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Subclinical epileptiform activity in children with electrical status epilepticus during sleep: Effects on cognition and behavior before and after treatment with levetiracetam

Helge Bjørnæs [a,*], Kristin A. Bakke [a], Pål Gunnar Larsson [b], Einar Heminghyt [a], Elisif Rytter [a], Line M. Brager-Larsen [c], Ann-Sofie Eriksson [a]

[a] National Centre for Epilepsy, Oslo University Hospital, Norway
[b] Department of Neurosurgery, Oslo University Hospital, Norway
[c] Vestre Viken Hospital Thrust, Drammen, Norway

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ABSTRACT

We performed a double-blind placebo-controlled crossover study of the effects of spike activity during sleep and when awake on learning, long-term memory, vigilance and behavior before and after treatment with levetiracetam in children with electrical status epilepticus during sleep.
At baseline, verbal learning declined with increasing spike activity, but there were no relations between spike activity and memory, vigilance or behavior.
Levetiracetam was effective in reducing sleep-related spike activity, but on a group level, this had no clear effects on behavior, vigilance or learning and memory.
Our results do not allow firm conclusions whether to treat nocturnal epileptiform activity or not; larger samples and longer follow-up may be needed.

1. Introduction

Patry et al. [1] described six children with epileptic seizures and/or cognitive deficits who all demonstrated a dramatic increase in epileptiform activity during non-REM (NREM) sleep. They termed this activity "electrical status epilepticus induced by sleep, ESES". Since then, a number of studies have addressed nocturnal epileptiform activity in children and linked it closely to the diagnoses of epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) [2], the Landau–Kleffner syndrome [3], and benign childhood epilepsy with centrotemporal spikes (BCECTS) [4–7]. Nocturnal epileptiform activity is also reported in a substantial proportion of children with autism [8], ADHD [9,10], and language problems [11]. Many of these children have never had epileptic seizures. Nocturnal epileptiform activity is now considered by many researchers as an epileptic encephalopathy with a specter of consequences on cognition and behavior that differs in form, degree and prognosis depending on the amount, age at onset, duration, localization, and treatment of the activity [12–19].

In its most extreme form, the CSWS syndrome, young children experience a dramatic global developmental regression with loss of most earlier acquired cognitive abilities, including language [14]. A somewhat less pervasive regression is seen in the Landau–Kleffner syndrome, where children develop severe aphasia or even, in some instances, generalized auditive agnosia [20]. In both syndromes, behavior deteriorates over time. Negative effects on cognition and behavior are described even in benign childhood epilepsies with centrotemporal spikes [21–23].

As one possible explanation of the devastating effect of epileptiform activity during NREM sleep, Tassinari et al. hypothesized that spike activity would interfere with the consolidation of memory traces and, thus, "wipe out" what was acquired during the day, the so-called "Penelope Syndrome" [24].

In the paper of Patry et al. [1], all the children had the EEG phenomenon ESES, and according to the definition of ESES, had more than 85% of their NREM sleep potentially disturbed by spike activity. However, the criterion of 85% or more is arbitrarily chosen, and many children with nocturnal spike activity during NREM sleep – perhaps most of them – donot fulfill the criterion [25,26]. Little is known about the effects on cognition and behavior of nocturnal spike activity in children. In addition, children may have different vulnerabilities to the potentially deteriorating effects of spiking during NREM sleep — implying,

* Corresponding author at: National Centre for Epilepsy, PO Box 53, 1306 Bærum Postterminal, Norway. Fax: +47 67501188.
E-mail address: helgeb@epilepsy.no (H. Bjørnæs).

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for instance, that the same amount of spiking may have different effects on cognition and behavior in different children. Consequently, we wanted to study the relationship between amount of spiking during NREM sleep, on the one hand, and cognition and behavior, on the other.

Moreover, even though spiking activity is more pronounced during NREM sleep than during REM sleep, in many children, it is not absent in REM sleep [27,28]. Studies of sleep deprivation in healthy people have suggested that NREM sleep and REM sleep have different effects on memory: While deprivation of NREM sleep seems to affect mainly consolidation of declarative memory, deprivation of REM sleep tends to hamper consolidation of procedural memory [29,30].

In addition, epileptiform activity may occur also during daytime when the child is awake [31]. Studies of inter-ictal spiking during daytime have led to the recognition of transient cognitive impairment directly related to spike activity [32,33], as well as the lasting impairment of cognitive functions and school performance in some children with excessive daytime spike activity [34,35].

Presumably, cognition and behavior may be affected by spike activity during one or more of these states. To get a more complete picture of how spike activity relates to cognition and behavior, we, therefore, included spike indexes for REM sleep and for the awake, daytime condition.

In a previous paper, we studied the effect of levetiracetam (LEV) on epileptiform activity during NREM sleep [36] and found a significant mean effect with half of the children obtaining 50% or more reduction in spike activity. The present paper is based on the same study and addresses the effects of epileptiform activity during NREM sleep on cognition and behavior just before the LEV treatment was started, as well as possible changes due to treatment. In addition, we wanted to assess effects on cognition and behavior of epileptiform activity during REM sleep and during waking.

