

# Epilepsy 2019: Clinical characteristics of the genetic generalized epilepsy patients with sleep convulsive seizure - Ayman Ashmawi - Epiclue Epilepsy Clinic

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**Objectives:** To explore the clinical characteristics of patients with generalized genetic epilepsies (GGEs) who experienced sleep generalized tonic clonic seizures (GTCs).

**Methods:** This retrospective observational descriptive study in which, we analyzed the medical records of consecutive patients who were newly or previously diagnosed with generalized genetic epilepsies in a specialized epilepsy clinic in Cairo, Egypt since January 1994 and till January 2015. Patients included had a definite diagnosis of GGE with generalized tonic-clonic seizures (GTCs) (either alone or in combination with myoclonic jerks and/or absence). The study cohort was divided into two groups, the first with sleep/wakefulness (S/W) GTCs and the other with only wakefulness (W) GTCs.

**Results:** 102 patients were included. Mean age of onset of epilepsy (SD/range) was 14.1 years ( $\pm$  4.6/ 4-30 years) and mean follow-up duration (SD/range) was 12.4 years ( $\pm$  2.6/10-20 years). 15 patients (14.7 %) experienced (S/W) GTCs. In univariate analysis, absence seizures ( $p=0.02$ ), Juvenile absence epilepsy syndrome (JAE) ( $p=0.002$ ) and Juvenile myoclonic epilepsy syndrome (JME) ( $p=0.01$ ) were significantly correlated to the patients with GGE who experienced sleep GTCs.

**Significance:** GTCs during sleep were experienced by one seventh of the patients with GGE. A link was observed between absence seizure type, JAE/JME epilepsy syndromes and sleep convulsive seizures in the patients with GGE.

**Keywords:** Generalized epilepsy, sleep seizures, absence, Sleep, Juvenile absence, Juvenile myoclonic

## Introduction

From the earliest times of epilepsy research, it was clear that many seizures exhibited temporal patterns and were affected by the sleep state. The sleep/wake cycle has been used for reference to classify seizures into nocturnal (during sleep), diurnal (during wakefulness) or diffuse (W. Gowers, 1885; M. Langdon-Down and W. Russell Brain, 1929; D. Janz, 1969). It was observed that diurnal seizures cluster at certain times of the day, namely upon awakening and in the late afternoon, and that nocturnal seizures tend to occur mainly at bedtime and in the hours before awakening (Langdon-Down & Brain, 1929; Griffiths & Fox, 1938).

Sleep/wake timing of seizures is associated with both epilepsy syndrome and seizure type. Seizures in focal epilepsy are more likely to occur during sleep than seizures in generalized epilepsy (Winawer, Shih *et al.*, 2016) especially those of frontal onset, (Bazil & Walczak, 1997), (Herman *et al.*, 2001; Minecan *et al.*, 2002), (Ramgopal, Vendrame *et al.*, 2012).

Seizures of awakening grand mal epilepsy and JME tend to occur in early morning hours shortly after awakening and sleep deprivation is known to be a crucial trigger (Janz D, Christian W, 1957; Genton, Thomas *et al.*, Janz 2000; Badawy, Macdonell *et al.*, 2009(Zarowski, Loddenkemper *et al.*, 2011, Winawer, Shih *et al.*, 2016) some patients have a second peak of occurrence in the early evening (Wolf P, Schmitt JJ, 2002), but seizures may also occur after a nap or during intermediate or provoked awakenings at night (Genton P *et al.*, 2013).

In 1962, Janz was the first to notice that up to 45% of patients with primarily generalized tonic-clonic seizures had nocturnal seizures (Janz 1962).

Sleep convulsive seizures is crucial for patients with GGE as they are believed to be bad prognostic indicator for long term remission (Ashmawi, Hosny *et al.*)

GGEs are believed to have genetic etiology and recently there was an emerging evidence for a genetic contribution to sleep/wake timing of seizures in a large group of individuals with common epilepsy syndromes(Winawer, Shih *et al.*, 2016) this subset of patients with GGEs having sleep convulsive seizures may share the same genetic background.

The coupling of seizures to a circadian phase in individual patients has direct implications for the clinical management of epilepsy, most notably in chronotherapeutics. Improved granularity in seizure tracking data offers new and potentially lifesaving approaches to seizure prevention and early treatment. (Guilhoto, Loddenkemper *et al.*, 2011)

Knowing the clinical characteristics of these patients may help predict course and prognosis, can improve seizure control and quality of life; explore the genetic background of this group. Moreover, reports about the clinical characteristics of the patients with GGEs having sleep GTCs are scarce. To our knowledge, only few reports, with the most recent published 2

decades ago (Oller 1996) (Doose H *et al.*, 1965, Wolf P 1992) (Obeid 1994).

In this study, we explored the clinical characteristics of the patients with GGEs who experience wakefulness and sleep convulsive seizures.

### Patients and methods

This is a retrospective observational descriptive study. The medical records of the patients who visited the Epicleu epilepsy clinic in Cairo, Egypt starting from 1994 and diagnosed having GGE were reviewed. All cases were treated by single senior epileptologist (H.H). To be included, patients must have had a definite diagnosis of GGE clinically and by EEG; presence of GTC (either alone or in combination with other seizure types). All the patients with EEG or clinical focal features were excluded. The study was approved by the ethical committee of the neurology department of Cairo University. One hundred and two patients were identified and divided into two groups, the first with sleep/wakefulness (S/W) GTCs and the other with only wakefulness (W) GTCs.

During the first visit, the senior epileptologist made (for newly diagnosed) or confirmed the diagnosis (for referred patients) of GGE by collecting the medical history and seizure details from the patients and any witnesses by using a structured questionnaire. A standard awake interictal EEG and brain computed tomography (CT) were performed in all cases, whereas a sleep EEG, video-EEG, and magnetic resonance imaging (MRI) brain was performed only when clinically indicated.

