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Sleep Spindle Alterations in Patients with Malformations of Cortical Development

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Abstract

Malformations of cortical development are disorders of altered brain anatomy and architecture that arise from abnormalities in the usual processes of cerebral cortical development. Although they often lead to epilepsy, cognitive delay, and motor impairment, little is known about their effect on sleep. Since malformations may anatomically or functionally disrupt the cerebral circuits that mediate sleep spindles, we hypothesized that these disorders would be associated with abnormal spindle characteristics. We analyzed the density, maximum frequency, laterality and distribution of sleep spindles seen in routine and long-term electroencephalographic recordings performed in ten brain malformation subjects and ten matched controls. There were no significant differences in spindle density or maximum frequency between the two groups, but malformation subjects had a significantly lower proportion of bilateral spindles and a significantly higher proportion of anterior and diffuse spindles compared to controls. In addition, unilateral malformations appeared to be associated with a skewing of unilateral spindles toward the contralateral side. Our findings suggest that brain malformations disrupt the thalamocortical circuits responsible for sleep spindle generation, and support the need for further studies on the relationships between cortical maldevelopment and sleep.

Keywords

sleep spindles; malformations of cortical development; epilepsy

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Introduction

Malformations of cortical development (MCDs) are congenital brain disorders arising during embryonic and fetal development that are characterized by abnormalities in the volume, location, or architecture of cerebral gray and white matter. Clinically, MCDs commonly cause epilepsy, cognitive delay, and motor impairment. The effect of these developmental malformations on the clinically and neurophysiologically important brain function of sleep, however, has not been well-studied.

MCDs are most readily recognized by the visible anatomical changes in gray matter [1]. However, there is now extensive evidence of functionally important disruptions in white matter connectivity associated with these disorders as well. For example, some patients with subcortical gray matter heterotopia (including subcortical band heterotopia and periventricular nodular heterotopia) have demonstrated deficits in reading fluency or processing speed that may be the result of abnormalities in cortico-cortical white matter pathways [2-4]. In addition, regions of gray matter heterotopia have been shown to be functionally co-active with the overlying cortex during the performance of simple tasks, suggesting the presence of aberrant cortical-subcortical white matter circuits in these disorders [5,6].

Sleep spindles are neurophysiologic signatures of stage II sleep that are easily identifiable on scalp electroencephalography (EEG) recording and depend on intact white matter connections for their normal expression. They appear to be generated by reciprocal interactions between subcortical thalamic structures and the cerebral cortex [7], and acquired lesions that may disrupt thalamocortical pathways lead to alterations in spindle characteristics [8-10].

We sought, therefore, to analyze the effect of cortical maldevelopment on the generation of sleep spindles. Here we demonstrate that patients with brain malformations indeed have significant and specific alterations in spindle expression compared to matched controls.

Methods

Subjects

Patients with neuroimaging-confirmed diagnoses of MCD who had a digital routine or long-term EEG monitoring study at our institution within the past seven years demonstrating at least a single sleep spindle were eligible for inclusion in this study. Ten such subjects were identified from clinical records, clinician referrals, and a research database of brain malformation patients at our institution.

For each malformation subject, an age- and sex-matched control subject was identified by selecting a patient without epilepsy who had had an EEG study of the same type (routine or long-term monitoring), demonstrating at least a single sleep spindle, within one year's time of the malformation subject's study. This was accomplished by progressively scanning consecutive procedure log numbers in our institution's EEG database and identifying patients who were within five years of age and of the same sex as the malformation subject. The control subjects had EEGs performed for evaluation of nonepileptic events, syncope, panic attacks, or, in two subjects, a remote history of seizures (more than ten years prior). Control subjects' neuroimaging with magnetic resonance imaging (MRI) demonstrated either entirely normal brain anatomy (in five) or incidental abnormalities (cerebellar encephalomalacia (one), nonspecific T2 white matter hyperintensities (three), or quadrigeminal cistern arachnoid cyst (one)).

