Role of various antiepileptic drugs in electrical status epilepticus during sleep and its complications

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ABSTRACT

Electrical Status Epilepticus during Sleep (ESES) is an uncommon epileptic encephalopathy typically seen in children. It features pronounced epileptiform activity during non-REM sleep stages and is linked with behavioral and cognitive impairments. This article introduces a novel method for managing patients with ESES.

Keywords: ESES, treatment protocol, antiepileptic drugs, cannabidiol, comorbidities approach

INTRODUCTION

First identified in 1971, Electrical Status Epilepticus during Sleep (ESES) is recognized by persistent EEG irregularities coinciding with sleep onset [1,2]. ESES is diagnosed based on the combination of 85% abnormal EEG patterns during non-REM sleep and an accompanying decline in neurocognitive functions [3]. This condition often appears in male children and is age-related [1,4-9].

CLINICAL FEATURES

ESES generally emerges between the ages of 2 and 12. Initial symptoms include seizures, often paired with a sudden or progressive cognitive decline, attention lapses, memory issues, subtle motor coordination difficulties, and behavioral problems. Prior to the disease’s manifestation, affected children typically display normal developmental patterns. The seizures they experience at the onset are generally mild, and can manifest as localized motor symptoms, generalized tonic-clonic seizures, or absences. Many patients experience multiple seizures daily. Typically, the cognitive and behavioral complications arise 2-3 years post the initial seizure episodes [1,6,10-14].

PARACLINICAL DATA

In ESES is the EEG recording shows over 85% complex spike-wave discharges between 1.5 to 3 hertz during non-REM sleep [1,3,10,15]. These spikes in the EEG are measured by the spike-wave index (SWI), representing the portion of non-REM sleep filled with spike waves [1,15]. While these discharges are generally localized in the frontotemporal or centrotemporal regions during wakefulness, they tend to become more generalized and frequent during sleep [1,3]. However,
abnormal waves from other sleep stages aren't diagnostic. When awake, the patient may exhibit localized or multifocal spikes, occasionally in bursts, which become more evident with the emergence of comorbidities [1,3].

While neuroimaging doesn't directly assist in diagnosis, it can reveal potential structural anomalies.

**PATHOPHYSIOLOGY**

The exact cause of ESES remains elusive, but prevalent theories suggest the involvement of hyperactive thalamic pathways. This may be due to a shift from GABAA-related inhibitory postsynaptic potentials to GABAB-mediated potentials, leading to extended latency and reduced frequency [16].

**OUTCOMES**

Clinical seizures often resolve naturally around puberty. Nonetheless, some electrical irregularities might persist in EEGs post-puberty. An improvement in cognition often follows these electrical rectifications. Various reports suggest that the duration of ESES can significantly influence neurocognitive outcomes [1,3,17-19].

**TREATMENT**

There are various treatment approaches for ESES, with none definitively superior. Common treatments include valproic acid, benzodiazepines, ethosuximide, corticosteroids, lamotrigine, levetiracetam, and sometimes a combination of these. Valproic acid, given its broad-range efficacy, is often a first choice. It's especially potent in regulating non-REM sleep discharges and reducing ESES-associated comorbidities [20,21]. Despite the potential side effects like tolerance and sedation, benzodiazepines, including clobazam and clonazepam, are used either alone or in combination [22,23]. Ethosuximide, recognized for its efficacy against absences, might also benefit some ESES cases [24,25]. Lamotrigine, when introduced cautiously, serves as an option for complex cases [26,27], while levetiracetam is an alternative for those unresponsive to primary treatments [28,29]. Corticosteroids, given their immunomodulatory properties, also present a viable option for treatment-resistant cases [20,30].

In what follows, we will present the results of an observational research study on 40 ESES patients who received classic antiepileptic therapy in specific combinations in order to control the disease. The study sample consisted of children aged between 4 and 12 years old. The gender distribution leaned more towards girls, and for the age categories, there was no specific representation regarding the prevalence in the population with the conditions under study. Furthermore, the study included 40 patients, and comparisons made to reveal statistically significant differences should be approached with caution. Samples included in the analysis can have sizes even smaller than 20; therefore, significant tests were not developed due to the lack of statistical representativeness (T-Test at 95% level of confidence).

One of the objectives of this study was to determine if there is a significant difference between patients who received AE at the time of ESES diagnosis - VPA+ETH - and those who didn't receive this medication. Additionally, it was important to establish whether this difference is influenced by the gender or age of the patients. Furthermore, the study aimed to ascertain if the stability of VPA+ETH, that was added at the time of diagnosis. The patients who came to the clinic with ESES presented varying degrees of attention deficit, ranging from mild to severe. The administration of VPA+ETH aimed to assess the extent to which this medication influenced these two medical conditions.

The main conclusion here is that patients who received VPA+ETH didn't require any additional treatment after one month, unlike those who received other medication. This indicates the effectiveness of VPA+ETH and its stability after just one month of treatment. Significantly fewer patients who received VPA+ETH needed additional medication after one month (T-Test at 95% level of confidence).

Considering the gender and age analysis, the effectiveness of VPA+ETH was observed to be more pronounced in girls and younger children (under the age of 8). The conclusion is that the treatment with VPA+ETH added at the time of ESES diagnosis, demonstrated its effectiveness by improving attention deficit conditions one month after their addition, as well as their stability over time. This symptom improvement was observed more prominently in girls and generally in younger children.

**Limits and Recommendation**

As previously mentioned, the sample size introduced in the study is too small to draw statistically significant conclusions. However, these results do reveal certain benefits that have emerged from the administration of these medications, and which could be the subject of a more extensive study.

The objectives and hypotheses are recommended to be formulated based on the results of this study.

**CONCLUSION**

The ideal pharmacotherapy for ESES varies from patient to patient. The association between VPA and ETH can be very effectiveness in cases of refractory to treat-
ment ESES. The primary goal is not only seizure control but, also improvement of cognitive and behavioral dis-
turbances.

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