

Autoimmune Epilepsy and/or Limbic Encephalitis Can Lead to Changes in Sleep Spindles

Otoimmün Epilepsi/Limbik Ensefalit, Uyku İğciklerinde Değişikliğe Neden Olabilir

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ABSTRACT

Introduction: Sleep disorders have been described in patients with autoimmune limbic encephalitis (LE). The changes in sleep structure were also reported. Recently sleep spindle abnormalities such as asynchronous or prolonged spindles were observed children with LE.

Methods: We studied the sleep and number of sleep spindles in the continuous electroencephalography-polysomnography (EEG-PSG) recordings of 6 patients with autoimmune epilepsy and/or LE. The longest NREM 2 period was selected. We evaluated the spindle density (spindles per minute), and compared that to the spindle densities of epilepsy patients with bilateral hippocampal sclerosis and healthy controls.

Results: We have demonstrated that patients with autoimmune epilepsy and/or LE had reduced slow wave sleep with decreased number of sleep

spindles. The mean number of spindles in 60 seconds was 5.86 ± 5.03 in patients with autoimmune epilepsy and/or LE. But spindle density was higher in two control groups (10.6 ± 1.65 and 9.95 ± 0.79).

Conclusions: The sleep abnormalities in LE can result from the disruption of thalamo-limbic circuits, and lead to changes in spindle wave activity. Although density of spindles decreased with acute lesions in thalamo-limbic circuits, the relations with structural lesions or chronicity of disease are not clear. That may be related to functional disruption of neural circuitry.

Keywords: Limbic encephalitis, autoimmune epilepsy, sleep, sleep spindle, polysomnography

ÖZ

Amaç: Otoimmün limbik ensefaliti olan hastalarda, uyku bozuklukları ve uyku yapısında değişiklikler tanımlanmıştır. Son zamanlarda, çocukluk çağı otoimmün limbik ensefalitlerinde, asenkron uyku iğcikleri veya uzamış iğcikler gösterilmiştir.

Yöntem: Otoimmün epilepsi ve/veya limbik ensefaliti olan altı hastanın uzun süreli elektroensefalografi-polisomnografi (EEG-PSG) kayıtlarında uyku yapısı ve uyku iğcikleri incelendi. En uzun NREM 2 dönemi seçildi. İğcik yoğunluğu (dakikadaki iğcik sayısı) hesaplanarak bilateral hipokampal sklerozu olan epilepsi hastaları ve sağlıklı kontrollerle karşılaştırıldı.

Bulgular: Otoimmün epilepsi ve/veya limbik ensefaliti olan hastaların yavaş dalga uyku döneminin kıaldığı ve uyku iğciklerinin azaldığını

gösterdik. Altmış saniyede ortalama iğcik sayısı otoimmün epilepsi ve/veya limbik ensefaliti olan hastalarda $5,86 \pm 5,03$ idi. Kontrol gruplarında ise iğcik yoğunluğu daha yüksekti ($10,6 \pm 1,65$ ve $9,95 \pm 0,79$).

Sonuç: Limbik ensefalitte uyku bozuklukları, talamo-limbik devrelerin bozulmasından kaynaklanabilir ve iğcik aktivitesi bozulabilir. Talamo-limbik devrelerdeki akut lezyonlar iğcik yoğunluğu ile birlikte azalıyor olsa da, yapısal lezyonların veya kronik durumların etkisi henüz aydınlatılamamıştır. Bu durum, nöral devrelerin işlevsel bozulmaları ile ilişkili olabilir.