Detailed clinical information was recorded on all 20 subjects, including MCD type, location and laterality, if appropriate, and the use of antiepileptic drugs (AEDs), including specifically benzodiazepines and barbiturates (because of their effect on fast EEG activity). This study was performed according to a protocol approved by the institutional review board of Beth Israel Deaconess Medical Center, Boston; due to its retrospective nature, the need for written informed consent was waived.

EEG Methods

All EEG studies were recorded using silver-chloride, gold-plated electrodes placed according to the 10-20 International system, with recorded impedances of less than 5 k Ω at all electrodes. All routine studies utilized both bipolar and average referential montages, while long-term monitoring studies utilized either a bipolar longitudinal montage or a bipolar longitudinal/transverse montage with subtemporal (T1/T2) electrodes. Initial analog signal conditioning included a 0.0-0.1 Hz high pass filter, a 30-70 Hz low pass filter and a 60 Hz notch filter. The digital sampling rate was 200-500 per second.

Sleep Spindle Analysis

For each subject, a 30-second epoch beginning with the first noted sleep spindle was analyzed by visual inspection. Sleep spindles were defined as waveforms distinct from the background with a frequency between 12-16 Hz [11], duration between 0.5-2 seconds and occurring in the context of EEG activity consistent with stage II sleep (slowing of posterior dominant rhythm and presence of vertex waves). Spindle density and maximum spindle frequency were measured for each subject's 30-second epoch. Sleep spindle laterality (bilateral, left, or right) and distribution (anterior, central, posterior or diffuse) for each noted spindle were recorded; distribution and laterality were determined by visual analysis based on region of greatest sleep spindle amplitude. Two electroencephalographers, blinded to subject status and diagnosis, independently scored each record and resolved differences by consensus.

Statistical Analysis

Differences in mean spindle density between malformation subjects and control subjects were analyzed for significance using a two-tailed Student t-test, while differences in mean maximum spindle frequency were analyzed using the Mann-Whitney U test as these two datasets had unequal variances. Differences in spindle laterality (unilateral or bilateral) and distribution (anterior, central, posterior, or diffuse) between malformation subjects and control subjects were analyzed using chi-squared tests. A threshold of $\alpha < 0.05$ was used in all cases for significance.

Results

The ten malformation subjects and ten control subjects were well-matched for age, sex and study type (Table 1). Malformation subjects were more likely to take AEDs at the time of the EEG recording, but this was not a significant difference (odds ratio 5.4, 95% confidence interval 0.80-36.88, $p=0.18$), and the rates of benzodiazepine and barbiturate use were similar between the two subject groups (OR 2.7, 95% CI 0.36-19.72, $p=0.63$). AED dosages were all within generally accepted ranges used in clinical practice. Four MCD subjects had unilateral malformations, while six had bilateral malformations (Figure 1). Specific malformation subtypes included periventricular nodular heterotopia, focal cortical dysplasia, polymicrogyria, and schizencephaly; malformation locations included diffuse, parietooccipital, temporal, parietal, and temporoparietal (Table 2).

There were no differences between the malformation subjects and control subjects in either mean spindle density (3.9 spindles/30 seconds vs 4.2 spindles/30 seconds, $p=0.79$) or in mean

maximum spindle frequency (13.1 Hz vs 13.9 Hz, $p=0.23$). However, significant differences were seen in the laterality (Figure 2) and anatomical distribution (Figure 3) of spindles between the two groups (Table 1). Malformation subjects had a significantly higher proportion of unilateral sleep spindles compared to controls (OR 2.7, 95% CI 1.1-6.80, $X^2=4.40$, $p=0.04$). Furthermore, subjects with unilateral malformations appeared to demonstrate a skewing of unilateral spindles toward the contralateral side, with fewer ipsilateral spindles, although the sample sizes were small. Finally, malformation subjects had a significantly different overall anatomical distribution of sleep spindles, with an increased proportion of both anterior and diffuse spindles ($X^2=4.19$, $p=0.04$).

