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Epilepsy beyond seizures: Predicting enduring cognitive dysfunction in genetic generalized epilepsies

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ABSTRACT

Reduced cognitive functioning has been documented in the genetic generalized epilepsies (GGE). Among a number of hypothesized causal mechanisms, some evidence from other epilepsy syndromes suggests the impact of epileptiform discharges. This study investigates the relationship between cognitive function in GGE and burden of epileptiform discharges within a 24-hour EEG recording, controlling for variables relevant to cognitive function in epilepsy.

As part of a larger prospective cohort study, 69 patients with EEG-confirmed GGE (11–58 years) underwent 24-hour EEG and detailed neuropsychological assessment using the Woodcock Johnson III Tests. Ten-second pages of the EEG were marked manually page-by-page on longitudinal bipolar montage with 0.5 to 70 Hz bandwidth by an experienced EEG reader. Multiple regression analyses were conducted. Epileptiform discharges were detected in 90% of patients. Less than 0.01% of electrophysiological events of two or more seconds were recognized by patients. Regression analysis demonstrated that the cumulative duration of epileptiform discharges over a 24-hour period predicted overall cognitive ability and memory function, accounting for 9.6% and 11.8% of adjusted variance, respectively. None of the epilepsy covariates included in multiple regression analysis added significantly to the model.

Duration of epileptiform discharges negatively predicts overall cognitive ability and memory function, even after accounting for other known determinants of cognition. Prolonged epileptiform discharges are common and remain unreported by patients, raising important questions regarding the management of GGE syndromes and their associated comorbidities. Further research is required to investigate causal mechanisms if we are to improve cognitive outcomes in this common group of epilepsies.

1. Introduction

Cognitive dysfunction in epilepsy is thought to reflect a combination of causal factors including the underlying disease process, seizures, antiepileptic drugs (AEDs), educational disruption, and more recently, the burden of epileptiform discharges (ED) [1,2]. Historically considered a benign disorder, genetic generalized epilepsy (GGE) has been associated with reduced outcomes across all domains of cognitive function on meta-analysis [3]. A small literature has examined consciousness during EEG activity and seizures in one GGE syndrome, childhood absence epilepsy, reporting associations between duration of long ED and absence seizures, and attention and visual memory tasks [4–6].

Studies of other epilepsy syndromes have demonstrated that ED are associated with reductions in reaction time [7], processing speed [8], memory [9], short-term memory [10], and overall IQ [9], although a recent review suggests that the impact on enduring functions remains unclear [11]. In addition, neurobiological differences between syndromes preclude the generalizability of these findings to GGE. Furthermore, EEG monitoring periods are typically of short duration and capture only wakefulness, not sleep, and EEG output is commonly described in categories such as "frequent" or "infrequent" ED, rather than in quantified terms. The possible confounding effects of other epilepsy-related variables are rarely addressed. Hence, many questions remain regarding the significance of electrophysiological abnormalities for cognitive functioning in GGE, particularly in syndromes other than childhood absence epilepsy.

We investigated the relationship between ED and cognitive function in a primarily adult GGE sample using 24-hour EEG which enabled comprehensive capture of diurnal and nocturnal events according to the circadian variation in EEG activity [12]. We used quantified EEG data by measuring the duration of all ED throughout the 24-hour recording. Given the relevance of duration of discharges in previous findings, we hypothesized that greater duration of ED would predict poorer cognitive function, independently of relevant clinical variables.

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2. Materials and methods

2.1. Participants

Patients were recruited prospectively as part of a larger prognosis study through epilepsy specialist clinics at two tertiary hospitals in Melbourne, Australia (St. Vincent's Hospital and Monash Medical Centre) and their outreach clinic (North West Regional Hospital, Tasmania). We established the diagnosis of GGE according to International League Against Epilepsy (ILAE) criteria [13,14]. All patients had EEG and brain MRI performed as per routine practice of the epileptologists. Included patients had a confirmed diagnosis of GGE based on the combination of consistent clinical features and a positive EEG showing generalized ED on at least one occasion, and consented to take part in the study. Exclusion criteria were the following: the presence of potentially epileptogenic structural abnormalities (such as hippocampal sclerosis) on MRI, coexistent focal and generalized epilepsies, secondary bilateral synchrony, and single seizure with generalized epileptiform abnormalities on EEG.

We classified patients into childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and generalized epilepsy with generalized tonic–clonic seizures (GTCS) only (GTCSO) according to ILAE criteria [13,14]. Patients who did not fulfill the criteria of the four major syndromes were classified as "GGE unspecified". All medical records including EEG and neuroimaging were reviewed independently by two epilepsy specialists (WD & US) with any discordance on diagnosis resolved by consensus based on ILAE criteria.

