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Original Research Article

A prospective observational study on understanding of idiopathic generalized epilepsies namely juvenile myoclonic epilepsy and epilepsy with generalized tonic-clonic seizure alone by electroencephalogram with updated terminology in a tertiary care hospital

Kazi Jannat Ara[1]*, Abu Nasir Rizvi[1], Kanuj Kumar Barman[1], Khair M. Sobhan[2]

[1]Department of Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[2]Department of Medicine, Dhaka Dental College, Dhaka, Bangladesh

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***Correspondence:**
Kazi Jannat Ara,
E-mail: rimmineuro@gmail.com

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ABSTRACT

Background: In 2017, the international league against epilepsy (ILAE) classification of epilepsies described the "genetic generalized epilepsies", which contained the "idiopathic generalized epilepsies". This study delineates the four syndromes comprising the IGEs: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic-clonic seizures alone (GTCA). JME patients usually present with myoclonic seizures, and GTCA patients present with GTCS only after awakening from sleep. Aim of the study was to identify the differences between juvenile myoclonic epilepsy and epilepsy with generalized tonic-clonic seizures alone by semiology and EEG with updated terminology under the observation of the clinicians.
Methods: This was a prospective observational study and was conducted in the epilepsy clinic, department of neurology, Bangabandhu Sheikh Mujib medical university, from February 2021 to July 2022. The sample size was 60.
Results: Among 60 patients, family history was present in 12 (20%) and 6 (10%) JME and GTCA patients, respectively. In this study, the EEG finding of generalized spike-wave (2.5-5.5 Hz) was seen in 26 (43%) and 19 (32%) among JME and GTCA patients, respectively. Generalized Polyspike wave (2.5-5.5 Hz) was seen in 26 (43%) JME patients, and EEG was normal in 15 out of 60 patients of epilepsy. In EEG findings, 2.5-5.5 Hz generalized spike-wave should be diagnosed in JME and GTCA patients as a special group of IGEs.
Conclusions: In this study, we have recognized and differentiated between juvenile myoclonic epilepsy and generalized tonic-clonic seizures alone by semiology and EEG in IGE syndromes as a special grouping among the IGEs is helpful as they carry prognostic and therapeutic implications.

Keywords: Epilepsy with generalized tonic-clonic seizures alone, Juvenile myoclonic epilepsy, Myoclonic

INTRODUCTION

Epilepsy is a disease of the brain defined by any of the following conditions: at least two unprovoked (or reflex) seizures that occur more than 24 hours apart; one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years; diagnosis of an epilepsy syndrome. An epileptic seizure is a transient occurrence of signs and symptoms due to abnormal excessive or synchronous neuronal activity in the brain. According to the world

health organization (WHO), 50 million people throughout the world have epilepsy. At the same time, the centers for disease control and prevention estimate that approximately 4 billion people (50% of the global population) live in Asia, of whom about 23 million have epilepsy. Historically, idiopathic generalized epilepsies (IGEs) included four syndromes childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic–clonic seizures alone (GTCA). In 2017 international league against epilepsy (ILAE) classification suggested that the term "genetic generalized epilepsies" (GGEs) be used for the broad group of epilepsies with generalized seizure types and generalized spike-wave based on a presumed genetic etiology arising from twin and family research study data.[1] IGE is a common group of epilepsies, accounting for approximately 15%-20% of persons with epilepsy.[2] Population-based studies of new onset epilepsy in children and adolescents have found that 23%-43% have generalized epilepsy, and of these, 53%–58% have one of the four IGE syndromes.[3-5] Juvenile myoclonic epilepsy is a typical, well-defined, age-related epileptic syndrome with a prevalence of 4-11% of all epilepsies and an incidence of 0.4 -0.9%.[6-8] JME has been classified as an idiopathic generalized epilepsy in the classification proposed by the ILAE.[9] JME is common, with a prevalence ranging from one to three per 10 000 persons in population-based studies.[10,11] It accounts for approximately 9.3% of all epilepsies.[12] The typical age at onset is 10–24 years (range = 8-40 years). There is a slight female preponderance. Five to 15% of cases evolve from CAE to JME.[13,14] GTCA syndrome (originally called epilepsy with grand mal seizures on awakening) is a common IGE syndrome. Epidemiological data are limited, although, in one study, GTCA accounted for one-third of all adolescent onset IGEs. The typical age at onset is 10-25 years (80% have their first tonic-clonic seizure in the second decade), ranging from 5-40 years.[15,16] In this study, we provided updated diagnostic criteria for Juvenile myoclonic epilepsy (JME) and epilepsy with generalized tonic-clonic seizures alone. The aim of the study was to identify the differences between JME and GTCA by semiology and EEG with updated terminology under the observation of the clinicians.

