Clinical characteristics and prognosis according to focality of epilepsy patients reporting generalized tonic-clonic seizures alone

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ABSTRACT

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Distinguishing focal epilepsy from idiopathic generalized epilepsy in patients reporting only generalized tonic-clonic seizures (GTCS) is important but not easy in the outpatient setting. We attempted to clarify the clinical characteristics of patients with clinically GTCS alone without focal semiological features according to magnetic resonance imaging (MRI) and electroencephalography (EEG) abnormalities. Patients (n = 139) were classified into three groups: A (n = 55, generalized interictal epileptiform discharges), B (n = 73, unremarkable EEG and MRI), and C (n = 11, focal epileptiform discharges or slowing on EEG or abnormal MRI findings). The onset age of group A was significantly earlier than that of groups B and C ($P = 0.02$). A higher proportion of females was also documented in group A than in groups B and C ($P = 0.008$). Favorable treatment responses were noted in all groups. Despite the limitations of a small sample size and evaluation at the outpatient clinic, this study suggested that patients with GTCS alone had either focal or generalized origin, as expected. The age at onset, in addition to EEG and MRI findings, may be helpful in the differential diagnosis between focal and generalized origins. However, if strict EEG criteria in generalized epilepsy are considered, epilepsy classification may not be possible in the majority of patients with GTCS alone (73/139, 52.5%). Approximately half of the patients may have primary GTCS according to only a semiological basis, or some of these patients may have focal to bilateral tonic-clonic seizures.

Key words: generalized tonic-clonic seizure, idiopathic generalized epilepsy, semiology, focality, electroencephalography

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I. INTRODUCTION

It is important to distinguish between idiopathic generalized epilepsy (IGE) and focal epilepsy in patients with no focal neurological deficits and normal intelligence, as this affects treatment choices, investigation, prognosis and counseling. It is easy to diagnose childhood or juvenile absence epilepsy (CAE or JAE), or juvenile myoclonic epilepsy (JME) in IGE types because of the characteristic seizure types of absence or myoclonus. In clinical practice, generalized tonic-clonic seizures (GTCS) alone is difficult to classify. GTCS alone may be idiopathic (primarily) or secondarily. The absence of focal semiological features, normal brain magnetic resonance imaging (MRI) findings, and presence of generalized epileptiform discharges on electroencephalography (EEG) are highly suggestive of IGE. However, normal EEG findings may not exclude the diagnosis of IGE in patients with clinically GTCS alone.[1-3] As a rule, the older the patient, the less likely that the seizure is truly of generalized origin, and for practical purposes new-onset seizures in patients older than 30 years of age may be considered to be focal unless proven otherwise. This study aimed to clarify the clinical characteristics of patients with GTCS alone without focal semiological features.

II. MATERIALS AND METHODS

We investigated 3,606 consecutive patients who visited the epilepsy clinic of Severance Hospital by a physician between January 2000 and December 2019 (Yonsei Epilepsy Registry). Patients who had at least two or more GTCS alone without focal semiological features documented, by the outpatient evaluation, were included. Patients who had at least two or more GTCS alone without focal semiological features documented, by the outpatient evaluation, were included. Patients were excluded if they had the following conditions: insufficient information about seizure semiology, including GTCS alone during sleep; provoked seizures; significant etiological histories (moderate to severe head trauma, stroke, central nervous system infection) except for a family history of epilepsy and febrile seizures; and neurological deficits including mental retardation. Also, patients were excluded if they experienced seizures with focal semiological features, absence seizures, or myoclonic seizures during follow-up. Patients with follow-up longer than a year were included, and 1-year seizure freedom was demonstrated only in patients with follow-up longer than 2 years.

Clinical information concerning sex, age at seizure onset, total seizure numbers, follow-up years, family history of epilepsy, febrile seizure history, and presence or absence of seizure in outpatient visit was collected. All patients underwent scalp EEG recording and epilepsy-dedicated MRI. Routine scalp EEG recording using the international 10/20 system included sleep deprivation, photic stimulation, and hyperventilation as provocations. EEG or MRI data acquired during the follow-up as well as at the initial evaluation were analyzed. All included patients were classified into three groups according to EEG and MRI findings: group A with generalized interictal epileptiform discharges (IEDs), group B with unremarkable EEG and MRI findings, and group C with consistent focal IEDs or slowing on EEG or abnormal MRI findings. This study was approved by the institutional review board of Severance Hospital.

