DOI: 10.4274/forbes.galenos.2022.82474
Forbes J Med 2023;4(1):21-7

Original Article / Orijinal Araştırma

Electroclinical and Demographic Evaluation of Cases with Self-limited Epilepsy with Centrotemporal Spikes

Kendini Sınırlayan Sentrotemporal Dikenli Epilepsili Hastaların Elektroklinik ve Demografik Değerlendirilmesi

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Cite as: Badem M, Sarıkaya Uzan G, Hız Kurul S. Electroclinical and Demographic Evaluation of Cases with Self-limited Epilepsy with Centrotemporal Spikes. Forbes J Med 2023;4(1):21-7

ABSTRACT

Objective: This study aims to contribute to our understanding of unknown aspects of this syndrome by evaluating the characteristics of patients with rolandic epilepsy (RE), who applied to our hospital.

Methods: The cases diagnosed with "self-limited epilepsy with centrotemporal spikes (SeLECTS)", who applied to the Pediatric Neurology Department of Dokuz Eylül University Faculty of Medicine between July 2016, and July 2020, were evaluated clinically, electroencephalographically, and psychometrically retrospectively.

Results: Ninety-two cases diagnosed with RE were included in the study. The age of seizure onset was mostly observed between the ages of 5-10, with a frequency of 51.1%. Twenty-nine (31.5%) of these cases were followed up by the Child and Adolescent Psychiatry department due to psychiatric comorbidities such as anxiety, anxiety disorder, depression, and attention deficit. After the evaluation of the patients' first seizure type, it was identified that the seizures of the "generalized tonic-clonic" type were the most common (43.5%). The second most common type of seizure was "focal orofacial motor seizures" (21.8%). Finally, focal clonic seizures took third place (12%). Considering the success rates of the first-line drugs, it was seen that levetiracetam was 86% effective, valproic acid 79.3%, carbamazepine 100%, and oxcarbazepine 100%.

Conclusion: Our study suggested considering the necessity of further evaluation of SeLECTS even in patients with generalized tonic-clonic seizures. The presence of psychiatric comorbidities reveals the necessity and importance of assessing these cases, especially in terms of anxiety, anxiety disorder, depression, and attention problems.

Keywords: Rolandic epilepsy, self-limited epilepsy with centrotemporal spikes, electroencephalography, centrotemporal spike wave discharge, anti-seizure medication

Received/Geliş: 29.04.2022
Accepted/Kabul: 10.06.2022

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ÖZ

Amaç: Bu çalışmanın amacı hastanemize başvuran kendini sınırlayan sentrotemporal dikenli epilepsi hastalarının özelliklerini değerlendirerek bu sendromun bilinmeyen yönlerini anlamamıza katkıda bulunmaktır.

Yöntem: Dokuz Eylül Üniversitesi Tıp Fakültesi Çocuk Nöroloji Anabilim Dalı'na Temmuz 2016-Temmuz 2020 tarihleri arasında klinik, demografik, elektroensefalografik ve psikometrik açıdan retrospektif olarak değerlendirildi.

Bulgular: Doksan iki hasta çalışmaya alındı. Nöbet başlangıç yaşının sıklıkla 5-10 yaş olduğu görüldü (%51,1). Hastaların %31,5'i (n=29) anksiyete, anksiyete bozukluğu, depresyon veya dikkat eksikliği gibi psikiyatrik komorbiditeler nedeniyle Çocuk ve Ergen Psikiyatrisi bölümü tarafından izlenmekteydi. Hastalarımızın en sık görülen ilk nöbet tipi jeneralize tonik-klonik tip nöbet olarak tanımlandı (%43,5). İkinci en yaygın nöbet tipi fokal orofasiyal motor nöbet olarak tanımlanmıştı (%21,8). Son olarak üçüncü

en sık nöbet görünümü ise fokal klonik nbet tipiydi. İlk basamak ilaçların başarı oranları levetirasetam (%86), valproik asid (%79,3), karbamazepine (%100) ve okskarbazepin (%100) şeklindeydi.

