Generalized Tonic–Clonic Seizures after Self-Limited Epilepsy with Centrotemporal Spikes: A Case Series

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Purpose: Patients with self-limited epilepsy with centrotemporal spikes (SLECTS) rarely experience generalized tonic-clonic seizures (GTCS) after remission, and post-remission GTCS has not been thoroughly described in earlier studies. Herein, we describe the clinical and electrographic features of GTCS after a substantial period of seizure freedom in patients with SLECTS.

Methods: This study included six patients (three boys and three girls) diagnosed with SLECTS who later developed GTCS after or near remission. Medical records, including clinical data and serial electroencephalography (EEG) recordings, were retrospectively reviewed for all patients.

Results: Patients' age at SLECTS onset ranged from 5.2 to 10.2 years (mean, 8.4 years), while seizure cessation was achieved between 8 and 12.2 years. During SLECTS, typical centrotemporal spikes were observed in all patients, and generalized spike-and-wave discharges were observed in three patients. The age at the first episode of subsequent GTCS ranged from 14.4 to 17.3 years (mean, 15.8 years), constituting an average interval of 5.6 years after the last episode of seizures (range, 4.1 to 8.1 years). EEG at subsequent episodes of GTCS revealed generalized discharges in two patients, focal discharges in two other patients, and normal discharges in the remaining two patients. Two patients had multiple episodes of GTCS.

Conclusion: Although rare, GTCS may occur near or after remission in patients with SLECTS, and clinicians should be aware of this. Subsequent GTCS may be a manifestation of idiopathic generalized epilepsy. However, large-scale studies are needed to determine the nature of such episodes of GTCS and their associated risk factors.

Keywords: Epilepsy, rolandic; Seizures; Epilepsy, generalized

Introduction

Self-limited epilepsy with centrotemporal spikes (SLECTS) or benign childhood epilepsy with centrotemporal spikes is the most frequent type of self-limited focal epilepsy, accounting for 15% to 25% of syndromic pediatric epilepsy cases [1,2]. The age of onset ranges from 2 to 12 years, with a peak age between 7 and 9 years. Onset before 2 or after 12 years of age is unusual [3]. Seizures mostly present with focal hemifacial sensorimotor symptoms with brief durations and predominantly occur during sleep. Seizures...
may become focal to bilateral tonic-clonic seizures, which were formerly termed "secondary generalization." Characteristic electroencephalography (EEG) findings include normal background activity with stereotypical centrotemporal spikes. SLECTS shows an excellent prognosis, where patients usually enter remission within 1 to 3 years from onset, and most patients are free of seizures after the age of 15 to 16 years [4,5].

The occasional occurrence of generalized tonic-clonic seizures (GTCS) after SLECTS has been mentioned in the literature. The subsequent presentation of generalized seizures, such as absence seizures, and less often, GTCS, was reported to occur in 1% to 2% of patients with SLECTS. A few published studies have reported GTCS following SLECTS [5-7]. Loiseau et al. [8] described that SLECTS was associated with a 10-fold higher relative risk of GTCS than observed in the normal population. However, other authors consider subsequent GTCS to be an independent de novo event [9,10]. Nevertheless, to date, there is a lack of detailed descriptions of patients with subsequent GTCS after SLECTS. In addition, the pathophysiological mechanisms of such seizures have yet to be determined.

In accordance with the favorable prognosis of SLECTS, most patients with SLECTS present infrequent seizures, relatively short periods of disease, and a good response to antiseizure medication (ASM). However, we recently observed rare occurrences of GTCS in patients near or after SLECTS remission. Some experienced a single GTCS episode, as in most previous studies, whereas others experienced multiple seizure episodes, sometimes with generalized epileptiform discharges. Thus, we retrospectively reviewed the characteristics of six children who developed GTCS after SLECTS. This study aimed to inform clinicians that GTCS may occur in patients with SLECTS, albeit rarely. In addition, we intend to provide detailed descriptions of our experiences to improve the clinical understanding of subsequent GTCS.

Materials and Methods

Among patients from the pediatric neurology departments of Seoul National University Bundang Hospital and Seoul National University Children’s Hospital, six patients (three boys and three girls) from 1998 to 2021 were identified as having GTCS after SLECTS. A few published studies have reported GTCS following SLECTS [5-7]. Loiseau et al. [8] described that SLECTS was associated with a 10-fold higher relative risk of GTCS than observed in the normal population. However, other authors consider subsequent GTCS to be an independent de novo event [9,10]. Nevertheless, to date, there is a lack of detailed descriptions of patients with subsequent GTCS after SLECTS. In addition, the pathophysiological mechanisms of such seizures have yet to be determined.

