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Temporal patterns of epileptiform discharges in genetic generalized epilepsies

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ABSTRACT

Objective: We sought to investigate the temporal patterns and sleep–wake cycle-related epileptiform discharges (EDs) in genetic generalized epilepsies (GGEs).
Methods: We studied 24-hour ambulatory electroencephalography (EEG) recordings of patients with GGE, diagnosed and classified according to the International League against Epilepsy criteria. We manually coded the type of discharge, time of occurrence, duration, and arousal state of each ED. We employed mixed effects Poisson regression modeling to study the temporal distribution of epileptiform discharges. Additionally, we used multinomial regression analysis to explore the significance of the relationship between different states of arousal and types of epileptiform discharges.
Results: We analyzed 6923 EDs from 105 abnormal 24-hour EEGs. Mixed effects Poisson regression analysis demonstrated significant changes in ED counts across time blocks. This distribution was largely influenced by the state of arousal. Generalized fragments (duration < 2 s) and focal discharges were more frequent during non-REM sleep while paroxysms (duration ≥ 2 s) were more frequent in wakefulness. Overall, 67% of epileptiform discharges occurred in non-REM sleep and only 33% occurred in wakefulness. Twenty-four patients (23%) had ED exclusively in sleep. Epileptiform discharges peaked from 23:00 through 07:00 h.
Significance: There is a time-of-day dependency of ED with a significant influence exerted by the state of arousal. Our observations suggest that the generation of epileptiform discharges is not a random process but is the result of complex interactions among biological rhythms such as the sleep–wake cycle and the intrinsic circadian pacemaker. High density of ED in sleep suggests that 24-hour EEG recording with the capture of natural sleep may be more useful than routine EEG to diagnose GGE.

1. Introduction

Temporal patterns in the occurrence of epileptic seizures have been described by researchers for several decades [1–3]. Only a few studies have investigated temporal patterns of epileptiform discharges [4–7]. Even those studies were based on relatively small numbers of patients (n = 19, 17, 5, and 5, respectively) from cohorts with mixed focal and generalized epilepsy.

The close relationship between the sleep–wake cycle and epileptiform discharges (EDs) has been highlighted [8]. Generalized spike–wave discharges are more frequent during nonrapid eye movement (NREM) sleep than in wakefulness and least common during REM sleep [9].

These studies suggest that circadian rhythms are relevant to epileptogenicity and highlight the influence of sleep–wake cycle on epileptiform discharges. However, it is difficult to draw robust conclusions because of methodological problems such as small sample size and the lack of a uniform protocol for EEG recording.

Against this backdrop, we sought to investigate two research questions in relation to genetic generalized epilepsy (GGE): (1) Is there a temporal pattern (time-of-day dependency) in the occurrence of ED? (2) Is there a difference in ED quantity between sleep and wakefulness? To explore these questions, we conducted the current study based on 24-hour ambulatory EEG recordings in a well-characterized cohort of patients diagnosed with GGE. We also sought to assess the diagnostic yield of EEG based on temporal patterns. We hypothesized that epileptiform discharges follow an intrinsic rhythm influenced by the sleep–wake cycle.

2. Materials and methods

2.1. Case ascertainment

The methodology of our research has been previously described [10,11]. In summary, we prospectively recruited patients through

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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. The diagnosis of GGE was established using International League against Epilepsy (ILAE) criteria [12,13].

2.2. Inclusion and exclusion criteria

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, secondary bilateral synchrony as defined by Blume and Pillay [14], and a single seizure with generalized epileptiform abnormalities on EEG.

2.3. Syndromic classification

We classified patients into childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and generalized epilepsy with generalized tonic–clonic seizures only (GTCSO) according to the ILAE criteria [12,13]. Those who did not fulfill the criteria of four major syndromes were grouped together as genetic generalized epilepsy unspecified (GGEU) for the purpose of this study. All medical records were reviewed independently by two epilepsy specialists (US & WDS) with any discordance on syndromic diagnosis resolved by consensus based on the ILAE criteria.

2.4. Clinical and demographic data

One investigator (US) interviewed all participants on the day of their 24-hour ambulatory EEG recording and reviewed medical records to obtain their demographic and clinical information. The seizure-free duration was calculated based on the date of the last seizure and the date of the ambulatory EEG.

