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Yield of outpatient sleep EEG for epileptiform alterations detection in children

Running title: sleep EEG for IED in children

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Abstract

Introduction: Ambulatory EEGs in children are frequently ordered as sleep studies. However, the yield according to different clinical situations has received little attention to date. We aimed to quantify the added value in terms of detection of epileptiform features of an EEG containing sleep, as compared to only wakefulness, according to the referral diagnoses.

Methods: We retrospectively selected consecutive outpatients EEG recordings of patients between 6 months to 16 years old, performed between January 2014 and February 2015. We excluded those lacking at least 10 minutes of waking and/or at least 5 minutes of behavioral sleep. Interictal epileptiform activity (IEA) in wakefulness and sleep was compared among referral suspected diagnoses. Additional yield of sleep was considered if at least one of the following was observed: Appearance of IEA or increase by $> 50\%$, 2, IEA change in localization or morphology, seizure occurrence.

Results: A total of 425 recordings, (mean age $6,9 \pm 4,7$ years) were analyzed. Of them, 194 (45,6%), presented an additional yield during sleep, which was dependent on the occurrence of IAE during wakefulness: 77/251 (30.7%) in those without, versus 117/174 (67.2%) in those with wakefulness IAE ($p < 0.001$, χ^2). The yield was markedly lower in studies performed for non-epileptic referral diagnoses (7%, versus 43%-100%; $p < 0.001$, Fisher).

Conclusions: When wakefulness EEG lacks epileptiform features, the yield of sleep EEG in our pediatric population appeared modest, especially in patients without a suspected epileptic syndrome. This information may be used to optimize the request of sleep EEG in children.

Introduction

Epilepsy is one of the most common neurologic conditions occurring in the pediatric population, with a prevalence in Europe around 4.5-5.0 per 1,000 among children and adolescents (Forsgren *et al.*, 2005) (Jallon *et al.*, 1997). Although the diagnosis of epilepsy is primarily clinical, EEG is a noninvasive, safe, and relatively inexpensive test playing a crucial role in the diagnosis, characterization and clinical management (Binnie & Prior, 1994). The complex relationship between seizures and sleep cycles or sleep-related oscillations has been identified decades ago (Kellaway *et al.*, 1980; Steriade & Amzica, 2003). The yield of the first EEG study to identify interictal epileptiform abnormalities (IEA) after a first unprovoked seizure in children ranges from 32% to 59% in adults (Baldin *et al.*, 2014). Sleep may activate IEA in approximately a third of patients with epilepsy and up to 90% of those with epilepsies related to sleep or awakening (Donat & Wright, 1989; Vaughn & D'Cruz, 2004). In this context, sleep deprivation is frequently used to increase the EEG sensitivity (Pratt *et al.*, 1968).

EEGs in the pediatric age are very frequently ordered as sleep studies; while this allows an artifact-free reading in subjects that are restless during wakefulness and to study sleep activity and brain maturation in the youngest, studies are longer and more expensive than routine EEGs, and require sometimes specific preparation (sedation). To the best of our knowledge, the yield of sleep studies according to different referral diagnoses has not been definitely assessed in this population. The aim of this study consists of quantifying the added value of sleep EEG in children in terms of detection of epileptiform features, as compared to wakefulness EEG only, according to different referral diagnoses.

Methods

Design and Patients

In this retrospective cohort study, which was approved by our Ethics Commission, we retrieved the reports of 765 consecutive pediatric patients who had an ambulatory EEG between January 2014 and February 2015 at the EEG/epileptology unit, Neurology department of the University hospital of Lausanne (CHUV). We included only EEGs of children aged between 6 months to 16

years on an outpatient basis, since sleep transients such as K complexes and spindles develop by 3-6 months of age, and allow a reliable detection of sleep. We excluded EEGs lacking at least 10 minutes of wakefulness and/or at least 5 minutes of sleep recording. Children recorded as inpatients because of acute conditions were also excluded. In our center, the vast majority of ambulatory pediatric recordings last between 60 and 120 minutes (“nap EEG” performed under continuous supervision of a registered EEG technician); children up to 4-5 years are preferentially recorded during their spontaneous afternoon nap, whereas older subjects will be recorded in the morning after sleep deprivation.

