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Secondary causes of restless legs syndrome in older people

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Abstract

Background: secondary causes of restless legs syndrome (RLS) have been reported to be more common in those with late-onset RLS. However, 'late-onset' in previous studies was defined as onset after 45 years.
Objective: to determine the prevalence of secondary causes of RLS and the relationship between aetiological factors and age of symptom onset in an older population.
Design: prospective study conducted over a 5-year period.
Participants: 80 consecutive non-related patients diagnosed with RLS.
Measurements: patients were assessed according to a standard protocol. Age at symptom onset, severity of symptoms, neurological findings and laboratory tests were examined.
Results: iron deficiency (serum ferritin <50 ng/ml) was present in 22% of patients with onset before 50 years, 39% of those with onset at 50 to 64 years and 58% in those with onset after 64 years ($P=0.009$). Clinical neuropathy was also more common in older-onset patients ($P=0.08$). Family history was positive in 39%, 23% and 8% of these groups, respectively ($P=0.008$).
Conclusion: secondary causes of RLS become more common and a positive family history less common with increased age of symptom onset.

Keywords: *restless legs syndrome, elderly, iron, ferritin*

Introduction

Restless legs syndrome (RLS) is a sleep disorder characterised by unpleasant leg sensations, which may be described as crawling, restless or fidgety in nature [1]. These sensations are felt deep within the limb and are usually bilateral; rarely, the arms may also be affected. Symptoms of RLS are invariably worse while resting and are particularly prominent at night. In more severe cases, symptoms may be present to some extent throughout the day. Moving the legs relieves discomfort, at least to some extent. The vast majority of patients with RLS also have repetitive jerking movements called 'periodic movements of sleep' (PMS) in the legs. PMS may repeatedly awaken the patient from sleep, although some are aware only that they sleep poorly at night or that their bed partner complains of being kicked. PMS are also common in older people without RLS or sleep disturbance [2].

RLS is a common and distressing condition that receives little attention in standard medical textbooks and is frequently misdiagnosed or unrecognised by physicians. Anxiety and depression are common consequences of RLS, and many patients report that their symptoms have been described as psychological in origin [3]. Accurate diagnosis of RLS is usually straightforward provided a good history is elicited from the patient. Even though muscle cramps and peripheral neuropathy often co-exist with RLS, patients

usually have no difficulty in distinguishing the different symptom complexes. There are similarities between neuroleptic-induced akathisia and RLS, and neuroleptics can exacerbate the symptoms of restless legs. Patients with akathisia move because of a feeling of inner restlessness, and restlessness is more prominent during the waking hours.

RLS can occur at any age, but epidemiological studies indicate that the prevalence of the condition is highest in later life [4–7]. In a telephone survey of 1,803 adults in Kentucky, 19% of those older than 79 years reported symptoms of restless legs at least five times a month [4]. An interview-based study of 369 Germans aged 65 years or over found an overall prevalence of 9.8% [5]. Although there may be long asymptomatic periods, the severity of the condition tends to increase with time [7].

RLS is idiopathic in most cases, and up to half of these patients have a positive family history consistent with autosomal dominant inheritance [8]. RLS has also been reported in association with a wide variety of conditions and medications. The associations between RLS and iron deficiency and end-stage renal disease are particularly strong, and are likely to be of pathognomic significance since iron repletion or successful kidney transplantation often results in cure or major improvement in restless legs. Secondary causes of RLS have been reported to be more common in those with late-onset RLS, while a positive family history seems most common in those with early-onset RLS [9, 10]. However, 'late onset' in these studies was defined as onset after 45 years. This study examines the association between risk factors for RLS and age of onset in a predominantly elderly group of patients.

Methods

Subjects

Subjects were 80 consecutive non-related RLS patients seen over a 5-year period by a single geriatrician and general physician with an interest in RLS. The diagnosis of RLS was based on the four criteria of the International RLS Study Group (IRLSSG): (1) urge to move limbs associated with unpleasant sensations; (2) motor restlessness; (3) worsening with inactivity and temporary improvement with activity; and (4) worsening at night [11].

