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FULL-LENGTH ORIGINAL RESEARCH

The impact of epilepsy on sleep architecture during childhood

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Summary

Purpose: The effect of etiology on the relationship between epilepsy and sleep during childhood has not been studied in detail. The aim of this study was to evaluate differences in sleep structure in drug-resistant epilepsies with different underlying causes.

Methods: We studied 31 patients with drug-resistant epilepsies with or without a structural lesion (lesional and nonlesional) and compared their sleep architecture with that of normal controls and with that of a group of children with benign epilepsy with rolandic spikes (BERS). Subjects underwent a single-night polysomnographic recording. Sleep recordings were scored according to the American Academy of Sleep Medicine (AASM) and cyclic alternating pattern (CAP) criteria.

Key Findings: Compared to normal controls, patients with drug-resistant epilepsy showed a significant reduction of time in bed, total sleep time, rapid eye movement (REM) sleep, sleep stage N3, and sleep efficiency, and a significant increase in wake after sleep onset. The lesional subgroup showed a reduction in total sleep time and sleep latency and an increase in REM latency and wake after sleep onset. No significant differences, however, were found comparing the lesional and nonlesional subgroups. When compared to BERS, patients with drug-resistant epilepsy showed a significant reduction in sleep stage N3, REM sleep, and sleep efficiency. Regarding CAP analysis, when compared to controls, the drug-resistant group had an increased A1% and a decreased A2%, with a decrease of A1 index in N3 and a global decrease of A2 and A3 indexes. The lesional subgroup showed a slight increase of A1% with a decrease of A1 index in N3 and a global decrease of A2 and A3 indexes. Drug-resistant epilepsy, compared to benign epilepsy showed an increase of CAP rate in N2 and of A1 index in N1 and N2 but not in N3; A2 and A3 indexes were similar in both, but patients with drug-resistant epilepsy showed a significant reduction of A3 index in N1.

Significance: Our findings suggest that the presence of structural cerebral abnormalities may play an important role in disrupting sleep architecture.

KEY WORDS: Sleep, Drug-resistant epilepsy, Lesional epilepsy, Benign epilepsy childhood, Cyclic alternating pattern.

The etiologic repertoire of childhood epilepsies has increased in the past decade, mostly as a result of advances in neuroimaging and molecular genetics. Cases previously regarded as ''cryptogenic'' are now often reclassified as symptomatic to some structural or molecular abnormalities (Duchowny, 2000).

Seizure frequency and degree of control with antiepileptic drugs (AEDs) vary widely in childhood epilepsies, even in the same syndrome category. It has been shown that epilepsies accompanied by magnetic resonance imaging (MRI)–identified structural lesions are often associated with high seizure frequencies and a high degree of refractoriness to AEDs (Duchowny & Harvey, 1996; Kloss et al., 2002; Gupta et al., 2007; Nabbout & Dulac, 2008). In particular, the group of malformations of cortical development is generating a great deal of interest as the most common form of lesional epilepsy in children, often associated with refractory seizures, yet amenable to surgical treatment in several patients (Palmini et al., 1991; Krsek et al., 2008).

There has been a growing interest in the relations between sleep and epilepsy, kindled by the realization that there are many potentially relevant two-way interactions (Bourgeois, 1996). Seizures are frequent during sleep, and both seizures and epileptogenic discharges can disrupt sleep architecture and feed forward in a deleterious cycle of ''covert'' sleep deprivation, leading to an overall increase in seizure frequency (Bourgeois, 1996; Dinner, 2002; Foldvary-Schaefer & Grigg-Damberger, 2009). Furthermore, a number of AEDs may contribute to sleep disruption (Foldvary-Schaefer, 2002).

