Clinical Neurophysiology 126 (2015) 1493–1497

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Occurrence of epileptiform discharges and sleep during EEG recordings in children after melatonin intake versus sleep-deprivation

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ARTICLE INFO

Article history:
Accepted 4 October 2014
Available online 18 October 2014

Keywords:
Melatonin
EEG
Sleep deprivation
Epileptiform discharges
Children
Epilepsy

HIGHLIGHTS

- The occurrence rate of epileptiform discharges in the EEG of children 1–16 years of age does not differ in sleep induced by melatonin and sleep deprivation.
- Melatonin is equally efficient as partial sleep deprivation in inducing sleep.
- Melatonin may be preferable in younger children as they fall asleep easier than after partial sleep deprivation, and also from the parent's perspective.

ABSTRACT

Objective: To determine if melatonin is equally efficient as partial sleep deprivation in inducing sleep without interfering with epileptiform discharges in EEG recordings in children 1–16 years old.
Methods: We retrospectively analysed 129 EEGs recorded after melatonin intake and 113 EEGs recorded after partial sleep deprivation. Comparisons were made concerning occurrence of epileptiform discharges, the number of children who fell asleep and the technical quality of EEG recordings. Comparison between different age groups was also made.
Results: No significant differences were found regarding occurrence of epileptiform discharges (33% after melatonin intake, 36% after sleep deprivation), or proportion of unsuccessful EEGs (8% and 10%, respectively). Melatonin and sleep deprivation were equally efficient in inducing sleep (70% in both groups). Significantly more children aged 1–4 years obtained sleep after melatonin intake in comparison to sleep deprivation (82% vs. 58%, $p \leqslant 0.01$), and in comparison to older children with melatonin induced sleep (58–67%, $p \leqslant 0.05$). Sleep deprived children 9–12 years old had higher percentage of epileptiform discharges (62%, $p \leqslant 0.05$) compared to younger sleep deprived children.
Conclusion: Melatonin is equally efficient as partial sleep deprivation to induce sleep and does not affect the occurrence of epileptiform discharges in the EEG recording. Sleep deprivation could still be preferable in older children as melatonin probably has less sleep inducing effect.
Significance: Melatonin induced sleep have advantages, especially in younger children as they fall asleep easier than after sleep deprivation. The procedure is easier for the parents than keeping a young child awake for half the night.

1. Introduction

One of the cornerstones in the diagnosis of epilepsy in children is the results from electroencephalography (EEG). Performing EEG recordings in young children may, however, be challenging since a good quality requires that the patient does not move. Therefore, the method of choice so far has been EEG performed during sleep. Sleep also improves the sensitivity of the examination, by increasing the amount of epileptiform activity in the EEG (Niedermeyer and Lopes da Silva, 2005a). Natural sleep is desirable since many pharmacological agents influence brain activity and as a consequence decrease the occurrence of epileptiform discharges

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http://dx.doi.org/10.1016/j.clinph.2014.10.015
1388-2457/

(Ashrafi et al., 2010; Niedermeyer and Lopes da Silva, 2005a). Many neurophysiology clinics use sleep deprivation to obtain reliable recordings (Degen, 1980; Giorgi et al., 2013; Leach et al., 2006; Wassmer et al., 1999). The incidence of epileptiform discharges in sleep deprived EEGs does, however, vary widely from 32% to 72% in different reports (Marinig et al., 2000). Furthermore, sleep deprivation is not easy to achieve in young children and could be burdensome for both children and parents. Therefore melatonin, given prior to the investigation, is currently used in a number of laboratories to induce sleep before the EEG recording (Eisermann et al., 2010; Sander et al., 2012; Wassmer et al., 2001a,b).

Melatonin is a hormone produced in the pineal gland. It regulates circadian rhythms and some aspects of the sleep–wake cycle. It is widely used to treat jet lag and sleep disturbances (e.g. sleep onset delay) (Cortese et al., 2013; Herxheimer and Petrie, 2002). During the last two decades, studies reporting a sleep inducing effect of melatonin (Wassmer et al., 2001a; Milstein et al., 1998), as well as its safety in children (i.e., lack of side-effects and tolerability) (Sander et al., 2012) have been published. Melatonin is well tolerated also in children with behavioural problems (Eisermann et al., 2010; Mohammadi et al., 2012; Wassmer and Whitehouse, 2006). Doses of melatonin vary between different studies ranging from 2 mg up to 20 mg (Eisermann et al., 2010; Wassmer et al., 2001a,b), and there is no clear consensus regarding when and in which doses melatonin should be administrated in children. To the best of our knowledge there are no studies that have described the effect of melatonin intake on epileptiform discharges during sleep in different age groups or compared it to the effects of sleep deprivation. The issue of whether to use melatonin or sleep deprivation as a sleep inducer and in which age groups they should be chosen therefore remains controversial (Giorgi et al., 2013; Marinig et al., 2000).

