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ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

NREM Parasomnias: An Important Comorbidity in Epilepsy Patients of Pediatric Age

Pediyatrik Yaş Grubu Epilepsi Hastalarında Önemli Bir Komorbidite: NREM Parasomnileri

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Summary

Objectives: We here aimed to investigate our pediatric group of patients to reveal the comorbidity of epilepsy and non-rapid eye movement (NREM) parasomnias and their clinical and polysomnographic characteristics.

Methods: We retrospectively investigated all patients at the age of 18 or younger internalized within the last two years patients for a full night polysomnographic evaluation in our Sleep and Wake Disorders Unit. The diagnosis of epilepsy was made on the basis of clinical findings and electroencephalography findings; and the diagnosis of NREM parasomnia was made according to the International Classification of Sleep Disorders.

Results: A total of 29 male (67.4%) and 14 female (32.6%) patients were investigated. Nineteen (44.2%) out of 43 patients were diagnosed as epilepsy. Nine (47.4%) of the patients with epilepsy also had delta-alpha paroxysms (DAP) and partial wakefulness during sleep – which are the characteristics polysomnographic features of NREM parasomnias.

Conclusion: We observed a high comorbidity of epilepsy and NREM parasomnia in pediatric group of patients investigated in our sleep center. The arousal parasomnias are increasingly being reported to be more common in patients with epilepsy, probably due to shared common physiopathological mechanism characterized by pathological arousals originating in abnormal thalamo-cortical circuits produced by the central pattern generators.

Key words: Epilepsy; NREM parasomnias; pediatric age group.

Özet

Amaç: Çalışmamızda pediyatrik yaş grubu hastalarımızda epilepsi ve NREM (non-rapid eye movement) parasomnilerinin birlikteliğini ve klinik-polisomnografik özelliklerini incelemeyi amaçladık. Bu amaçla, Uyku ve Uyanıklık Bozuklukları Merkezi'mizde son iki yıl içinde tüm gece polisomnografi incelemesi yapılan 18 yaş ve altı tüm hastaların dosyalarını geriye dönük olarak inceledik.

Gereç ve Yöntem: Tıbbi kayıtlarına göre, klinik ve elektroensefalografi bilgilerine göre epilepsi tanısı konulan ve Uluslararası Uyku Bozuklukları Sınıflaması kriterlerine göre NREM parasomnisi tanısı alan hastalar çalışmaya dahil edildi.

Bulgular: Toplam 29 erkek (%67.4) ve 14 kadın (%32.6) hasta incelendi; 43 hastanın 19'unda (%44.2) epilepsi tanısı mevcuttu. Polisomnografi incelemesinde, epilepsi tanısı olan hastaların 9'unda (%47.4) NREM parasomnilerinin karakteristik bulgusu olan delta-alfa paroksizmleri ile uykunun yüzeyelleştiği saptandı.

Sonuç: Uyku merkezimizde incelenen pediyatrik yaş grubunda oldukça yüksek oranda epilepsi ve NREM parasomnisi birlikteliği saptadık. Özellikle son yıllarda, uyanma bozukluğu ile seyreden NREM parasomnilerinin epilepsi hastalarında daha sık görüldüğü bildirilmektedir. Bu durumun, ortak bir fizyopatolojik mekanizma olarak, santral patern jeneratörleri ile talamo-kortikal döngülerde patolojik uyanıklık reaksiyonlarına bağlı olduğu düşünülmektedir.

Anahtar sözcükler: Epilepsi; NREM parasomnileri; pediyatrik yaş grubu.