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Results

Six SLECTS patients (three boys and three girls) developed GTCS at an average of 5.6 years after the last episode of seizures (range, 4.1 to 8.1 years). Detailed clinical descriptions of the patients are provided below.

1. Case reports

Patient 1 (female) developed focal motor seizures during sleep at 5.2 years of age. The semiology included unilateral upper extremity stiffening and clonic movements. Focal to bilateral tonic-clonic seizures were sometimes observed in later episodes. She had a history of simple febrile seizures at 3 years of age. The patient had no family history of febrile seizures or epilepsy. The patient achieved her developmental milestones. Physical and neurological examinations revealed no abnormalities. Her EEG revealed frequent high-voltage spike-and-wave discharges from C3–T3 and C4–T4, which were activated during sleep. Brain magnetic resonance imaging (MRI) revealed no remarkable findings. Upon diagnosis of SLECTS, carbamazepine was administered. She became seizure-free at the age of 9 years, and ASMs were discontinued at 14 years of age. Six months after withdrawal, the patient experienced daytime GTCS. At that time, her EEG revealed generalized bursts of spike-and-
wave discharges. She was diagnosed with possible idiopathic generalized epilepsy (IGE), for which valproic acid (VPA) was administered. She had three more episodes of daytime GTCS until she was 21 years old, and no further seizures were reported until the last follow-up conducted at 29 years of age.

Patient 2 (female) experienced GTCS 30 minutes after falling asleep at 7 years of age. The patient had a history of simple febrile seizures at 18 months of age. She had a positive family history of febrile seizures (maternal uncle) and epilepsy (father and paternal aunt; specific syndrome information was not available). The patient did not exhibit any neurodevelopmental problems. Physical and neurological examinations did not reveal any abnormalities. EEG revealed spikes or spike-wave discharges from C3 and C4. Brain MRI findings were normal. Oxcarbazepine (OXC) was administered, and she was seizure-free from the age of 8 years. OXC was withdrawn when she was 12 years old. At 16 years of age, she developed daytime GTCS while awake. Her EEG revealed frequent generalized spike- or polyspike-wave discharges. Suspecting IGE, levetiracetam (LEV) was administered. No further seizures were reported until the age of 17 years.

Patient 3 (male) developed focal motor seizures at the age of 9.8 years. He had a tonic deviation of the unilateral face during sleep, followed by focal to bilateral tonic-clonic seizures. His past and family histories were unremarkable, and his developmental profile was normal. The EEG findings were abnormal, with spike-wave discharges at C3-T3 and C4-T4, and the brain MRI findings were normal. After establishing the diagnosis of SLECTS, OXC was administered. The patient was seizure-free from the age of 10 years, and OXC was discontinued at 13 years of age. At 17 years of age, the patient developed daytime GTCS. The EEG findings were normal, VPA was prescribed to prevent GTCS. Two more episodes of GTCS occurred during treatment, and he was seizure-free at the last follow-up conducted at the age of 18 years.

Patient 4 (female) developed focal motor seizures while taking a nap at 10.2 years of age. The semiology included clonic movement of one side of her face, which propagated to the upper extremities. Idiomatic episodes occurred on several occasions, sometimes with focal to bilateral tonic-clonic seizures. She had a negative personal history and an unremarkable family history. The patient showed normal psychomotor development. EEG revealed high-voltage spikes or spike-and-wave discharges from C4-T4 during sleep, and brain MRI revealed no abnormal findings. After being diagnosed with SLECTS, OXC was administered. A year later, when she was 11 years old, she was seizure-free, but presented clinically with abrupt and clear impairment of consciousness and electronically with generalized 3-Hz spike-wave discharges. Centrocortical spikes persisted at this time. VPA was administered instead of OXC until electrographic and clinical normalization of both SLECTS and childhood absence epilepsy (CAE). During ASM tapering, the patient developed daytime GTCS. EEG revealed a few sharp wave discharges from F3 and F4. LEV was administered, and no further seizures were observed until the last follow-up conducted at 16 years of age.

Patient 5 (male) experienced a focal seizure at 8.11 years of age. He presented with focal motor seizures and tonic contraction of the right face during sleep. He experienced a simple febrile seizure at years of age and had an unremarkable family history. His neurodevelopment was normal, and the neurological examination results were unremarkable. EEG recordings showed spike-wave discharges from C3–T3, and brain MRI findings were normal. After being diagnosed with SLECTS, OXC was administered. The patient was seizure-free from 11 years of age, and OXC was withdrawn after normalization of EEG at 14 years of age. When the patient was 15 years old, he developed daytime GTCS. At the time of evaluation, the EEG findings were normal. VPA was administered, and no further seizures occurred until the last follow-up conducted at 17 years of age.

