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Original article

Restless legs syndrome in 218 patients: associated disorders

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Abstract

Background: Restless legs syndrome (RLS) is a disorder characterized by disagreeable sensations in the legs that occur at rest and are relieved by movement. These symptoms, which are worse at night, may result in sleep onset or sleep maintenance insomnia. Most patients are found on polysomnography (PSG) to have periodic limb movements in sleep (PLMS). The disorder, idiopathic in most cases, may be sometimes associated with specific disorders.

Methods: Using the Province of Manitoba Health database, we compared the diagnoses made in the 5 years prior to sleep laboratory evaluation of 218 patients (103 men and 115 women) with RLS and 872 matched control subjects from the general population.

Results: We found that 43.7% of male RLS patients vs. 10.4% of male controls and 46.1% of female RLS patients vs. 22.8% of female controls had been diagnosed as having psychological/psychiatric (most often depression) disorders ($P < 0.05$). Extrapyramidal disease or movement disorders were previously diagnosed in 17.5% of male RLS patients vs. 0.2% of male controls and in 23.5% of female patients vs. 0.2% of female controls ($P < 0.05$). Many patients had been previously diagnosed with disorders of the musculoskeletal system: 35.9% of male patients vs. 22.8% of male controls and 49.6% of female RLS patients vs. 23.3% of female controls had been diagnosed as having diseases of joints (male; $P =$ ns, female; $P < 0.05$). Disorders of the back were also more frequently diagnosed in RLS patients: 21.4% of male patients vs. 13.1% of male controls and 38.3% of female patients vs. 15.0% of female controls (male; $P =$ ns, female; $P < 0.05$).

Conclusions: We conclude that RLS patients are much more likely to have previously been diagnosed with extrapyramidal disorders, musculoskeletal disorders, depression, and painful conditions such as joint and back disorders.

Keywords: Restless legs syndrome; Etiology; Sleep; Periodic movements

1. Introduction

Restless legs syndrome (RLS), a very common disorder, is characterized by discomfort in the legs described as creeping, crawling, tingling, or painful [1]. The unpleasant sensations are precipitated by rest and relieved by activity. These symptoms are worse at bedtime and thus RLS patients complain of sleep disturbance, especially insomnia. Most RLS patients have periodic limb movements in sleep (PLMS) documented by polysomnography (PSG). These findings are diagnostic of periodic limb movement disorder (PLMD) [2]. It may be that RLS is simply a manifestation or a presentation of PLMD, and that the separation into distinct diagnostic entities may not be appropriate. It is likely that RLS may be present in

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10–15% of the population [3]. The physiological mechanisms causing RLS are unknown. The disorder, idiopathic in most cases, has been associated with iron deficiency [4], polyneuropathy [5], rheumatoid arthritis [6], and hemodialysis [7,8]. Patients may become symptomatic at any age and have been reported to wait a mean of 2 years after first seeking medical attention before a diagnosis is made [9]. In an attempt to shed light on the reason for delayed diagnosis, and to confirm that RLS was more common in groups of patients with certain diseases, we compared the diagnoses patients had received in the 5 years prior to sleep laboratory evaluation to a matched control group from the general population.

2. Patients and methods

2.1. Selection of patient and control subjects

We selected all patients diagnosed as having RLS/PLMS at the St. Boniface General Hospital Sleep Disorders Center from 1990 to 1998. We excluded those with a sleep breathing disorder (apnea/hypopnea index > 5). All patients met the diagnostic criteria of International Classification of Sleep Disorders for RLS [10]. They had most often been referred for assessment of a sleep complaint of insomnia (sleep onset and/or sleep maintenance) or daytime sleepiness, or suspected sleep apnea. These patients were matched (see below) to control subjects using the Manitoba Health Database, described in detail elsewhere [11,12]. All residents of Manitoba have equal access to government funded health services. This database includes the complete health care utilization information of all residents of the Province of Manitoba, including diagnosis with every contact with a physician. Each physician contact results in a claim which includes the diagnosis for that contact. The database includes 779 diagnoses based on the ICD 9CM.