Sonuç: Çalışmamız jeneralize tonik-klonik nöbetli hastalarda bile ileri nörolojik inceleme gerekliliğini göstermiştir. Psikiyatrik eş tanıların varlığı bu hastaların özellikle anksiyete, anksiyete bozukluğu, depresyon ve dikkat sorunları açısından değerlendirilmesinin gerekliliğini ve önemini ortaya koymaktadır.

Anahtar Kelimeler: Rolandik epilepsi, kendini sınırlayan sentrotemporal dikenli epilepsi, elektroensefalografi, sentrotemporal diken dalga deşarjı, antinöbet ilaç

INTRODUCTION

Epilepsy is the most common childhood neurological disorder, and the second most common neurological disorder diagnosed in adults. The seizures are temporary symptoms and signs that occur because of abnormal and excessive activity of neurons. A seizure refers to a single unprovoked attack. The epileptic syndrome explains clinical presentations with a specific seizure type and similar accompanying clinical and laboratory findings.[1]

Rolandic epilepsy (RE) or self-limited epilepsy with centrotemporal spikes (SeLECTS) is the most common childhood epileptic syndrome.[1] It often starts at the ages of 3-13 and, most commonly appears between the ages of 8-9, and seizures stop at the age of 14-18. Therefore, it is considered to be benign. Seizure activity starts around the central sulcus of the brain. This area is also called centrotemporal area, which is located around the rolandic fissure. The presence of a centrotemporal spike wave in electroencephalography (EEG) is characteristic. Typically, antiepileptic drugs easily control seizures. However, some cases that have unbenign prognosis, resistant to treatment, and who experience cognitive and motor regressions may be observed.[1] This study aims to contribute to our understanding of the unknown aspects of this electroclinic syndrome by evaluating the characteristics of patients with SeLECTS, who applied to our hospital.

METHODS

Ethical approval was obtained from the Ethics Committee of Dokuz Eylül University Faculty of Medicine on July 6, 2020, with the decision number 2020/15-38. Also, approval was obtained from the Chief Physician of the Faculty of Medicine Hospital to conduct research in the database of our hospital.

The cases diagnosed with "SeLECTS", who applied to the Pediatric Neurology Department of Dokuz Eylül University Faculty of Medicine between July 1, 2016, and July 1, 2020, were evaluated clinically, electroencephalographically, and psychometrically retrospectively. The cases were diagnosed according to the clinical and electroencephalographic manifestations published by the ILAE.[2] The files with incomplete medical records were excluded from the study.

Statistical Analysis

The gender of the patients, the province of residence, the age of onset of the seizure, the onset type of seizure, the duration of the seizure, the existence of any additional disease after a seizure, the presence of a family member diagnosed with epilepsy, a history of consanguinity parents, EEG results, the brain magnetic resonance images (MRI), treatment protocols, and the accompanying medical and psychiatric comorbidities were evaluated using the Statistical Package for the Social Sciences 26.0 statistics program after recording all data in a registration form. Informed parental consent was not required for this study

RESULTS

Ninety two cases with SeLECTS were included in the study. Forty-seven (51.1%) cases were boys and 45 (48.9%) of them were girls. The boy/girl ratio was found to be 1.04. The age of diagnosis of the cases ranged from 3 to 17 years. The clinical and demographic characteristics of our patients are given in Tables 1 and 2.

The various additional medical conditions were identified in 38 (41.3%) cases. Twenty-nine (31.5%) of these cases were followed up by the Child and Adolescent Psychiatry department due to psychiatric comorbidities such as anxiety, anxiety disorder, depression, and attention deficit. The medical conditions other than psychiatric comorbidity were non-specific and they did not influence the diagnosis and prognosis of RE. Ten of the cases had WISC-R assessments and only one of them had an IQ score of 70, which indicates poor performance. However, this case was responsive to medical treatment and had a good prognosis.