The aim of this study was to determine whether melatonin is equally efficient as partial sleep deprivation in inducing sleep without interfering with epileptiform discharges in EEG in children as well as the technical quality of EEG recordings. We also analysed the sleep inducing effects of melatonin in comparison to partial sleep deprivation, as well as occurrence of epileptiform discharges in EEG recordings in different age groups.

2. Materials and methods

2.1. Subjects and study design

We retrospectively analysed 129 EEG recordings from 121 patients with melatonin induced sleep and 113 EEGs from 111 patients after partial sleep deprivation, aged 1–16 years. The EEGs were performed at a Swedish university hospital during two different time periods: 2010–2011 for melatonin induced sleep and 2007–2008 for sleep deprivation. The routines in our department changed in 2009 when we began to use melatonin in clinical practise to induce sleep in paediatric patients during EEG recordings. Partial sleep deprivation was routinely used before 2009. Children undergoing sleep deprived EEG during 2010–2011 were excluded from further analyses. Patient selection and mean age of the participants are shown in Fig. 1. All children were referred by paediatric neurologists or paediatricians. The indications for EEG were suspected epilepsy, unclear spells, or treatment control in patients with established epilepsy. Reasons for performing sleep EEG in children with established epilepsy were to get an EEG recording without movement artefacts. Clinical background data, such as epilepsy diagnosis, developmental delay and behavioural problems were obtained from referrals, as well as self-reported data from patients and parents documented in the medical records when referred to the EEG recording. EEG recordings were divided into four groups depending of the age of the children (i.e., 1–4 years, 5–8 years, 9–12 years and 13–16 years).

2.2. EEG recordings

For partial sleep-deprived EEGs, caregivers were told to put the child to sleep between 7 p.m. and 9 p.m. the night prior to the examination, and to wake the child at 4 a.m. Sleep deprived EEGs were recorded at 8 a.m. For sleep EEGs using melatonin, children between 1 and 4 years of age were given 3 mg melatonin in liquid form orally and children between 5 and 16 years of age 6 mg, 15 min prior to electrode application. No specific instructions were given regarding prior sleep. These EEGs usually were performed in the early afternoon between noon and 2 p.m.

EEGs were performed using a standard procedure with silver cup scalp electrodes placed according to the international 10–20 system modified adjusted to the patients' age. A Nicolet One EEG Recorder/Reader v.5.30.1.1178 (Copyright 2007 – VIASYS Healthcare Inc.) EEG equipment was used. Electrode impedances were less than 10 kΩ and the high-pass filter was set at 70 Hz. All EEG recordings were performed in a dark and quiet room, and the children were instructed to lie calmly and try to go to sleep. The EEG examination lasted between 30 and 40 min.

EEGs were evaluated by physicians specialised in clinical neurophysiology. All EEGs with epileptiform discharges were re-evaluated by the first author (G.G.). Epileptiform discharges were considered present only if they had well defined morphology and were seen recurrently without influence of muscle or movement artefacts and from electrodes with high conductance. Single isolated epileptiform discharges were not accounted for because of uncertain clinical specificity (Niedermeyer and Lopes da Silva, 2005b). Unsuccessful EEG was defined as either an EEG that was impossible to record due to an uncooperative child or a recording that was difficult to evaluate due to artefacts.

2.3. Statistical analyses

Statistical analyses were performed in Statistica, version 10 (Copyright StatSoft, Inc 1984–2011) and via web-site www.openepi.org. Comparisons were made in three steps. In the first step comparisons were made between melatonin induced sleep and sleep deprived EEGs in children 1–16 years old as a whole group. In the second step comparisons were made between the two EEG modalities (i.e., melatonin induced sleep EEG and sleep deprived EEG) in four different age groups. In the third step comparisons were made between different age groups within each EEG modality. In each step comparisons were made concerning occurrence of epileptiform discharges, the number of children who fell asleep and proportion of unsuccessful EEG recordings.

Statistical analyses of baseline characteristics were performed with chi-square test for categorical variables and Student's t test for continuous variables.

Chi-square test or Fisher's exact test, when appropriate, were used to compare the occurrence of epileptiform discharges and occurrence of sleep and proportion of EEGs that were defined as unsuccessful. Statistical significance was set at $p \leqslant 0.05$.

3. Results

There were no significant differences in the number of EEG recordings showing epileptiform discharges, types of epileptiform activity or occurrence of other abnormalities (i.e., general or focal slowing of background activity) in children between 1 and 16 years of age who received melatonin prior to EEG, as compared to those who were sleep deprived (Table 1). Furthermore, no statistical