There were 218 patients (103 men and 115 women) with RLS. Each patient was matched to four individuals selected at random from the general population by postal code (to correct for socioeconomic factors and access to health care), age, and gender. All patients and control subjects were residents of Manitoba for the length of the study period.

The patients and control subjects were divided into two groups based on gender. We determined what physicians had diagnosed in the patients and control subjects in the 5-year period prior to the year in which the patient was diagnosed as having RLS. One of the 779 diagnoses based on the ICD 9CM was said to be present in a patient if it was made at least twice in the database in the 5-year period. Statistical analysis of the data was performed by the Mantel–Haenszel χ^2 test to determine what diagnoses were statistically significant in RLS patients compared to controls. We used a variant of the test which compares three or more matched samples with respect to measurements made on a dichotomous categorical scale. If four or more patients for each gender had a diagnosis in the database, we compared the proportion of patients to the proportion of controls who had received that diagnosis. We thus compared findings for 81 diagnoses for males and 94 for females. Because of the many possible comparisons we performed a Bonferroni correction and calculated the χ^2 value required for $\alpha = 0.05$.

The analysis was done in such a way as to protect patient and control subject confidentiality by scrambling the health insurance number of patients and controls and using the scrambled number as the only unique identifier. We were not permitted or able by the regulations allowing use of the database to be able to identify or contact the control subjects. This project was reviewed by the Ethics Committee of the University of Manitoba and the Access and Confidentiality Committee of Manitoba Health.

3. Results

The age distribution of the RLS patients is shown in Table 1. The 103 male patients had a mean age of 49.2 ± 14.8 (standard deviation, SD) years, the 118 female patients had a mean age of 48.5 ± 15.3 years.

3.1. Clinical presentation

The patients with restless legs syndrome most often presented with insomnia, daytime sleepiness, and snoring (Table 2). There were no differences between the proportion of males and females presenting with these features. The duration of their chief presenting symptoms was as follows: insomnia: mean $126.2 \pm$

Table 1
Age distribution of the RLS patients

Age (years)	Females	Males
11–20	5	2
21–30	8	11
31–40	20	20
41–50	28	22
51–60	26	24
61–70	20	17
71–80	7	6
81–90	1	1

23.3 (SEM) months for males vs. 134.1 ± 19.7 months for females; daytime sleepiness: mean 49.8 ± 12.3 months for males vs. 76.2 ± 15.2 months for females; snoring: mean 80.4 ± 21.8 months for males vs. 117.6 ± 46.5 months for females. The patients who complained of insomnia as a group had a prolonged subjective sleep onset latency (mean 69.6 ± 9.3 min for males, 62.2 ± 8.2 min for females), and an Epworth sleepiness scale (ESS) score in the normal range latency (mean 7.2 ± 0.7 for males, 6.9 ± 0.7 for females). The RLS patients who complained of excessive daytime sleepiness as a group had a shorter subjective sleep onset latency (mean 21.7 ± 7.3 min for males, 23.4 ± 5.3 min for females), and a higher Epworth sleepiness score (mean 14.0 ± 0.9 for males, 15.4 ± 0.8 for females) than those with insomnia (see above) ($P < 0.001$). None of the differences between males and females were significant.

3.2. Medication use on presentation

Many of the RLS patients (65% of males, 71% of females) were on a wide variety of medications for various medical disorders (Table 3). At the time the patients were assessed in the Sleep Disorders Centre twice as many women as men were being treated with antidepressants of various types (see Table 3) and they were also much more likely to be on thyroid replacement therapy. It is of interest that the female but not the male patients on benzodiazepines had a lower ESS score than those not on benzodiazepines; mean 8.3 ± 1.1 for males on benzodiazepines vs. 9.4 ± 0.6 for males not on benzodiazepines; mean 5.6 ± 1.2 for females on benzodiazepines vs. 10.5 ± 0.7 for females not on benzodiazepines (male; not significant, female; $P < 0.001$). All 14 male RLS patients on antidepressants and 26 of 27 female RLS patients on antidepressants had been diagnosed as having depression in the Manitoba Health Database (see below).