2.1.1. Standard protocol approvals, registrations and patient consents

This research was approved by the Human Ethics Research Committees of all participating sites. Participants provided their written informed consent as per the Declaration of Helsinki.

2.2. Procedure

All participants were interviewed during 24-hour ambulatory EEG recording. Medical records were also reviewed to obtain their sociodemographic (age, gender, education, employment) and clinical information (seizure types, ages of onset, the date of last seizure, past history of febrile seizures, family history of febrile seizures and epilepsy in first degree relatives, history of antiepileptic drug therapy and current dosages, previous EEG findings and neuroimaging findings).

Standard protocol for 24-hour ambulatory EEG was employed as previously described [15]. Electroencephalogram signals were acquired with 32-channel, Compumedics Siesta ambulatory EEG system (Compumedics Ltd., Melbourne, Australia) according to the international 10–20 system. The recording was commenced in the morning, usually between 9 am and 10 am. The patient was then allowed to resume routine activities, returning home wearing the small ambulatory EEG device around the waist. Patients were asked to complete a record of their activities during the recording period and to signal the presence of seizures by pressing a button on the device.

Patients were encouraged to have at least 7 to 8 h of sleep during the night. The recording was ceased, and patients were disconnected from the EEG device 24 h later. Twenty-two patients completed the cognitive assessment during EEG recording. Due to patient and clinician availability, the remaining 47 completed the assessment in the week prior or following the EEG recording.

An experienced EEG reader (US) reviewed all 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 undertaken on common average referential montage [16]. A measuring tool incorporated in the software was used to manually measure amplitude and duration of discharges.

Each epileptiform discharge was assessed for discharge type (focal, generalized fragment, generalized paroxysm), duration (seconds), time of occurrence, state of arousal, and individual components (spike–wave, polyspike–wave, polyspike). The sleep onset and offset times were recorded. Total ED duration was obtained by adding up the total duration of all ED (in seconds) over the 24-hour period of the EEG recording. Total number of discharges was obtained by calculating the total number of ED over the 24-hour length of the EEG recording.

The Woodcock Johnson III Tests of Cognitive Abilities (WJ-III) were used to measure cognitive functioning. These tests were developed on the basis of the comprehensive Cattell–Horn–Carroll (CHC) model, which has a demonstrated factor structure that explains cognitive domains underlying the majority of validated cognitive tests, including tests of executive functioning [17,18]. "Brief Intellectual Ability" is a subscale of the WJ-III measuring overall cognitive ability that incorporates measurement of comprehension–knowledge, fluid reasoning, and processing speed, as per the CHC factor structure. Two additional broad CHC factors—short-term memory and long-term (anterograde) memory retrieval—were measured using the WJ-III tests (see Online Supporting Information for details). The CHC factor "short-term memory" is synonymous with "working memory". Long-term memory retrieval includes learning and retention of new information, and retrieval of existing knowledge.

All investigators were blinded; none of the data were available to either the person interpreting EEGs or administering/scoring cognitive tests.

Variables used as covariates in the analysis were obtained from current patient medical records and structured validated interviews. Epilepsy duration was included to account for the potential cumulative effects of disease. Antiepileptic drug therapy is considered a risk factor for cognitive dysfunction, and such side effects are commonly reported by patients [19]. A continuous variable—number of AEDs currently prescribed—was dichotomized to 2 levels: 1) No AED or monotherapy, and 2) polytherapy (>1 AED). There was insufficient power to include monotherapy as a separate level. Additionally, current use of valproate, levetiracetam and lamotrigine was included to account for possible side-effects specific to each of these most frequently used AEDs. Three seizure variables were also included as covariates given the previously demonstrated association of this seizure type with reductions in cognitive function: history of absence seizures, days since last GTCS, and seizure-free duration [5,20]. The impact of education level on cognitive function is well known and was included as a covariate to account for the possibility that any association between ED and cognitive function was not simply reflecting this relationship [21].

2.3. Analysis

Standard linear regression was used to test associations between duration of ED and the three cognitive outcomes: overall cognitive functioning, short-term memory, and long-term memory retrieval. Tests of these three a priori hypotheses that duration of ED would be negatively associated with cognitive outcomes were conducted using Bonferroni-adjusted alpha levels of 0.017 per test (0.05/3).

We used single and multiple linear models to explore other possible hypotheses regarding associations between number of ED and the three cognitive outcomes, the potential role of covariates, and time of day variables. Corrections for multiple comparisons were not made for these exploratory analyses to ensure that potentially important findings were not overlooked [22]. Analyses were conducted using R version 3.2.0 and the *lm.beta* and *gvlma* packages.