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Restless leg syndrome and sleep quality in granulomatosis with polyangiitis

Granülomatöz polianjit hastalarında uyku kalitesi ve huzursuz bacak sendromu

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Abstract

Objective: We investigated the frequency and severity of restless leg syndrome (RLS) and sleep quality in granulomatosis with polyangiitis (GPA) patients.

Methods: A cross-sectional study was conducted on GPA patients. A control group was formed from patients of similar age and gender. Demographic, clinic and laboratory data were recorded. In the GPA group, disease activity was evaluated with Birmingham Vasculitis Activity score for Wegener Granulomatosis, disease-related damage by vasculitis damage index (VDI), quality of life (QoL) was by health assessment questionnaire (HAQ). In both groups, RLS diagnosis was confirmed and severity was measured according to the International Restless Legs Study Group criteria. Sleep quality was evaluated by the Pittsburgh Sleep Quality index (PSQI), sleepiness the Epworth Sleepiness scale, level of depression by the Beck Depression index (BDI).

Results: Out of total 55 GPA patients, 36 who could be reached and who agreed to participate and meet the inclusion criteria were enrolled. The control group comprised 35 subjects. Age and sex were similar between groups. The frequency of RLS was similar between groups (19.4% vs. 17.1%, p=0.802). RLS severity score was indifferent. PSQI and BDI scores were increased in GPA. When parameters in GPA patients with and without RLS were compared, no significant differences were observed except for the cardiovascular damage domain of VDI. RLS severity scores did not correlate with other parameters. PSQI scores had significantly correlated with HAQ and BDI.

Conclusion: The frequency of RLS was not increased in GPA compared with controls. Sleep quality was impaired and was observed to be related to worse QoL and higher scores for depression.

Keywords: Granulomatosis with polyangiitis, ANCA, restless leg syndrome, sleep quality

Öz

Amaç: Bu çalışmada, granülomatöz polianjit (GPA) hastalarında huzursuz bacak sendromu (HBS) sıklığının, şiddetinin ve uyku kalitesinin değerlendirilmesi amaçlanmıştır.

Yöntem: Kliniğimizde takip edilen erişkin GPA hastaları kesitsel olarak çalışmaya dahil edildi. Benzer yaş ve cinsiyet özelliklerine sahip sağlıklı gönüllülerden bir kontrol grubu oluşturuldu. Demografik, klinik ve laboratuvar bilgileri kaydedildi. Hasta grubunda hastalık aktivite düzeyi Birmingham Vaskülit Aktivite skoru-Wegener Granülomatozu (BVAS/WG), GPA ilişkili hasar vaskülit hasar indeksi (VHİ), yaşam kalitesi Sağlık Değerlendirme Anketi (SDA) ile skorlandı. Her iki grupta HBS tanısı ve şiddeti Uluslararası Huzursuz Bacak Sendromu Çalışma Grubu tanı ve hastalık şiddeti kriterlerine göre belirlendi. Uyku kalitesi, Pittsburgh Uyku Kalitesi indeksi (PUKİ), uykululuk hali Epworth Uykululuk skalası, depresyon düzeyi Beck Depresyon indeksi (BDİ) ile ölçüldü.

Bulgular: Elli beş GPA hastasından ulaşılan, katılmayı kabul eden ve dışlama kriteri olmayan 36 hasta çalışmaya dahil edildi. Otuz beş sağlıklı gönüllüden kontrol grubu oluşturuldu. İki grup arasında yaş ve cinsiyet yönünden anlamlı fark saptanmadı. GPA grubunda HBS sıklığı %19,4 kontrol grubunda %17,1 olarak saptandı (p=0,802). HBS şiddet skorları iki grup arasında anlamlı olarak farklı değildi. PUKİ ve BDİ skorları GPA grubunda daha yüksekti. HBS olan ve olmayan GPA hastaları karşılaştırıldığında BVAS/WG, VHİ skorları benzerdi. VHİ alt gruplarına bakıldığında sadece kardiyovasküler hasar HBS grubunda anlamlı olarak daha fazlaydı. HBS şiddet skorları ile diğer parametreler arasında korelasyon saptanmazken, PUKİ ile BDİ ve SDA arasında anlamlı korelasyon saptandı.

