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Research Article

Prevalence and Features Associated With Restless Leg Syndrome in Postmenopausal Females

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Summary

Background: Animal and human studies have shown that estrogen modulates dopaminergic activity. The hypoestrogenic state associated with menopause, characterized by a decreased ovarian follicular response to gonadotropins and estrogen, affects the nervous system at multiple anatomical or functional sites.
Aims: We investigated the prevalence of restless leg syndrome (RLS) in postmenopausal females and assessed the relationship between RLS and the clinical features of menopause.
Methods: We enrolled 523 menopausal females in the study. Of those, 334 (63.86%) did not meet the inclusion criteria and were excluded. Of the remaining 189 postmenopausal patients, 73 met all of the diagnostic criteria for RLS; however, 47 of those had at least one factor related to secondary RLS and were excluded from the study. The remaining 26 (18.3%) postmenopausal patients with idiopathic RLS were categorized as group 1. The control group included 56 postmenopausal females free of RLS and matched by age (+2 years) to group 1.
Results: Onset age of menopause was earlier and surgical menopause was more frequent in group 1. The Pearson's correlation test revealed a strong and significant correlation between the onset ages of menopause and RLS.
Conclusions: Estrogen receptors are widely distributed throughout the central and peripheral nervous systems. Estrogen modulates dopaminergic activity in the nigrostriatal system. Menopause is characterized by hypoestrogenemia, and may be a risk factor for the development or worsening of RLS symptoms.

Key words: Menopause, Restless Legs Syndrome, Estrogen, Hypoestrogenemia

Postmenopozal Dönemdeki Kadınlarda Restless Legs Sendromunun Prevalansı ve İlişkili Özellikler

Özet

Amaç: İnsan ve hayvan çalışmaları östrojenin dopaminerjik aktiviteyi değiştirebileceğini göstermiştir. Ovaryan follekülerin gonadotropinler ve östrojene verdiği yanıtın azalmasıyla karakterize menopoz döneminde, hipoöstrojenemik durumun sinir sistemini pek çok anatomik ve fonksiyonel bölgede etkileyebileceği kabul edilir. Çalışmamızın amacı postmenopozal dönemdeki kadınlarda Restless Legs Sendromunun (RLS) sıklığını değerlendirmektir. Ayrıca menopozun klinik özellikleriyle RLS arasındaki ilişkiyi de araştırdık.
Yöntem: Bu çalışmaya menopoz döneminde olan 523 kadın dahil edildi. 334 (63.86%) kadın bu çalışmada kullanılan kriterleri karşılamadığı için çalışmadan çıkarıldı. Sonuç olarak 189 postmenopozal dönemdeki kadın değerlendirildi. Bunlar içinde 73'ü RLS'nun tüm kriterlerini karşılıyordu. Bunların 26'sında RLS'nin sekonder nedenlerinden en az biri vardı. Bu nedenle

bu hastalarda elendi. 142 hastanın 26'sı (18.3%) RLS'ye neden olan herhangi bir faktör taşımıyordu. Bu hastalar grup 1 olarak sınıflandı. Kontrol grubu, bu grubla benzer yaşta (+2), RLS semptomları olmayan 56 postmenopozal kadından oluştu.
Bulgular: Grup 1 hastalarında menopoz başlama yaşı daha erken ve cerrahi menopoz çok daha yüksek orandaydı. Menopoz başlama yaşlarıyla RLS arasında güçlü ve anlamlı korelasyon vardı.
Tartışma: Sinir sisteminin hem santral hemde periferik kısmı yaygın olarak östrojen reseptörü içermektedir. Östrojen, nigrostriatal sistemde dopaminerjik aktiviteyi değiştirebilmektedir. Hipoöstrojenemi ile karakterize menopoz dönemi, RLS semptomlarını başlatan yada kötüleştiren bir risk faktörü olarak olabilir.

Anahtar Kelimeler: Menopoz, Restless Legs sendromu, östrojen, hipoöstrojenemi

INTRODUCTION

Restless leg syndrome (RLS) is a common sensorimotor disorder with a female preponderance and an increasing prevalence with age[14]. RLS may be idiopathic or secondary. Idiopathic RLS appears to run in families, suggesting a genetic basis for the syndrome[24,11]. Secondary RLS may be associated with various diseases such as iron deficiency (with or without anemia), uremia, pregnancy, rheumatoid arthritis, and several neurological conditions[11].