More specifically, at baseline, before treatment was started, we wanted to assess whether spike activity during NREM sleep would impair recall on the following morning of memory tasks acquired the evening before, in accordance with the "Penelope syndrome" [24].

We also wanted to study possible negative effects on memory of spike activity during REM sleep and during waking.

As epileptiform activity during sleep could lead to poor quality of sleep with effects upon the child's alertness the following morning, we wanted to relate measures of vigilance to spike activity during NREM sleep and REM sleep as well as to spike activity in the awake state.

In addition, we hypothesized that degree of spike activity would be reflected in the child's behavior.

After treatment with levetiracetam, we wanted to assess whether improvement in spike activity would be beneficial for cognition and behavior. We did not include a study of placebo effects.

2. Material and methods

A new method for quantifying spike activity [37] was applied on 24-hour EEG registrations. Spike indexes (SI) defined as percentage of time with less than 3 s between spikes in 10-minute epochs were calculated for the awake state (SI-AW), during NREM sleep (SI-NREM), and during REM sleep (SI-REM).

All children referred to the children's department at the National Centre for Epilepsy have a 24-hour ambulatory EEG recording. The reasons for referring children to the Centre may not always be epileptic seizures, but concerns about attention, behavior, school performance, or to investigate possible EEG abnormalities in children with ADHD or autism.

Thus, children who had a 24-hour EEG recording with a spike index of at least 30% during NREM sleep and who had at least a fourfold increase in SI-NREM from awake state were consecutively considered for inclusion. In addition, children had to be between 5 and 10 years of age and have an IQ over 50. They should have been seizure free for at least six weeks prior to inclusion. Twenty-three children fulfilled these criteria and were invited to participate in the study. We found this randomization to either LEV or placebo ethical for the following reasons: Seventeen of the children had paediatric diagnoses (ADHD, Asperger syndrome o.a.) but no diagnoses of epilepsy. Eleven of them were treated with methylphenidate and continued on this medication throughout the study. Only four children had epilepsy and were receiving antiepileptic drugs. In these children, LEV (or placebo) were given as add on medications.

Following inclusion, the children were blindly randomized to either treatment with levetiracetam (LEV) first or placebo first. The patients, then, had a 24-hour ambulatory EEG recording and a baseline neuropsychological assessment, as outlined below (T1), followed by a four-week titration period with either LEV or placebo. Levetiracetam was titrated up to 20–25 mg/kg. The titration period was followed by an eight-week treatment period. Then, a four-week wash-out/titration period followed before the children were changed from LEV to placebo or vice versa for eight weeks. Twenty-four-hour EEG recordings and neuropsychological testing were performed at the end of both treatment periods (T2 and T3). The effect of levetiracetam (LEV) treatment on the epileptiform activity during NREM sleep is reported elsewhere [35] and will be only briefly summarized in the present paper. Electroencephalograms were successfully recorded at baseline in 21 patients.

The children were tested using the Norwegian version of the Wechsler Abbreviated Scale of Intelligence (WASI) [38] on the day they were going to have the baseline (T1) EEG recording. We had decided to exclude children with IQ substantially below 70 from further cognitive testing but not from analyses of treatment effects on the epileptiform activity and on behavior. One patient with total IQ of 62 was excluded, leaving 20 for further testing. On the same day, during late afternoon, those included for cognitive assessment were tested with three brief memory tests consisting of a 10-word list learning task and tests for learning/recognition of 16 faces and five abstract designs. Immediate performance was scored: For the 10-word list, we recorded number of words recalled in the best trial during acquisition, "best trial", and for faces and designs number of items correctly recognized during acquisition. On the following morning, the children were tested for recall of the 10 words, and for recognition of the faces and designs among foils. Scores were number of items correctly recalled (words) or recognized (faces and designs), respectively. Percent remembered was calculated by dividing the score in the morning by the respective score during acquisition in the evening, multiplied by 100. This score reflects how well the learned material is preserved during the night and is regarded as an estimate of the efficiency of the consolidation process. In addition, they were tested with three tests supposed to measure attention, concentration and vigilance: a simple reaction time task, a choice reaction time task, and a semantic word fluency task (for short we name these tests "vigilance tests;" for closer description of the test methods, see Appendix A). The test procedures were repeated at T2 and T3 with parallel versions of the memory tests but with the same vigilance tests.

At baseline, the test results were deemed invalid in two children due to insufficient cooperation, leaving 18 test protocols for the baseline analyses. Additionally, five children dropped out of the testing later on: two discontinued the study because of adverse effects on behavior, one because of a positive effect on behavior while on LEV which the parents would not jeopardize by continuing the study, one refused to participate in testing for the third time, and the test protocol was canceled in one child because there was insecurity about the administration of LEV. Thus, only 13 test protocols remained for analyses of treatment effects.

On each of the three test occasions, one of the parents filled in two questionnaires: Norwegian versions of the Strength and Difficulties Questionnaire, SDQ [39,40] and of the Child Health Questionnaire (CHQ) [41,42]. Both questionnaires require description of the children's health conditions and behavior during the last weeks prior to admittance, SDQ rendering scores on 7 clinical scales, CHQ on 15 scales (se Appendix A). Complete data on behavioral measures were available for baseline analyses in 19 children, and for assessment of treatment effects in 17 children.