Sonuç: GPA hastalarında HBS sıklığı kontrol grubuna göre anlamlı artış göstermemekle beraber uyku kalitesi skorları GPA hastalarında daha kötü olarak izlendi, depresyon ve yaşam kalitesi bozukluğu ile ilişkili olduğu görüldü.

Anahtar Kelimeler: Granülomatöz polianjit, ANCA, huzursuz bacak sendromu, uyku kalitesi

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Introduction

Granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis) is an anti-neutrophil cytoplasmic antibody associated vasculitis (AAV), which affects various organ systems including the upper air ways, lungs, kidneys, nervous system, gastrointestinal system, and musculoskeletal system leading to mortality and varying degrees of morbidity, inevitably causing significant deterioration in the individual's quality of life (QoL).[1,2] In chronic rheumatic conditions like GPA, in addition to disease-related organ damage, several other factors may contribute to altered QoL, such as socio-economic impairment, mood disorders, neurocognitive changes and hampered sleep quality.

Restless leg syndrome (RLS) is a neurologic disorder characterized by sensorimotor symptoms comprising unpleasant sensations and urgency to move the limbs occurring especially at rest and/or at night, predominantly affects the lower limbs, causing sleep disturbance even to the point of insomnia.[3] RLS is a common disorder with an incidence of 5-15% in the general population.[4,5] Several studies have investigated the frequency of RLS and effects on sleep quality in rheumatic disorders, indicating an increased incidence.[6-13] However, the frequency of RLS and its impact on sleep quality and overall QoL in GPA are yet to be elucidated.

The impact of GPA on QoL has been demonstrated in various studies.[2,14,15] Results from several studies imply that sleep quality may be a factor affecting overall QoL in AAV. In a systematic review of the literature, Mercuzot et al.[15] identified sleep disturbances as one of the main aspects affecting the physical component scale of short form 36 in patients with AAV. Likewise, Basu et al.[16] demonstrated that sleep disturbance is a factor strongly associated with physical and mental component scale scores in AAV. Accordingly, as a disorder significantly impairing sleep quality, RLS may be an overlooked comorbidity in GPA, further contributing to deteriorated QoL.

Here in this study, we investigated the frequency and severity of RLS and sleep quality in our GPA patients and their impact on QoL. We additionally evaluated patient characteristics, which may be related to RLS occurrence. To the best of our knowledge, this is the first study to investigate RLS in GPA patients.

Materials and Methods

A cross-sectional, single-centre study was conducted in a cohort formed from adult patients who had been followed up in our clinic with a diagnosis of GPA for at least 3 months. Patients of this cohort were either evaluated during follow-ups or reached via telephone and a visit was arranged upon consent to participate. Patients who did not meet the American College of Rheumatology 1990 Classification Criteria for Wegener's Granulomatosis or 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for GPA and patients who did not want to participate were excluded.[17,18] A control group was formed of healthy volunteers with similar age and sex characteristics. Informed consent was obtained from all the participants.

Data regarding demographics, clinical characteristics, treatment history and active treatment agents were collected. The last value in the hospital database for each laboratory parameter was recorded. The disease activity was evaluated by the Birmingham Vasculitis Activity Score for Wegener Granulomatosis (BVAS/WG) while disease-related damage was measured by the Vasculitis Damage Index (VDI).[19,20] Baseline Five Factor Scale (FFS) was calculated.[21]

RLS diagnosis was made in accordance with the International Restless Legs Study Group (IRLSSG) Diagnostic Criteria for RLS.[22] In subjects with a diagnosis of RLS, symptom severity was assessed by calculation of International RLS Rating Scale (IRLSRS) scores.[23]

In GPA patients and healthy volunteers, sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI), daytime sleepiness by the Epworth Sleepiness Scale (ESS), the level of depression the Beck Depression Index (BDI).[24-26] QoL was assessed by Health Assessment Questionnaire (HAQ) in GPA patients.[27]