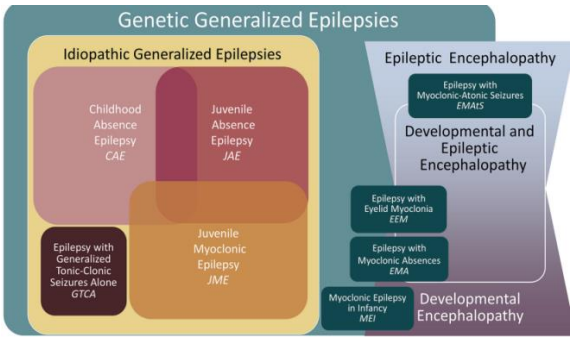

Figure 1: Concept of genetic generalized epilepsy versus idiopathic generalized epilepsy.[1]

The concept of genetic generalized epilepsy versus idiopathic generalized epilepsy is shown in (Figure 1) in which it is found that idiopathic generalized epilepsies (IGEs) are a subgroup of genetic generalized epilepsies (GGEs), comprised of the following four syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures alone. These four syndromes may show some degree of overlap. In addition to the IGEs, GGEs include; individuals with generalized seizure types who do not meet the criteria for a specific syndrome and less common generalized epilepsy syndromes. These latter syndromes also have a genetic basis and may occur in the setting of normal intellect or intellectual disability. Some present with epileptic encephalopathy, such as epilepsy with myoclonic, atonic seizures, whereas other syndromes, such as epilepsy with myoclonic absences and epilepsy with eyelid myoclonia, may be associated with a developmental and epileptic encephalopathy, an epileptic encephalopathy, or a developmental encephalopathy. The features that can be seen in JME and GTCA in general is shown in (Table 1). It shows that the usual age onset for JME is 10-24 years, whereas for GTCA is 10-25 years. The seizure type of JME is myoclonic seizures, and on the other hand, GTCA has generalized tonic-clonic seizures as the main type of seizure. In JME, febrile seizures may occur approximately 4% to 5%, whereas in GTCA, they may occur about 15% of patients. Generalized 3-5.5 Hz spike-wave and polyspike-wave can be seen in all states in JME but only in sleep in GTCA.

Objectives

Objectives of current study were to identify the differences between JME and epilepsy with GTCA by semiology and EEG with updated terminology under the observation of the clinicians.

METHODS

This prospective observational study was conducted in the epilepsy clinic, department of neurology of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from February 2021 to July 2022. The sample size was 60. Among these 60 patients with IGEs, 35 were JME patients, and 25 were GTCA patients. Generally, the age onset for IGE patients ranges from 3-25, but they can be occurred up to as late as 40 years. The typical age of onset of JME patients is 10-24 years (range=8-40 years), and for Epilepsy with GTCA age of onset is 10-25 years (range=5-40 years). This study provided updated diagnostic criteria of JME and epilepsy with GTCA at their adult age of presentation in the clinic. We included only the patients with JME and Epilepsy with GTCA aged over 18. The patients should be evaluated by diagnostic seizure type, a CT scan of the brain and MRI of the brain with epilepsy protocol with normal imaging findings should be done from the radiology department of BSMMU and outside of

BSMMU. Mandatory diagnostic interictal long duration routine EEG (3 hours) showing generalized spike-wave and Polyspike wave at 2.5-5.5 Hz and morphology were available for view for differentiating between JME and GTCA patients. In this study, those patients with: clinical evidence of myoclonic jerks secondary to hypoxia and metabolic disease, other structural brain abnormalities, EEG abnormalities but no clinical evidence of any type of seizures and family history of progressive myoclonic epilepsy were excluded. Statistical comparison was performed by using the student t-test for the frequency and x2 or Fisher's exact tests for the other categoric variables (significance, $p<0.05$). Statistical analysis was conducted using IBM Statistical Package for Social Sciences version 25 (SPSS version 25.0) for windows 10.