The pathophysiological mechanisms underlying RLS are not unknown; however, most investigations of the condition have focused on the dopamine and iron systems[1,7]. The more than 90% efficacy rate of levodopa for RLS is the primary basis for the dopaminergic hypothesis. Several radiographic techniques have been used to examine the involvement of the dopamine system in RLS, including positron emission tomography, magnetic resonance imaging (MRI), and single-photon emission computed tomography (CT). Although the results are mixed, support exists for involvement of the dopaminergic nigrostriatal loop[6].

Human and animal studies indicate that estrogen modulates dopaminergic activity. Estrogen may influence dopamine synthesis, metabolism, and transport; however, no consensus exists as to the direction, locus, or mechanism of the effect of the hormone on the dopaminergic system, and the relationship is likely to be complex[4,19,17,25].

Estrogen receptors are distributed widely throughout the central and peripheral nervous systems[3,12,15,16,21,22]. Thus, hypoestrogenism after menopause, characterized by decreased ovarian follicular responsiveness to gonadotropins and estrogen[10], affects the nervous system at multiple anatomical and functional sites.

Although RLS has been studied in a wide range of settings, including clinical trials, population-based studies, patient support groups, and patient and family registries, few studies have evaluated the effect of menopause on RLS[14].

Our study investigated the prevalence of RLS in postmenopausal females and assessed the relationship between RLS and clinical features of menopause.

MATERIAL AND METHODS

We enrolled 523 consecutive postmenopausal females who attended the Obstetrics and Gynecology Disease outpatient clinic of the medical faculty at our university.

The study was performed in accordance with the Helsinki Declaration. The patients were given a detailed explanation of the study and all provided written informed consent.

Case evaluations

Menopause was defined as cessation of menses for ≥12 continuous months as ascertained by self-report. The gynecologic exclusion criteria were: gynecologic or non-gynecologic malignancies, currently undergoing chemotherapy or radiotherapy treatment, peripheral vascular disease, and currently taking or had taken hormone replacement therapy for >6 months.

The patients were evaluated in two phases. In the first phase, RLS was diagnosed according to the criteria proposed by the International Restless Leg Syndrome Study Group (IRLSSG)[(2)]: 1. an urge to move the legs, 2. relief of symptoms by movement, 3. worsening of symptoms when at rest, and 4. circadian variation in the urge to move with the most severe symptoms during the evening or night. Only patients who fulfilled all four criteria were included in the study.

In the second phase, the patients diagnosed with RLS were assessed for factors related to secondary RLS, and each patient underwent a neurological examination.

Biochemical tests (measurement of erythrocyte sedimentation rate, hemogram, glucose, transaminases, urea, creatinine, protein electrophoresis, iron levels, thyroid function test, and urine analysis) were performed to exclude causes of secondary RLS.

We excluded patients with a history of familial RLS, diabetes mellitus, uremia, anemia, iron deficiency, rheumatoid arthritis, caffeine and alcohol abuse, malnutrition, a chronic systemic disease, peripheral neuropathy, radiculopathy or myelopathy, spinal cord compression, multiple sclerosis, Parkinson's disease, and using drugs such as metoclopramide, neuroleptics, tricyclic antidepressants, and serotonin reuptake inhibitors.

Patients meeting the inclusion criteria were designated as group 1.

Control subjects

The control group consisted of postmenopausal females without RLS or neurological and gynecological conditions. The inclusion and exclusion criteria for the control group were the same as those used for the patient group.

We used a structured questionnaire to assess sociodemographic characteristics including age, marital status, occupation, education, and number of pregnancies; reproductive history including age at menarche, age at menopause, and type of menopause (natural or surgical); body mass index (BMI), and iron levels. Menopause was classified as natural when there was no procedure causing the cessation of menses.

Statistical analysis

The Statistical Package for the Social Sciences version 15 (SPSS Inc., Chicago, IL, USA) was used to conduct the statistical tests, and the results are expressed as the means±standard deviations. Continuous variables were compared between groups using t-tests for independent samples. Non-parametric data were compared using Fisher's exact test or the likelihood ratio chi-square test. The hypothesis test was used to compare two proportions of independent samples between groups. Pearson's correlation test was used to establish the relationship between the ages at onset of RLS and menopause. P-values <0.05 were deemed to indicate statistical significance.

RESULTS

A total of 523 females with symptoms of menopause attended the Obstetrics and Gynecology Department during the study period. Of those, 334 (63.86%) did not meet the gynecologic inclusion criteria and were subsequently excluded. Thus, we evaluated 189 postmenopausal patients. Of those, 73 (38.62%) met all of the diagnostic criteria for RLS; however, 47 of those had at least one factor related to secondary RLS and were excluded from

the study. The remaining 26 (18.3%) postmenopausal patients with idiopathic RLS were categorized as group 1. The control group was selected from the 116 postmenopausal patients without idiopathic or secondary RLS.