III. RESULTS

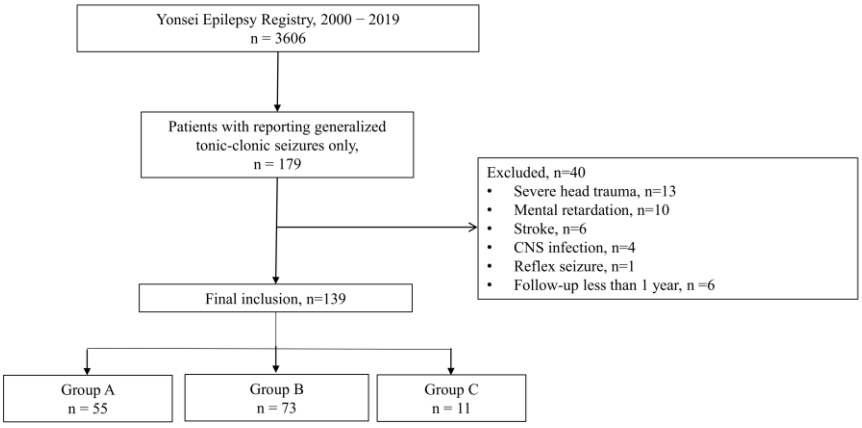

Figure 1. Flow chart depicting epilepsy patients in this study

In a total of 3,606 epilepsy patients, 139 patients were finally enrolled, and classified into 55 patients (39.6%) in groups A, 73 patients (52.5%) in group B, and 11 patients (7.9%) in group C (Figure 1). In the Yonsei Epilepsy Registry during the study period, there were 34 patients with CAE, 62 patients with JAE, and 195 patients with JME. Also, there were 123 secondarily GTCS alone preceded by focal semiological features patients without significant etiological histories or neurologic deficits.

The clinical profiles of each group are presented in Table 1. The proportion of females was higher in group A (60.0%) than in groups B (32.9%) and C (36.4%) ($P = 0.008$). The age of seizure onset was lower in group A (16.3 ± 5.1 years) than in groups B (20.5 ± 12.5 years) and C (23.3 ± 9.7 years) ($P = 0.023$). The number of EEGs (median, range) was higher in group A than in groups B and C ($P < 0.001$). The number of antiepileptic drugs used (AEDs) (median, range) was lower in group B (1, 1–4) than in groups A (2, 1–5) and C (2, 1–6) ($P = 0.011$). No difference was noted in the total number of seizures, family history of epilepsy, history of febrile seizures, follow-up years, number of MRIs, and 1-year seizure freedom.

Table 1. Demographic and clinical characteristics of patients according to each group

	Total (n=139)	**Group A (n=55)**	**Group B (n=73)**	**Group C (n=11)**	***P***
Sex, female n, (%)	62 (43.9)	33 (60.0)	24 (32.9%)	4 (36.4)	0.008
Age at seizure onset, mean (range)	19.1 (5-68)	16.3 (6-30)	20.5 (5-68)	23.3 (13-43)	0.02
Seizure onset ≥30 years, n, (%)	15 (10.8)	1 (1.8)	11 (15.1)	3 (27.3)	0.01
Total seizure numbers, median (range)	8.8 (10.2)	9.6 (9.7)	7.7 (8.4)	12.6 (19.7)	0.26
Follow up years, mean (range)	7.4 (1-19)	7.5 (1-18)	7.0 (1-18)	9.6 (2-19)	0.34
Family history, n, (%)	17 (12.2)	6 (10.9)	8 (11.0)	3 (12.2)	0.28
Febrile seizure, n, (%)	13 (9.4)	7 (12.7)	5 (6.8)	1 (9.1)	0.53
Number of MRIs, median (range)	1 (1-4)	1 (1-2)	1 (1-1)	1 (1-2)	0.28
Number of EEGs, median (range)	2 (1-9)	4 (1-9)	2 (1-5)	2 (1-6)	<0.001
Number of AEDs, median (range)	1 (1-6)	2 (1-5)	1 (1-4)	2 (1-6)	0.01
1-year seizure freedom/ follow-up more than 2 years, (%)	127/129 (98.4)	48/48 (100)	69/70 (98.6)	10/11 (90.9)	0.16