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On the other hand, disrupted sleep architecture may negatively interfere with spike frequency and seizure control. Enhanced sleep fragmentation and high proportions of wakefulness and light sleep, with a decrease in non–rapid eye movement (NREM) sleep stages 3 and 4 and REM are common polysomnographic findings in individuals with epilepsy (Touchon et al., 1991). Moreover, subjects with epilepsy might show a marked NREM sleep instability, evaluated by means of the cyclic alternating pattern (CAP) analysis. Brief bursts of spikes, polyspikes, and spike-wave discharges are frequently associated with the slow-wave containing A1 subtypes of CAP (and become an integrating part of the A1 phase), leading to an activating effect on epileptiform discharges (whereas phase B seems to exert a powerful and prolonged inhibitory action) (Parrino et al., 2006; Terzaghi et al., 2008).

The effect of the epilepsy etiology on sleep architecture and microstructure during childhood has not been studied in detail.

The aim of this study was to evaluate the differences in sleep architecture and microstructure between drug-resistant epilepsies with different underlying causes and benign epilepsy or controls.

Methods

Participants

Subjects were recruited for this study at the Epilepsy Unit of São Lucas Hospital, Pontifícia Universidade Católica do Rio Grande do Sul, Brazil. Thirty-one consecutive patients (19 male and 12 female; age range 1.5–16.4 years, mean 8.7 years) who met clinical and electroencephalographic criteria for the diagnosis of partial drug-resistant epilepsy were included (Kwan et al., 2009) and classified according to their seizure frequency, following the Engel scale (Engel et al., 1993). The same patients were analyzed and subgrouped according to the presence of a lesion: lesional and nonlesional (normal MRI).

Ten children (six male and four female; age range 6–10, mean 8.1 years) with benign childhood epilepsy with centrotemporal spikes were recruited at the Sapienza University of Rome Department of Developmental Neurology and Psychiatry. They all met the inclusion criteria: diagnosis of benign epilepsy with rolandic spikes (BERS) on the basis of the typical age of onset, seizure semiology, typical wake and sleep electroencephalography (EEG) pattern (centrotemporal spikes), normal development, and no medication at the time of the study.

The normal control group consisted of 23 healthy, nonsnoring children (nine male and 14 female; age range 3–15.4 years, mean 8.3 years) who were retrospectively enrolled from our database of sleep recordings, selecting normal healthy children with no history of severe organic and mental illness and, in particular, without any neurologic or psychiatric disability.

All parents were asked to sign an informed consent form, and the project was approved by the local ethical committee.

Recordings

Subjects with drug-resistant epilepsies underwent a whole-night video-polysomnographic recording using a digital system that consisted of at least 16 EEG channels, electrooculography, electromyography, electrocardiography, nasal airflow, and abdominal respiratory movements. None of the patients had seizures during the night of the recording.

Sleep was subdivided into 30-s epochs and sleep stages were visually scored according to the standard American Academy of Sleep Medicine (AASM) criteria (Iber et al., 2007).

The following conventional sleep parameters were evaluated:

1. Time in bed (TIB);
2. Sleep period time (SPT): time from sleep onset to sleep end;
3. Total sleep time (TST): the time from sleep onset to the end of the final sleep epoch minus time awake;
4. Sleep onset latency (SOL): time from lights out to sleep onset, defined as the first of two consecutive epochs of sleep stage 1 or one epoch of any other stage, in minutes;
5. REM latency (FRL): time from sleep onset to the first REM sleep epoch, in minutes;
6. Number of stage shifts per hour (SS per hour);
7. Number of awakenings per hour (AWN per hour);
8. Sleep efficiency (SE%): the percentage ratio between total sleep time and time in bed (TST/TIB*100);
9. Percentage of SPT spent in wakefulness after sleep onset (WASO%), that is, the time spent awake between sleep onset and end of sleep;
10. Percentage of SPT spent in sleep stages N1 (N1%), N2 (N2%), N3 (N3%), and REM sleep (REM%).