The mean age of the patients in group 1 was 55.12 ± 7.59 years and that of the 116 patients without RLS was 61.45 ± 9.36 years (t = -3.671, p = 0.001). Because age was significantly different between the groups, the control subjects were matched by age (±2 years). Thus, the control group comprised a total of 56 postmenopausal patients.

Sociodemographic characteristics

We found no significant difference in age, marital status, education, occupation, or number of pregnancies between the groups. The sociodemographic characteristics of the groups are shown Table 1. The mean ages of group 1 and the control group were 55.12 ± 7.59 (range: 38–75) and 53.66 ± 6.69 (range: 40–75) years, respectively (t = 0.877, p = 0.383; Table 2).

Comparison of reproductive characteristics, iron levels, and BMI

The groups were similar in terms of age at menarche, iron levels, and BMI. The onset age of menopause was earlier (t = -4,204, p < 0.001) and surgical menopause was more frequent (x^2 = 6.337, p = 0.012) in group 1 than in the control group. The reproductive characteristics, iron levels, and BMI according to group are shown in Table 2. In group 1, the mean age at menopause onset was 47.23 ± 5.47 and mean age at RLS onset was 51.8 ± 56.28 years. Pearson's correlation test revealed a strong and significant correlation between the onset ages of menopause and RLS (r = 0.772, p = 0.001).

Table 1. Sociodemographic characteristics according to group.

Parameter		Group 1 (*n* = 26)		Control group (*n* = 56)		x^2	***p*-value**
		n	%	*n*	%		
Marital status	Married	22	84.6	48	85.7		
	Single	3	11.5	6	10.7	0.017	0.992
	Other	1	3.8	2	3.6		
Occupation	Working	9	34.6	26	46.4	0.588	0.443
	Not working	17	65.4	30	53.6		
Education	No education	4	15.4	6	10.7		
	Primary school	8	30.8	20	35.7		
	Secondary school	11	42.3	20	35.7	1.132	0.886
	High school	1	3.8	4	7.1		
	University	2	7.7	6	10.7		
	Nulliparous	5	19.2	13	23.2		
Parity	1–3	15	57.7	29	51.8	0.271	0.873
	≥4	6	12	14	25		

Table 2. Reproductive characteristics, iron levels, and body mass index according to group.

Parameter Mean ± SD		Group 1 (*n* = 26)	Control group (*n* = 56)	*t*	*p*-value
Age (y)		55.12 ± 7.59	53.66 ± 6.69	0.877	0.383
Age at menarche (y)		13.15 ±1.66	12.39 ±1.77	0.069	0.761
Age at menopause (y)		47.23 ±5.47	52.23 ± 4.79	-4.204	**<0.001**
Iron levels (µg/dL)		75.61 ± 16.60	73.53 ± 16.65	0.527	0.600
Body mass index		30.15 ± 6.31	29.29 ± 5.29	0.649	0.518
Type of menopause	natural vs. surgical	15/11	48/8		**0.012***

***** Fisher's exact chi-square test.

DISCUSSION

The prevalence of RLS was 18.3% in postmenopausal females with no secondary RLS factors in our study. The worldwide prevalence of RLS is estimated to be between 1 and 15%[6]. A higher-than-normal prevalence (20–30%) of RLS has been reported in patients with anemia, uremia, neuropathies, multiple sclerosis, and rheumatoid arthritis[6,18]. Furthermore, based on the results of five epidemiological studies, the rate of RLS in pregnant females is between 11 and 27%[13,14]. However, the only study carried out using the IRLSSG criteria found the prevalence of RLS to be 18.3%[2].

We used several inclusion and exclusion criteria to obtain a highly selected group of cases with idiopathic RLS so that potential effects of menopause would be related to idiopathic rather than secondary RLS. Although our inclusion criteria were strict, the prevalence of RLS in our study was higher than that reported in previous community-based studies and was comparable to the rate among females during pregnancy.

The age at menopause onset was earlier in patients with RLS than in the control group, and we found a strong, significant positive correlation between the onset ages of RLS and menopause.

These findings suggest that the etiopathogenetic mechanism underlying the correlation between RLS and menopause may involve a neurobiological interaction between estrogen and the dopaminergic system. Our finding is supported by previous studies linking nigrostriatal dopaminergic activity and RLS and others showing an interaction between estrogen and the nigrostriatal dopaminergic system.

