental trajectory[9,23]. In most patients, the effects of correct treatment and the restoration of normal sleep interictal epileptic activity, and normal EEG on behavioral difficulties, are still contentious[7,24]. In the current patient group, 33.3% (n = 11) had learning disabilities or other psychiatric disorders, and 9.1% (n = 3) had regression of bright normal intelligence; however, due to the retrospective and observational nature of the study, not every patient was followed-up at equal time intervals, and these tests could not be performed at equal time intervals, nor could a standard treatment protocol be applied. Therefore, further analyses were not possible. Although neuropsychological tests were performed at the time of BCECTS diagnosis, neuropsychological tests were at times not performed during or after the onset of ESES. In these cases, a decision was made based on clinical observations and in consultation with the family and teacher of the patient. The lack of standardized formal neurocognitive assessment during and after ESES development hindered further analysis to prevent bias. However, other than 1 patient who was determined as having mild MR, all of the patients were able to attend formal education. Hence, despite showing some learning deficits, most patients with BCECTS can attend formal education.

The mean duration of ESES was determined as 10.5 months (range 4-28) until remission and 8.8 months (range 3-36) until resolution. This finding was consistent with the literature. In terms of age, the mean time to resolution was 7.9 months for patients ≤8 years of age and 22.7 months in patients >8 years of age ($p < 0.005$). These results raised the question of whether older patients required more aggressive treatment. However, this hypothesis needs to be verified with prospective, randomized, controlled, and multicenter studies. The most important limitation of most of the relevant studies has been that they did not investigate the effect of AEDs and blood test results on the neuropsychological findings[25]. Moreover, external factors, such as parents, can have a large impact on quality of life. Available evidence has suggested that even though the atypical evolution of BCECTS due to AEDs is unlikely[26], carbamazepine treatment has been shown to potentially lead to true ESES in children with BECTS[27]. In the current study, 15 patients used CBZ before ESES, 10 of whom were >8 years of age. Of these patients, 2 used another AED in addition to CBZ. Although CBZ was the most commonly preferred AED, there was no statistically significant relationship. It was not possible to investigate any possible correlation between the AED choice and BCECTS-to-ESES evolution.

In the patient group, 78.8% (n = 26) had typical ESES and 21.2% (n = 7) had atypical. This difference may have been ascribed to the SWI being calculated from the EEG recordings of at least 45 min, and included 1 NREM cycle. Indeed, ESES discharges are known to be most pronounced during the first hour of sleep and to decrease towards the morning. In the current study, demographic characteristics were not significantly associated with typical and atypical ESES. In ESES, spikes are typically scattered over the frontocentral regions, while they are characteristically CT in BECTS. In the current study, CT and non-CT localization and anterior or posterior EEG dominance were not significantly associated with the SWI (typical/atypical ESES), prognosis, or restoration of the findings to normal. This finding was consistent with recent studies in the literature[28,29].

Nevertheless, it was determined to be strongly associated with high cortical function disorders, morphology, organization, and interictal anomalies. Many studies evaluating the distinctive features of interictal anomalies in atypical BECTS have associated them with fluctuations in cognitive signs in the severe stage of idiopathic focal epileptic syndromes (IFE), such as the intensity of interictal anomalies while awake[30,31], activation degree during sleep, and particularly, its near-continuity, and continuous SW during slow-wave sleep[7-9]. Furthermore, while the mean number of interictal paroxysms was not statistically different in typical and atypical ESES, a direct cause-and-effect relationship was not confirmed. The descending slope/slow-wave measurements performed while awake and asleep showed sig-

nificant differences between different children and between measurements made on different days, and there was also an overlap between typical and atypical cases. Although the mean number of paroxysms per minute while awake was reported as between 1 and 40 in BECTS, and 5 and 60 in atypical forms, this number was reported as between 1 and 90/min, and 5 and 120/min, respectively, during slow sleep. Moreover, it has been argued that the quantification of interictal paroxysms is not sufficient for the prediction of the prognosis of BECTS. In contrast, some studies have argued that some EEG parameters, such as the duration of ESES, are also effective in predicting the severity and prognosis of ESES. These are quantitative parameters, such as background activity, sleep pattern, sleep architecture, and spike amplitude, frequency, and distribution during sleep[4,12,32].