3.3. Diagnoses made in the 5 years prior to sleep laboratory evaluation

Data analysis is presented separately for males and females in Tables 4 and 5. These tables do not have identical categories because some disorders are unique to one gender. Because we are examining many diagnostic entities, some differences may be significant purely based on chance. We are thus presenting the results in terms of uncorrected probability and probability corrected to account for the multiple testing. In addition, in Tables 4 and 5 we are presenting some diagnostic categories in which the differences were not significant or the number of cases was small but, in which previous literature has suggested an association with RLS (e.g. diabetes mellitus). Each table shows the number of patients or control subjects who had been diagnosed two or more times for each diagnostic class. Male RLS patients had been more frequently diagnosed as having depression, diseases of musculoskeletal and connective tissue, movement disorders, respiratory disorders and peripheral vascular disease. Females with RLS had been more frequently diagnosed with depression, movement disorders, arthropathies, disorders of the back, and respiratory diseases. There was a trend toward anemia and hypothyroidism being more common in the female patients.

Table 2
Chief presenting complaint on referral to sleep disorders center

Chief complaints	Males	(%)	Females	(%)
Insomnia	40	38.8	53	46.1
Excessive daytime sleepiness	21	20.4	26	22.6
Snoring	21	20.4	12	10.4
Fatigue	7	6.8	8	7.0
Apnea (observed)	7	6.8	4	3.5
Restless legs	3	2.9	8	7.0
Others[a]	4	3.9	4	3.5

[a] Shortness of breath, headache, sleep walking, nightmare, choking, moaning and groaning.

4. Discussion

For several years before the RLS diagnosis was established, our patients were diagnosed as having various disorders more frequently than controls. Our data suggests the possibility that development of RLS is associated with many etiologic factors. All the RLS patients we reported had been referred to the sleep disorders center because of chronic sleep-related complaints. Although insomnia was by far the most common presenting complaint, some patients presented with features that suggested a sleep breathing disorder. Thus, these patients may not be representative of the RLS patient in the community in whom symptoms may not be serious enough to warrant evaluation. In addition, because RLS in some patient groups is now widely known to be common (e.g. renal failure) such patients are no longer being referred. Nevertheless, our results suggest that more detailed assessment of sleep is warranted in the management of the conditions mentioned below.

4.1. Mood disorders

Forty-five male RLS patients (43.7%) and 53 female RLS patients (46.1%) had been diagnosed as having mood disorders (depression or affective psychosis) confirming the impression of previous reports. Gorman et al. reported the high frequency of overt depression and anxiety in RLS patients [13]. Young et al. reported that of the 140 patients with RLS, 128 were diagnosed as having conditions often associated with a tension state or depression [14]. The sleep complaints of RLS may be incorrectly interpreted as a symptom of depression [15]. It is possible that chronic discomfort caused by RLS is a trigger for depression or affective disorder.

Depression is a common cause of insomnia. However, certain antidepressants may cause RLS as an adverse effect [16]. On the other hand, insomnia caused by RLS may theoretically result in depression. The risk of developing new depression is reported to be higher in those who have insomnia compared with those without insomnia [17,18]. Thus, there are several possible reasons that might explain the previous diagnosis of depression in RLS patients.