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Introduction

Parasomnias are defined as undesirable physical events or experiences that occur during entry into sleep, within sleep or during arousals from sleep by the International Classification of Sleep Disorders.[1] They involve complex, purposeful, goal-directed, behaviours without consciousness. Parasomnias are divided into three categories according to sleep stage they arise as NREM (non-rapid eye movement) parasomnias, REM parasomnias and others occurring irrespective to sleep stages. NREM parasomnias, also called as the disorders of arousal, are commonly encountered in children and adolescent age group, which include confusional arousals, somnambulism (sleepwalking) and sleep terrors.[2] Because of clinical similarities, NREM parasomnias should be differentiated from nocturnal epileptic seizures.[3] A common pathophysiologic mechanism has been hypothesized in both disorders involving cholinergic pathways in the ascending arousal system, which leads to the activation of common pattern generators responsible from the overlapping semiology of nocturnal seizures and NREM parasomnia attacks.[4] Furthermore, sleep-related epileptic seizures and NREM parasomnias may also coexist in the same patient. High prevalence of sleep disturbances in epilepsy patients compared to the general population has been increasingly reported in recent studies, making the differential diagnosis for these two conditions important to prevent mistreatment derived from misdiagnosis in epilepsy patients.[5] Here we investigated our pediatric group of patients to reveal the comorbidity of epilepsy and NREM parasomnias, and their clinical and polysomnographic characteristics.

Materials and Methods

In this study, we retrospectively investigated all patients at the age of 18 or younger internalized within the last two years for a full night polysomnographic (PSG) evaluation in our Sleep and Wake Disorders Unit to reveal the comorbidity of epilepsy and NREM parasomnias, and their clinical and polysomnographic characteristics.

Sixteen channel-electroencephalography (EEG) recordings were used in PSG montage and electrode placement was performed according the international 10-20 system. Sleep was recorded and scored according to the American Academy of Sleep Medicine (AASM) Manual for the Scoring of

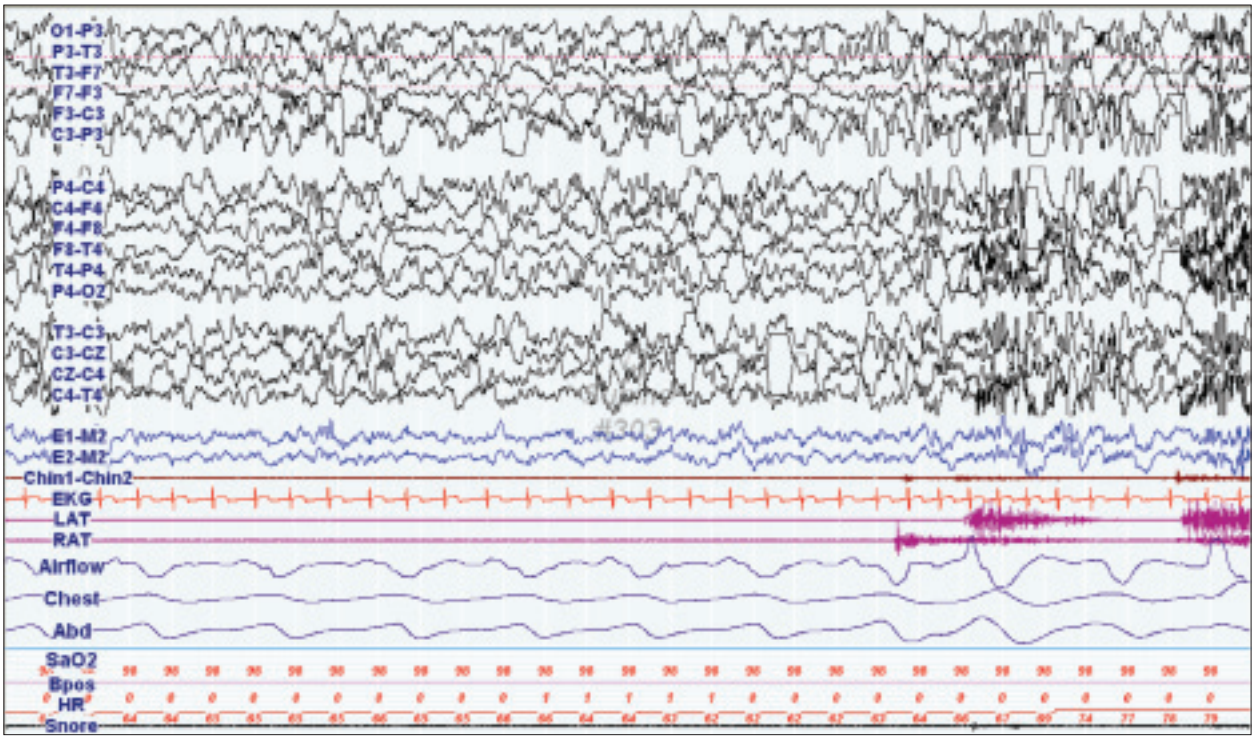


Figure 1. NREM parasomnia attack characterized by delta-alpha paroxysms (DAP) and partial wakefulness during sleep (last 7 seconds of the trace).