Furthermore, intracortical disinhibition of foot and hand muscles in patients with RLS suggests that the nigrostriatal dopaminergic system (A8 and A9) may be involved in motor excitation[23]. However, the higher frequency of symptoms in lower extremities than in regions, such as the face, suggest that other dopaminergic systems, such as the mesocorticolimbic system (A10 system), located in the caudal of pons or spinal cord may play a role in RLS[20]. Furthermore, the diencephalic dopamine neurons (A11 group) a significant source of CNS dopamine, may be involved in the pathogenesis of RLS.

Although the exact role of this system is not known, the diencephalic dopaminergic neurons are involved in nociceptive control, and disinhibition of the A11 neurons, which normally suppress sensory input, may explain the pain reported by patients with RLS[5].

We found no significant difference between groups in the frequency of natural menopause (gradual decline in estrogen levels; group 1:15/26; 62.5%; control group: 48/56; 85.71.1%). However, the rate of surgical menopause (abrupt decline in estrogen levels) was significantly higher in group 1 than in the control group (group 1: 11/26, 42.3%; control group: 8/56; 14.3%). These findings suggest that surgical menopause, which causes sudden hypoestrogenism, may be related to the increased risk of RLS in postmenopausal females.

Evidence from animal experiments suggests that estrogen modulates dopaminergic activity in the nigrostriatal system[9]. Estrogen receptors are located in brainstem dopaminergic neurons, and several possible estrogen targets have been identified in the nigrostriatal dopaminergic system. Furthermore, investigations of amphetamine-stimulated dopamine release have found estrogen-dependent variations in basal extracellular concentrations of striatal dopamine and in striatal dopamine-mediated behaviors. Most of these experiments were performed in ovariectomized female rats receiving potent estrogen, estradiol, or estradiol benzoate treatment. Estrogens increase dopamine concentration by increasing tyrosine hydroxylase activity and inhibiting dopamine breakdown, or by increasing dopamine receptor density. Additionally, estrogen may modulate dopamine levels by altering monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT) enzyme activity. Furthermore, estrogen may provide neuroprotection by inhibiting dopamine transporter function, increasing mitochondrial activity, and acting as an antioxidant. Alternatively, estrogen may directly suppress dopaminergic function by shifting D2-dopamine receptors from a high- to low-affinity state or indirectly via prolactin release, which has an inhibitory effect on the dopaminergic system[9].

Low estrogen levels after menopause have a long-term cumulative effect on many tissues[10]. Estrogen receptors are widely distributed throughout the central and peripheral nervous systems[3,12,15,16,21,22]. As a result, the hypoestrogenic state that characterizes menopause may affect the nervous system. Postmenopausal females do not experience absolute estrogen deficiency in the peripheral nervous system because adrenal and ovarian androgens are aromatized to estrogen[10]. As a result, the effects of menopause differ among individual females.

Our findings, together with those of previous investigations of the neurobiological interactions between estrogen and the nigrostriatal dopaminergic system, suggest that hypoestrogenemia may contribute to the development of RLS in menopausal females.

To our knowledge, no previous descriptive study has assessed the relationship between menopause and RLS. Furthermore, a retrospective study of female patients with RLS found that the majority of patients (69%) reported an increase in the severity of RLS symptoms following menopause, despite being on hormone replacement therapy[8].

Our study had several limitations. First, we used self-reported data for age at menopause, which may have been subject to recall bias. Second, previous studies have shown that the prevalence of RLS increased in males and females between the ages of 50 and 60 years, with a marked increase with age in females[14]. Our patient group comprised subjects older than 50 years of age; thus, age may have a contributed to the high RLS prevalence in

our study. Third, we made a hospital-based study. The prevalence value determined in our study may be different than that of community-based studies. Furthermore, we compared serum iron, but not serum ferritin, levels in group 1 and the control group.

Despite these limitations, our study had several strengths. First, our primary goal was to assess the frequency of RLS in postmenopausal females. We found an increased frequency of RLS in this special population. Second, we enrolled a relatively large number of postmenopausal subjects. Third, to our knowledge, our study is the first investigation of the prevalence and associated features of RLS in postmenopausal females.

We conclude that a high proportion of postmenopausal females experience RLS, particularly those with early onset of menopause or surgically induced menopause. Estrogen modulates dopaminergic activity in the nigrostriatal system. Menopause is characterized by hypoestrogenemia and may be a risk factor for the development of or worsening RLS symptoms. Larger epidemiological, neurophysiological, and neuroradiological studies are needed to verify the degree of risk and further characterize the relationship between RLS and hypoestrogenemia.

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