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) v22.0 was used to analyse data. Continuous variables were checked for normal distribution with Kolmogorov-Smirnov test and additionally with visual analyses by plots and histograms. According to normality, continuous variables were presented either with median [interquartile range (IQR) or minimum (min)-maximum (max)] or mean ± standard deviation (SD). Mann-Whitney U or Students t-tests were used to compare continuous variables according to normality. Categorical variables were presented with numbers and percentages and compared by x^2 test. Correlations between continuous and ordinal variables were investigated by Spearman's Rho. Correlations with a coefficient (r) between 0.5-0.7 considered moderate, ≥0.7 considered strong and <0.5 considered week. P-values ≤0.05 were considered statistically significant for all analyses.

Ethics approval (E1-22-2633) was obtained from institutional ethics committee. Accordingly, the study was conducted in the guidance of the ethical standards laid down by 1964 Declaration of Helsinki and its later amendments.

Results

Out of a total 55 GPA patients, 36 who could be reached, agreed to participate, and met the inclusion criteria were enrolled. The control group comprised 35 healthy subjects. Demographics of both groups and clinical characteristics of GPA patients are presented in Table 1. No significant differences between age, gender and body mass index were observed between the groups. Among GPA patients 69.4% had at least one comorbidity, with hypertension being the most common (33.3%). Median (min-max) VDI score was 1.0 (0.0-4.0) and BVAS/WG score was 1.0 (0.0-7.0) in the GPA group.

The number of patients with RLS according to the IRLSSG criteria was similar between GPA patients and control group (19.4% vs 17.1%, p=0.802). Among patients with the RLS, the severity score was also similar [median (IQR): 17.0 (17.0) vs 12.5 (11.8), p=0.164]. PSQI scores [median (IQR): 5.0 (4.8) vs 3.0 (4.0), p=0.001] and BDI scores [median (IQR): 12.0 (10.5) vs 4.0 (9.0), p=0.003] were significantly higher in GPA patients. ESS scores showed no significant difference among the groups (Table 2).

A comparison of demographics, clinical characteristics, baseline FFS, VDI and BVAS/WG scores and treatment history among GPA patients with and without RLS is

Table 1. Demographics and clinical characteristics of granulomatosis with polyangiitis patients and control subjects

	GPA n=36	Control n=35	p
Age, years, median (IQR)	51.0 (17.5)	46.0 (16.0)	0.455
Gender, male, number (%)	16 (44.4)	14 (40.0)	0.705
BMI, median (IQR)	27.5 (6.5)	26.6 (6.5)	0.675
Patients with ≥1 comorbidities, number (%)	25 (69.4)		
Comorbidities, number (%)			
Hypertension	12 (33.3)		
Chronic kidney disease	6 (16.7)		
End-stage renal disease	2 (5.6)		
Osteoporosis	5 (13.9)		
Diabetes	2 (5.6)		
Cataract	1 (2.8)		
Avascular necrosis	1 (2.8)		
Malignancy	2 (5.6)		
Coronary artery disease	1 (2.8)		
Other	14 (38.9)		
Active smokers, number (%)	4 (11.1)		
Time from symptom onset, months, median (IQR)	40.0 (68.0)		
Time from diagnosis, months, median (IQR)	36.0 (69.0)		
cANCA positivity in IFA, number (%)	22 (77.8)		
PR3 positivity in ELISA, number (%)	27 (75.0)		
VDI score, median (min-max)	1.0 (0.0-4.0)		
FFS at baseline, median (min-max)	0 (0.0-2.0)		
BVAS/WG, median (min-max)	1.0 (0.0-7.0)		
Treatments			
Glucocorticoids, ever users, number (%)	36 (100)		
CTX ever users, number (%)	25 (69.4)		
RTX ever users, number (%)	10 (27.8)		
MMF ever users, number (%)	6 (16.7)		
AZA ever users, number (%)	18 (50.0)		
MTX ever users, number (%)	10 (27.8)		