4.2. Movement disorders

Not surprisingly, movement disorders and extrapyramidal disorders were often previously diagnosed

Table 3
Medications used by RLS patients on presentation

	Male	(%)	Female	(%)
Antihypertensives	15	14.7	14	12.2
Angiotensin II receptor antagonists	1	1.0	1	0.9
Calcium channel blockers	4	3.9	2	1.7
ACE inhibitors	5	4.9	2	1.7
β-Adrenergic blocking agents	6	5.8	4	3.5
α_1-adrenergic blocking agents	1	1.0	0	0
Diuretics	5	4.9	6	5.2
Peptic ulcer therapy	2	1.9	8	7.0
H_2-receptor antagonists	1	1.0	6	5.2
Proton pump inhibitors	1	1.0	2	1.7
Lipid lowering agents	5	4.9	2	1.7
Antidepressants	14	13.6	31[a]	27.0
Selective serotonin reuptake inhibitors	10	9.7	13	11.3
Non-selective monoamine reuptake inhibitors	3	2.9	11	9.6
Serotonin-norepinephrine reuptake inhibitors	1	1.0	2	1.7
Monoamine oxidase inhibitors	1	1.0	1	0.8
Other antidepressants	1	1.0	4	3.5
Antipsychotics	2	1.9	1	0.9
Phenothiazines	0	0	1	0.9
Butyrophenone derivatives	2	1.9	0	0
Antiparkinsonian agents	2	1.9	2	1.7
CNS stimulants	2	1.9	1	0.9
Analgesics	15	14.6	20	17.4
Acetic acid derivatives	2	1.9	7	6.1
Propionic acid derivatives	2	1.9	2	1.7
Opioids	1	1.0	1	0.9
Aspirin	4	3.9	1	0.9
Acetaminophen	7	6.8	12	10.4
Anticonvulsant	4	3.9	2	1.7
Barbiturates and derivatives	1	1.0	0	0
Carboxylic acid derivatives	1	1.0	0	0
Iminostilbene derivatives	1	1.0	1	0.9
Hydantoin derivatives	1	1.0	1	0.9
Benzodiazepines	14	13.6	18	15.7
Asthma therapy	6	5.8	6	5.2
β-2-Adrenergic agonists (inhaled)	3	2.9	4	3.5
Corticosteroids (inhaled)	1	1.0	2	1.7
Anticholinergics (inhaled)	2	1.9	0	0
Theophylline	1	1.0	1	0.9
Thyroid hormone	2	1.9	13[a]	11.3

[a] Difference between males and females using medication $P < 0.05$ by the χ^2 test.

Table 4
Diagnoses in males with RLS[a]

	Case	(%)	Controls	(%)	χ^2	Odds ratio
Mental disorders and diseases of the nervous system						
Psychological/psychiatric disorders[b]	45	43.7	43	10.4	60.545***	5.3‡
Other extrapyramidal disease and abnormal movement disorders	18	17.5	1	0.2	66.329***	72.0‡
Disease of the musculoskeletal system and connective tissue						
Rheumatoid arthritis and other inflammatory polyarthropathies	1	1.0	2	0.5	0.333	2.0
Arthropathy[c]	37	35.9	94	22.8	7.290	1.9†
Disorder of back[d]	22	21.4	54	13.1	4.219	1.8*
Disorders of muscle, ligament, and fascia[e]	17	16.5	45	10.9	2.593	1.7
Diseases of the respiratory system						
Upper respiratory infections[f]	15	14.6	16	3.9	16.690***	4.7‡
Asthma	12	11.7	18	4.4	7.759	2.8†
COPD[g]	27	26.2	45	10.9	16.266***	3.0‡
Symptoms involving respiratory system and chest symptoms	40	38.8	71	17.2	24.149***	3.4‡
Endocrine, nutritional, and metabolic diseases						
Thyrotoxicosis with/without goiter	2	1.9	0	0.0	8.000	>1000.0**
Acquired hypothyroidism	2	1.9	4	1.0	0.667	2.0
Diabetes mellitus	9	8.7	27	6.6	0.643	1.4
Disorders of lipoid metabolism	20	19.4	29	7.0	15.300***	3.3‡
Obesity and other hyperalimentation	9	8.7	10	2.4	9.657	4.3†
Diseases of the blood						
Anemia[h]	7	6.8	11	2.7	4.129	2.7*
Miscellaneous						
Renal failure[i]	4	3.9	3	0.7	6.036	5.3*
Inflammatory diseases of prostate	7	6.8	7	1.7	8.167	4.5†
Essential hypertension	27	26.2	61	14.8	7.946	2.1†
Peripheral vascular disease[j]	9	8.7	7	1.7	13.565***	5.8‡
Cerebrovascular disease[k]	4	3.9	5	1.2	3.361	3.2
Disorders of skin[l]	28	27.2	46	11.2	18.0***	3.1‡
Other symptoms involving abdomen and pelvis	21	20.4	39	9.5	10.025	2.6†

