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Memory consolidation in children with epilepsy: Does sleep matter?

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ABSTRACT

Introduction: Children with epilepsy have frequent sleep disturbance and challenges in learning and memory. There is little research on the consolidation of memory during sleep in this population. The goal of this pilot study was to determine whether children with epilepsy are able to consolidate memories better after a sleep versus wake period as has been demonstrated in typically developing children.
Methods: This study was a prospective evaluation of children with epilepsy to determine if sleep improved episodic memory (using word lists) as compared with memory following a wake period of similar duration. The study was conducted in patients in the Epilepsy Monitoring Unit at a single academic health science center. In the sleep recall condition, the learning trials were presented in the evening, and delayed recall of the words was tested in the morning. In the wake condition, the learning took place in the morning, and the delayed recall took place later in the day. Subjects wore an actigraph to evaluate sleep/wake patterns. Data regarding the children's epilepsy, antiepileptic medications, and frequency of interictal epileptiform discharges were also documented.
Results: Ten children (agd 8–17 years) participated in the study. For the entire sample, recall after sleep was better than recall after awake ($p = 0.03$), and 7 of the 10 children showed this effect. However, reanalyses removing an outlier showed no difference between the two recall conditions. The mean number of interictal epileptiform discharges was 8.8 during the recall after sleep and 7.8 during the recall after awake. Three children had seizures during the evaluation.
Conclusion: In this pilot study, we demonstrated that a small cohort of children with epilepsy, with similar interictal epileptiform discharges during sleep and wake, showed no advantage in memory for a word list after a period of sleep than after a period of being awake. This finding requires further study in a larger cohort. Poor memory consolidation during sleep may contribute to the cognitive deficits in children with epilepsy.

1. Introduction

Sleep is important for the consolidation of memory. Jenkins and Dallenbach [1] were the first to demonstrate the "existence of a 'sleep effect', i.e., better memory recall when learning is followed by a period spent asleep" [2]. Although learning is one of the most important tasks of childhood, the sleep–memory relationship has not been thoroughly studied in the pediatric population, and even less is known about how children's memory abilities are impacted when sleep is disrupted by seizures and interictal epileptiform discharges (IEDs).

The study of memory in children with epilepsy is an important area of research as it is well known that these children commonly have comorbid cognitive dysfunction. It has recently been proposed that disruption of sleep architecture by IEDs may contribute to cognitive impairment in children with epilepsy [3]. It is known that memory consolidation occurs during sleep in both adults [2] and children [4]. A recent pilot study examined memory consolidation during sleep in children with focal idiopathic epilepsies of childhood and healthy controls [5]. The control group showed an improvement in memory after sleep compared with a similar awake delay period during the daytime. The children with epilepsy not only failed to show the advantage after sleep but also actually had poorer memory after sleep than after an awake delay interval. These results suggest impaired sleep-related memory consolidation in children with epilepsy syndromes who have marked increases in IEDs during sleep. However, the study requires replication due to the small sample size in this research (only four children) and also confirmed in children with other types of epilepsy syndromes.

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There are other factors to consider in the evaluation of sleep and memory in children with epilepsy which require exploration in future research. These factors include the possibility of comorbid disorders that can disrupt sleep. Children with epilepsy may have coexisting primary sleep disorders including behavioral insomnia, restless leg syndrome, parasomnias, and sleep-disordered breathing [6]. In addition, the ultradian pattern of sleep, which is the oscillation during sleep between nonrapid eye movement (NREM), rapid eye movement (REM), and waking that occurs in a predictable pattern each night, may be disrupted by IEDs in children with epilepsy. The frequency and amount of sleep disruption in children with epilepsy have only been studied in a limited way, mainly with retrospective data gathered through parent reports. Few studies have evaluated sleep using objective measurements such as polysomnography or actigraphy. One study using polysomnography demonstrated sleep disruption in 80% of the children with epilepsy [7].

The evidence that specific physiologic processes take place during sleep leading to memory consolidation raises the possibility that the sleep disturbances commonly seen in children with epilepsy may be affecting learning in this patient population. The goal of this pilot study was to determine whether children with epilepsy are able to consolidate memories better after a sleep versus awake period as has been demonstrated in typically developing children. Existing data on the sleep effect in children with epilepsy are based on a small series of only four children. The topic has important implications for further understanding, evaluating, and treating children with epilepsy to promote optimal learning and memory consolidation in this vulnerable patient population.