Treatment was initiated or adjusted according to the opinion of the treating epileptologist. At each follow up visit, seizure frequency, timing of the seizures in relation to sleep/wake cycle, AED daily doses, and compliance were routinely recorded.

For each case, the following number of variables were searched and collected for the purposes of this study: Epilepsy syndrome, sex, status epilepticus, history of febrile seizures, family history of epilepsy, age of onset of seizures, disease duration at diagnosis, number and type of seizures, number of sleep GTCs, Timing of the sleep seizures in relation to the disease onset, number of seizure types, presence of nocturnal enuresis, precipitation of the seizures by sleep deprivation, most commonly AEDs used by the patients.

### Statistical Analysis

#### Results

120 patients were recruited, 18 patients were excluded for having clinical and/or EEG focal features and/or lack of GTC seizure type. Included were 102 patients followed up for mean

(standard deviation, SD) 12.4 ( $\pm$ 2.6) years (range 10-20 years). The mean disease duration at last follow up visit (range,  $\pm$ SD) was 19.18 years (9-60,  $\pm$ 9.9). 41 patients (40.2%) were males and 61 (59.8%) were females. Age of onset of seizures was less than 10 years in - %, from 10 to 19 years in - % and 20 years or older in - %. The mean age at onset (SD) was 14.1 years ( $\pm$  4.6) (range 4-30 years). The general characteristics of the sample are illustrated in the mean (rangeSD) disease duration before the first visit to our clinic was 7.18 (0-48, 9.96) years. Only 34% of patients were newly diagnosed. Family history of epilepsy was present in 11.8 % of cases and history of febrile seizures was even less common (2.9%). Fifteen patients (14.7 %) experienced seizures during sleep. Six patients had only one nocturnal seizure, 5 has from 2 to 9 while another 4 patients had at least 10 nocturnal seizures. Timing of sleep seizures varied in relation to the duration of the disease, 8 patients got sleep seizures within the first 2 years after the disease onset, 4 patients got late sleep seizures while another 3 got early and late sleep seizures. Almost three fourths of cases reported combination of 2 seizure types while only one and 3 seizure types were reported in 10.8% and 14.7% respectively. Primary generalized GTCs (PGTCs) were found in all cases, myoclonic jerks in 70.6 % while absence seizures were found in 33.3 %. The commonest epilepsy syndromes were, in decreasing order, JME (62.7%), JAE (27.5%) and GTCs only (9.8%). Sleep deprivation precipitated seizures in 18.6% of cases. Status epilepticus was reported in 4.9% and nocturnal enuresis in 2.9%. Inter-ictal generalized epileptiform discharges were detected in all cases either in the first or in follow up EEG records. Valproate (VPA) was used by patients 94 (92.2%).

Nocturnal seizures were significantly associated with absence seizures, JAE or JME and history of nocturnal enuresis but multivariate analysis confirmed only - which had an HR - (95% CI - - ) as an independent variable.

### Discussion

Another study found that most patients with epilepsy (75%) have seizures while asleep and awake; 20% of patients with epilepsy have seizures solely while asleep.

Our study found that nocturnal/diurnal seizures were experienced by 14.7% of patients with IGE, diurnal seizures in 84.3% while none had exclusively nocturnal seizures. Compared to other reports (Gower, 1885; Langdon-Down and Russell Brain, 1929; Janz, 1969) the number is low and this may be attributed to the difficult ascertainment by a witness (Bazil 2004).

Our study found a significant association between nocturnal seizures and that JAE or JME. This contrasts previous studies which report that JME patients experience seizures in the early morning shortly after awakening (Janz D, Christian W, 1957;

Genton, Thomas et al., Janz 2000) and the study in 2009 that showed that cortical excitability increases which meant increased seizure susceptibility in patients with IGE, particularly in JME, but not in subjects with focal epilepsy or controls without epilepsy, in the early morning using transcranial magnetic stimulation (Badawy, Macdonell *et al.*, 2009).

Our study supports contributes to the understanding of IGE and focal idiopathic epilepsy as related variants of a system disorder of the brain, with an ictogenesis making pathological use of existing functional anatomic networks.”(Wolf 2006) as there was a significant association in patients with IGE between well-known absence seizures and nocturnal GTCs, which are found to be related to focal epilepsies. This is in line with the proposed focal origin of IGE.

As Neuropsychological studies (Swartz, Halgren *et al.*, Devinsky, Gershengorn *et al.*, 1997, Fountain 2008) and Neuroradiological studies (Swartz, Simpkins *et al.*, 1996, Woermann, Free et al. 1999, Savic, Lekvall *et al.*, 2000, Savic, Osterman *et al.*, 2004) had showed in JME.

### Conclusion

A proportion of patients with IGE did not only experience seizures during wakefulness as proposed by earlier studies, but also during sleep. Absence seizures were significantly associated with the occurrence of additional sleep GTCs and this raises a number of questions to be investigated in the future: 1. what is the patient posture during the sleep/wake cycle just preceding the investigated GTCs? 2. Knowing that absence is epilepsy of the sleep system (Suntsova, Kumar et al. 2009) and that spike and wave paroxysms as EEG substrate of absences emerge from the same circuit that normally produces sleep spindles and the former are epileptic transformation of sleep spindles (Kostopoulos 2000). What is the incidence of witnessed sleep absence seizures either alone or preceding nocturnal GTCs in the patients with GGE? 3. Knowing the theory of absence related micro arousals, were the sleep convulsive seizures preceded by micro arousal absence seizures? Were those patients having other co-existing unknown frontal lobe lesions?

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