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Reduced NREM sleep instability in benign childhood epilepsy with centro-temporal spikes

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ABSTRACT

Objective: To analyze sleep architecture and NREM sleep instability by means of the cyclic alternating pattern (CAP) in children with benign epilepsy with rolandic spikes (BERS).
Methods: Ten children with BERS, drug free at the time of the study and 10 age-matched normal controls were included in this study. Sleep was visually scored for sleep architecture and CAP using standard criteria.
Results: Sleep architecture in BERS showed only few significant differences vs. controls with a reduction of total sleep time, sleep efficiency, and REM sleep percentage. CAP analysis revealed several significant differences: reduced total CAP rate, mainly in sleep stage 2, and reduced EEG slow oscillations and arousals during stages N1 and N2.
Conclusions: Sleep architecture is not importantly affected in BERS but CAP analysis reveals a decrease of NREM instability, mainly in sleep stage 2. Since there is a spindle-related spike activation in BERS, we speculate that the decrease of CAP and of EEG slow oscillations and arousals might be linked with the inhibitory action of spindling activity and spikes on arousals.
Significance: CAP analysis discloses sleep structure abnormalities in children with BERS not shown by the classical sleep scoring. Spike activity and CAP A1 subtypes seem to be mutually exclusive probably because centro-temporal spikes disturb the physiological synchronization mechanisms needed for the generation of slow-wave components of CAP.

1. Introduction

Benign childhood epilepsy with rolandic spikes (BERS) is the most common epileptic syndrome in childhood, with idiopathic etiology, a high genetic predisposition and a benign course (Kramer, 2008). Typical seizures are characterized by hemifacial motor seizures and may be preceded by somatosensory symptoms involving the inner cheek, tongue, and lips (Aicardi, 1979; Lombroso, 1967). By definition, centro-temporal spikes (CTS) are the hallmark of BERS. CTS are often bilateral and typically activated by drowsiness and slow (non-REM) sleep, but not by overbreathing (Clemens and Majoros, 1987). In the same child, CTS may occur right or left, infrequently or frequently, and appear small or giant, alone or with spikes in other locations (Panayiotopoulos et al., 2008).

The seizures occur during sleep, mostly night sleep but also during day sleep, in approximately 75% of the affected children, and usually appear just after the children falls asleep or close to the time of awakening (Lerman and Kivity, 1975).

Although the rolandic seizures occur mainly during sleep, studies on sleep in patients with BERS are scarce. One of the first study on this topic (Clemens and Olah, 1987) showed that no specific or clear-cut pathological alterations of sleep can be found. These authors concluded that epileptic malfunctioning of neuronal aggregates does not affect sleep organization and that the lack of detrimental interactions between epilepsy and sleep in this group may be related to the benign course of BERS. The same authors

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showed a clear increase of the spike activity in the first cycle of sleep related to slow sleep stages but also they observed a decrease in spike density during stages 1–2 on the descending slope of consecutive cycles in the hypnogram, and an increasing rate of activation on the ascending slopes (Clemens and Majoros, 1987).

Sleep structure is usually affected by lesional epilepsy with an increase of sleep fragmentation and high percentage of wakefulness and light sleep, with a decrease in slow-wave sleep (SWS) and REM sleep (Touchon et al., 1991). In addition, marked sleep instability is often observed in epileptic patients, even in the absence of nocturnal seizures (Herman, 2006). On the other hand, in primary forms of epilepsy (absence or primary generalized epilepsy, juvenile myoclonic epilepsy, partial benign epilepsies of childhood) sleep architecture is often normal but nocturnal interictal discharges basically have different effects on cyclic alternating pattern (CAP) parameters (Parrino et al., 2006).

It has been observed that both interictal and ictal discharges are more frequent during NREM sleep and show a strict association with K-complexes (Niedermeyer, 1965; Passouant et al., 1962) or spindles (Nobili et al., 2001). Moreover, Steriade and Amzica (1998) showed that epileptic spike and waves are driven by conversion of slow cortical oscillation (<1 Hz) into recurrent paroxysmal discharges.

