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Cognitive correlates of interictal epileptiform discharges in adult patients with epilepsy in China

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ABSTRACT

Objective: Learning difficulties or cognitive impairment has been observed in many patients with epilepsy. Evidence from neurophysiologic and functional neuroimaging suggests that epileptic seizures and/or epileptiform activity can be the dominant factors inhibiting specific brain areas. However, most previous studies were focused on cognitive performance in children. In this study, we analyzed a new cohort of adult patients with frequent interictal epileptiform discharges (IEDs).

Methods: Data from 67 adult patients with epilepsy were reviewed. Electroencephalography (EEG)-video recording and cognitive testing were performed, and the IED index was estimated as a percentage assigned to one of four categories (<1%, 1–10%, 10–50%, and >50%) during either wakefulness or sleep. Correlations of cognitive test results and clinical characteristics of IED categories were analyzed. The effects of the frequency, duration, location, and sleep–wake cycles of IEDs on cognition (intelligence and memory capacity) were analyzed.

Results: Patients with an IED index >10% showed impaired performance on the Chinese Wechsler Adult Intelligence Scale (WAIS-RC) and the Chinese Wechsler Memory Scale (WMS). This effect was detected independently from other IED frequencies and other IED-related variables, such as duration, distribution, and location. The impact of waking or sleeping IEDs was of equal importance in contributing to impaired WAIS-RC and WMS performance.

Conclusion: An IED frequency of more than 10% in both waking and sleeping EEGs is associated with impaired cognitive performance in adult patients. However, whether patients with a high IED frequency but low seizure frequency will benefit from antiepileptic treatment should be examined in future studies.

1. Introduction

A deleterious impact of focal interictal epileptiform discharges (IEDs) on behavior and cognition has been presumed for a long time. However, whether IEDs (such as spikes or spike–wave complexes) can affect cognitive development remains to be elucidated [1–4]. To identify a possible contribution of IEDs to cognition and behavior in children, Borusiak et al. [5] and Eeg-Olofsson et al. [6] reported that the prevalence of focal IEDs in children without epilepsy with behavior or cognition disorders was significantly higher than the 3% to 6% prevalence observed in two normative pediatric studies. Holtmann et al. [7] and Richer et al. [8] reported that children with an attention-deficit hyperactivity disorder had an IED incidence ranging from 6% on waking electroencephalograms (EEGs) to more than 50% on sleep EEGs [9]. Several other factors such as the characteristics of IEDs (frequency, localization, occurrence, and duration of spike or serial spike–wave complexes) and epileptic syndromes may also contribute to cognitive impairment. With respect to the frequency of spikes, Aldenkamp and Arends [10] showed that an occurrence of IEDs higher than 1% is associated with a delay in information processing. With respect to localization, Bedoin et al. [11] found that left-sided IEDs are associated with poor language abilities, and right-sided or occipital IEDs are associated with poor visual or spatial information processing. Riva et al. [12] indicated that specialization of a hemisphere can be affected by unilateral IEDs. In addition to the characteristics of IEDs, the cognitive profiles in children with epilepsy are as diverse as the epileptic syndromes themselves [13], such as an epileptic encephalopathy or electrical status epilepticus during slow-wave sleep (ESES) [14].

In analyzing the relationship between IEDs and cognition (including different characteristics of IEDs), one difficulty is segregating the effects of IEDs from those of other confounding variables. Therefore, well-designed studies are needed to address this issue and to exclude some other confounding factors, such as seizure frequency, duration, epilepsy syndrome, AEDs, short nonconvulsive seizures, and underlying brain diseases.

Previous studies have analyzed cognitive function in children with epilepsy and determined the effect of IEDs on intelligence and memory [15]. In our present study, we have explored these in adult patients independently, which may be crucial to the further therapy for such patients with epilepsy, who have few seizures but significant IEDs. The

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question of whether AED administration will reduce cognitive impairment needs to be addressed.

2. Methods

2.1. Patient selection criteria

Sixty-seven adults, aged from 18 to 48 years old, were included in a standardized, open, and comparative study during the period of 2010–2012. The primary inclusion criteria were as follows: (1) a history of at least one or more certain seizures and fluctuations in cognitive performance; (2) definite IEDs on a recent EEG; (3) subjects with focal IEDs treated with oxcarbazepine (OXC) as monotherapy in doses from 600 mg/day to 900 mg/day; subjects with generalized IEDs treated with levetiracetam (LEV) as monotherapy in doses from 1.5 g/day to 2.5 g/day; and (4) seizure frequency between several times a day to less than 5 times a year. In support of #3, Eun et al. [16] showed no difference in the effectiveness of OXC between intellectually normal and impaired children, and Tumay et al. [17] reported that LEV disrupts cognition to a lesser extent that valproate (VPA) and carbamazepine (CBZ). Therefore, restricting AED use to OXC and LEV likely reduced the direct impact of AEDs on cognitive performance in this study. Exclusion criteria were as follows: (1) malignant epilepsy syndromes that affect cognitive function (such as ESES or continuous spike–waves during slow sleep [CSWS]); (2) short nonconvulsive seizures defined as short ictal activity in seconds with semiology difficult to detect (no falling or continuous jerking, only with staring and subtle movements); and (3) brain diseases that may affect cognitive function (such as traumatic brain injury, brain tumors, gray matter heterotopia, tuberous sclerosis, and stroke). All study participants were patients at the epilepsy center of the First Hospital of Jilin University, and all patients underwent 24-h ambulatory EEGs and cognitive tests. All participants provided written informed consent before the study. This study design has been approved by the Research Ethics Board of the First Hospital of Jilin University.

2.2. IED frequency

Interictal epileptiform discharges were defined as spikes or spike–wave complexes, isolated or occurring serially without evident seizures. On the basis of previous literature [18], we used a "1 s = 10%" rule (explained in detail in Fig. 1): if a spike or spike–wave complex occurs within 1 s of one page (10 s), the index is set as 10%. Sporadic IEDs (≤1 IED/10 pages) are categorized as an index of ≤1%. If generally on each page, IEDs occur within more than half of the page (5 s), the index is categorized as ≥50%, and if IEDs occur within less than half of the page (5 s), the index is categorized as 10–50%. If the spikes are not sporadic but not every page contains IEDs, the category is set as 1–10%. An estimation was made by globally reviewing at least 30 EEG pages throughout each recording.

2.3. IED type and laterality

Interictal epileptiform discharges were categorized as focal or generalized on the basis of the electrode positions where the epileptiform activity clearly appeared. Focal IEDs were categorized as frontal, temporal, centrotemporal, or occipital, which were limited in several neighborhood channels, whereas generalized IEDs were identified as bilateral and synchronized, as is usually found in absence seizures and myoclonic seizures. Laterality was categorized as dominant or nondominant.

2.4. Neuropsychological tests

The Chinese Wechsler Adult Intelligence Scale (WAIS-RC; age ≥ 18 years) and the Chinese Wechsler Memory Scale (WMS) were used to test for intelligence and memory in all study participants.

2.5. Statistical analysis

Statistical analysis was performed with SPSS version 12.0 for Windows (IBM, Armonk, NY, USA). We used t-tests for comparison of

Fig. 1. Method of estimating the IED index in a 10-s EEG page. Common average display. Eight of the 10-s pages contained one or more isolated spike–waves. Only two of the 10-s pages were free of epileptiform abnormalities. The estimated index of this page is approximately 80%, which was categorized as ≥50%.