2.5. EEG data acquisition

All patients had 24-hour ambulatory EEG performed according to a standard protocol [10]. The EEG signals were acquired with a 32-channel, Compumedics Siesta ambulatory EEG system (Compumedics Ltd, Melbourne, Australia). The recording was commenced in the morning, usually between 9 and 10 AM, and the patient was allowed to resume routine activities, returning home wearing the small ambulatory EEG device around the waist.

We advised patients to have their natural sleep while the EEG was being recorded. They were encouraged to have at least 7–8 h of nighttime sleep to ensure optimum capture of epileptiform discharges in relation to their sleep–wake cycle. The recording was ceased when patients were disconnected from the EEG device 24 h later.

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

Each ED was assessed for characteristics including discharge type (generalized fragment, generalized paroxysm, focal), duration (seconds), time of occurrence, and state of arousal (Supplementary Fig. 1). The sleep onset and offset times were taken note of. The EEG and clinical data were entered into a custom-made electronic database.

2.6. Visual scoring of sleep stages

We followed the guidelines of the American Academy of Sleep Medicine (AASM) in scoring the sleep stages [15]. However, our EEG setup did not include electromyogram (EMG) and electro-oculogram channels as we did not employ polysomnography setup. Hence, we used the eye-movement artifact visible on frontal electrodes as an alternative for electro-oculogram. We classified sleep stages into NREM and REM sleep according to AASM criteria. However, we did not subclassify NREM sleep into stages N1, N2, and N3. The AASM guidelines define REM sleep based on three features: low amplitude mixed frequency background, rapid eye movements, and low EMG tone in chin muscles [15]. In the absence of a chin EMG channel, we adopted saw tooth waves and the lack of muscle artifact on EEG channels as supportive evidence in place of the third criterion [15]. If we detected an ED during daytime sleep, it was coded as a sleep-related ED.

For our Poisson regression analysis, we needed to know whether the discharge occurred in wakefulness, NREM sleep, or REM sleep. These stages were determined according to the AASM rules. For example, when an ED was found in an epoch satisfying criteria for stage W (wakefulness), it was scored as an ED during wakefulness. Similarly, when an ED occurred in an epoch satisfying criteria for stage N1, N2, or N3, it was scored as an ED during NREM sleep. Major body movements were scored according to the AASM criteria. If alpha rhythm was found anytime during the epoch with body movements, it was coded as W (wakefulness). Similarly, when the preceding or ensuing epoch was scored as W, the epoch with movements was scored as wakefulness. Otherwise, the epoch in question was considered to be in the same stage as the following epoch [15].

2.7. Definitions of EEG data

2.7.1. Discharge type

Epileptiform discharges were classified into generalized fragments (duration < 2 s), generalized paroxysms (duration ≥ 2 s), [16], and focal discharges (confined to a single lobe or part of a lobe) (Fig. 1) [10]. Focal discharges tend to occur as brief isolated activity lasting <1 s as shown in Fig. 1. Hence, we did not define an upper and lower limit of duration for focal discharges. For a more detailed account of the definitions and classification of epileptiform EEG abnormalities, the reader is referred to Supplementary file 1 and Seneviratne et al. [11].

2.7.2. Duration of epileptiform discharges

The duration of each ED was measured from the beginning of the first spike or polyspike to the end of the last wave and expressed in seconds.

2.8. Statistical analyses

Descriptive statistics included frequencies/percentages for categorical variables and mean/median and standard deviation for continuous variables. We considered a p value <0.05 as significant. All data analyses were conducted with Stata (version 14) statistical software package (StataCorp LP, Texas, USA).

2.8.1. Sleep–wake cycle changes

We performed mixed effects linear regression analysis to examine the difference of the epileptiform discharge duration between sleep and wakefulness. Additionally, we used clustered analysis of the multinomial regression model to explore the relationship between different states of arousal and types of epileptiform discharges.

2.8.2. Proportion of epileptiform activity in sleep and wakefulness

In order to ascertain the proportion of the total duration of all epileptiform discharges between sleep and wakefulness, we created a variable labeled as “spike density (SD)”. The sleep SD was defined as the total