SD, standard deviation; MRI, magnetic resonance imaging; EEG, electroencephalography; AED, antiepileptic drug

In group C, focal abnormalities were in MRI (6/11, 54.5%) and EEG (6/11, 54.5%). MRI abnormalities were calcified granuloma (3/6, 50.0%), cavernous malformation (1/6, 16.7%), encephalomalacia (1/6, 16.7%), and subependymal heterotopia (1/6, 16.7%). Lesions were in frontal (2/6, 33.3%), temporal (2/6, 33.0%), parietal (1/6, 16.7%), and subependymal (1/6, 16.7%). All EEG findings had epileptiform discharges and one was accompanied by focal slowing. Epileptiform discharges were frequently localized in frontal (4/6, 66.7%) than in temporal (1/6, 16.7%) and hemispheric (16.7%) (Table 2).

Table 2. MRI and EEG findings in group C

MRI, n (%)			
Localization		Abnormalities	
Frontal	2/6 (33.3)	Calcified granuloma	3/6 (50.0)
Temporal	2/6 (33.3)	Cavernous malformation	1/6 (16.7)
Parietal	1/6 (16.7)	Encephalomalacia	1/6 (16.7)
Subependymal	1/6 (16.7)	Subependymal heterotopia	1/6 (16.7)
EEG, n (%)			
Localization		Abnormalities	
Frontal	4/6 (66.7)	Focal IEDs	5/6 (83.3)
Temporal	1/6 (16.7)	Focal IEDs & focal slowing	1/6 (16.7)
Hemispheric	1/6 (16.7)		

MRI, magnetic resonance imaging; EEG, electroencephalography; IED, interictal epileptiform discharge

IV. DISCUSSION

This study suggests that epilepsy classification in a half of patients with GTCS alone without focal semiological features (group B in this study) exist in the “gray zone” between definite IGE and focal epilepsy. EEG performed in the earlier period after seizure attack or in sleep deprivation may be helpful in showing epileptiform discharges.[4,5] However, even repeated EEGs may not be useful in patients with IGE with GTCS alone.[1] Functional neuroimaging and highly advance MRI techniques may be helpful in showing some focal abnormalities but are never practical. The age at onset seems to be very useful in differentiating between idiopathic and secondarily GTCS if MRI and EEG do not provide information. However, there have been previous studies about adult-onset IGE including GTCS.[1-3,6-11] Adult-onset IGE (at the age of 18 or 20 years or later) comprised 8.5%–28.1% of IGE.[1,2,6,8] IGE has been reported to occur after 30 years of age in only 1.2%–5.7% of all patients with IGE.[2,3]

As a rule, the older the patient, the less likely that the seizure is truly of generalized origin, and for practical purposes new-onset seizures in patients older than 30 years of age considered to be focal unless proven otherwise.

According to the types of IGE, GTCS alone accounted for a greater proportion of adult-onset IGE compared with childhood- and adolescent-onset IGE.[2,3,7,8] In previous IGE prevalence studies, the prevalence of GTCS alone is known to be slightly more than half that of JME in adult epilepsy patients.[12,13] The Yonsei Epilepsy Registry, which included the patients in this study, had JME in 192 patients and 139 patients reporting GTCS alone during the same period, comparable to the previous studies. In addition, since previous studies included IGE patients for whom generalized IEDs were not identified, it is thought that prevalence is likely to be lower according to the strict criteria that include generalized IEDs.