[a] χ^2 values uncorrected for multiple testing: *χ^2 value >3.84 is significant at $P < 0.05$; †χ^2 value >6.63 is significant at $P < 0.01$; ‡χ^2 value > 10.83 is significant at $P < 0.001$; **Odds ratio not meaningful because none of the controls had this diagnosis; ***Using Bonferroni correction, χ^2 values > 11.724 indicate $P < 0.05$.

[b] Affective psychosis, depressive disorder not elsewhere classified, neurotic disorders.

[c] Osteoarthritis and allied disorders, other and unspecified arthropathies, other and unspecified disorders of joint, other disorders of synovium, tendon, and bursa.

[d] Intervertebral disc disorders, other and unspecified of back.

[e] Disorders of muscle, ligament, and fascia, peripheral enthesopathies and allied syndromes.

[f] Acute tonsilitis, chronic laryngitis and laryngotracheitis, influenza.

[g] Chronic bronchitis, emphysema, chronic airway obstruction, not elsewhere classified.

[h] Iron deficiency anemias, other deficiency anemias, hereditary hemolytic anemias, other and unspecified anemias.

[i] Acute renal failure, chronic renal failure, renal failure, unspecified.

[j] Other peripheral vascular disease, phlebitis and thrombophlebitis, other venous embolism and thrombosis.

[k] Acute, but ill-defined cerebrovascular disease, other and ill-defined cerebrovascular disease.

[l] Contact dermatitis and other eczema, erythematous conditions, pruritus and related conditions, symptom involving skin, and other integumentary tissue, burn of lower limbs.

Table 5
Diagnoses in females with RLS[a]

	Case	(%)	Controls	(%)	χ^2	Odds ratio
Mental disorders and diseases of the nervous system						
Psychological/psychiatric disorders[b]	53	46.1	105	22.8	24.781***	2.9‡
Other extrapyramidal disease and abnormal movement disorders	27	23.5	1	0.2	102.223***	108.0‡
Cataplexy and narcolepsy	4	3.5	0	0.0	16.000	>1000.0**
Hereditary and idiopathic peripheral neuropathy	4	3.5	1	0.2	11.250	16.0‡
Disease of the musculoskeletal system and connective tissue						
Rheumatoid arthritis and other inflammatory polyarthropathies	3	2.6	3	0.7	3.375	4.0
Arthropathy[c]	57	49.6	107	23.3	33.427***	3.5‡
Disorder of back[d#]	44	38.3	69	15.0	31.453***	3.6‡
Disorders of muscle, ligament, and fascia[e]	27	23.5	55	12.0	10.252	2.4†
Other disorders of soft tissues	34	29.6	40	8.7	36.283***	4.4‡
Symptoms involving head and neck	21	18.3	43	9.3	7.309	2.1†
Diseases of the respiratory system						
Upper respiratory infections[f]	8	7.0	26	5.7	0.295	1.3
Asthma	19	16.5	29	6.3	12.137***	2.7‡
COPD[g]	35	30.4	79	17.2	10.003	2.2†
Symptoms involving respiratory system and other chest symptoms	39	33.9	74	16.1	18.272***	2.7
Endocrine, nutritional, and metabolic diseases						
Thyrotoxicosis with or without goiter	1	0.9	6	1.3	0.143	0.7
Acquired hypothyroidism[#]	12	10.4	16	3.5	9.660	3.5†
Diabetes mellitus	9	7.8	19	4.1	2.676	1.9
Diseases of the blood						
Anemia[h]	13	11.3	23	5.0	6.570	2.6*
Miscellaneous						
Renal failure[i]	1	0.9	3	0.7	0.063	1.3
Peripheral vascular disease[j]	5	4.3	6	1.3	4.667	3.8*
Cerebrovascular disease[k]	4	3.5	2	0.4	8.167	8.0†
Disorders of skin[l]	42	36.5	74	16.1	23.500***	3.3‡
Other symptoms involving abdomen and pelvis	36	31.3	74	16.1	13.842***	2.6‡
Contusion of lower limb and of other and unspecified sites	9	7.8	10	2.2	9.389	4.3†

