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# Atypical EEG abnormalities in genetic generalized epilepsies

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HIGHLIGHTS

- Bilateral and symmetric generalized epileptiform activity is typical in genetic generalized epilepsies.
- Deviation from the classic abnormality is defined as "atypical".
- 66% of patients have at least one atypical abnormality on EEG.

ABSTRACT

*Objective:* Bilateral, symmetric and synchronous generalized epileptiform activity is considered to be the typical electroencephalographic (EEG) abnormality in genetic generalized epilepsy (GGE). We sought to study atypical EEG abnormalities in a systematic way based on 24-h ambulatory EEG recordings.
*Methods:* The diagnosis of GGE was validated and classified into syndromes according to the International League against Epilepsy criteria. All participants underwent 24-h ambulatory EEG recording. Epileptiform discharges were counted and detailed information was entered into an electronic database. Amplitude asymmetry, focal onset/offset of paroxysms, focal discharges, atypical morphology and generalized paroxysmal fast rhythm were defined as atypical abnormalities.
*Results:* Of the total of 120 patients, 107 had abnormal EEGs, of which 66.4% had at least one atypical epileptiform abnormality on EEG. Atypical morphology was the most frequent abnormality in 93.4% of patients, followed by amplitude asymmetry (28.0%), focal discharges (21.5%), focal onset of paroxysms (13.1%), focal offset of paroxysms (8.2%) and generalized paroxysmal fast rhythm (1.9%). The analysis of individual discharges revealed that 76% of paroxysms were of atypical morphology. Significant associations were found between (a) amplitude asymmetry and state of arousal ($p < 0.001$) as well as seizure-free duration ($p$ 0.013); (b) atypical morphology and state of arousal ($p < 0.001$).
*Conclusion:* In GGE, there are both common and rare atypical epileptiform EEG abnormalities that may vary according to the state of arousal and seizure-free duration.
*Significance:* Awareness of these variations is important to avoid misdiagnosis.


## 1. Introduction

Bilateral, symmetrical and synchronous generalized spike-wave activity, occurring on a normal background, is the classic electrographic abnormality of genetic generalized epilepsy (GGE) (Seneviratne et al., 2012). Other typical EEG abnormalities described in the literature are generalized polyspikes, generalized polyspike-wave discharges, photoparoxysmal response, eye-closure sensitivity, fixation–off sensitivity and occipital intermittent rhythmic delta activity (Seneviratne et al., 2012).

Several authors have reported atypical EEG abnormalities in GGE. This includes focal, unilateral, and asymmetric discharges, (Seneviratne et al., 2012) generalized paroxysmal fast activity, (Fakhoury and Abou-Khalil, 1999; Halasz et al., 2004) and distortion of spike-wave morphology during non-rapid eye movement (NREM) sleep (Sato et al., 1973).

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Due to wide heterogeneity among studies, it is difficult to generalize the results on atypical EEG abnormalities in GGE. None of the published studies have provided a detailed quantitative assessment of atypical EEG abnormalities. Hence, it is difficult to get an estimate of the prevalence of various atypical EEG changes in the GGE population. Atypical EEG abnormalities in GGE can potentially lead to misdiagnosis and inappropriate choice of antiepileptic drug therapy. Hence, a systematic study to evaluate this phenomenon has practical implications.

Against this backdrop, we designed the current study to evaluate atypical epileptiform EEG abnormalities of GGE by minimizing the shortcomings of previous studies with the use of a standardized protocol for recording EEG in a well-characterized cohort of patients diagnosed with GGE. We devised a method of manually quantifying the EEG abnormalities in order to provide a better understanding of the frequency of atypical EEG abnormalities.

## 2. Methods

### 2.1. Case ascertainment

We recruited patients for this prospective study through consecutive referrals from epilepsy clinics at two tertiary hospitals in Melbourne, Australia (St. Vincent's Hospital and Monash Medical Centre) with a large proportion of patients from outer metropolitan and rural regions of the states of Victoria and Tasmania. This study was part of an ongoing study on the prognosis of GGE. The diagnosis of GGE was established according to the International League against Epilepsy (ILAE) criteria (ILAE, 1989; Berg et al., 2010). All patients had EEGs and brain Magnetic Resonance Imaging (MRI) performed prior to recruitment as per routine practice of the epileptologists. Some patients had further investigations such as video-EEG monitoring and positron emission tomography (PET) scans to rule out focal epilepsy on clinical suspicion.

An investigator (US) interviewed all patients on the day of ambulatory EEG recording and collected clinical and demographic information which were then cross-checked with medical records. The collated information included age at the time of interview, gender, seizure types, age at the first seizure, current antiepileptic drugs and date of last seizure. The seizure-free duration was calculated based on the date of last seizure and the date of interview whereas epilepsy duration was based on the age of the first seizure and the date of interview.