In the current study, the mean spike count during the first 60 s of NREM was 97 during ESES, 49.8 at the time of BECTS diagnosis, 50.9 before ESES, and 32 after ESES. Furthermore, the time between BECTS diagnosis and the onset of ESES was shorter when the spike count per minute was higher. Again, a higher spike count per minute at the time of BECTS diagnosis indicated higher spike counts before and after ESES.

Spike count per minute during ESES was not statistically associated with seizure freedom, prognosis, or the presence of resolution or remission. This was potentially ascribed to the fact that the SW can show variations between individuals and between measurements made on different days. Nevertheless, the positive correlation between the novel SWI-short introduced in the current study and the conventional SWI for measurements made at the time of BECTS diagnosis, during ESES, and 6 months after ESES showed that the SWI-short was a novel, practical, and inexpensive method that can be used in the diagnosis and follow-up of BECTS patients and ESES evolution.

Strengths and Limitations

The major limitations of the study included its retrospective nature, differences in the treatments received by the patients, and differences in the follow-up and treatment durations. It was, at times, difficult to determine the first 180 s of NREM sleep due to the disrupted sleep architecture in patients with ESES. Transition to sleep was determined according to technician notes and video EEG recordings. The EEG recordings to be evaluated were determined by 1 researcher who reviewed technician notes and video EEG recordings, and 2 electroencephalographers who were blinded to the nature of the study evaluated the selected recordings. The coefficient of agreement between the 2 electroencephalographers was high, and any disagreements during the assessments were resolved by the opinion of the third researcher (who originally selected the recordings to be reviewed) and consensus. Further limitations of the study included not having conducted simultaneous standard neuropsychological tests at the time of ESES development, during ESES, and before and after ESES, and not having studied the effects of the AEDs and blood test results on the neuropsychological findings.

Conclusions

The data demonstrated that age at ESES diagnosis, the time between BCECTS diagnosis and the onset of ESES, time to resolution of ESES, ESES remission, and seizure freedom after ESES were associated with prognosis. The remission and resolution of ESES and seizure freedom were significantly associated with a younger age (<8 years) at last follow-up.

The early recognition of ESES evolution in children with BECTS, the better understanding of the relationship between age at ESES diagnosis and remission and prognosis, and timely intervention can prevent long-term sequelae. This raises the question concerning the need for medical treatment without delay.

Moreover, a novel short method to determine the SWI was presented in the current study. It was demonstrated that the SWI-short was positively correlated with the conventional SWI at the time of BECTS diagnosis and during and 6 months after ESES. This study was significant in that it demonstrated, with a small sample, how this novel short method can be a practical and inexpensive method that can be used in the diagnosis and follow-up of BECTS patients and ESES evolution. Further larger prospective studies are needed.

Conflict of Interest
The authors declare that they have no conflicts of interest.

Disclosure

All co-authors have read and agreed to the content of the manuscript. None of the authors has any conflict of interest to disclose, any financial or commercial involvement, and any contribution of industry-sponsored research or corporate participation in preparing the manuscript. We confirm that we have read the Journal's position on ethical publication issues and affirm that this report is consistent with those guides.

Ethical Approval

All of the procedures performed in study involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Authors' Contribution

HKU and EA conceptualized and designed the study, designed the data collection instruments, collected data, and reviewed and revised the manuscript. KA conducted the data analysis, interpreted the data, and critically reviewed the manuscript. TH and AS coordinated and supervised the data collection, interpreted the data analysis, drafted the manuscript, and critically reviewed the initial manuscript as well as the subsequent revised versions. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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