ANCA: Antineutrophil cytoplasmic antibody, AZA: Azathioprine, BMI: Body mass index, BVAS/WG: Birmingham Vasculitis Activity Score for Wegener's Granulomatosis, CTX: Cyclophosphamide, ELISA: Enzyme-linked immunosorbent assay, FFS: Five factor Scale, GPA: Granulomatosis with polyangiitis, IFA: Immunofluorescence assay, IQR: Interquartile range, MMF: Mycophenolate mofetil, MTX: Methotrexate, PR3: Proteinase 3, RTX: Rituximab, VDI: Vasculitis Damage Index

Table 2. Data regarding restless leg severity, sleep quality, sleepiness and depression in groups

	GPA n=36	Control n=35	p
Subjects with restless leg syndrome, number (%)	7 (19.4)	6 (17.1)	0.802
IRLSRS score, median (IQR)*	17.0 (17.0)	12.5 (11.8)	0.164
PSQI score, median (IQR)	5.0 (4.8)	3.0 (4.0)	**0.001**
ESS score, median (IQR)	2.5 (3.8)	3.0 (4.0)	0.852
BDI score, median (IQR)	12.0 (10.5)	4.0 (9.0)	**0.003**

**Calculated only in subjects with restless leg syndrome. BDI: Beck Depression Index, ESS: Epworth Sleepiness Scale, GPA: Granulomatosis with polyangiitis, IRLSRS: International Restless Legs Study Group Rating Scale, IQR: Interquartile range, PSQI: Pittsburgh Sleep Quality Index*

presented in Table 3. No significant differences were observed except for cardiovascular damage domain of VDI between groups (14.3% vs 0%, p=0.028). Among laboratory parameters, the median ferritin level was lower and frequency of proteinuria was higher in patients with RLS, without reaching statistical significance (Table 3).

Restless leg severity scores did not significantly correlate with VDI, BVAS/WG, PSQI, BDI, HAQ and ESS scores (Table 4). PSQI scores significantly positively correlated with HAQ and BDI scores (r=0.487, p=0.003 and r=0.457, p=0.005, respectively). The mean ± SD HAQ score was 0.19±0.39 in the GPA group. When PSQI, BDI, ESS and HAQ scores were compared between GPA patients with and without RLS, no significant differences were observed (p=0.505, p=0.480, p=0.206, p=0.165, respectively).

Discussion

In our study, we observed a frequency of 19.4% for RLS in GPA patients, which was similar to the control group. PSQI scores indicate a significant impairment of sleep quality in the GPA group. PSQI scores correlated with BDI and HAQ, which may indicate the deteriorating effect of sleep impairment on mood and QoL. We did not observe such a correlation with RLS symptom severity in our patient population. No significant risk factor for the occurrence of RLS could be identified except for cardiovascular damage. Our results imply a similar effect of increased rates of renal and musculoskeletal damage without reaching statistical significance.

Increased rates of RLS under rheumatic conditions have been reported in various studies. The prevalence of RLS has been reported to be 14.3% and 19.1% among patients with rheumatic diseases.[6-13,28-31] More specifically, a frequency of approximately 20-31% had been reported in rheumatoid arthritis, 30% in ankylosing spondylitis, 15-64% in psoriatic arthritis, 31-38% in lupus, 15% in Sjögren's disease, 41% in systemic sclerosis, and 29% in Behçet's syndrome.[6,9-13,28-31] In two studies involving adults from our country originating from two different geographical regions, the prevalence of RLS was observed to be 3.4% and 5.5% in the general population.[32,33] We observed a frequency of 19.4% in our GPA patients, implying an increased prevalence compared to the general population with a similar rate as in other rheumatic diseases. However, when compared to our control group with similar age and gender characteristics, a significantly increased frequency was not observed.