Patient 6 (male) developed GTCS during sleep at 8.9 years of age. His past medical history was unremarkable, and his family history was negative. The patient exhibited a normal developmental profile. EEG revealed high-voltage spike-wave discharges from C3–T3 and C4–T4, and brain MRI revealed no abnormal findings. The neurological examination results were normal. After being diagnosed with SLECTS, OXC was administered. He became seizure-free at 9 years of age. However, because of persistent centro-temporal spikes on EEG, ASMs were continued. When the patient was 14.4 years of age, he developed daytime GTCS. EEG revealed spikes or sharp wave discharges from Fp2–F8 or Fp1–F7. After replacing OXC with VPA, the patient remained seizure-free until the last follow-up conducted at 16 years of age.

2. Clinical characteristics

The general characteristics of the patients are summarized in Table 1. A history of febrile seizures was found in three patients, and a positive family history was observed in one patient. Patient 2 had a family history of febrile seizures and epilepsy within second- and third-degree relatives. All six patients' neurodevelopmental profiles were normal. The age of onset for SLECTS ranged from 5.2 to 10.2 years (mean, 8.4 years). The age at the first subsequent GTCS ranged from 14.4 to 17.3 years (mean, 15.8 years), occurring after remission of SLECTS in three patients and near remission in the other three. The mean interval between the last seizure in SLECTS and the onset of subsequent GTCS was 5.6 years, ranging from 4.1 to 8.1 years. The SLECTS seizure types included focal motor sei-
Table 1. General characteristics of the patients

| Case | Age (yr)/ Sex | Past Hx of febrile seizure | FHx of epilepsy/febrile seizure | Developmental delay | Age at onset (yr) | Seizure type | Brain MRI | Initial ASM | Last seizure (yr) | Interval (yr) | Age at onset (yr) | Brain MRI | ASM |
|------|---------------|----------------------------|---------------------------------|---------------------|------------------|-------------|-----------|-------------|------------------|-------------|------------------|-----------|-----|
| 1    | 29/F          | Yes                        | No/No                           | Normal              | 5.2              | FS+FBTC     | Normal    | CBZ         | 9.10             | 5.5          | 15.3             | Normal   | VPA |
| 2    | 22/F          | Yes                        | Yes/Yes                         | Normal              | 7.0              | GTCS        | Normal    | OXC         | 8.0              | 8.1          | 16.1             | NP        | LEV |
| 3    | 18/M          | No                         | No/No                           | Normal              | 9.8              | FS+FBTC     | Normal    | OXC         | 10.6             | 6.9          | 17.3             | Normal   | VPA |
| 4    | 16/F          | No                         | No/No                           | Normal              | 10.2             | FS+FBTC     | Normal    | OXC         | 12.2             | 4.1          | 16.3             | Normal   | LEV |
| 5    | 17/M          | Yes                        | No/No                           | Normal              | 8.11             | FS+FBTC     | Normal    | OXC         | 11.0             | 4.1          | 15.4             | Normal   | VPA |
| 6    | 16/M          | No                         | No/No                           | Normal              | 8.9              | GTCS        | Normal    | OXC         | 9.2              | 5.2          | 14.4             | NP        | VPA |

Hx, history; FHx, family history; SLECTS, self-limited epilepsy with centrotemporal spikes; GTCS, generalized tonic-clonic seizure; ASM, antiseizure medication; FS, focal seizure; FBTC, focal to bilateral tonic-clonic seizure; CBZ, carbamazepine; VPA, valproic acid; OXC, oxcarbazepine; NP, not performed; LEV, levetiracetam.

We described six patients with SLECTS who experienced GTCS after being seizure-free. These children had some common features. All six patients showed electrographically and clinically typical SLECTS at onset, such as sleep-related seizures in children with normal neurodevelopment, characteristic EEG recordings, and the absence of structural brain abnormalities.

Additionally, at the time of evaluation for subsequent GTCS, the patients showed changes in electrographic and clinical features from their previous SLECTS. Every episode occurred during the day, without a sleep association, and centrotemporal spikes no longer existed on EEG. All patients except one were off medications at the time of the first subsequent GTCS. SLECTS disappeared between 8 and 12 years of age in our patients, which is consistent with previous reports stating that the resolution of seizures is achieved by the age of 16 [3-5,12]. Three patients did not achieve complete remission by definition; however, they had subsequent GTCS close to the upper limit of the remission age.