Anahtar Kelimeler: Limbik ensefalit, otoimmün epilepsi, uyku, uyku iğciği, polisomnografi

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INTRODUCTION

Autoimmune limbic encephalitis is frequently recognized as a cause of subacute encephalopathy with seizures. Sleep dysfunction and sleep disorders such as insomnia, hypersomnia, and parasomnia have been also described in patients with autoimmune limbic encephalitis (LE) (1-5). Almost all of these sleep problems has been written within voltage gated potassium channel related limbic encephalitis (VGKC-LE) (1-4), and central sleep apnea or severe periodic limb movements of sleep were

reported in patients with NMDA receptor mediated limbic encephalitis (6). Furthermore, the significant improvement of these sleep disturbances with immunotherapy suggested as a supporting data for an autoimmune basis for the sleep dysfunction (2, 6).

Besides these clinical findings of sleep disorders, the changes in sleep structure were also reported in electrophysiological studies in patients

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with LE (2, 5–7). A decrease of the slow waves in non-rapid eye movement (NREM) in patients with N-methyl-D-aspartate receptor associated limbic encephalitis (NMDAR-LE) (8) and presence of phasic electromyography activity during REM periods with insufficient REM sleep in patients with VGKC-LE (9) reduced total sleep time with frequent awakenings as a sign of decreased sleep efficiency (2, 10), and brief sleep fragments consisting of theta activity interspersed with faster rhythms were reported (2, 10). Recently sleep spindle abnormalities such as asynchronous or prolonged spindles were also observed in 38% of children with autoimmune encephalitis (11).

During the generation of spindles, the reticular thalamic nucleus acts as a pacemaker, and induces activation of thalamo-cortical neurons. Thalamo-cortical neurons connect to neurons in different cortical areas giving rise to the spindle waves (12). Sleep spindles are widespread, and occur in different intracerebral structures at the time of scalp spindles. Physiological hippocampal or limbic spindles were also reported in subjects having intracerebral EEG recording during NREM sleep (13–16). The sleep abnormalities documented in LE can result from the disruption of thalamo-limbic circuits and lead to changes in spindle wave activity. Therefore, we have investigated sleep spindle changes in patients with autoimmune LE and/or autoimmune epilepsy.

METHODS

Between 2011–2016, seven patients with autoimmune epilepsy and/or limbic encephalitis had long term EEG and at least one-night polysomnography (PSG) recording in our video EEG monitoring (VEM) unit. The study was conducted according to the declaration of Helsinki. All patients underwent magnetic resonance imaging (MRI) and cancer screening in addition to routine laboratory tests. Additionally, all patients had blood and cerebrospinal fluid (CSF) examination for autoimmune antibodies including NMDA, VGKC (LGI 1 and Caspr 2), GAD, and Glycine. One patient who had paraneoplastic limbic encephalitis with anti-Hu antibodies was excluded.

Continuous video-EEG recordings were performed over 1–2 days with scalp electrodes which were placed according to the International 10–20 System with additional anterior temporal electrodes. Electrooculogram, electrocardiogram and submental electromyogram were included. Sleep stage was determined by the criteria described by AASM (17). The longest NREM 2 period was selected. For each subject, the NREM 2 sleep periods of 200 s which had no ictal changes or sleep disorder findings, such as apnea or limb movement, were analyzed for spindle density. Sleep spindles were visually scored according to the published criteria as sleep EEG spindles with a frequency between 11 and 16 Hz and a duration >0.5 s (17).

To compare our findings related to spindle density of patients with autoimmune epilepsy and/or limbic encephalitis, we also selected two groups having PSG recordings. One of them was epilepsy patients group with bilateral hippocampal sclerosis on MRI, and the other one healthy control group who had no sleep disorder or epilepsy. Again for each subject, the NREM 2 sleep periods of 200 s which had no ictal changes or sleep disorder findings were analyzed for spindle density.

Basic descriptive statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients with autoimmune epilepsy and/or limbic encephalitis

We had 6 patients with autoimmune epilepsy and/or limbic encephalitis with PSG recordings. Beside routine tests, all had blood and cerebrospinal fluid examination for autoimmune antibodies, and viral encephalitis.

Accordingly, 4 patients had antibodies against voltage gated potassium channels (seropositive for the VGKC-LGI1 antibody), one had anti-glycine, and the last one had anti-GAD antibodies.