CAP was scored according to the criteria by Terzano et al. (2001). CAP is a periodic electroencephalography activity of NREM sleep characterized by repeated spontaneous sequences of transient events (phase A), recurring at intervals up to 2 min in duration. The return to background activity identifies the interval that separates the repetitive elements (phase B). In particular, phase A candidates are scored within a CAP sequence only if they precede and/or are followed by another phase A in the temporal range of 2–60 s.

CAP A phases have been subdivided into a three-stage hierarchy of arousal strength:

1. A1: A phases with synchronized EEG patterns (intermittent alpha rhythm in N1; sequences of K-complexes or delta bursts in the other NREM stages), associated with mild or trivial polygraphic variations;
2. A2: A phases with desynchronized EEG patterns preceded by or mixed with slow high-voltage waves

(K-complexes with alpha and beta activities, K-alpha, arousals with slow-wave synchronization), linked with a moderate increase of muscle tone and/or cardiorespiratory rate;

3 A3: A phases with desynchronized EEG patterns alone (transient activation phases or arousals) or exceeding two-thirds of the phase A length, and coupled with a remarkable enhancement of muscle tone and/or cardiorespiratory rate.

Sleep and CAP parameters were visually scored using the Hypnolab 1.2 sleep software analysis (SWS Soft, Italy).

Statistical analysis

Comparisons between the control group and subgroups of patients with epilepsy (lesional and nonlesional) were performed using the nonparametric Kruskal-Wallis analysis of variance (ANOVA) for unpaired datasets. Because of multiple comparisons, a Tukey post hoc test was applied. Comparisons between the benign epilepsy with rolandic spikes (BERS) group and the drug-resistant epilepsy group were performed using the Mann-Whitney test.

All statistical analyses were performed with the Statistical Program for Social Sciences software package (SPSS for Windows, version 20; SPSS, Inc., Chicago, IL, U.S.A.).

Results

Table 1 shows the individual clinical features of the drug-resistant patients, as type of epilepsy, frequency of seizures, and antiepileptic drug therapy in use at the time of the study. All patients were taking benzodiazepines in association with other antiepileptic drugs.

Sleep parameters

Compared to normal controls, patients with drug-resistant epilepsy showed a significant reduction of TIB, TST, REM%, N3% and SE. They also showed a significant increase in WASO (see Table S1).

Table 1. Clinical characteristics of the patients with drug-resistant epilepsy

Subject	Age (years)/gender	Epilepsy type	EEG	Engel[a]	AED
1	2.2/M	L2	LT	10	CBZ; VPA; LMT
2	14/F	L2	LF	7	CBZ; VPA
3	4.8/M	L2	RFT	9	CBZ
4	9.5/M	L1	LF	7	VPA
5	15/F	L2	LT	7	VPA; LMT
6	13/F	L2	RT	8	CBZ; VPA
7	3.7/F	L2	LT	9	VPA; TPM
8	13/M	L2	LF	8	VPA; LMT; PBT
9	5.5/M	L2	RT	8	VPA; LMT
10	6.4/M	L1	RT	8	CBZ
11	12.9/M	L2	RT	10	VPA; PHT; LMT
12	16.4/M	L1	LF	9	CBZ
13	6/F	L1	RT	8	VPA; LMT
14	15/F	L1	LF	8	CBZ; VPA
15	2/M	L2	RT	8	OXC
16	13.8/M	L1	LCT	10	VPA; TPM; OXC
17	3.4/M	L1	LT	10	VPA; CBZ
18	10.3/F	L2	LT	7	TPM
19	12.5/F	L2	RFT	7	PHT; OXC
20	2.5/M	L2	RFT	8	OXC; TPM
21	4/M	L2	LT	8	OXC
22	11/F	L2	LFT	9	CBZ
23	2/F	L2	RT	7	CBZ; PBT
24	16.3/F	L2	RF	7	CBZ
25	1.5/F	L2	FP	7	CBZ; TPM
26	14/M	L2	LT	8	CBZ; VPA; PHT
27	6.6/M	L2	RO	10	VPA
28	9/M	L1	LF	8	CBZ
29	7.2/F	L2	LT	10	VPA; LMT
30	11.4/M	L1	RF	7	VPA; OXC
31	4.6/M	L1	LFT	10	VPA; VGB