The true etiology of RLS is yet to be fully clarified. Nevertheless, several factors have been demonstrated to be associated with the occurrence of RLS, such as age, gender, presence of comorbidities like iron deficiency, diabetes mellitus and nervous system disorders.[32] Furthermore, immune system alterations have also been suggested to play a role in the development of RLS. In an immune-mediated clinical scenario-like GPA in various organ systems can be involved leading to significant deteriorations in QoL, disease-related damage, disease activity and long-term administration of immunosuppressants may also be related to the presence of RLS. In our study, when we compared the demographic and clinical characteristics of our GPA patients with and without RLS, we did not observe any significant differences between demographics, frequency of comorbidities and iron deficiency parameters. Regarding disease-related parameters, again no significant differences were observed in symptom duration, disease activity, overall disease-related damage and treatment regimens. When disease-related damage was investigated organ system wise, only cardiovascular damage was observed to be potentially related to RLS development and despite similar trend being observed with musculoskeletal and renal damage, it did not reach statistical significance. There are contradictory results in the literature regarding the risk of RLS occurrence among patients with cardiovascular disease. Several large population-based cohorts failed to demonstrate a relationship between RLS and cardiovascular disease.[34] Yet, it has also been reported that there may be a time-dependent association between RLS and cardiovascular disease, particularly in patients with RLS symptoms over three years. However, our sample size is too small to demonstrate such time-dependent relation. Interestingly, none of the five patients with neuropsychiatric damage had symptoms of RLS.

Table 3. Clinical and laboratory characteristics of granulomatosis with polyangiitis patients with and without restless leg syndrome

	With RLS n=7	Without RLS n=29	p
Age, years, median (IQR)	50.0 (24.0)	51.0 (18.0)	0.387
Gender, male, number (%)	3 (42.9)	13 (44.8)	0.925
BMI, median (IQR)	27.9 (7.2)	26.8 (6.6)	0.789
Patients with ≥1 comorbidities, number (%)	6 (85.7)	19 (65.5)	0.298
Time from symptom onset, months, median (IQR)	27 (36)	48 (71)	0.387
BVAS/WG, median (min-max)	1.0 (0.0-3.0)	1.0 (0.0-7.0)	0.584
FFS at baseline, median (min-max)	0 (0.0-1.0)	0 (0.0-2.0)	0.410
VDI score, median (min-max)	1.0 (0.0-2.0)	1.0 (0.0-4.0)	0.318
Patients with involvement in VDI domains, number (%)			
Musculoskeletal	1 (14.3)	2 (6.9)	0.455
Skin/mucous membranes	0 (0)	1 (3.4)	0.638
Ocular	0 (0)	1 (3.4)	0.638
ENT	1 (14.3)	16 (55.2)	0.072
Pulmonary	0 (0)	0 (0)	
Cardiovascular	1 (14.3)	0 (0)	**0.028**
Peripheral vascular disease	0 (0)	1 (3.4)	0.638
Gastrointestinal	0 (0)	0 (0)	
Renal	2 (28.6)	5 (17.2)	0.395
Neuropsychiatric	0 (0)	5 (17.2)	0.262
Other	0 (0)	2 (6.9)	0.500
Treatments			
Glucocorticoids, ever users, number (%)	7 (100)	7 (100)	1.000
CTX ever users, number (%)	5 (71.4)	20 (68.9)	0.899
RTX ever users, number (%)	2 (28.6)	8 (27.6)	0.958
MMF ever users, number (%)	2 (28.6)	4 (13.8)	0.346
AZA ever users, number (%)	3 (42.9)	15 (51.7)	0.674
MTX ever users, number (%)	2 (28.6)	8 (27.6)	0.958
Laboratory parameters			
Haemoglobin, g/dL, median (IQR)	12.3 (1.9)	12.9 (1.7)	0.165
Serum iron, ug/dL, median (IQR)	49.0 (50.0)	54.0 (34.0)	0.257
Total iron binding capacity, ug/dL, median (IQR)	263.0 (108.0)	277.0 (110.0)	0.647
Serum ferritin, μg/L, median (IQR)	14.5 (349.4)	48.0 (380.5)	0.308
Patients with iron deficiency anaemia, number (%)	1 (14.3)	4 (13.8)	0.973
TSH, mU/L, median (IQR)	1.9 (0.7-2.2)	1.5 (0.1-3.4)	0.746
Free T4, ng/dL, median (IQR)	0.9 (0.8-1.0)	1.1 (0.0-1.3)	1.000
Patients with > 1+ proteinuria in urinalysis, number (%)	3 (42.9)	5 (17.2)	0.143