Variables

Based on our EEG reports, following variables were retrieved: age at the EEG recording, gender, learning disability, referral (putative) diagnosis appearing on the EEG request (categorized into epileptic syndrome (1993; Berg *et al.*, 2010) or non-epileptic condition). Occurrence of interictal epileptiform activity (IEA) was considered for multifocal, bilateral, independent or generalized spikes, sharp waves, polyspikes, spike and waves, polyspike and waves; diffuse electrodecrements, periodic lateralized (PLEDs or LPDs) or generalized epileptiform discharges (GPEDs or GPDs); furthermore we scored the occurrence of epileptic seizures (electrographic: at least 10 seconds; electroclinical: any duration >2 seconds of rhythmic or periodic epileptiform discharges or waves >3 Hz, or if less frequent, association with a clear evolution in amplitude, field or frequency (Chong & Hirsch, 2005)). The standardized nomenclature of the American Clinical Neurophysiology Society (ACNS) (Hirsch *et al.*, 2013) is routinely used in our Unit since early 2014 to quantify IEA (<1/h=rare; 1/h to 1/min=occasional; 1/min. to 1/10 sec. = frequent, and > 1/10 seconds =abundant). When the reports did not allow assessing the difference in the frequency of IEA, one investigator (SO) performed a new inspection of the raw EEG traces and discussed it with the senior authors/ (JN, AOR).

Variation of epileptiform activity and seizures during sleep versus preceding wakefulness were compared using the following four criteria: 1. Appearance or increase of more than 50 % of IEA; 2. A change in localization and / or morphology of IEA (additional focus or generalization, presence of a new epileptiform activity), or 3. Both , and 4. Occurrence of epileptic seizures.

Statistical analyses

Calculations were performed using SPSS Statistics 20 (2011 version). Normally distributed data were described using mean and standard deviation (SD). Comparisons among categorical variables were performed by χ^2 or two-tailed Fisher's exact tests, as appropriate.

Results

Patients

From the 765 recordings initially retrieved, 425 (mean age 6.9, SD \pm 4.7 years; 50.4% girls) fulfilled the inclusion criteria, while 340 were excluded (128 inpatients studies; 18 monitorings, and 194 having an age < 6 months or >16 years).

Referral diagnoses were: West syndrome (n=21); Genetic generalized epilepsy (GGE) (n=61) (3 childhood absence epilepsy, 3 juvenile absence epilepsy, 7 juvenile myoclonic epilepsy, 2 myoclonic absences epilepsy, 3 eyelid myoclonic absence epilepsy and 2 absence status, but not myoclonic atstatic epilepsy, see below); Idiopathic focal benign epilepsies (n=30) (Benign epilepsy of childhood with centro temporal spikes (BECTS) and benign occipital epilepsy (BOE)); Focal-multifocal lesional of different etiologies (e.g., cerebral tumor; cortical dysplasia, ischemic/ hemorrhagic stroke, infections, arteriovenous malformation) or of unknown origin (n=121); Electric status epilepticus in sleep (ESES) (n=14); myoclonic atstatic epilepsy (MAE) (n=20). Rarer conditions were grouped as "Others/miscellaneous" (n=47) (Angelman syndrome=2, Rett syndrome =3, generalized epilepsy with febrile seizures (GEFS)=2, GEFS "plus"= 6, Wolf-Hirschhorn syndrome = 3, subacute sclerosing panencephalitis (SSPE)=2, Aicardi syndrome=1, Pseudo-Lennox syndrome =1, X fragile syndrome= 2, late epileptic spasms=7, epileptic encephalopathies of unknown origin=7, atypical absences not otherwise specified =4, Idiopathic photosensitive occipital lobe epilepsy (IPOE)=2, Sturge-Weber syndrome =1, Lennox-Gastaut syndrome = 2, Dravet syndrome=1, GLUT-1 deficiency =1).

Finally, behavioral and attentional problems such as pervasive developmental disorder and autistic spectrum disorder, attention deficit hyperactivity disorder (ADHD), and non epileptic

paroxysmal events (i.e., psychogenic non-epileptic seizures, vertigo, migraine, other paroxysmal somato-sensory symptoms) were summarized as “non-epileptic referrals” (n=111).