When the first seizure type of the patients was evaluated, it was identified that the seizures of the "generalized tonic-clonic" type were the most common with a 43.5% frequency

Table 1. Demographic features of our patients

Gender (n, %)	Male, 47 (51.1%)
	Female, 45 (48.9%)
The age of seizure onset (mean, years)	9.2 (±3.5)
Family history of epilepsy (n)	24 (26.1%)
Related parents (n)	16 (17.4%)

(Table 2). The duration of the first seizure was less than 5 min at 66.3% of the cases, and it was between 5-30 min at 29.4% of the cases and more than 30 min at 4.3%.

Neurological examination findings of all cases were normal. Transient non-specific neurological findings were detected in 11 (12%) cases during the neurological examinations performed after a seizure. One patient was intubated due of status epilepticus.

After the first EEG manifestations of the cases were examined, the normal manifestations were detected in 18.5% of cases, focal manifestations in 35.9% of cases, multifocal manifestations in 26.1% of cases, and generalized manifestations in 19.6% of cases. When the 2nd and 3rd EEG manifestations of the patients were assessed, it was identified that they returned to the baseline with 44.4% and 48.2%, respectively (Table 3).

Because of evaluating the brain imaging findings performed by MRI or computed tomography (CT), it was determined that non-specific findings were reported in 9.8% of the cases. After the brain imaging findings of MRI or CT were assessed, it was detected that non-specific findings were reported in 9.8% of cases.

Drug treatment was initiated in 92.4% (85 cases) of the cases. As the first treatment, levetiracetam treatment was mostly used one with a 46.8% frequency. Valproic acid treatment was the second choice as the first drug with a 30.4% frequency. Carbamazepine was preferred as the first drug in 9.8% and oxcarbazepine in 5.4% of the patients (carbamazepine was the first drug chosen in 9.8% of patients and oxcarbazepine in 5.4% of the patients) (Table 4). In 73 (85.5%) cases in whom treatment was initiated, the seizures either stopped completely or decreased more than 50%. Considering the success rates of the first-line drugs, it was identified that levetiracetam was 86% effective, valproic acid 79.3%, carbamazepine 100%, and oxcarbazepine 100%.

22.8% of cases who used second-line drugs respond well to the treatment. The third-line antiepileptic treatment was initiated in 8.7% of cases who did not benefit from second-line drugs, and all cases were quite responsive to the treatment except one (1.1%) case, in whom EEG manifestations converted to ESES.

Table 2. First seizure presentation of our patients

First seizure type	Patient number and percentage
Generalized tonic-clonic seizure (n)	40 (43.5%)
Focal orofacial motor seizures (n)	20 (21.8%)
Focal clonic seizure (n)	11 (12%)
Generalized tonic seizure (n)	9 (9.7%)
Generalized atonic seizure (n)	4 (4.2%)
Generalized clonic seizure (n)	3 (3.3%)
Focal tonic-clonic seizure (n)	3 (3.3%)
Generalized tonic-clonic seizure and focal clonic seizure (n)	1 (1.1%)
Focal clonic seizure and behavioral arrest (n)	1 (1.1%)
Total	92 (100%)

DISCUSSION

After reviewing the studies in the literature related to RE, it was identified that the cases were frequently diagnosed between the ages of 3 and 16 years. The peak age was detected between 7 and 9 years. Although there was no major difference between gender, the majority of the cases were boy patients in our study.[3-7]

In our study, 47 (51.1%) of all cases were boys and 45 (48.9%) were girl patients. The boy/girl ratio was found to be 1.04. The mean age of our patients was 9.2±3.5 years. The age of seizure onset ranged from 3 years to 18 years, and the mean age was 9.2±3.586 years. After the estimation of the age distribution, the median age was 9. Only one patient, who suffers from a seizure at the age of 17 and experienced only

Table 3. Seizure type according to the EEG

EEG order	Normal	Focal	Multifocal	Generalized	Total
First	17	33	24	18	82
Second	32	20	10	10	72
Third	28	12	6	12	58
Fourth	17	12	5	2	36

EEG: Electroencephalography

Table 4. The response rate of the first-line antiepileptic treatment

Drug	Levetiracetam	Valproic acid	Carbamazepine	Oxcarbazepine
Count of responsiveness	37/43	23/29	7/7	6/6
Percentage of responsiveness (%)	86%	79.3%	100%	100%

one seizure. The present findings are generally consistent with the literature.