L1, idiopathic localization-related epilepsy; L2, symptomatic localization-related epilepsy; RT, right temporal; LT, left temporal; RF, right frontal; LF, left frontal; RO, right occipital; RFT, right frontotemporal; LFT, left frontotemporal; AED, antiepileptic drug; CBZ, carbamazepine; VPA, valproate; LMT, lamotrigine; OXC, oxcarbazepine; PHT, phenytoin; VGB, vigabatrin; TPM, topiramate; PBT, phenobarbital.

[a]Seizure frequency classification: 5, 1–3 seizures per year; 6, 4–11 seizures per year; 7, 1–3 seizures per month; 8, 1–6 seizures per week; 9, 1–3 seizures per day; 10, 4–10 seizures per day; 11, >10 seizures per day.

Table 2. Comparison between sleep variables of the two subgroups of patients with drug-resistant epilepsy and controls

	C (n = 23) Mean ± SD	EL (n = 21) Mean ± SD	ENL (n = 10) Mean ± SD	p-Value[a]	Post hoc Tukey C vs. EL p-Value	Post hoc Tukey C vs. ENL p-Value
TIB min	553.7 ± 53.72	509.19 ± 86.35	469.50 ± 38.81	<0.001	0.009	<0.001
SPT min	525.5 ± 56.72	444.26 ± 90	446.15 ± 46.09	<0.001	<0.001	0.001
TST min	512.8 ± 60.36	347.86 ± 82.94	367.90 ± 86.28	<0.001	<0.001	<0.001
SOL min	21.7 ± 15.21	42.71 ± 49.51	13.30 ± 23.98	NS	NS	NS
FRL min	107.8 ± 38.19	214.60 ± 111.31	125.07 ± 83.80	0.013	0.009	NS
SS h	5.3 ± 1.59	2.71 ± 1.22	2.67 ± 1.41	<0.001	<0.001	<0.001
AWN h	0.6 ± 0.64	0.89 ± 0.85	0.74 ± 0.30	NS	NS	NS
SE%	92.6 ± 5.39	69.98 ± 19.39	79.05 ± 20.27	<0.001	<0.001	NS
WASOspt	2.5 ± 2.91	19.01 ± 20.57	17.03 ± 20.38	0.004	0.004	0.033
N1spt	3.8 ± 3.85	17.88 ± 24.05	16.43 ± 18.38	0.042	0.048	NS
N2spt	47.2 ± 5.29	50.41 ± 25.58	50.53 ± 27.98	NS	NS	NS
N3spt	23.7 ± 5.31	7.16 ± 7.47	6.87 ± 9.57	<0.001	<0.001	<0.001
REMspt	22.9 ± 5.04	5.52 ± 5.38	9.14 ± 9.94	<0.001	<0.001	<0.001

[a]Kruskal-Wallis ANOVA; C, controls; EL, epilepsy lesional; ENL, epilepsy nonlesional.

The group of drug-resistant epilepsy was subdivided into two subgroups, according to a presence of a cerebral lesion. Table 2 shows the statistical comparison between the sleep architecture parameters obtained from children with epilepsy (lesional and nonlesional) and controls. The lesional subgroup showed a reduction in TST and SE and N3% and an increase in N1%, REM latency, and WASO when compared to controls. The nonlesional subgroup also showed a reduction in TST, N3%, and REM sleep, but no differences were observed concerning first REM latency (FRL) and SE% when compared to controls. No statistically significant differences were found between the lesional and nonlesional subgroups.

Compared with BERS subjects, children with drug-resistant epilepsy had a significant reduction in N3%, REM%, SE, and in number of stage shifts per hour (see Table S2).