EEG recordings

EEG was done with long-duration routine interictal EEG (3 hours) in the neurology department of BSMMU. Interictal EEG was done after evaluation of seizure type in both cases of JME and epilepsy with GTCA patients in the Epilepsy clinic. EEG was done with sleep deprivation. We used 21-channel digital recording with common average reference, average reference, bipolar longitudinal and transverse montages, and standard 10-20 electrode placement. Recordings lasted for 3 hours for both resting awake and sleep states, including hyperventilation and intermittent photic stimulation at 1-20 Hz with an eye open and eye closed at each frequency. Sleep-deprived recordings lasted for 30 minutes at the onset of EEG. Intermittent photic stimulation and hyperventilation were done before awake from sleep in the last 30 minutes of EEG.

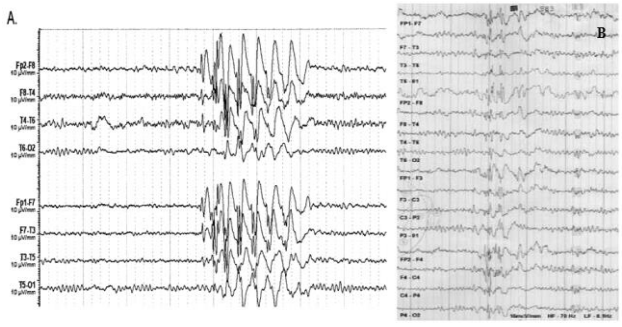

Figure 2: Example of diagnostic EEGs of a JME patient; A) a patient with JME, age 18 years, showing characteristic generalized poly spike-wave and B) a patient with JME, age 24 years, showing characteristic generalized poly spike-wave patterns on a normal awake background.

Evaluation of EEG

Following confirmation of the kind of diagnostic seizure, EEGs from both types of epileptic individuals were analyzed. The posterior dominant rhythm, symmetry, amplitude, and frequency of the background rhythm were evaluated. This study examined the background rhythm, symmetry, regularity, amplitude, generalized spike-wave complex, and generalized polyspike wave complex with duration and frequency. A photoparoxysmal response to intermittent photic stimulation is present in more than one-third of patients. Interictal irregular, generalized polyspike-wave, and spike-wave at a frequency of 3-5.5 Hz are required to diagnose JME. For diagnosis, an ictal recording is not necessary. Interictal GTCA must be diagnosed with a generalized spike-wave or polyspike-wave at 3-5.5 Hz. The diagnosis requires a generalized spike-wave or polyspike-wave at 3-5.5 Hz.

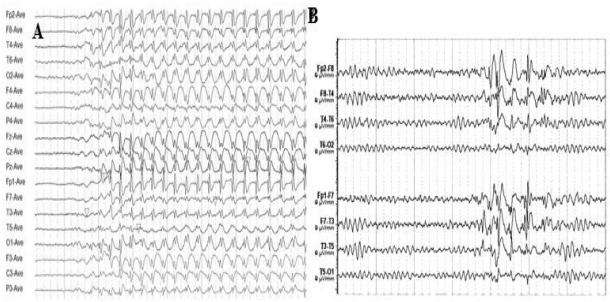

Figure 3: A diagnostic EEG of a patient with GTCA; A) An interictal electroencephalogram (EEG) of a young man aged 21 years old with epilepsy with GTCA, showing his generalized spike wave on awakening from sleep, B) a patient with GTCA, age 25 years, showing characteristic generalized spike-wave patterns on a normal awake background.

RESULTS

In our study, we showed the age distribution of the study people in where least people 3 & 3 were aged between 61-70 years, 5 & 3 were between 51-60 years, 5 & 7 were 41-50 years, 7 & 9 were 31-40 years, and 11 & 7 were 18-30 years among JME and GTCA patients respectively. In this study, among the study people, most of the respondents, 35 (58%), were female, and 25 (42%) were male (Figure 4). In this study, we showed the diagnostic criteria of JME which is one of the syndromes of idiopathic generalized epilepsy (Figure 5). The criteria that can be used to diagnose JME are seizures and EEG findings. The mandatory seizures that have to be present in JME is myoclonic seizures, and as an exclusion, myoclonic absence, tonic, atonic, and typical absence seizures can also be seen. In EEG findings, we can see a 3-5.5 generalized poly spike wave as a case of JME, and an exclusionary, generalized slow spike-wave at a frequency can be seen less than 2.5 HZ (Table 2). Here, the study shows the criteria to diagnose epilepsy with generalized tonic-clonic seizures alone. The criteria that have been used are seizures and EEG. As a mandatory seizure type, generalized tonic-clonic seizures must be seen in patients, and as an exclusion, any other seizure type may also be seen. On EEG findings, generalized spike-wave or polyspike wave can be found as 3-5.5 Hz, and on the other hand, exclusionary polyspike wave can

be found less than 2.5 Hz same as JME (Table 3). In our study myoclonic, absence+myoclonic, and myoclonic+GTCS seizure was seen in 19 (54%), 9 (26%) & 7 (20%), respectively, among JME patients, on the other hand, GTCS was seen in 25 (100%) patients (Table 4).