Sleep and Associated Events.[6] PSG recordings included left and right electrooculogram, chin electromyogram, left and right tibialis anterior EMG, electrocardiogram, nasal pressure transducer, oronasal thermistor, thoracal and abdominal strain gauges, pulse oxymetry, and synchronized video recording. The following conventional sleep parameters were evaluated: time in bed (TIB), total sleep time (TST), total NREM/REM time, sleep onset latency (SOL), sleep efficiency (SE), duration and percentage of wakefulness, and sleep stages N1, N2, N3 and REM, respiratory disturbance index (number of apneas, hypopneas and respiratory effort-related arousals divided by TST) and periodic leg movement (PLM) index (number of PLM divided by TST).

The diagnosis of epilepsy was made on the basis of clinical findings and EEG findings observed in PSG investigation as recommended by the Commission on Classification and Terminology of the International League Against Epilepsy.[7] The diagnosis of parasomnia was made according to the International Classification of Sleep Disorders.[1]

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, Chicago, IL, U.S.A.). The differences between demographic and PSG variables were analyzed by means of chi-square test for nominal variables, Mann Whitney U and Kruskal-Wallis test for nonparametric variables. A p value of <0.05 was taken to indicate statistical significance.

Results

A total of 29 male (67.4%) and 14 female (32.6%) patients were investigated. The mean age of the patients was 11.5±4.3 years (ranging between 3 and 18 years). Nineteen (44.2%) out of 43 patients were clinically diagnosed as epilepsy, and 14 (73.6%) of them were under treatment with antiepileptic drugs. Remaining 24 patients without epilepsy, who had normal PSG findings were comprised as the control group. PSG recordings, 14 patients (73.6%) had epileptic activity, and two (10.5%) had seizures during PSG recording. Focal epileptiform activity was present in 10 patients, and generalized epileptic discharges were present in 4 patients. Focal activities were localized at frontotemporal region in 8 patients, at temporoparietal region in one patient and at parietooccipital region in another patient.

Nine (47.4%) of the patients with epilepsy also had delta-alpha paroxysms (DAP) and partial wakefulness during sleep-which are the characteristics features of NREM parasomnias (Figure 1). Seven (36.8%) of them had parasomnia attacks during the recording. All of the patients which had DAP during PSG recordings also had epileptic activity on EEG. One patient had periodic leg movements in sleep. None of them had obstructive sleep apnea syndrome, REM-sleep behaviour disorder (RBD), restless legs syndrome or any other sleep disorder.

Polysomnographic data are given in Table 1. None of these parameters showed significant differences between patients with epilepsy along with or without parasomnia, or as compared to subjects without epilepsy with normal clinical and PSG evaluation.

Table 1. Polysomnography parameters of the study population

PSG data	Patients with epilepsy without parasomnia (n=10)	Patients with epilepsy with parasomnia (n=9)	Control group (n=24)	*p*
TIB - minutes	454.9±25.0	459.9±24.1	512.6±10.3	0.091
TST - minutes	406±41.8	403.8±44.4	405.8±133.3	0.876
SOL - minutes	13.3±9.2	14.5±20.2	22.8±23.4	0.463
SE - %	89.2±7.8	87.8±8.7	78.2±14.7	0.329
N1 - minutes (%)	14.4±10.6	11.2±8.8	15.7±5.5	0.925
	(3.3±2.4)	(2.6±2.1)	(3.3±3.1)	(0.891)
N2 - minutes (%)	167.4±55.1	174.7±39.4	161.7±67.1	0.529
	(38.4±12.5)	(41.0±10.7)	(33.5±10.9)	(0.312)
N3 - minutes (%)	149.7±57.5	160.2±68.2	154.3±37.4	0.941
	(35.2±14.4)	(36.5±13.3)	(32.3±2.6)	(0.866)
REM - minutes (%)	71.7±21.0	57.5±14.7	74.0±41.2	0.641
	(16.4±4.3)	(13.3±3.0)	(15.0±5.4)	(0.586)