Two epilepsy specialists (US and WDS) independently reviewed all medical records including EEG and neuroimaging. Any discordance on syndromic diagnosis was resolved by consensus according to ILAE criteria (ILAE, 1989; Berg et al., 2010). We classified patients into four main syndromic groups; childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and generalized epilepsy with generalized tonic-clonic seizures only (GTCSO). Those who did not fit into four main syndromes were grouped together as "GGE unspecified (GGEU)". We included patients with a definitive diagnosis of GGE based on the combination of consistent clinical features and a positive EEG showing generalized epileptiform discharges at least on one occasion. Exclusion criteria were potentially epileptogenic structural abnormalities on MRI, coexistent focal and generalized epilepsies and secondary bilateral synchrony as defined by Blume and Pillay (Blume and Pillay, 1985). We also excluded single seizure presentation with generalized epileptiform abnormalities on EEG, even though a more recent ILAE report has defined a single unprovoked seizure with at least 60% recurrence risk as epilepsy (Fisher et al., 2014). This definition was not established when our study was launched.

### 2.2. EEG data

All patients had 24-h ambulatory EEG planned and performed prospectively according to a standard protocol. EEG signals were acquired with 32-channel, Compumedics Siesta ambulatory EEG system (Compumedics Ltd, Melbourne, Australia) using compact flash card for data storage. Gold cup electrodes were attached with electrode paste according to the international 10–20 system and affixed with collodion adhesive. The recording was commenced in the morning, usually between 9 and 10 am. Then, the patient was allowed to resume routine activities, returning home wearing the small ambulatory EEG device around the waist or over the shoulder.

We advised patients to have at least 8 h of night-time sleep to ensure optimum capture of circadian variations in epileptiform discharges. They were given a diary to document symptoms and events, in addition to pressing the "event button" of the portable EEG device. The recording was ceased and patients were disconnected from the EEG device 24 h later. The EEG data were downloaded from the memory card subsequently.

An experienced EEG reader (US) reviewed all EEGs with ProFusion 4 software (Compumedics Ltd, Melbourne, Australia). Ten-second pages were reviewed page-by-page on longitudinal bipolar montage with 0.5–70 Hz bandwidth. When an epileptiform abnormality was detected, detailed evaluation of the waveform was done on the common average referential montage. A measuring tool incorporated in the software was used to manually measure amplitude and duration of discharges.

We classified epileptiform discharges into generalized fragments (duration <2 s), generalized paroxysms (duration $\geqslant$2 s) and focal discharges (confined to a single lobe or part of a lobe). Bifrontal discharges (both symmetric and asymmetric) were considered to be fragments of frontal expression of generalized epileptiform activity and not classified as focal. We excluded cases of frontal lobe epilepsy with bifrontal epileptiform discharges based on clinical evaluation, video-EEG and neuroimaging. The spike-wave complex was defined as surface-negative spike with duration of 20–70 ms followed by a surface negative slow wave. Polyspikes were defined as a sequence of two more spikes with each spike having duration of 20–70 ms. When a polyspike was followed by a surface-negative slow wave, it was called polyspike-wave complex (Chatrian et al., 1974).

Details of each discharge were entered into an electronic database specifically designed for the study. The details included time of discharge, state of arousal, type of discharge (spike-wave, polyspike, polyspike-wave), frequency of discharges, site of amplitude maximum, amplitude symmetry, paroxysm organization, paroxysm morphology (typical/atypical), paroxysm onset (focal/generalized), paroxysm offset (focal/generalized), duration of discharges and symptoms associated with paroxysms. Sleep onset and offset times as well as background rhythm were also recorded. We defined more than 50% amplitude difference between hemispheres as amplitude asymmetry. Paroxysms were defined as irregular and disorganized when there were disruptions of the regular rhythmic ictal discharges by slow waves or complexes of different frequency and/or morphology or brief (<1 s), transient, interruptions of seizure discharges (Sadleir et al., 2009). We defined focal lead-in discharges lasting >200 ms as focal onset. A similar definition was used for focal offset. For atypical morphology, we did not perform further evaluation of the spike-wave complex as per two previous studies (Weir, 1965; Blume and Lemieux, 1988). Any deviation from the classic surface negative spike/s followed by dome-shaped wave based on visual analysis was considered as atypical morphology for the current study. When $\geqslant$50% of discharges of a paroxysm had abnormal morphology, we classified it as a paroxysm of abnormal morphology. We found it difficult to