The assessment of CAP revealed several differences between subjects with drug-resistant epilepsy and normal controls including increased indexes of all A subtypes (see Table S3). The comparisons between the epilepsy subgroups and controls are summarized in Table 3. The lesional subgroup showed a lower CAP rate in N1 and reduction of A2 and A3 indexes.

With respect to BERS, patients with drug-resistant epilepsy showed an increase of CAP rate in N2 and of A1 index in N1 and N2 but not in N3. A2 and A3 indexes were similar in both, but patients with drug-resistant epilepsy showed a significant reduction of A3 index in N1. (see Table S4).

Discussion

We found that children with drug-resistant epilepsy have longer sleep-onset latency, increased number and duration of awakenings after sleep onset, reduced SE, and REM sleep with delayed REM latency. We also observed an important decrease in TST and SWS.

Sleep organization in children with epilepsy has been generally assessed in small groups of patients and mostly with respect to gross sleep architecture parameters (Baldy-Moulinier, 1992; Hunt & Stores, 1994; Bruni et al., 1995; Barreto et al., 2002; Nunes et al., 2003; Maganti et al., 2005; Kaleyias et al., 2008). Epilepsy per se and/or the seizures themselves may promote sleep disruption and significantly affect the quality, quantity, and the architecture of sleep (Kothare & Kaleyias, 2010). Patients with epilepsy generally have sleep architecture abnormalities such as increased number and duration of awakenings, reduced sleep efficiency, reduced or abnormal K complexes and sleep spindles, reduced and fragmented REM sleep, and increased stage shifts (Nunes et al., 2003).

In a collaborative study, Nunes et al. (2003) evaluated sleep organization in pediatric patients with partial refractory epilepsy showing that they have only mild sleep structure abnormalities, and this can be considered either an effect of the epileptic syndrome or the result of the chronic antiepileptic drug treatment. These authors reported a reduction of TIB and TST, and the percentage of stage 2 was significantly reduced in patients with epilepsy who presented seizures during the recordings, whereas the percentage of stages 3–4 was increased. In children with epilepsy and tuberous sclerosis, Bruni et al. (1995) found sleep abnormalities represented by a decrease of sleep efficiency and of REM sleep and an increase of light sleep and WASO.

Drug-resistant seizures are related to sleep abnormalities more often than infrequent seizures. Kaleyias et al. (2008) studied the possible association between sleep abnormalities and seizure control and observed that the subgroup of children with poor control of seizures exhibited a decrease

Table 3. Comparison between CAP parameters between the two subgroups of drug-resistant epilepsy and controls

	C (n = 23) Mean ± SD	EL (n = 21) Mean ± SD	ENL (n = 10) Mean ± SD	p-Value[a]	Post hoc Tukey C vs. EL p-Value	Post hoc Tukey C vs. ENL p-Value
CAP rate%	32.17 ± 10.92	29.08 ± 23.09	27.13 ± 17.86	NS	NS	NS
In N1	27.85 ± 21.22	13.05 ± 19.67	22.11 ± 17.98	0.026	0.018	NS
In N2	27.17 ± 12.50	30.21 ± 24.64	31.38 ± 18.17	NS	NS	NS
In N3	43.56 ± 12.38	32.07 ± 27.91	30.88 ± 30.97	NS	NS	NS
A1%	72.93 ± 12.39	84.62 ± 17.09	82.34 ± 8.78	0.002	0.001	NS
A2%	15.81 ± 8.83	3.98 ± 5.76	4.36 ± 3.77	<0.001	<0.001	<0.001
A3%	11.26 ± 5.13	11.38 ± 16.75	13.33 ± 6.81	NS	NS	NS
A1 index	38.26 ± 16.86	40.38 ± 37.76	29.80 ± 19.28	NS	NS	NS
In N1	24.55 ± 21.04	20.44 ± 26.32	34.12 ± 36.02	NS	NS	NS
In N2	34.32 ± 17.24	44.46 ± 40.51	38.59 ± 22.29	NS	NS	NS
In N3	70.35 ± 22.82	29.81 ± 36.32	19.49 ± 34.75	<0.001	<0.001	<0.001
A2 index	7.60 ± 5.35	0.99 ± 1.28	1.40 ± 1.71	<0.001	<0.001	<0.001
In N1	7.04 ± 7.37	2.53 ± 4.32	0.58 ± 1.13	0.016	NS	0.021
In N2	10.52 ± 6.49	1.42 ± 1.83	2.22 ± 2.62	<0.001	<0.001	<0.001
In N3	6.76 ± 4.41	1.67 ± 5.23	0.57 ± 1.30	<0.001	<0.001	<0.001
A3 index	4.64 ± 2.97	1.64 ± 1.88	3.40 ± 3.24	0.001	<0.001	NS
In N1	17.70 ± 12.46	3.48 ± 4.78	6.67 ± 5.26	<0.001	<0.001	NS
In N2	7.57 ± 3.05	2.96 ± 2.99	5.12 ± 4.62	<0.001	<0.001	NS
In N3	2.62 ± 1.82	1.59 ± 2.78	1.18 ± 2.45	0.003	0.007	0.009