The seizures with accompanying oropharyngeal symptoms occur in more than half of the cases and typically begin with sensory symptoms resembling numbness, tingling, pinning, and electrification in the unilateral tongue, lips, palate, inner part of the cheek, and pharyngolaryngeal region. This is followed by ipsilateral tonic deviation of the mouth, the clonic contractions at the edge of the mouth ranging from a few seconds to a minute, and the contractions may also spread to the ipsilateral arm and more rarely to the leg. As a rule, consciousness is preserved.[8] The generalized or focal atonic atypical seizures in RE could be observed.[9] Besides, the seizures could convert to generalized tonic-clonic seizures.[9] Seldomly, partial status epilepticus could be seen.[10-13]

After we evaluated the first seizure characteristics of 92 patients with RE, the generalized tonic clonic type was detected in 40 (43.5%) cases. The number of patients experiencing focal orofacial motor seizures was 20 (21.8%). In addition, the number of cases with focal clonic seizures was 11 (12.0%). The existence of different types of seizures in our patients was found to be compatible with the literature. Orofacial motor seizures characteristic of SeLECTS were not mostly defined as the first seizure type in our cases. We considered that the reason for this might be the lack of questioning and recording about the awareness of these types of seizures by the observers and child due to the retrospective nature of our study. Similarly, as stated above, notably focal motor seizures with orofacial involvement are not frequently reported in the literature.

The average seizure duration in SeLECTS is 2-3 minutes.[14] Rarely, it may even evolve into status epilepticus.[15] Sixty-one (66.3%) of 92 patients diagnosed with SeLECTS had a seizure fewer than 5 min. Twenty-seven patients had seizures between 5-30 min and 4 patients over 30 min. The current findings are consistent with the literature. The etiology of SeLECTS is often idiopathic. However, studies revealed that its complex genetic pattern may play a role in the etiology.[16] In families experiencing centrotemporal spike wave discharges, the related gene was found on chromosome 15q14.[17] In particular, there is a study showing that mutations in 15q14 lead to changes in potassium chlorine cotransport channels, and that the current picture increases neuron excitability.[18] The presence of dysarthria in patients diagnosed with SeLECTS may arise from a phenotypic feature associated with 11p, 15q, 16p12, and Xq22.[19] In our study, we identified that any genetic examinations were not carried out in our cases. This is due to the lack of a genetic panel or targeted testing recommended in the guidelines for SeLECTS. The copy-number variations mentioned above are expensive examinations that could only be used for scientific curiosit; therefore, these examinations are not routinely performed.

The genealogy of 92 cases included in the study was evaluated. Of 23 cases, only one individual had a family member diagnosed with epilepsy. However, no family history of epilepsy was detected in 68 cases. Also, the family histories of epilepsy in 92 cases were evaluated. There were two cases whose family members were diagnosed with an epileptic syndrome. Only one individual had a family member diagnosed with Rett syndrome. The other patient had a family history of unspecified epilepsy. Sixteen (17.4%) of 92 cases diagnosed with SeLECTS, the consanguinity was detected between the parents. However, there was no consanguinity in seventy-four cases.

Neurological examinations, neurological development, and cognitive functions of the patients are often normal except during the seizure periods.[20] Neuropsychological disorders can be detected in patients with SeLECTS. These may consist of linguistic problems often associated with reading and phonetics.[21] Since the origin of RE mainly derived from the lower part of the rolandic sulcus and affects the perisylvian region that supports the language networks, mild and temporary defects may emerge in all linguistic abilities such as auditory attention, oromotor skills, reading, and writing.[22] Seldomly, retardation in visual spatial abilities, neurocognitive impairment, and dyslexia could be observed.[23] Also, in some cases, drug side effects may influence the clinical picture.[24] The side effects of medical treatments include symptoms such as headache, abdominal pain, nausea, and sleep disturbance.[25]