Discussion

Here we demonstrate that developmental brain malformations are associated with significant and specific alterations in sleep spindle expression, with a decreased proportion of bilateral and an increased proportion of unilateral spindles. Our findings suggest that unilateral malformations may be associated with a skewing of spindles toward the hemisphere contralateral to the malformation. In addition, the increased proportion of anterior spindles seen with malformations in our study may represent a similar phenomenon, since our malformation subjects had predominantly posterior lesions. Our findings imply that MCDs can functionally disrupt the normal thalamocortical projections that mediate sleep spindle generation in the human brain.

Our study has several limitations. Most importantly, our sample size was small, given the relative infrequency of these malformations. Nonetheless, even with limited numbers of subjects we were able to detect a robust difference in spindle laterality and distribution, suggesting a strong biological effect. Further studies with larger series of patients would allow for more refined analyses of the effects of malformation location and specific malformation type on spindle expression. For our retrospective case-control design, we attempted to match control subjects as closely as possible to malformation subjects based on age, sex, and type and timing of EEG study. However, potential unidentified confounding factors could of course remain. Malformation subjects showed a nonsignificantly higher rate of AED use; while these drugs have been shown to affect sleep staging [12], there is less reason to suspect that they should produce focal changes in sleep spindle expression.

Our findings complement reports in the literature on the effect of acquired brain lesions on sleep spindles. A decrease in proportion of bilateral spindles was also seen with unilateral thalamic strokes, for example [8]. The decrease in ipsilateral spindle expression that we observed in the presence of unilateral malformations was also seen with acute unilateral hemispheric strokes [9], suggesting that both developmental and acquired lesions that interfere with thalamocortical projections unilaterally may lead to a decrease in symmetric, bilateral spindles and a skewing of unilateral spindles toward the contralateral side. Furthermore, a decreased expression of posterior spindles was also seen with unilateral cortical strokes; this may reflect a greater predominance of posterior strokes (although stroke locations were not reported) or may suggest difficulty with projection of sleep spindles posteriorly with cortical strokes. Interestingly, the hemisphere in which the seizure focus resides in patients with symptomatic partial epilepsy has been associated with an increase in ipsilateral spindle expression, rather than a decrease; this has been theorized to result from increased irritability (and possibly rhythmicity) of the epileptogenic cortex [10].

Since depth electrode studies of brain malformations suggest that regions of dysplasia or heterotopia themselves have an intrinsic epileptogenicity [13], the relative changes in sleep architecture due to anatomical malformations and their functional hyperexcitability warrant further study. A simplistic view of the effect of MCD location on spindles might predict that

cortical abnormalities would be expected to lead to an increase in sleep spindles resulting from increased rhythmicity and hyperexcitability, while subcortical abnormalities would be more likely to interrupt thalamocortical projections and focally decrease the expression of spindles. However, it is likely that much more complicated effects are at work, based on the complex network of cellular interactions that have been shown to mediate cerebral synchrony and spindle oscillations [14,15].

Further neurophysiological studies, including those targeting evoked potential responses, other EEG patterns during sleep, or baseline EEG activity during wakefulness (using quantitative spectral methods) would expand our understanding of the functional effects of cortical maldevelopment. In addition, a better understanding of sleep architecture may hold direct importance for the clinical care of patients with developmental brain malformations, since there is a high incidence of medically refractory epilepsy in this population and seizures and interictal epileptiform discharges are known to be activated by non-rapid eye movement sleep [12]. Furthermore, since sleep has been demonstrated to improve memory consolidation and learning [16], potential changes in sleep architecture with MCDs may also be relevant to a complete understanding of the cognitive difficulties observed in many patients with these disorders. Prospective studies using sleep symptom questionnaires, clinical sleep evaluations, and polysomnography in this population may help to shed light on the relationship between the neurophysiologic alterations we report here and broader effects on sleep quality and architecture.