Discussion

Sleep is of crucial importance in children's and adolescents' physical growth as well as their memory, attention, mood, behavior and cognition.[2] Sleep and its disturbances in epileptic children should therefore better be evaluated. Sleep disturbances in epileptic children may be secondary to nocturnal seizures, abnormal architecture of sleep due to epilepsy and antiepileptic drugs prescribed, in addition to coexistent primary sleep disorders.[8] Sleep disorders commonly observed in patients with epilepsy are reported as excessive daytime sleepiness, obstructive sleep apnea syndrome and periodic limb movement disorder in sleep.[9,10] In our retrospective survey, obstructive sleep apnea syndrome or periodic limb movement disorder in sleep did not show significant difference, but a high comorbidity of arousal parasomnias with epilepsy was observed.

The arousal parasomnias are increasingly being reported to be more common in patients with epilepsy.[11] Both personal past medical history and family history indicated a comorbidity of epilepsy-especially of frontal lobe-and arousal parasomnias up to 35%.[12,13] Here we observed a high comorbidity (47.4%) of epilepsy and parasomnia in pediatric group of patients investigated in our sleep center. Epilepsy types observed in our study were generalized in four patients, focal in 10 patients. Localizations were frontotemporal in 8 patients, temporoparietal in one patient and parietooccipital in another patient. Epilepsies with fronto-temporal origin are especially reported in the literature to coexist together with arousal parasomnias, probably due to shared common neuronal pathways.[14,15] Although retrospective design of the study constitutes a bias in patient selection, this comorbidity should draw attention for the clinicians dealing with epilepsy, as some of the nocturnal attacks reported by the family may not be of epileptic in origin.

The relationship between epilepsy and parasomnia is complex and reciprocal. Both disorders are characterized by paroxysmal episodes of affective and/or ambulatory behavioral changes. In spite of video-EEG recordings, it may still be challenging in some cases to differentiate a nocturnal epileptic or parasomnia attack, especially if they coexist in the same patient. The gating effects of arousal were regarded as the common permissive background for the appearance of both motor phenomena.[15] Epileptic discharges may also act as an internal trigger, increasing arousal instability and facilitating the occurrence of arousal parasomnias, as well.[11,16]

Both arousal parasomnias and seizures especially of frontotemporal origin consist of pathological arousals originating in abnormal thalamo-cortical circuits produced by the central pattern generators, suggesting a shared physiopathological mechanism.[14,15] It was hypothesized that these disorders have abnormal arousal mechanisms in the dorsal cholinergic arousal pathways resulting in peculiar motor patterns in the medial frontal lobe regions,[17] but probably triggered by different stimuli. Proposed mechanisms are *(i)* liberation due to functional inactivation especially of the frontodorsal convexity during NREM sleep in both conditions, *(ii)* state dissociation between local/regional nature of sleep and wake states, and *(iii)* pathological arousals accompanied by confused behavior with alarm like behaviors activated by the frontal cholinergic arousal system during the condition of depressed cognition in NREM sleep.[18] In our previous study, we investigated cyclic alternating pattern in patients with epilepsies with frontal and/or temporal lobe origin and arousal parasomnias and demonstrated that arousal parasomnias were associated with milder activation in specific brain areas, mainly restricted to the frontal lobe, while fronto-temporal lobe epilepsies were associated with a moderate to powerful activation in wider brain networks.[19]

These findings suggest that common pathways are involved in epilepsy (especially of frontotemporal lobe) and parasomnia (especially in arousal parasomnias), which result in overlapping clinical and physiopathological phenomena. For this reason, a careful medical history and detailed investigation including video-monitoring EEG and polysomnography are necessary in evaluation of these patients for an accurate diagnosis and treatment. It should also be kept in mind that these two disorders commonly co-exist in the same patient, which may challenge the differential diagnosis of nocturnal attacks.