2. Methods

This study was a prospective evaluation of children with epilepsy to determine if sleep improved declarative memory (using word lists) as compared with memory following an awake period. The study was conducted with subjects who were inpatients electively admitted to the Epilepsy Monitoring Unit (EMU) at the Hospital for Sick Children, Toronto, Canada over a 3-month period (June–August 2012). Approval from the institutional Research Ethics Board was obtained prior to study commencement. Informed consent was obtained from all subjects and their parent/caregiver before participation. This study was part of a larger study evaluating the role of actigraphy in sleep and wake patterns in children with epilepsy. Participants wore an actigraph (the Motionlogger® Micro Sleep Watch® Actigraph, Ambulatory Monitoring, Inc (AMI)) to record sleep/wake patterns. The parent stayed in the room at night during the EMU evaluation and completed a sleep diary during the course of monitoring, including the nights of this research trial.

2.1. Participants

Patients between ages 8–18 years, with a history of medically refractory epilepsy, (defined by one or more seizures within 6 months prior to enrollment, despite a trial of at least two antiepileptic medications), who were being electively admitted to the epilepsy monitoring unit (EMU), were approached for participation in this study.

Children/teenagers who were expected to be in the EMU for a minimum duration of 48 h were eligible to participate. Participants who were included had the following characteristics: ability to cooperate with EEG lead placement and continuous video-EEG (VEEG) monitoring as well as to wear an actigraph on the nondominant wrist, no significant motor disabilities or movement disorders involving the extremities (including dystonia, chorea, or tremor), and ability to cooperate with the evaluation. The participant's ability to cooperate was determined by asking the parent(s) if they predicted that their child would be able to listen to a list of words and remember and recall some of the words.

2.2. Participant characteristics

Demographic information including age and gender as well as the seizure type, ictal onset, neuroimaging findings, duration of epilepsy, and type and number of antiepileptic medication(s) were obtained through questionnaires completed by parents and designed for this study.

2.3. Information about epilepsy during the EMU admission

Details during the EMU admission were evaluated including the following: length of stay (hours), number of seizures in the awake versus sleep condition, changes to AEDs during the admission, sleep duration in the sleep condition, and daytime sleep (naps). The ictal data were recorded through simultaneous video-EEG. A spike index was done in a blinded fashion by one of the researchers to determine the number of interictal epileptiform discharges. Interictal spike frequency was counted visually for 25 min (5 × 5 minute epochs) randomly selected during the waking and NREM sleep periods. The average spike index was calculated (combining sleep and wake epochs) for spikes/min.

2.4. Sleep data

Sleep data, including total sleep time, sleep onset latency, and wake after sleep onset, were determined from the actigraph recording, which was worn continuously on the non-dominant wrist for 90.5 h during the sleep–memory evaluation. Correlation between the parent reported sleep diary and the actigraph was performed to ensure the actigraphy data were interpreted correctly. Actigraphy data were analyzed using Action4 software (Ambulatory Monitoring Inc., Ardsley, NY USA). Actigraph data were analyzed by activity counts to determine sleep versus awake time using the following method: Cole-Kripke PCD ZCM 1 min.

2.5. Memory Evaluation

Memory was tested using a verbal learning and delayed recall task. The task involved presentation of 15 nouns for five learning trials. On each trial the words were read aloud with a 1-second interval between each word for five consecutive trials, with each trial followed by a free recall test. The order of presentation of the words remained the same across trials. Two word lists were used; one list was from the Auditory Learning Test [8] and the second was from the World Health Organization/UCLA version of the Auditory Verbal Learning Test [9]. Each participant was tested twice. In the awake condition, the learning trials were presented in the daytime and delayed recall was tested after a long delay during which the participant was awake. The subject was requested to not sleep during the day, and this was verified by the actigraph and VEEG recording. In the sleep condition, the learning trials were given in the late afternoon/early evening and delayed recall was tested the following morning after waking. There was one day between the two conditions. The order of the conditions was counterbalanced among participants, and the order of presentation of the word lists was counterbalanced across the awake and sleep conditions. The length of the awake and sleep delay intervals were matched for each child, and were on average 11.43 h (range 10.75 – 13.25 h).

A clinical psychologist (MLS) trained the co-authors, a medical student (SS) and a staff physician (SW), to perform the memory testing using a script.

3. Results

3.1. Participants

A total of 12 children from the epilepsy monitoring unit were consecutively recruited to participate in this cross-sectional study at the Hospital for Sick Children. Two patients were uncooperative with the