Their clinical and laboratory-imaging findings were summarized on Table 1. The mean age was 39.2±18.9 years. The mean number of spindles in 60 seconds was 5.86±5.03. Two of the patients' (Patient 1 and 2) clinical presentation and their findings were given below in detail.

Patient 1 (FG): A 63-year-old male patient presented with hypersomnia after an operation for retinal detachment. He was admitted to our center due to memory problems and seizures almost for 6 months. He had focal seizures originated from temporal lobe during his first routine EEG recording. His brief seizures like faciobrachial dystonic seizures and cognitive dysfunction were also reported during his clinical follow-up in our clinic. Standardized mini mental state examination (SMMSE) result was 26/30 with a mild impairment of spatiovisual and executive abilities. Instrumental activities of daily living (IADL) showed mild impairment.

His MRI revealed right hippocampal and bilateral temporal lobe hyperintensity on T2 weighted series. His routine blood tests were normal except mild hyponatremia. Paraneoplastic panel was negative on his blood sample. His CSF findings showed slightly increased in protein level.

His blood and CSF were investigated for any etiology including viral infections. The diagnosis of autoimmune limbic encephalitis was supported after finding of antibodies against the Lgi1 protein in the cerebrospinal fluid and sera samples.

He was given intravenous immunoglobulin, antiepileptic treatment of levetiracetam, and phenytoin before his long term video-EEG-PSG recordings. He did not have seizures, periodic leg movements or sleep apnea during his two days of monitoring. His full-night VEEG-PSG on his 9th day of admission revealed low sleep efficiency (52%) and REM sleep (8%), mostly with phasic electromyography activity but REM sleep behavior disorder (RBD) was not recorded. During day-time recordings multiple jerky and kicking-like behaviors were observed during REM sleep with phasic electromyographic activity.

Interictal EEG baseline activity was 6–8 Hz, and very frequent paroxysmal bilateral temporal slow and sharp-slow waves were revealed. There was no clinical or subclinical ictal activity.

He later received pulse steroid followed by oral maintenance dose, and his antiepileptic treatment was given as levetiracetam, clonazepam, and oxcarbazepine. After 1 month, we observed prominent improvement in his sleep-related disorders and cognitive dysfunction.

He had no more seizures. His antiepileptic drugs were decreased in first year of follow up.

Patient 2 (DG): A 29-year-old male patient presented with confusion, behavior change, increased appetite, and focal seizures. These clinical features had been found almost for 3 months, and he had received intravenous pulse steroid treatment in another center two months ago. Upon admission to our hospital he was drowsy with frequent seizures. During his examination numerous focal-faciobrachial seizures were seen daily.

His MRI showed bilateral medial temporal T2 hyperintensity involving hippocampi and amygdala. His blood and CSF were investigated for any etiology leading to encephalopathy and seizures, including viral infections. The diagnosis of autoimmune limbic encephalitis was supported after finding of antibodies against the Lgi 1 protein in the cerebrospinal fluid and sera samples.

Table 1. Summary of clinical and laboratory-imaging findings of 6 patients with autoimmune epilepsy and/or limbic encephalitis