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Figure 1. Bilateral and unilateral malformations of cortical development

A T2-weighted axial magnetic resonance image from a patient with bilateral periventricular nodular heterotopia (left) demonstrates multiple confluent nodules of heterotopic gray matter lining the lateral walls of the ventricles bilaterally, often protruding into the lumen (white arrowheads). A T2-weighted coronal magnetic resonance image from a patient with unilateral focal cortical dysplasia (right) demonstrates an abnormally broad gyrus with increased cortical thickness and blurring of the gray matter-white matter junction in the left suprasylvian region (white arrow).

Figure 2. Laterality of sleep spindles in subjects with malformations of cortical development

Examples of bilateral (left), left-predominant (middle), and right-predominant (right) spindles observed in EEG recordings from cortical malformation subjects in this study are highlighted (yellow). EEG was obtained using electrodes placed according to the 10-20 International system; montage is indicated by labels on left side of image. Spindles were defined as waveforms distinct from the background with a frequency between 12-16 Hz, duration between 0.5-2 seconds and occurring in the context of EEG activity consistent with stage II sleep. The dark and yellow vertical lines represent time markers on the digital recordings.

Figure 3. Anatomical distribution of sleep spindles in subjects with malformations of cortical development

Examples of diffuse, anterior, posterior, and central spindles (from left to right) observed in EEG recordings from cortical malformation subjects in this study are highlighted (yellow). EEG was obtained using electrodes placed according to the 10-20 International system; montage is indicated by labels on left side of tracings. Spindles were defined as waveforms distinct from the background with a frequency between 12-16 Hz, duration between 0.5-2 seconds and occurring in the context of EEG activity consistent with stage II sleep. The dark and yellow vertical lines represent time markers on the digital recordings.

Table 1
Group characteristics and sleep spindle analysis of cortical malformation subjects and matched controls

	Malformation	Control
Subjects, number (sex)	10 (9 female)	10 (9 female)
Age, mean (SD)	35.7 (12.2)	35.6 (14.3)
Study type	6 LTM, 4 routine	6 LTM, 4 routine
Medication usage		
Number using AEDs	7	3
Number using benzodiazepines or barbiturates	4	2
Spindles by laterality, total number		
Unilateral	19	9
Bilateral	20	33
Spindles by distribution, total number		
Anterior	17	12
Central	8	10
Posterior	3	3
Diffuse	11	17

Statistical analyses are presented in text of Results. Abbreviations: SD = standard deviation; LTM = long-term monitoring; AEDs = antiepileptic drugs.

Table 2
Detailed characteristics of developmental lesions and sleep spindles in cortical malformation subjects.

Subject	Malformation Type	Malformation Laterality and Location	Neurological Features	Laterality of Spindles Number (%)			Location of Spindles Number (%)			
				Symmetric	Left Dominant	Right Dominant	Anterior	Central	Posterior	Diffuse
1	Schizencephaly	R temporoparietal	DD, seizures	1(50)	1(50)	0	1(50)	0	0	1(50)
2	Pachygyria and PNH	R parietooccipital	DD, seizures	3(43)	2(29)	2(29)	3(43)	1(14)	1(14)	2(29)
3	FCD	L lateral temporal	Seizures	5(83)	0	1(17)	1(17)	0	0	5(83)
4	FCD	L medial temporal	Seizures	1(50)	0	1(50)	2(100)	0	0	0
5	Pachygyria	B parietal	Aggression, seizures	3(75)	1(25)	0	4(100)	0	0	0
6	PNH	B diffuse	Seizures	2 (22)	5(56)	2(22)	1(11)	5(56)	2(22)	1(11)
7	PNH	B diffuse	MR/CP, night terrors	1(100)	0	0	0	0	0	1(100)
8	PNH	B diffuse	Seizures	1(100)	0	0	0	1(100)	0	0
9	Polymicrogyria	B parietooccipital	DD, seizures	3(100)	0	0	3(100)	0	0	0
10	FCD and encephalomalacia	B parietooccipital and L frontal	Mild MR, seizures	1(25)	1(25)	2(50)	2(50)	1(25)	0	1(25)

R = right; L = left; B= bilateral; PNH = periventricular nodular heterotopia; FCD = focal cortical dysplasia; DD = developmental delay; MR = mental retardation; CP = cerebral palsy