Neurological examination after the first seizure was found to be normal in 81 (88%) of our patients. According to the medical records of the cases, the neurological symptoms during the neurological examination in the emergency department were identified in 11 (12%) cases. However, these symptoms were temporary, and none of the patients had permanent neurological symptoms. After the assessment of our patients in terms of comorbid diseases during the follow-up, it was identified that twenty-nine (31.5%) cases had accompanying mental health disorders. Nine cases experienced other comorbid disorders such as hyperlipidemia, urinary incontinence, hypothyroidism, allergy, asthma, permanent deformity due to fracture in the arm, abdominal pain, vitamin D deficiency, and headache, which were not associated with SeLECTS. One of 92 cases had a history of intubation due to clinical status (1.1%). Fever was detected in two cases (2.2%). Therefore, it was evaluated as a fever-triggered seizure. The current findings are consistent with the literature. Besides, neurological

examinations, neurological development, and cognitive functions were normal.

Patients diagnosed with SeLECTS may go into spontaneous remission without treatment.[26] Levetiracetam and carbamazepine treatment is accepted as primary treatment.[27,28] Lamotrigine was also effective for treating SeLECTS. However, levetiracetam is considered more advantageous since lamotrigine reaches the desired levels of therapeutic effect within 5-6 weeks.[29] Valproic acid may be taken into account in the presence of myoclonus, which is accompanied by generalized spike wave discharge.[19,20] Oxcarbazepine, sultiam, clonazepam, barbiturates, pyrimidone, clobazam, and phenytoin are other antiepileptic drugs effective for treating SeLECTS.[29,30] Besides, patients with epilepsy with SeLECTS wave discharge often benefit from treatment.

Anti-epileptic drugs initiated after the first seizure in 92 patients with SeLECTS who applied to our hospital were evaluated. Similar findings were identified in the literature. Levetiracetam treatment was initiated in 41 (44.6%) patients. Valproic acid treatment was used in 28 patients (30.4%). Other drugs consist of phenytoin, carbamazepine, oxcarbazepine, and diazepam. Four patients (4.3%) did not use any medication. Also, the duration of the first-line drugs of the patients was examined. Fourteen cases (15.2%) had continued current treatment for 2 years. Fifty-six patients maintained recommended treatment for less than 2 years and 22 patients for more than 2 years. 84.8% of 92 patients diagnosed with SeLECTS benefited from the treatment after the first seizure. There was a decrease in the frequency and duration of the seizures. Eleven (12%) cases did not benefit from the first-line medications. Although treatment was not initiated in three (3.3%) patients after the first seizure, the seizure recurrence was not observed in these patients.

Additionally, the second-line anti-epileptic drug use was examined in our cases. Sixty-eight patients (73.9%) did not require any second-line medications. Treatment was continued with valproic acid in 8 cases (8.7%), levetiracetam in 8 cases (8.7%), carbamazepine in 5 cases (5.4%), oxcarbazepine in 2 cases (2.2%), and clobazam in one case (1.1%). It was detected that 4 of the antiepileptic drugs (4.3%) were used for 2 years and 4 (4.3%) of them for 3 years. One drug had been continued for 7 years. Of these 24 cases, 21 (87.5%) benefited from the treatment. Thus, there was a decrease in the frequency and duration of the seizures. However, three (12.5%) cases did not benefit from the second-line treatments.

As similarly, third-line drugs were also examined. It was identified that eighty-four patients (91.3%) no longer require any medications. Also, eight cases benefited from the treatment. Consequently, the obtained results related to the prescribed antiepileptic drugs, their duration, and the treatment benefit rate were consistent with the literature.

EEG is an invaluable tool used to guide the clinical management of epilepsy diagnosis. It helps determine whether the attacks are of epileptic origin and allows the prediction of relapse risk after the first seizure. The classic EEG sign of SeLECTS is centrotemporal spike wave discharge. Occasionally, focal rhythmic slow EEG activity could be observed in the same area. This finding is not associated with a structural lesion. Therefore, it may be considered to be a symptom of SeLECTS.[31]

A stereotypic dipole waves may be observed in the centrotemporal region. The negative pole is in the centrotemporal region, and the positive pole extends to the bifrontal region. The origin of it is located in the lower rolandic region. Besides, a generalized spike wave and multifocal independent spike waves could be detected.[32] Although observed rarely, cases converted to ESES.