Yield of sleep versus awake EEG

Among the 425 recordings, 194 (45.6%) presented an additional yield during sleep; the detailed description, stratified for referral diagnoses, is given in **Table 1**. Of note, recordings performed for referrals other than epilepsy syndromes were clearly less likely to provide additional information during sleep (7% versus 43% to 100%, $p < 0.001$, Fisher). If the EEG during wakefulness failed to show any IEA (n=251), 77 (30.7%) of the sleep studies disclosed an additional yield; in contrast, when the awake EEG contained IEA (n=174), 117 (67.2%) of the sleep studies provided an additional information ($p < 0.001$, χ^2) (**Table 2**). Globally, during sleep, 14 recordings showed epileptic seizures (referral diagnoses: 8 focal lesional or unknown origin, 4 in “others”, 1 in GGE and 1 in ESES), and 15 epileptic myoclonus (6 in GGE, 4 in “others”, 2 in MAE and 2 in focal lesional or unknown origin); all of them were preceded by IEA in their sleep EEG. Finally, our results did not show significant differences between sleep-deprived (5 years or more years) and not sleep-deprived children (4 years or less); an additional yield was found in 70/171 (40.9%) and in 124/254 (48.8%) EEGs, respectively ($p = 0.110$, χ^2).

Discussion

This analysis, addressing the yield of pediatric outpatient sleep EEGs according to different referral diagnoses in terms of IEA, suggests that studies recorded for suspected diagnoses other than epileptic syndromes, especially without any IEA during preceding wakefulness, seem not likely to have an added value related to sleep.

Previous assessments of the yield of EEG in epilepsy focused either on the absolute value of the study type (wakefulness versus sleep), or on the use of sleep deprivation (Shinnar *et al.*, 1994; Carpay *et al.*, 1997; DeRoos *et al.*, 2009; Giorgi *et al.*, 2013). As far as we are aware, this is the first study to evaluate the yield of the sleep versus awake EEG according to different pediatric referral diagnoses.

The rich interplay between epilepsy and sleep is known since antiquity: Aristotle and Hippocrates described the occurrence of epileptic seizures during sleep, and Galen even prevented his patients with epilepsy against sleepiness (Passouant, 1991). Analysis of sleep microstructure has led to establishing a relationship between the frequency of IEA and the phases of sleep Cyclic Alternating Pattern (CAP) (Terzano *et al.*, 1989): IAE seem to be linked to the slow sleep oscillations, and especially to the reactive delta burst characterized by the A1 subtype in the CAP (Halasz, 2013), and are modulated especially by sleep in epilepsies that affect the thalamo-cortical circuit involved in the arousal system (Terzano *et al.*, 1991a; Terzano *et al.*, 1991b; Gigli *et al.*, 1992) .

Our global IEA yield in a pediatric population (45.6%) appears comparable with previous data in adults showing that sleep may activate IEA in approximately one third of patients with epilepsy (Vaughn & D'Cruz, 2004). A study about the circadian variation of IEA in GGE (Pavlova *et al.*, 2009) showed an increase of IEA frequency in NREM sleep in 60 % of patients, and the highest ratio NREM /wake was as high as 14:1; these numbers seem in line with our findings (yield of 47.5%).

Referrals related to focal and multifocal lesional epilepsies represented the highest sample of our pediatric records (n=121), with a sleep yield in 59.5% of them. In comparison, adult patients with temporal lobe seizures are well known to present during NREM sleep an increase of spiking rate, extension of electrical field, and an increase in the rate of bilateral independent discharges (Halasz, 2013). A study of 40 patients with temporal lobe epilepsy observed a new focus in 53% during NREM sleep (Sammaritano *et al.*, 1991). In our cohort, ESES, BOE, and BECTS groups displayed the highest rate of increase in IEA during sleep, in accordance with one of the main characteristics of these pediatric epileptic syndromes : indeed, IEA may be seen only in sleep in 2,5-35% of patients (Dinner, 2002), which corresponds to our findings (5/30; 16%). Furthermore, as logically expected, ESES was the only group that had a sleep yield of 100%. In West syndrome patients, our sleep yield (42.9 %) lies again in the range of previous descriptions (Jeavons & Bower, 1961; Kellaway *et al.*, 1979; Gomez & Klass, 1983). Regarding rarer conditions (classified as “others”), the small sample size did not allow drawing any conclusions.