References

1. American Academy of Sleep Medicine. The international classification of sleep disorders second edition: diagnostic and coding manual. Westchester, IL: American Academy of Sleep Medicine; 2005.
2. Lazaratou H, Soldatou A, Dikeos D. Medical comorbidity of sleep disorders in children and adolescents. Curr Opin Psychiatry 2012;25(5):391-7. [CrossRef]
3. Kothare SV, Kaleyias J. Sleep and epilepsy in children and adolescents. Sleep Med 2010;11:674-85. [CrossRef]
4. Tassinari CA, Gardella E, Cantalupo G, Rubboli G. Central pat-

tern generators relationships to parasomnias and sleep-related epileptic seizures. Sleep Med Clin 2012;7(1):125-34. [CrossRef]

5. Grigg-Damberger M, Ralls F. Primary sleep disorders and paroxysmal nocturnal nonepileptic events in adults with epilepsy from the perspective of sleep specialists. J Clin Neurophysiol 2011;28(2):120-40. [CrossRef]
6. Iber C, Ancoli-Israel S, Chesson SF, Quan AL. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
7. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010;51(4):676-85. [CrossRef]
8. Bazil CW. Sleep and epilepsy. Curr Opin Neurol 2000;13:171-5.
9. Zanzmera P, Shukla G, Gupta A, Singh H, Goyal V, Srivastava A, et al. Markedly disturbed sleep in medically refractory compared to controlled epilepsy - a clinical and polysomnography study. Seizure 2012;21:487-90. [CrossRef]
10. Chihorek AM, Abou-Khalil B, Malow BA. Obstructive sleep apnea is associated with seizure occurrence in older adults with epilepsy. Neurology 2007;69(19):1823-7. [CrossRef]
11. Pincherle A, Proserpio P, Didato G, Freri E, Dyljgeri S, Granata T, et al. Epilepsy and NREM-parasomnia: a complex and reciprocal relationship. Sleep Med 2012;13(4):442-4. [CrossRef]
12. Provini F, Plazzi G, Tinuper P, Vandi S, Lugaresi E, Montagna P. Nocturnal frontal lobe epilepsy. A clinical and polygraphic overview of 100 consecutive cases. Brain 1999;122(Pt 6):1017-31. [CrossRef]
13. Bisulli F, Vignatelli L, Naldi I, Licchetta L, Provini F, Plazzi G, et al. Increased frequency of arousal parasomnias in families with nocturnal frontal lobe epilepsy: a common mechanism? Epilepsia 2010;51(9):1852-60. [CrossRef]
14. Tassinari CA, Rubboli G, Gardella E, Cantalupo G, Calandra-Buonaura G, Vedovello M, et al. Central pattern generators for a common semiology in fronto-limbic seizures and in parasomnias. A neuroethologic approach. Neurol Sci 2005;26 Suppl 3:225-32. [CrossRef]
15. Parrino L, Halasz P, Tassinari CA, Terzano MG. CAP, epilepsy and motor events during sleep: the unifying role of arousal. Sleep Med Rev 2006;10(4):267-85. [CrossRef]
16. Nobili L. Nocturnal frontal lobe epilepsy and non-rapid eye movement sleep parasomnias: differences and similarities. Sleep Med Rev 2007;11(4):251-4. [CrossRef]
17. Montagna P, Provini F, Bisulli F, Tinuper P. Nocturnal epileptic seizures versus the arousal parasomnias. Somnologie 2008;12(1):25-37. [CrossRef]
18. Halász P, Kelemen A, Szűcs A. Physiopathogenetic Interrelationship between Nocturnal Frontal Lobe Epilepsy and NREM Arousal Parasomnias. Epilepsy Res Treat 2012;2012:312693.
19. Benbir G, Kutlu A, Gozubatik-Celik G, Karadeniz D. CAP characteristics differ in patients with arousal parasomnias and frontal and temporal epilepsies. J Clin Neurophysiol 2013;30(4):396-402. [CrossRef]