AZA: Azathioprine, BMI: Body mass index, BVAS/WG: Birmingham Vasculitis Activity Score for Wegener's Granulomatosis, CTX: Cyclophosphamide, ENT: Ear nose throat, FFS: Five factor Scale, IQR: Interquartile range, MMF: Mycophenolate mofetil, MTX: Methotrexate, RLS: Restless leg syndrome, RTX: Rituximab, TSH: Thyroid-stimulating hormone, VDI: Vasculitis Damage Index

Table 4. Correlations between IRLSRS, ESS, PSQI, BDI, HAQ scores and BVAS/WG, VDI scores in GPA patients

		IRLSRS	ESS	PSQI	BDI	HAQ	BVAS/WG	VDI
IRLSRS	r	1.000	0.207	0.157	0.116	0.294	0.094	-0.204
	p		0.227	0.359	0.502	0.081	0.586	0.246
ESS	r	0.207	1.000	0.253	0.305	0.309	0.041	-0.120
	p	0.227		0.137	0.071	0.067	0.813	0.500
PSQI	r	0.157	0.253	1.000	**0.457**	**0.487**	0.285	-0.287
	p	0.359	0.137		**0.005**	**0.003**	0.092	0.099

BDI: Beck Depression Index, BVAS/WG: Birmingham Vasculitis Activity score for Wegener's Granulomatosis, ESS: Epworth Sleepiness Scale, GPA: Granulomatosis with polyangiitis, HAQ: Health Assessment Questionnaire, IRLSRS: International Restless Legs Study Group Rating Scale, PSQI: Pittsburgh Sleep Quality Index, VDI: Vasculitis Damage Index

The impact of deprived sleep quality in AAV has been reported previously.[15,16] RLS is a condition that strongly deteriorates sleep and eventually overall QoL.[3] Our results demonstrated higher PSQI scores in GPA patients, suggesting impaired sleep quality in GPA. Furthermore, PSQI scores significantly correlated with worse HAQ and BDI scores, revealing the effects of impaired sleep on mood and QoL. However, none of the PSQI, ESS, HAQ, BDI scores had no significant differences between GPA patients with and without RLS. Additionally, IRLSRS scores did not correlate with PSQI, BDI, HAQ or ESS. Therefore, our results did not demonstrate significant effects or RLS on sleep quality, mood and QoL.

Study Limitations

There are several limitations to our study. Although we did not observe an increased frequency of RLS in GPA patients in comparison with healthy volunteers with demographics, small sample size hinders making more accurate assumptions regarding the true incidence of RLS in GPA. Furthermore, not all possible confounders could be evaluated, due to small sample size again. Lastly, electrophysiologic evaluation was not made in asymptomatic patients, therefore the presence of possible subclinical nerve and muscle impairment was not demonstrated.

Conclusion

All in all, in our study although the frequency of RLS was increased compared to literature reports involving the general population, we did not observe a significant difference from the healthy controls. However, sleep quality was impaired nevertheless. Although impaired sleep quality seemed to be related to worse QoL and higher scores for depression in the GPA group, our results did not demonstrate effects of RLS symptom severity on sleep quality, QoL or depression. We did not observe any significant risk factor for the occurrence of RLS, except for cardiovascular damage. A small sample size warrants cautious interpretation of our results, yet there is limited data in the literature for GPA patients regarding the impact of impaired sleep quality and RLS as a comorbidity on QoL. Larger studies are needed to further elucidate the prevalence and effects of RLS in GPA.

Ethics

Ethics Committee Approval: Ethics approval was obtained from institutional ethics committee (Ankara City Hospital - E1-22-2633).

Informed Consent: Informed consent was obtained from all the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.C.G., B.A., A.E., O.K., A.O., Design: S.C.G., B.A., A.E., O.K., A.O., Data Collection or Processing: S.C.G., P.A.D., S.K., Analysis or Interpretation: S.C.G., A.O., Literature Search: S.C.G., P.A.D., S.K., Writing: S.C.G., A.O.

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