[a] χ^2 values uncorrected for multiple testing: *χ^2 value > 3.84 is significant at $P < 0.05$; †χ^2 value > 6.63 is significant at $P < 0.01$; ‡χ^2 value > 10.83 is significant at $P < 0.001$; **Odds ratio not meaningful because none of the controls had this diagnosis; #Difference between males and females of diagnosis $P < 0.05$ by χ^2 test; ***Using Bonferroni correction, χ^2 values > 12.000 indicate $P < 0.05$.

[b] Affective psychosis, depressive disorder not elsewhere classified, neurotic disorders.

[c] Osteoarthritis and allied disorders, other and unspecified arthropathies, other and unspecified disorders of joint, other disorders of synovium, tendon, and bursa.

[d] Intervertebral disc disorders, other and unspecified of back.

[e] Disorders of muscle, ligament, and fascia, peripheral enthesopathies and allied syndromes.

[f] Acute tonsilitis, chronic laryngitis and laryngotracheitis, influenza.

[g] Chronic bronchitis, emphysema, chronic airway obstruction, not elsewhere classified.

[h] Iron deficiency anemias, other deficiency anemias, hereditary hemolytic anemias, other and unspecified anemias.

[i] Acute renal failure, chronic renal failure, renal failure, unspecified.

[j] Other peripheral vascular disease, phlebitis and thrombophlebitis, other venous embolism and thrombosis.

[k] Acute, but ill-defined cerebrovascular disease, other and ill-defined cerebrovascular disease.

[l] Contact dermatitis and other eczema, erythematous conditions, pruritus and related conditions, symptom involving skin, and other integumentary tissue, burn of lower limbs.

in our patients. Although the exact role of dopamine in the pathogenesis of RLS is not clear, dopamine agonists reduce the symptoms and polysomnographic features of RLS [19–22]. It is possible that the pathogenesis of RLS may overlap with that of extrapyramidal disorders. For example, patients taking neuroleptics may have symptoms of akathisia, which has similarities to the symptoms of RLS [23]. Voderholzer et al. reported that PLMS were found in five of seven patients with Gilles de la Tourette's syndrome [24]. Patients with Parkinson's disease may show periodic movements in sleep which suggests basal ganglia dysfunction, as reported by Askenasy et al. [25].

4.3. Peripheral neuropathy

There was a trend of hereditary idiopathic peripheral neuropathy being more often diagnosed in female RLS patients but not in male RLS patients. Classic forms of RLS may be associated with mild predominantly sensory polyneuropathy, as reported by Rutkove et al. [5]. It is possible that RLS may be a manifestation of the symptoms of polyneuropathy such as painful, tingling, or tormenting sensation. It is also possible that such abnormal sensations may lead to a misdiagnosis of a skin disorder, which was much more commonly made in both our male and female RLS patients.

4.4. Painful disorders

Disorders of the back and arthropathies were unexpectedly common in the female RLS group. Walters et al. reported that lumbosacral radiculopathy may play a role as a trigger of RLS [26]. Disorders of the back may lead to RLS via spinal cord or rootlet dysfunction. Hartmann et al. described three cases of RLS associated spinal cord lesions [27]. It is possible that such neurologic problems may result in RLS. It is also possible that the sometimes distressing discomfort of RLS patients was misdiagnosed as indicating a disorder of the back or arthropathies.