Non-epileptic referral diagnoses showed by far the lowest yield (7.2%) of sleep EEG. While a

reason to request a sleep EEG in conditions such as ADHD, autism spectrum, and other behavioral and learning problems may be to evaluate the structure of sleep and signs of dysmaturity, the aim of our study was specifically directed towards IEA. This findings are in contrast with other studies suggesting a high rate of IEA in sleep in conditions as autism (Spence & Schneider, 2009; Zappella, 2010), although their role in the condition remains controversial. One the one side, the modest yield in our study may temper the policy of routinely ordering a sleep-EEG in this category of patients. On the other side, IEA identification, especially if related to clinical correlates, can have an important impact on patient management, highlighting that policies have to be tailored to each specific situation.

This study has limitations: its retrospective character implies that referral diagnoses were not verified independently, but this reflects a common situation for the EEG interpreter. It is a single center analysis, which calls for caution regarding generalization. A large proportion of records were in patients under antiepileptic treatment (a situation that could decrease the number of seizures and/or IEA), but it was not the aim of our study to evaluate the effects of the treatment in the sleep EEG. Finally, the evaluation of the sleep structure represents an important issue, both to assess development and to allow at times a comfortable interpretation in young subjects who are steadily moving during wakefulness; we did not assess these issues in the present analysis.

In conclusion, under consideration of the aforementioned limitations, this study suggests that a pediatric sleep EEG recording seems to have a relatively low yield of disclosing IEA in pediatric patients referred for diagnoses other than epilepsy, especially if the preceding wakefulness lacks epileptiform transients. While these findings, if confirmed, may contribute to guide the policy of EEG requests in this particular population, decisions upon ordering sleep studies should always rely on a patient by patient basis.

Tables

Table 1: Yield of sleep EEG for interictal epileptiform abnormalities detection stratified by referral diagnoses

Syndrome. Sleep yield.	Non epileptic sd.	West sd.	GGE.	BOE/ BECTS.	Focal l/c.	ESES.	MAE	Others.
No yield	103 (92,8%)	12 (57,1%)	32 (52,5%)	7 (23,3%)	49 (40,5%)	0 (0%)	9 (45%)	19 (40,4%)
Increase >50% of IEA	0	4 (19%)	9 (14,8%)	15 (50%)	30 (24,8%)	7 (50%)	1 (5%)	3 (6,4%)
New IEA localization	0	2 (9,5%)	6 (9,8%)	0	6 (5%)	0	0	4 (8,5%)
Both	8 (7,2%)	3 (14,3%)	14 (23%)	8 (26,7%)	36 (29,8%)	7 (50%)	10 (50%)	21 (44,7%)
Total	111	21	61	30	121	14	20	47

Table 2: Yield of sleep EEG according to occurrence of interictal epileptiform abnormalities in wakefulness, stratified by referral diagnoses.

		Non-epileptic syndrome	West syndrome	GGE	BOE/ BECTS	Focal l/c	ESES	MAE	Others
No IEA Awake	No yield in sleep.	101 (91 %)	5 (24 %)	17 (28%)	4 (13%)	32 (26%)	0	6 (30%)	9 (19%)
IEA awake.	No yield in sleep.	2 (2 %)	7 (33 %)	15 (25%)	3 (10%)	17 (14%)	0	3 (15%)	10 (21%)
	Yield in sleep.	1 (1 %)	6 (28 %)	16 (26%)	18 (60%)	46 (38%)	14 (100%)	3 (15%)	13 (28%)
Total		111	21	61	30	121	14	20	47

Abbreviations:

IEA: Interictal epileptiform activity.

GGE: Genetic generalized epilepsy.

BOE. Benign occipital epilepsy.

BECTS: Benign epilepsy of childhood with centrotemporal spikes (Rolandic epilepsy).

ESES: Encephalopathy with electrical status epilepticus during slow wave sleep.

Focal l/c: Focal lesional or cryptogenic.

MAE: Myoclonic atstatic epilepsy (Doose sd.).

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