Although important evidence is in favor of CAP as a modulating factor of epileptiform discharges and seizures in epilepsy (Eisensehr et al., 2001; Manni et al., 2005; Parrino et al., 2001, 2006; Terzaghi et al., 2009; Terzano et al., 1991b), the only epileptic syndrome that has shown an independence from CAP seems to be BERS that, despite the high spike index during NREM sleep, does not seem to be modulated by CAP oscillations. In general, in all the benign forms of epilepsy in childhood, focal spike discharges seem to show no significant relationship with CAP (Terzano et al., 1991a,b). The first study on CAP in children with BERS was conducted more than 15 years ago evaluating how the CAP and non-CAP conditions affected CTS distribution during sleep (Terzano et al., 1991b). These authors showed no significant differences in spike distribution throughout CAP and NCAP modalities and stated that, despite the high burst frequency during NREM, interictal discharges of CTS are not modulated by the arousal-related mechanisms of CAP.

The independence of CTS from CAP cannot exclude a possible relation between them and other microstructural events, such as sleep spindles which are generally disjoined from the CAP (especially phase A) patterns (Parrino et al., 2000). It has been demonstrated that the interictal discharges in BERS coincide with the peaks of sigma (sleep spindles) activation (Nobili et al., 1999b) suggesting that during sleep of BERS patients, CTS are sensitive to the promoting action of the spindle generating mechanism, while slow-wave activity does not seem to play a facilitating role or is even inversely correlated with CTS distribution (Nobili et al., 1999b, 2000).

The strict relationship of CTS with spindles might explain the relative independence of CTS from the CAP A phase modulation since during the entire duration of phase A there is a sustained depression of the sigma spectral band activities (Bruni et al., 2009; Ferri et al., 2005) and, therefore, the neurophysiological substrate for the occurrence of CTS is lacking.

Since spindling activity is commonly associated with a reduction of arousals and slow EEG oscillations during sleep (Naitoh et al., 1982; Steriade et al., 1993) and CTS are independent from CAP modulation and linked with sigma activity, we can expect that in BERS there might be a reduction of CAP rate (due to the inhibitory influence of spindles on arousals) and a decrease of the A phases with special effect on the A1 subtype.

Since the previous old study on CAP in BERS (Terzano et al., 1991b) evaluated only the CAP/NCAP condition and did not take into account the role of the different CAP A phases, the aim of our new study was to analyze in details CAP in sleep polysomnographic recordings of children with BERS and to confirm our hypothesis of a decreased NREM sleep EEG oscillations in these subjects.

2. Method

2.1. Participants

For the purpose of this study, we recruited 10 children with BERS (mean age 8.1 years, range 6–10), who met the following inclusion criteria:

- Diagnosis of BERS on the basis of the typical age of onset, seizure semiology, typical wake and sleep EEG pattern (CTS) and normal development.
- Absence of known daytime consequences of sleep disorders (e.g., daytime sleepiness, cataplexy, hyperactivity, morning headache, mouth breathing).
- No medication at the time of the study.

Patients with BERS were recruited at the Child Neuropsychiatry Unit of the second faculty of Medicine and Surgery, of the "Sapienza" University of Rome.

Ten age-matched normal controls (mean age 7.8 years, range 6–10) 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 neurological or psychiatric disability.

All parents were asked to sign a consent form approved by the institution in which sleep recordings were carried out.

2.2. Polygraphic sleep recordings

For this study, subjects underwent an overnight polysomnographic recording (PSG) after one adaptation night, in order to avoid the first-night effect.

The EEG recordings and electrode placement were performed according the 10–20 system and the PSG montage included at least 4 EEG channels (C3, C4, O1, O2) referenced to the contralateral mastoid, left and right electrooculogram (EOG), chin electromyogram (EMG), left and right tibialis anterior EMG and electrocardiogram (ECG). All recordings started at the subjects' usual bedtime and continued until spontaneous awakening.

2.3. Sleep stage scoring

Sleep was subdivided into 30-s epochs and sleep stages were scored according to the standard AASM criteria (Iber et al., 2007). The following conventional sleep parameters were evaluated:

- Time in bed (TIB);
- Sleep period time (SPT): time from sleep onset to sleep end;
- Total sleep time (TST): the time from sleep onset to the end of the final sleep epoch minus time awake;
- 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
- R latency (RL): time from sleep onset to the first REM sleep epoch, in minutes;
- Number of stage shifts/hour (SS/hour);
- Number of awakenings/hour (AWN/hour);
- Sleep efficiency (SE%): the percentage ratio between total sleep time and time in bed (TST/TIB * 100);