Patient (age-sex)	Antibody	Clinical symptoms	MRI Findings	Time duration between the onset of symptoms and VEEG-PSG monitoring	EEG Findings	PSG findings	Spindle density (number/60 s)
Patient 1-FG: 63-M	LG11	Hypersomnia, seizure, cognitive dysfunction	Bilateral temporal and right hippocampal hyperintensity	6 months	Decreased in baseline activity with bilateral temporal slow waves (with AEDs)	Low sleep efficiency (53%), loss of atonia during REM with mild RBD. 38% N1 51% N2 3% N3 8% REM	2.4
Patient 2-DG: 29-M	LG11	Personality changes, faciobrachial seizures	Bilateral temporal and hippocampal hyperintensity	3 months	*Decreased in baseline activity with bilateral temporal epileptiform activities (with AEDs)	*Low sleep efficiency (52%) with no REM sleep. 18% N1 76% N2 6% N3	1.8
Patient 3-PG: 64-F	LG11	Visual-auditory hallucinations, cognitive changes, hyponatremia, seizures	Bilateral symmetrical T2 hyperintensity of mesial temporal lobe, uncus, hippocampi	2 months	Right temporal epileptiform activities. 4 subclinical seizures on right temporal lobe. (with AEDs)	Significant reduction of REM sleep (2%) with decreased sleep efficiency (77%) and frequent apnea and hypopnea (AHI: 20) 12% N1 81% N2 2% N3 5% REM	8.19
Patient 4-MG: 25-F	LG11	Seizures, cognitive problems	Bilateral hyperintensity of medial temporal lobe, uncus, hippocampi, amygdala and caudate on T2 weighted images	2 months	Decreased in baseline activity with left temporal epileptiform activities 6 focal seizures on left temporal in 48 hours. (with AEDs)	Low sleep efficiency with (77%) reduction of REM and deep NREM sleep 25% N1 62% N2 3% N3 10% REM	3
Patient 5-AD: 27-F	Glycine	Headache, left focal seizures	Normal	3 months	Rare mild epileptiform activities on left temporal (with AEDs)	Mild decrease in sleep efficiency (79%) 14% N1 56% N2 17% N3 13% REM	15
Patient 6-HY: 27-F	GAD	Seizures, stiff-person	Bilateral hippocampal hyperintensity (stable-increases when seizures are increased)	6 years	Epileptiform activities on right temporal. 3 seizures either right or left hemisphere (with AEDs)	Mild decrease in sleep efficiency (78%)	4.8

*He had two PSG recordings with 2 weeks' interval. These findings were about the second PSG recordings.

AED, antiepileptic drugs; AHI, apnea-hypopnea index; EEG, electroencephalography; F, female; GAD, glutamic acid decarboxylase; LG11, leucine-rich glioma-inactivated 1; M, male; MRI, magnetic resonance imaging; N1/2/3, non-rapid eye movement stages 1/2/3; PSG, polysomnography; REM, rapid eye movement; s, seconds; VEEG, video electroencephalography.

He had fragmented unrefreshing night sleep, and very frequent nocturnal seizures. Therefore, he had two video-EEG and PSG recording in a month, one of them was at the beginning of admission, the other one 2 weeks after treatment with intravenous immunoglobulin. He was receiving valproate, levetiracetam, and clonazepam.

First video-EEG-PSG recordings revealed loss of sleep architecture with very frequent faciobrachial seizures. Nearly all sleep was in NREM sleep, N1 stage. There were almost no K complexes or sleep spindles (less than 10 per night). He had loss of muscular atonia in brief REM sleep. Interictal EEG changes showed bilateral temporal epileptiform activities with decreased baseline activity.

During his second video-EEG-PSG recordings faciobrachial dystonic seizures were no longer present. Sleep architecture was still disturbed and REM sleep was not observed. But K complexes and sleep spindles were now formed. He had reduced sleep efficiency at 52% with no evidence of sleep apnea, parasomnia or behavioral disorders.

After 16 months of follow up he had no seizures with two antiepileptic drugs, and he could work in his office.