[a]Kruskal-Wallis ANOVA; C, controls; EL, epilepsy lesional; ENL, epilepsy nonlesional.

in sleep efficiency, a higher arousal index, and an increased percentage of REM sleep compared with children who were seizure-free or exhibited good seizure control.

In this new study, when we subdivided the drug-resistant epilepsy group into two subgroups, according to the presence or absence of cerebral lesions, we observed a greater reduction in TST, SE, and REM sleep time and increased sleep latency in patients with lesional epilepsy, compared to the normal control group and the nonlesional subgroup, suggesting that the presence of structural cerebral abnormalities may play an important role in disrupting sleep architecture. These findings seem to be in some agreement with those of previous studies reporting that children affected by symptomatic partial epilepsy show permanent modifications in sleep architecture, including an increased number of stage shifts, a reduced number of REM periods, and percentage of sleep stage 2 and REM sleep (Deray & Epstein, 1991; Bruni et al., 1995).

The localization-related epilepsies are believed to result from a focal region of cerebral dysfunction and presumably reflect a more severe pathophysiology than that seen in primary generalized epilepsies because individual neurons in the focus exhibit sudden depolarization shifts, which probably represent giant excitatory postsynaptic potentials (Gloor & Fariello, 1988).

The pathogenetic mechanism underlying the spike generation during sleep is complex: it has been demonstrated that within NREM sleep, the facilitating influences on IED production is exerted separately by either spindle activity or delta synchronization mechanisms and that the activating properties of sleep are not due to the stage per se but depend largely on the level of activity of synchronizing mechanisms (Ferrillo et al., 2000). Synchronization of epileptiform spikes and slow oscillation during sleep involve the synchronous bursting-mode of the thalamocortical system, where spikes of the cortical neurons are highly synchronized, driven by the γ-aminobutyric acid (GABA)ergic gating machine of the thalamic reticular nucleus. Therefore, during slow sleep, the cortex is prone to abnormal synchronizing processes. Nobili et al. (1999) suggested that in lesional partial epilepsy a regional hyperexcitability in the epileptogenic cortex can transform the thalamic volley that normally induces sleep spindles in a spike and wave burst inducing mechanism. The thalamic origin of spike-wave was proposed in the late 1940s and was replaced by the idea that sleep spindles develop into spike wave seizures because of an enhanced excitability of neocortical neurons (Gloor & Fariello, 1988). On the other hand, the slow wave activity mode of activation in adult partial epilepsy seems to be linked to the hyperpolarization-activated spike bursts that occur in isolated pools of thalamocortical neurons that generate delta wave oscillations.