Table 2: Diagnostic criteria for juvenile myoclonic epilepsy.

	Mandatory	Alerts	Exclusionary
Seizures	Myoclonic seizures	Generalized tonic-clonic status epilepticus. Consistent unifocal semiology (i.e., always affecting the same body part on the same side) at onset of generalized tonic-clonic seizures. Consistent unifocal myoclonus.	Myoclonic-absence seizures, atonic seizures, tonic seizures, atypical absence seizures, focal impaired awareness seizures, myoclonus predominantly or exclusively during sleep, myoclonic seizures that occur exclusively with reading, cortical tremor with myoclonus.
EEG	3-5.5-Hz generalized spike wave or generalized polyspike-wave on EEG (may be obtained historically)	-	Habitual myoclonic event captured on EEG in the absence of polyspike and spike-wave discharge. Focal slowing. Consistently unilateral focal epileptiform abnormalities. Generalized slow spike-wave at frequency <2.5 Hz (unless it is at the end of a higher frequency burst). Diffuse background slowing that is not limited to the postictal period.
Age at onset		8-9 years or 25-40 years	<8 years or >40 years (CAE may occasionally evolve to JME; in such cases, persons may have onset of absence seizures, but not GTCA or myoclonic seizures prior to age 8 years).

Table 3: Diagnostic criteria of generalized tonic-clonic seizures alone.

	Mandatory	Alerts	Exclusionary
Seizures	Generalized tonic-clonic Seizures	Consistent unifocal semiology (i.e., always affecting the same body part on the same side) at seizure onset	Generalized myoclonic-tonic-clonic seizures (suggest JME) any other seizure type
EEG	3-5.5-Hz generalized spike wave or generalized polyspike-wave on EEG (may be obtained historically)		Focal slowing. Consistently unilateral focal epileptiform discharges. Generalized slow spike-wave at frequency <2.5 Hz (unless it is at the end of a higher frequency burst) Diffuse background slowing that is not limited to the postictal period
Age at onset		5-9 years or 26-40 years	<5 years or >40 years

Table 4: Frequency of different seizure types in JME and GTCA.

Type of seizure	JME N (%)	GTCA N (%)
Myoclonic	19 (54)	-
GTCS	-	25 (100)
Absence+Myoclonic	9 (26)	-
Myoclonic+GTCS	7 (20)	-

In the study, it was shown that the EEG patterns of idiopathic generalized epilepsy among JME and GTCA patients. The total sample size for this study is 60. Among these 60 patients, JME patients 35 (58%), and GTCA patients 25 (42%). Among of JME patients, family history was seen in 12 (20%), normal EEGs was seen in 9 (15%), GSW occurrence was seen in EEG by 26 (43%), GPSW was seen by 26 (43%), GSW with frontally predominance was seen in 12 (20%) patients, hyperventilation activation of GSW in EEG was seen in 22 (37%), maximum frequency SW resting was 2.5-5.5 (Hz), photic sensitivity was seen by the number of 20 (33%). Among of GTCA patients family history was seen in 6 (10%), normal EEGs was seen in 6 (10 %), GSW occurrence was seen in EEG by 24 (32%), GSW with frontally predominance was seen in 2 (3%) patients,

Hyperventilation activation of GSW in EEG was seen in 10 (17%), Maximum frequency SW resting was 2.5-5.5 (Hz), photic sensitivity was seen by the number of 6 (10%) (Table 5).