Control Groups

We had 5 epilepsy patients with bilateral hippocampal sclerosis on MRI. They had video-EEG recordings due to their antiepileptic drug resistant

Table 2. Features of patients with bilateral hippocampal sclerosis and drug resistant epilepsy

Patients	age	gender	MRI	Interictal EEG	Ictal EEG	Spindle density (number/60 s)
Epilepsy control 1, HB	28	M	L>R bilateral hs	R>L temporal spikes R TIRDA	Right Temporal	12.3
Epilepsy control 2, HT	34	M	R>L bilateral hs	R temporal spikes R TIRDA	Right temporal	10.8
Epilepsy control 3, CK	29	M	L>R bilateral hs	L>R temporal spikes	Left temporal	12.1
Epilepsy control 4, CS	31	F	R>L bilateral hs	L>R temporal spikes	Bilateral temporal	9
Epilepsy control 5, GG	38	M	L>R bilateral hs	R>L temporal spikes	Right temporal	8.8

hs, hippocampal sclerosis; L, left; R, right; TIRDA, temporal intermittent rhythmic delta activity.

focal seizures. The mean age was 32 ± 4.06 years. Their mean duration of epilepsy was 15.2 ± 7.3 years.

Although they had no sleep problems, electrooculogram, electrocardiogram and submental electromyogram were also included in their recordings so we can determine the sleep stages. EEG samples of equal duration (200 s) containing spindles were selected from nights without any seizure. Their clinical and EEG findings were summarized on Table 2.

The mean number of spindles in 60 seconds was 10.6 ± 1.65 .

As a healthy control group we had 8 patients who had no sleep disorder or epilepsy but having PSG recordings in our VEEG-PSG monitoring unit. They had mild sleep complaints including insufficient sleep time or abnormal behaviors during sleep. They had no other systemic or neurological disorders. Their PSG recordings were normal. Of these healthy group 5 were female, 3 were male. The mean age was 34.5 ± 14.0 years. The mean number of spindles in 60 seconds was 9.95 ± 0.79 .

DISCUSSION

Herein we have demonstrated that patients with autoimmune epilepsy and/or limbic encephalitis had mild to moderate reduced sleep efficiency with decreased number of sleep spindles. Although N2 sleep was the longest stage; in all patients sleep spindles, a grapho-element of N2, were decreased. Sleep disturbance during the acute phase of limbic encephalitis is known, acute insomnia or hypersomnia has been described almost in one fourth of patients with positive VGKC antibodies (1) but there was no PSG finding in this series. Only in a few PSG studies insomnia, mild sleep apnea, vivid dreams, loss of REM atonia with and without REM behavioral disorder, and restless sleep were reported (2, 6, 7). Additionally, decreased sleep efficiency, presence of phasic electromyography activity during REM periods with insufficient REM sleep were described. Only in an EEG study of children with autoimmune encephalitis, sleep spindle abnormalities with asynchronous or prolonged spindles were also observed in autoimmune encephalitis (11). To our knowledge there is no report about changes in sleep spindles in autoimmune epilepsy and/or limbic encephalitis until now.

Reduction of spindle density in patients with autoimmune epilepsy and/or LE may simply be interpreted as a result of decrease in sleep efficiency due to increased interictal-ictal EEG changes or nocturnal seizures (18). But we have seen that the number of spindles decreased in spite of patients having moderate or good sleep with >70% efficiency. The durations of N3 or REM were decreased in our patients but not N2 stages. Also we selected the EEG sample periods which had no ictal changes or sleep disorder findings. Furthermore, our control groups of patients with drug resistant epilepsy due to bilateral hippocampal sclerosis had similar frequent interictal epileptiform activities but higher number of sleep spindles.

Our findings related to decreased frequency of sleep spindles in patients with autoimmune epilepsy and/or LE can be related to acute-subacute lesions in thalamo-limbic circuits. Limbic encephalitis is an autoimmune disease resulting in inflammation in limbic system, radiologically seen as signal change in MRI. Limbic-hippocampal spindles, although identified in the majority of nonepileptic hippocampi, occurred rarely simultaneously with scalp spindles (14, 15). We hypothesized that acute inflammation of hippocampus is leading to reduction of spindle generation. Therefore, we formed a control group of epilepsy patients with bilateral hippocampal sclerosis. Our second control group consisted of healthy subjects with mild sleep related complaints and normal PSG findings. Accordingly, chronic structural changes like bilateral hippocampal sclerosis did not diminish spindle density, and their spindle densities were similar to healthy controls without lesions. Furthermore, one patient with anti-glycine autoantibody positive autoimmune epilepsy who had a normal MRI, had spindle density similar to control groups. Also in the latter patient there was a slight improvement of sleep and number of sleep spindles after treatment in second week. So, autoantibodies which cause acute structural changes in hippocampi may lead to disruption in spindle generation.