After the first EEG manifestations of 92 cases with RE were examined, the EEG manifestations of 17 cases were evaluated as normal. Centrotemporal spike waves were present in 75 patients. Considering the classification of ILAE published in 2017, the assessment was performed on whether the symptoms were focal, multifocal, or generalized.[2]

There were 33 cases (35.9%) with focal onset. The number of focal-onset cases decreased to 20 (21.7%) in the second EEG and to 12 (13%) in the third EEG. A focal centrotemporal spike wave was detected in 12 (13%) cases on the fourth EEG. There were 24 cases (26.1%) with multifocal onset in the first EEG. Multifocal onset was detected in 10 (10.9%) cases in the second EEG, 6 (6.5%) cases in the third EEG, and 5 (5.4%) cases in the fourth EEG. Eighteen cases (19.6%) have shown generalized EEG patterns. In addition, there were generalized EEG manifestations in 10 cases (10.9%) in the second EEG, 12 (13%) cases inthe third EEG, and 2 (2.2%) cases in the fourth EEG.

EEG tests were performed every 6 months according to routine follow-up procedures. EEG manifestations of our patients tended to return to the normal baseline over time. Even after the assessment of the fourth EEG, any change was observed in EEG manifestations in 20.6% of our cases. It was identified that both seizure activities and EEG manifestations of our patients tended to improve over time, and, they benefited significantly from the treatments.

Neuroimaging is necessary to rule out any structural, inflammatory, or metabolic causes of seizures. Typically, in patients with SeLECTS, no clear pathology that cause

seizures is detected in cranial imaging. In fractional anisotropy, a reduction was observed in the left inferior frontal region and supra-marginal gyrus. This finding is associated with poor performance in language tasks.[33] In patients with SeLECTS, thinning of the cortex could be detected, which is most clear in the left perisylvian region. However, this is not associated with language development.[34]

The imaging results for our cases. The first 83 imaging results were obtained through MRI. Normal manifestations were detected in 74 cases. The results of eight of the nine patients who underwent CT were reported as normal. All the results reported by CT or MRI were non-specific and inadequate to exclude the diagnosis of SeLECTS.[35]

Study Limitations

The most important limitation of our study is the sample size. Therefore, studies with larger samples are needed to better evaluate the SeLECTs.

CONCLUSION

The obtained results of our study, in which we evaluated our patients, including gender distribution, age, family history, seizure-related parameters such as the age of onset, duration, EEG characteristics, medications, and response rates, were observed to be mostly compatible with the literature. However, although SeLECTS is among the childhood epileptic syndrome with focal-onset seizures, the first seizure type in our study was mainly the generalized tonic-clonic type. This finding may be related to the overlooked initial symptoms of seizures in patients with SeLECTS. Therefore, this highlights the fact that SeLECTS should be taken into account in patients who applied for generalized tonic-clonic seizures. Additionally, in our study, we identified a high rate of psychiatric comorbid disorders (31.5%) in our patients, most of whom had a good prognosis in terms of seizures and EEG manifestations. Although psychiatric comorbidities mostly seem to be observed in cases that were referred to the CSWS clinic, we consider that our results are noteworthy in terms of emphasizing the necessity and importance of evaluating cases with a good prognosis, especially in terms of anxiety, anxiety disorder, depression, and attention problems.

Ethics

Ethics Committee Approval: The study was approved by the Dokuz Eylül University of Local Ethics Committee (date: 06.07.2020, decision no: 2020/15-38).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.S.U., S.H.K., Concept: M.B., S.H.K., Design: M.B., S.H.K., Data Collection or Processing: M.B., G.S.U., Analysis or Interpretation: M.B., G.S.U., S.H.K., Literature Search: M.B., G.S.U., S.H.K., Writing: M.B., G.S.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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