Contrary to this traditional view, however, neuronal spiking during seizure initiation, and spread is highly heterogeneous and not hypersynchronous, suggesting complex interactions among different neuronal groups; even neurons outside the region of seizure onset showed significant changes in activity minutes before the seizure, suggesting

that it may be possible to obtain predictive information from individual neuronal activity without necessarily localizing what has been traditionally considered to be the seizure focus (Truccolo et al., 2011). This observation could explain the mechanism by which the epilepsy and spiking activity affect the sleep structure through the abnormal activation of different brain regions devoted to the sleep promoting mechanisms (Truccolo et al., 2011).

Although abnormalities in sleep architecture might be caused by AEDs, the results of the different studies are inconclusive. We compared children with drug-resistant epilepsy to a group of children with BERS without antiepileptic medication. In comparison with BERS, patients with drug-resistant epilepsy showed a reduction of TST and of number of stage shifts per hour, increased number and duration of awakenings after sleep onset, and a decrease of SE, N3, and REM sleep.

AEDs are able to modify the frequency and course of the epileptic phenomena and sleep architecture (Placidi et al., 2000). Their stabilizing sleep effect is represented mainly by the reduction in number of stage shifts per hour in patients with drug-resistant epilepsy, but despite the use of drugs, including benzodiazepines, they still showed increased number and duration of awakenings after sleep onset and lower TST, indicating that some effects might tend to disappear with treatment chronicity (Legros & Bazil, 2003).

This study is the most comprehensive analysis of CAP in drug-resistant epilepsies to date. This analysis showed a reduction of CAP rate and reduction of A2 and A3 indexes in association with an increase of A1%. However, A1 index was reduced in N3, when compared to normal control; this finding reflects a decrease of transient slow EEG oscillations during NREM sleep that has been related to poor cognitive functioning (Ferini-Strambi et al., 2004; Pereira et al., 2012). The same difference was found when we compared drug-resistant epilepsy and benign rolandic epilepsy: A1 index was significantly reduced in slow wave sleep in drug-resistant epilepsy.

The reduction of NREM sleep instability in our patients is represented by a decrease of A1 index in N3 but also of the A2 and A3 indexes that correspond to EEG arousals. This finding might be related to the underlying pathology and/or to the effects of antiepileptic drugs that affect sleep structure by reducing arousal number and the whole sleep EEG oscillatory patterns (Bruni et al., 2007; Miano et al., 2010). It is interesting to note that other types of variability, such as heart rate have also been reported to be decreased in treated children with partial epilepsy (Ferri et al., 2002).

We should take into account that the interictal EEG abnormalities could be in part responsible for the sleep microstructure changes. Furthermore, some limitations should be noted: (1) in the lesional subgroup we have included patients with different etiologies, (2) all patients with drug-resistant epilepsies were chronically treated with antiepileptic drugs including a benzodiazepine and the role of these drugs in biasing our findings cannot be definitely ruled out, (3) the AEDs related changes in the sleep architecture were not taken into consideration.

Our findings show a wide range of sleep abnormalities in children with drug-resistant epilepsies, and these abnormalities are more evident when there is a visible lesion, similar to what has been reported in children with symptomatic partial epilepsy. Further understanding of the relationships between epilepsy and disruption of sleep architecture is certainly important because it is common knowledge that in a sizable proportion of patients there operates a vicious cycle in which seizures disrupt sleep and such sleep disruption leads, in turn, to greater vulnerability to seizures. Breaking this cycle becomes a priority in many of these patients.

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Disclosure

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Comparison between sleep variables of patients with drug-resistant epilepsy and controls.

Table S2. Comparison between sleep variables of two groups of patients with epilepsy: drug-resistant and benign childhood with rolandic spikes (BERS).

Table S3. Comparison between CAP parameters of drug-resistant epilepsy and controls.

Table S4. CAP parameters in patients with drug-resistant epilepsy and BERS.

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