The later occurrence of GTCS in our patients with SLECTS was unexpected, particularly in situations where the children were thought to be in a state of post-remission or near remission from SLECTS. However, we encountered a few patients with subsequent GTCS in recent years, although this has scarcely been reported in the literature. The presentation of GTCS after SLECTS was first reported in 1972 [13]. Blom et al. [13] performed a retrospective follow-up study of 40 patients aged > 15 years with a history of SLECTS. They described a girl who had one episode of GTCS at 16 years of age, 3 years after the discontinuation of ASMs. However, clinical data, such as age at the onset of SLECTS, seizure semiology, past medical history, and electrographic recordings, were not documented. Loiseau et al. [8] conducted a more extensive, long-term study, in which 168 patients with SLECTS were followed up for 7 to 30 years. While 165 of 168 patients showed complete remission, three experienced generalized seizures a few years after recovery from SLECTS [8]. A 34-year-old woman presented with one episode of GTCS 24 years after ASM withdrawal. Similar to our cases, an 18-year-old girl whose ASM was discontinued at 12 years of age experienced a single GTCS event. Another woman had two episodes of generalized seizures at 22 years of age, 10 years after ASM withdrawal. The authors concluded that concerning the incidence of GTCS in the community, the relative risk of such seizures is 10-fold after SLECTS, making them unlikely to
be distinct entities. More recently, 29 patients with SLECTS were prospectively followed up for 12 to 17 years in a Dutch study of childhood epilepsy [14]. In a Dutch cohort of children with SLECTS, three developed GTCS after having a seizure-free interval of at least 6 months during their 15 years of follow-up. Further details of these patients with subsequent GTCS have not yet been documented. Although rare, our findings on subsequent GTCS after SLECTS are supported by observations from earlier reports. Unfortunately, descriptions of subsequent GTCS are relatively brief, as most previous studies aimed to investigate the long-term outcomes of SLECTS. Moreover, such issues seem to be overlooked by physicians, probably because of their rarity and favorable prognosis. Thus, we attempted to provide more detailed descriptions of our patients' clinical and electrographic features and inform pediatric neurologists that although GTCS is rare, it can be observed after being seizure-free from SLECTS.

Whether subsequent GTCS is only an occasional seizure episode following SLECTS or a manifestation of different epilepsy syndromes has not been determined in previous studies. GTCS in four of our patients (patients 1–4) appeared to be related to IGE. Indeed, EEG recordings for subsequent GTCS revealed generalized epileptiform discharges in patients 1 and 2. Moreover, four consecutive GTCS episodes occurred in patient 1. Such repetitive generalized seizures, along with generalized spike-wave complexes on EEGs, indicate IGE. Patient 3 was also likely to have IGE due to multiple GTCS episodes, even though his EEG revealed no abnormal findings. Interestingly, patient 4 had concurrent absence seizures, which is a phenotype of IGE. CAE is associated with a much higher rate of later GTCS occurrence. In fact, it has been estimated that GTCS occurs in 36% to 60% of patients with CAE, usually 5 to 10 years from the onset [15,16]. Thus, GTCS in patient 4 appears to have evolved from CAE. Owing to the short follow-up duration after its onset, the nature of sequential GTCS in patients 5 and 6 remains to be determined. However, both of them had relatively long seizure-free intervals and showed different semiology from their previous seizures of SLECTS. In addition, they no longer showed centrotemporal spikes on EEG. These common features of GTCS in patients 5 and 6 may indicate they shared the same etiologies. Nevertheless, long-term follow-up is needed to evaluate further seizure episodes and serial EEG findings.

Other forms of epilepsy may coexist in patients with SLECTS. Cerminara et al. [17] described two patients with CAE who developed SLECTS after remission of seizures and normalization of EEG recordings. Despite recent interesting observations in animal models suggesting a pathophysiological relationship between SLECTS and CAE, the authors considered both forms of epilepsy to be distinct entities owing to their rarity. Verrotti et al. [18] recently reported 11 cases of SLECTS and CAE occurring in the same patient. Four out of 11 patients presented with SLECTS and CAE concurrently, while the remaining seven experienced the two syndromes at different times. The authors suggested the possibility of a pathophysiological relationship with a genetic predisposition.