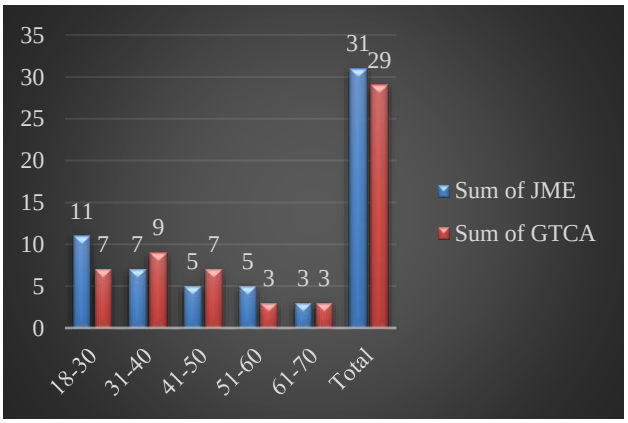

Figure 4: Age distribution of our study people.

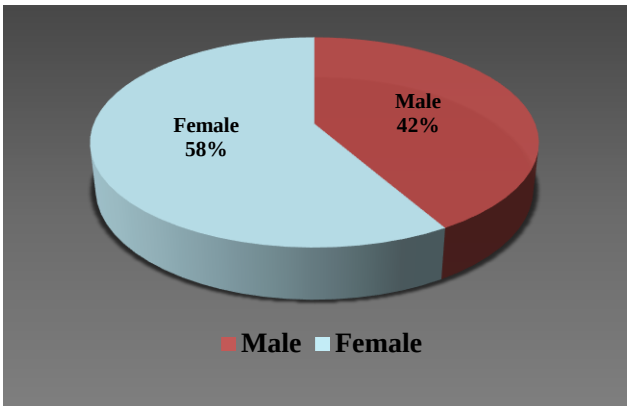

Figure 5: Gender distribution of our study people.

Table 5: EEG patterns of epileptiform discharges in patients with JME-onset and GTCA-onset idiopathic generalized epilepsy.

EEG findings	JME		GTCA	
	N	%	N	%
Number of patients	35	58	25	42
Family History	12	20	6	10
Normal EEGs	9	15	6	10
GSW occurrence (EEGs)	26	43	19	32
GPSW occurrence (EEGs)	26	43		0
GSW with frontally predominance	12	20	2	3
GSW in sleep record (EEGs)	26	43	20	33
GSW in drowsy record (EEGs)	7	12	4	7
GSW in awake record (EEGs)	6	10	5	8
Hyperventilation activation of GSW (EEGs)	22	37	10	17
Photic sensitivity (EEGs)	20	33	6	10

Maximum frequency SW resting and/or HV (2.5-5.5 Hz), G-generalized; SW-spike wave; PSW-polyspike wave; HV-hyperventilation.

DISCUSSION

This study shows the age distribution of the study people. The least people 3 and 3 were aged between 61-70 years, 5 and 3 were between 51-60 years, 5 and 7 were 41-50 years, 7 and 9 were 31-40 years and 11 and 7 were 18-30 years among JME and GTCA patients respectively **(**Figure 4). Another study like Thomas et al mentioned that juvenile myoclonic epilepsy begins between the ages of 8-26 years.[17] A study by Obeid et al in which it was mentioned that the majority of the patients had their first seizures between the ages of 12-18 years.[18] In our study, the mean age at the onset of JME and GTCA was 14 and 16 years, respectively. In other studies by Mehndiratta et al reported, the mean age of the onset of JME and GTCA was 14.46 and 15.95 years, respectively.[19] Our study showed slight female predominance (58% females) in both JME and GTCA patients (Figure 5). Gender distribution is considered to be equal but few studies (Thomas et al and Vijay et al) have shown female preponderance.[17,20] In our study, the earliest age of onset of JME and epilepsy with generalized tonic-clonic seizures alone was 10-24 and 10-25 years, respectively. Before starting treatment, juvenile myoclonic epilepsy in 35 (58%) patients and epilepsy with GTCA in 25 (42%) patients occurred most often immediately after awakening. This circadian rhythm was observed in other studies also.[17,21,22] In patients with absence seizures, these always preceded Juvenile myoclonic seizures and GTCA. A similar observation was made in other studies also.[22,23] In this study, the features of JME and GTCA have been mentioned, showing the usual age onset for JME is 10-24 years and for GTCA is 10-25 years. The seizure type of JME is myoclonic seizures, and on the other hand, GTCA has generalized tonic-clonic seizures as the main type of seizure. This study, as well as other studies, mentioned some criteria (Seizures, EEG findings) to be able to diagnose JME, one of the syndromes of IGE. It is also mentioned that myoclonic seizures have to be present in JME, and as an exclusion, myoclonic absence, tonic, atonic, and typical absence seizures can also be seen (Table 1). In this study, we found that a 2.5-5.5 Hz generalized spike wave was present in JME, and a generalized slow spike can be less than 2.5 HZ (Table 2). In this study, we also studied the criteria for diagnosing GTCA. As a mandatory criteria generalized tonic-clonic seizures must be seen in patients to be diagnosed as a GTCA patient. On EEG findings generalized spike-wave or polyspike wave should be found 2.5-5.5 Hz and as an exclusionary polyspike wave can be <2.5 Hz (Table 3). In our study myoclonic, absence+myoclonic, and myoclonic+GTCS seizure was seen in 19 (54%), 9 (26%) and 7 (20%), respectively, among JME patients. On the other hand, GTCS was seen in 25 (100%) patients (Table 4). In other studies by Shahnaz et al myoclonic, absence and myoclonic, and myoclonic and GTCS seizure was seen in 60 (100%), 2 (3.3%) and 46 (76.6%), respectively among JME patients.[24] In this study, we studied the diagnosis of idiopathic generalized epilepsy by using updated