In a recent study, GTCS alone occurred in two patients with very late onset age (61 and 80 years) in whom generalized IEDs were identified.[9] In this study, using strict IGE criteria, group A had significantly earlier onset compared with group C (focal epilepsy), and only one patient in group A was more than 30 years of age at onset. The higher proportion of females in group A than in groups B and C in this study is also thought to be related to the epidemiological characteristic that a higher proportion of female patients have IGE than focal epilepsy.[14]

Therefore, the results of this study and previous studies suggest that new-onset seizures including GTCS alone in patients older than 30 years of age considered to be focal epilepsy. However, the IGE type of GTCS alone may occur in a nonnegligible number of patients after the age of 30 years.[6-8] Some proportion of our patients in the “gray zone” (group B) may have IGE. In addition, unless strict EEG criteria are used, patients with secondarily GTCS alone may be erroneously regarded as having primarily GTCS. On the other hand, clinically GTCS alone by a thorough interview on an outpatient basis may exclude clear focal epilepsy in most cases, considering a small portion (7.9%) of clear focal epilepsy (group C).

This study has major limitations. The accuracy of seizure semiology, which

was related to the outpatient evaluation,[15] small number of seizures, and strong dependence on witnesses, could be insufficient. In addition, some patients with focal semiological features but IGE may have been excluded in this study.[16,17] EEGs were not repeated in 27.4% (20/73) of patients in group B, probably due to favorable seizure control, although repeated EEGs are necessary for appropriate classification. In this study, 7.9% (group C) of patients with GTCS alone had clear focal epilepsy considering focal EEG and MRI findings. They were more likely to have frontal lobe epilepsy, as expected.[18]

In this study, seizure outcomes with AED treatment were similar among the groups and excellent, suggesting good prognosis in patients with clinically GTCS alone. Previous studies of IGE prognosis demonstrated distinctly favorable outcome compared to focal epilepsy.[19] Thus, GTCS alone is comparable with IGE in terms of prognosis. This study suggests that GTCS alone without focal semiological features may show excellent AED responsiveness regardless of primarily or secondarily GTCS.

V. CONCLUSION

This study suggests that half of the patients with GTCS alone without focal semiological features were regarded as having IGE or focal epilepsy. The classification for patients in the “gray zone”, corresponding to half of the patients with GTCS alone in this study, still needs a solution although focal and generalized seizures did not represent a clear dichotomy. The distinction between IGE and focal epilepsy in patients with GTCS alone may not be important in terms of the prognosis.

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전신 강직 간대 발작만 호소하는 뇌전증 환자들의 국소성 유무에 따른 임상적 특성과 예후

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김경민

전신 강직 간대 발작(GTCS, generalized tonic-clonic seizures)만 보고하는 뇌전증 환자에서 국소 뇌전증과 특발성 전신 뇌전증을 구분하는 것은 중요하지만 실제 임상에서는 쉽지 않다. 본 연구에서는 국소 발작 증상이 없고 전신 강직 간대 발작만 있는 환자들을 뇌자기공명영상검사 및 뇌파검사의 이상에 따라 구분하여, 임상적 특징을 살펴보고자 하였다. 전체 139명의 환자는 A군(55명, 뇌파검사상 전반적인 뇌전증 모양파가 확인된 환자), B군(73명, 뇌파검사와 뇌자기공명영상검사가 정상인 환자), C군(11명, 뇌파검사상 국소적인 뇌전증 모양파 혹은 비정상적인 뇌자기공명영상검사 소견을 가진 환자)으로 분류되었다. A군의 발병연령은 B군과 C군과 비교할 때 빨랐고, A군에서 여성의 비율이 더 높은 것으로 나타났다. 본 연구에서는 전신 강직 간대 발작만 보고하는 환자들이 국소적이거나 전반적인 특성을 모두 가질 수 있음을 확인했고, 뇌파와 뇌자기공명영상 소견과 더불어 발병 연령이 국소성, 전신성 뇌전증을 감별 진단하는데 도움이 될 수 있음을 확인하였다. 절반(73/139, 52.5%)의 환자들이 국소 뇌전증과 전신 뇌전증으로 명확하게 구분되지 않아, 앞으로 이에 대한 연구가 필요하다.

핵심되는 말 : 전신 강직 간대 발작, 특발성 전신 뇌전증, 국소성, 뇌파, 발작증세