Within a broader scope, cases of coexistent focal and generalized epilepsy have also been reported by several authors. Twelve cases of CAE in patients with localization-related epilepsy were reported by Sofue et al. [19] Among those with focal seizures, four had frontal lobe epilepsy, two had occipital lobe epilepsy, and one was diagnosed with temporal lobe epilepsy, while the types of seizures were undetermined in the remaining five patients. Jeha et al. [20] documented seven patients with focal and IGE. Four patients showed electrographically and clinically proven focal and generalized epilepsy, while the remaining three patients had only focal seizures recorded, but developed clinically suspicious generalized epilepsy. The authors emphasized the importance of detailed seizure descriptions since they first suspected more than one epilepsy syndrome due to the coexistence of auras preceding focal impaired awareness seizures, along with sudden-onset GTCS.

Other types of focal epilepsy may follow the remission of SLECTS. Guerrini et al. [21] reported two cases of idiopathic photosensitive occipital epilepsy in patients who recovered from SLECTS. These cases suggest that two different epilepsy syndromes can appear in the same patient. However, the pathophysiology...
ology of this co-occurrence has not yet been elucidated. This seems more likely to be a distinct form of epilepsy that occurs independently, although more cases with detailed clinical information are necessary for further investigations.

Among the various electrographic and clinical features of our cases, we observed generalized epileptiform discharges in three patients with SLECTS. Similar findings were described in a previous study, in which 11 out of 12 patients with localization-related epilepsy showed generalized spike-waves prior to a later onset of CAE [19]. These generalized epileptiform discharges in focal epilepsy syndrome may predispose patients to the transition to GTCS. However, generalized spike-wave complexes are sometimes found in children with SLECTS and other focal epilepsies such as childhood epilepsy with occipital paroxysms [6,10,22]. Thus, there is insufficient support to assume that the presentation of generalized discharges before the occurrence of GTCS is a predictive factor.

In our patients, generalized epileptiform discharges, focal abnormalities, and normal findings were revealed on EEG at the time of subsequent GTCS evaluation. However, none of the patients showed 3 to 6 Hz spike- and polyspike-wave discharges on interictal EEG, a characteristic feature of juvenile myoclonic epilepsy. Although focal epileptiform discharges were observed in two of our patients, the semiologic features were primary generalized seizures without evidence of focal seizure onset. In fact, the existence of focal EEG abnormalities is common in IGE and has been found to be observed in about one-third of patients with IGE in previous studies [23]. Therefore, those patients with focal interictal EEG features can still be associated with IGE. In the aforementioned study by Loiseau et al. [8], EEG recordings upon GTCS were only noted in two out of three patients with GTCS after SLECTS. One patient with subsequent GTCS at the age of 34 years showed EEG without paroxysms, whereas the other 22-year-old patient had diffuse, erratic sharp waves on EEG. A large amount of EEG data must be collected to detect significant common electrographic features.

In this study, we sought to describe patients’ clinical and electrographic findings in detail, which were lacking in previous research. Such descriptions are essential to identify the cause of sequential GTCS for precise evaluation, diagnosis, and treatment. We have also thoroughly reviewed the previous literature to corroborate our findings. However, some limitations of this study should be mentioned. Due to the descriptive nature of the case series, risk factors and possible pathophysiologic mechanisms were not analyzed. Another limitation is that although the diagnosis of SLECTS and IGE in our patients was based on their electrographic and clinical characteristics, the findings of generalized EEG abnormalities in SLECTS and focal EEG features in IGE should be interpreted cautiously. Generalized spike-and-wave discharges are sometimes observed in patients with localization-related epilepsy and, likewise, focal discharges may be present in patients with generalized epilepsy. Therefore, serial EEG results and characteristic clinical manifestations should be considered upon diagnosis. In addition, our study included a small number of patients, who may not be representative of a larger group of patients. Further studies with a larger number of patients and longer follow-up duration would greatly improve our understanding of subsequent GTCS and help discover the associated risk factors.

In conclusion, although complete remission of SLECTS has been taken for granted for many years, we observed the subsequent occurrence of GTCS after seizure-free intervals of several years. Although not yet clarified, this form of GTCS may be a manifestation of a different epileptic syndrome, such as IGE. Lastly, pediatric neurologists who treat patients with SLECTS should be aware of the possibility of GTCS occurrence, even after several years of freedom from seizures.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contribution

Conceptualization: HJK, YJK, SYK, AC, HK, BCL, HH, JHC, JC, and KJK. Data curation: HJK, YJK, SYK, AC, HK, BCL, HH, JHC, JC, and KJK. Formal analysis: HJK, YJK, AC, and HK. Methodology: HJK, YJK, AC, and HK. Project administration: HJK. Visualization: HJK. Writing-original draft: HJK. Writing-review & editing: HJK and HK.

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