The changes in spindle density could be related to acute lesions of hippocampal-limbic system. But in contrast to that suggestion, we had a patient with a chronic autoimmune encephalitis with antiGAD antibodies. Although her MRI revealed bilateral hippocampal atrophy-sclerosis her spindle density was lower than control patients with bilateral hippocampal sclerosis. Without any relation to structural lesion, autoimmune antibodies can lead to functional disruption of spindle generation pathways. On the other hand, our control group patients with bilateral hippocampal sclerosis might have autoimmune antibodies for early limbic encephalitis. But we could not prove that because we did not investigate their blood or CSF samples. All these can support an autoimmune basis for the sleep disturbance, and suggest that the sleep manifestations are not due to irreversible structural changes but rather to functional disruption of neural circuitry.

Our findings may be a clue for importance of limbic system-hippocampus in generation of spindles. Although hippocampal spindles have been discussed to be related to epileptic activity (19), recent studies indicate that they are physiological (14–16, 20). Also, transformation of hippocampal spindles to hippocampal spikes or an occluding effect of hippocampal spikes on hippocampal spindles were suggested (13). In our study we had no intracranial EEG recordings, and we could not claim those are hippocampal spindles. But the number of spindles are not same in epilepsy patients having frequent hippocampal spikes with bilateral hippocampal sclerosis or limbic encephalitis. So, changes in spindles could not be a sign of hippocampal epileptogenicity because decrease in number of spindles can only be seen in acute-subacute structural lesions. But augmentation of spindle density in line with improvement of hippocampal lesions in our patients suggests an important role for hippocampus in generation of physiological spindles.

Our findings suggest that patients with autoimmune epilepsy and/or LE had less sleep spindle although their sleep was not poor. According to our patients, that could not be correlated with frequency of epileptiform activity. Although the density of spindles decreased with acute lesions, the relations with structural lesions or chronicity of disease are not clear. Therefore, there are several limitations to the study including a small sample size and a retrospective study design. Future large prospective, follow-up studies are necessary to determine the validity of our observations.

CONCLUSION

Autoimmune epilepsy and/or LE lead to changes in sleep structure with decrease in spindle density. The causality of spindle density reduction as a biomarker of autoimmune limbic encephalitis has to be investigated. The detailed electrophysiological sleep investigations of patients may give a clue or simple way of diagnosing LE, and clinical importance of hippocampal spindles.

Ethics Committee Approval: Our study was conducted and written according to the declaration of Helsinki.

Informed Consent: We obtained written informed consents for Video EEG monitoring unit admission and oral consents for publication of anonymised medical information.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – FIT; Design – FIT; Supervision – FIT, SS; Resource – FIT, SS; Materials –FIT, ES; Data Collection &/or Processing –ES, FIT; Analysis&/or Interpretation – FIT, ES; Literature Search – ES, FIT; Writing Manuscript– ES, FIT; Critical Review – FIT, SS;

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Hasta Onamı: Video EEG ünitesi yatışı için yazılı olarak, isim kullanılmadan tıbbi bilgilerin yayınlanması için sözel bilgilendirilmiş onam alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir – FIT; Tasarım – FIT; Denetleme – FIT, SS; Kaynak – FIT, SS; Malzemeler - FIT, ES; Veri Toplanması ve/veya İşlemesi – ES, FIT; Analiz ve/veya Yorum – FIT, ES; Literatür Taraması – ES, FIT; Yazıyı Yazan – ES, FIT; Eleştirel İnceleme – FIT, SS.

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