terminology and EEG on the JME group of IGE and a GTCA onset group of IGE. In our study, we showed the EEG findings of these two groups of patients, especially in the duration, amplitude, and frequency of GSW and the number of discharges during awake sleep state and also during provocation states. In this study, among the 60 patients, JME patients were 35 (58%), and GTCA patients were 25 (42%) (Table 5). In other studies by Shahnaz et al the diagnosis of JME was made in only 6 (10%) patients by the referring physicians.[24] In our study, family history was seen in 12 (20%) and 6 (10%) in JME and GTCA patients, respectively, whereas in the other study by Shahnaz et al found the presence of family history in 12 cases, 4 in first-degree relatives and 8 in second-degree relatives and Aggarwal et al observed family history of seizures was positive in 26 (25.24%) probands among first- and second-degree relatives.[19,24] In our study normal EEGs were seen in 9 (15%) and 6 (10%) in JME and GTCA patients, respectively, while in other studies by Shanaz et al reported 18 (30%) had normal EEGs.[24] In this study, GSW occurrence in EEG among JME and GTCA was 26 (43%) and 19 (32%) respectively, while in another study Shanaz et al found generalized spike waves in 7 (11.6%).[24] In our study, GPSW was only seen in 26 (43%) EEGs of JME patients, while other studies by Shanaz et al found an asymmetry of SW/PSW discharges was found in 6 (10%).[24] In the present study, the maximum frequency of SW resting was 2.5-5.5 (Hz) in both JME and GTCA patients; on the other hand Shahnaz et al found the frequency SW resting was 4-6 Hz.[24] Among JME and GTCA patients, hyperventilation activation of GSW in EEG was seen in 22 (37%) and 10 (17%), but Shanaz et al found that 27 (45%) had hyperventilation activation in EEG findings.[24] In our study, photic sensitivity was seen by the number of 20 (33%) and 6 (10%) in JME and GTCA, respectively, while Shahnaz et al observed photic sensitivity in 11 (18.33%) JME patients.[24] In other studies a low prevalence of photoparoxysmal response has been observed in African and Asian patients.[25] In this study, neuroimaging was normal in all patients, and genetic testing was not part of the current routine diagnostic evaluation. Clinical genetic studies, such as twin studies, have shown that JME has a strong genetic component. A family history is occasionally present; typically, affected family members have an IGE or GGE syndrome, but not necessarily JME or GTCA.[26]

The general age onset for IGE patients is 5-40 years. But in this study, the patients aged between 18-80 years who had idiopathic generalized epilepsy were only included. As the adult age of our presentation was 18-80, so we could only study the two syndromes (JME, GTCA) of IGE among our patients.

CONCLUSION

Recognition of the IGEs is essential for clinical care, as it informs diagnosis, prevents unnecessary investigation, allows optimal selection of ASMs, and provides prognostic guidance. It also enables the identification of a relatively homogeneous group of patients for clinical research and antiseizure therapy trials. The IGEs are a distinctive subgroup within the GGEs, and the term IGE is confined to the four syndromes- CAE, JAE, JME, and GTCA. In this study, we recognized juvenile myoclonic epilepsy and epilepsy with generalized tonic-clonic seizures alone in IGE syndromes as a special grouping among the GGEs are helpful as they carry prognostic and therapeutic implications. The definitions for epilepsy syndromes and the diagnosis of IGEs by EEG with updated terminology provided in this study will require validation in longitudinal studies and may be further refined for new research studies.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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