Although osteoarthritis was far more often diagnosed in female RLS patients, rheumatoid arthritis (RA) was not statistically more common in our patients. Reynolds et al. described that the prevalence of RLS was significantly higher in the group with RA [6]. In addition, Salih et al. reported that RLS symptoms were more frequent in RA patients (25%) than in non-RA controls with osteoarthritis or seronegative arthropathy (4%) [28]. It is possible that the prevalence of RLS in RA patients is high but these patients are not being referred to the sleep laboratory.

4.5. Respiratory disease

Our data revealed that RLS patients had been diagnosed more often as having chronic respiratory disorders. Spillane et al. reported eight RLS patients suffering from COPD [29]. Although smoking was reported to be a low risk factor for RLS by Lavigne et al. [30], it has been reported that RLS is relieved by cessation of smoking [31]. It is possible that chronic hypoxemia caused by COPD is more closely linked with the pathogenesis of RLS than smoking.

4.6. Endocrine and metabolic disorders

Our data shows a trend toward a previous diagnosis of acquired hypothyroidism in female RLS patients. Female patients were twice as likely to be on thyroid replacement. Schlienger reported RLS due to moderate hypothyroidism [32]. Further investigation is required to determine the impact of thyroid function on RLS. We found no statistically significant association between RLS and diabetes mellitus (DM). Banerji et al. found that 17.0% of 53 DM patients vs. 2.0% of 50 controls had RLS [33]. O'Hare et al. also found that 8.8% of 800 DM patients vs. 7.0% of 100 controls had RLS ($P = 0.02$) [34]. We found that diabetes was relatively common in both patients and controls and that although there was a trend to diabetes being more common in the RLS patients, the differences were not significant.

4.7. Anemia

We found a trend toward RLS patients being diagnosed with anemia more frequently than control subjects in both genders. O'Keeffe et al. reported that serum ferritin levels were reduced in the RLS patients compared with control subjects, and were inversely correlated with the severity of RLS symptoms [4]. Sun et al. reported a significant inverse correlation between serum ferritin and RLS severity [35]. But non anemic RLS patients despite normal serum ferritin levels may have abnormally low CSF

ferritin, as reported by Earley et al. [36]. The evolving data suggests that two factors may be linking RLS and iron metabolism. One may be iron depletion in the central nervous system (CNS), most often caused by iron deficiency. The other is abnormal iron distribution and transport in the CNS, caused by abnormal iron regulation in the CNS.

4.8. Renal failure

We found a trend toward renal failure being more common in male RLS patients, but not in female RLS patients. RLS is a frequent specific complaint in patients with renal failure [7,37]. Roger et al. reported that RLS was more common in female than in male renal dialysis patients and that RLS symptoms improved with the correction of anemia with epoetin alfa [8]. The anemia caused by renal failure may be playing a role in the pathogenesis of RLS. We believe that renal failure patients are now being treated for restless legs without referral for sleep laboratory evaluation because this has been a topic of interest in the literature, and most nephrologists are now aware of the relationship. Winkelman et al. reported that 20% of 204 end-stage renal disease patients had moderate to severe RLS symptoms [38]. Walker et al. reported that approximately 60% of 54 renal failure patients on dialysis had mild or severe RLS [7].

Our data raises some therapeutic issues. Although all of these patients gave a history characteristic of restless legs syndrome when evaluated in the sleep disorders center, less than 2% of the patients were receiving the medications usually first recommended, the anti-Parkinsonian agents [39]. A substantial number of the patients, both men and women, had been diagnosed with depression and many of the patients were being treated for depression, some with medications that could potentially worsen the movements. A systematic examination of the relationship between restless legs syndrome and depression and anti-depressants is warranted.

5. Conclusions

We conclude that RLS is associated with many disorders. It seems reasonable that a clinician should include a sleep history in evaluation of patients with these disorders, since these patients may require treatment of the distressing RLS symptoms.

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