Methods

All subjects were assessed according to a standard protocol. Age of onset of symptoms was noted. Patients were asked about similar symptoms in close relatives; family history was accepted as positive if any first-degree relative was reported to have had such symptoms. The severity of RLS was assessed using a 10-point RLS severity scale [12]. Patients were asked about leg symptoms suggestive of distal sensory neuropathy, and a clinical diagnosis of peripheral neuropathy was made if there were bilateral distal sensory symptoms (with or without signs) that could clearly be distinguished from RLS. A history of other factors associated with RLS, including rheumatological disease, diabetes mellitus and neuroleptic exposure, was sought. Blood chemistry tests included full blood count, creatinine, urea, glucose, ferritin, thyroid function tests, and vitamin B12 and folate levels. Additional investigations were performed if clinically indicated.

Analyses

Clinical and laboratory findings at presentation were compared in pre-determined groups according to age at onset with RLS (<50 years, 50–64 years and >64 years). Serum ferritin was analysed as a continuous variable; the proportions of patients with serum ferritin <20 ng/ml and <50 ng/ml were also examined. Continuous data were examined with analysis of variance (ANOVA) and categorical variables by chi-square tests for trend.

Results

The mean age (SD) of the 80 patients was 71.2 (7.8) years (range 42–89 years). There were 49 women and 31 men. Twenty-two patients were less than 65 years old (range 42–64 years), and 58 were 65 years or older (range 65–89 years) at the time of presentation. Eighteen patients had first developed RLS before they were 50 years, 26 when aged between 50 and 64 years, and 36 at 65 years or over.

Details of patients according to age of onset of RLS are shown in Table 1. Serum ferritin levels at presentation differed significantly between the three groups (P=0.05). Pair-wise comparisons using the Tukey–Kramer test showed a significant difference in ferritin levels between those with onset of

Table 1. Clinical and laboratory data according to age of onset with RLS

	Age of onset			
	<50 years (N=18)	50–64 years (N=26)	>64 years (N=36)	P
Age of onset, mean (SD)	35.2 (6.3)	46.5 (5.8)	70.1 (6.9)	
Serum ferritin, mean (SD)	82.7 (43.0)	68.4 (54.3)	50.9 (39.0)	0.05
Serum ferritin <50 ng/ml	4 (22.2%)	10 (38.5%)	21 (58.3%)	0.009
Serum ferritin <20 ng/ml	2 (11.1%)	4 (15.4%)	7 (19.4%)	0.4
Family history of RLS	7 (38.9%)	6 (23.1%)	3 (8.3%)	0.008
Sensory neuropathy	0 (0%)	3 (11.5%)	6 (16.7%)	0.08
Serum ferritin <50 ng/ml or clinical neuropathy	4 (22.2%)	12 (46.2%)	26 (72.2%)	0.0004
RLS severity[a], mean (SD)	6.4 (2.1)	6.3 (1.5)	6.0 (1.7)	0.6

Data are number (%) unless otherwise noted.
[a]Dublin RLS severity score.

RLS at <50 years and those with onset at 65 years or over (P=0.05). Other blood chemistry results did not differ between the groups (data not shown). RLS severity did not differ between the groups. The proportion of patients with serum ferritin <50 ng/ml increased significantly with increased age of onset of RLS, whereas the proportion of patients with a positive family history showed a significant decline.

Of the 35 patients with serum ferritin <50 ng/ml, 21 (60%) had haemoglobin levels of 12 g% or over and mean corpuscular volumes of 80 fl or over. Upper and lower gastrointestinal (GI) evaluation was recommended for 19 of the 35 patients who did not have one or more of: obvious non-gastrointestinal cause of blood loss (2 patients), known GI disease associated with iron deficiency or blood loss (7), GI investigation within the previous 2 years (4) or recent surgery (4). Six of these 19 patients refused full GI evaluation. Diagnoses in the remaining 13 patients were: oesophagitis (2 patients), oesophageal cancer (1), erosive gastritis (1), duodenal ulcer (1), colonic polyp (1), colon cancer (1) and no cause (5).

One patient with onset of RLS at 65 years or over had seropositive rheumatoid arthritis in addition to a serum ferritin level of <50 ng/ml. A clinical diagnosis of bilateral distal sensory or sensory/motor neuropathy in the legs was made in nine patients, of whom five had type 2 diabetes mellitus, one had chronic renal failure (serum creatinine >200 mmol/l) and one patient had both.

Discussion

The results of this study show that secondary forms of RLS are increasingly important in patients who develop the condition for the first time in later life, occurring in over 70% of those with onset at 65 years or over. This is consistent with previous reports. Ondo and colleagues noted that ferritin levels were lower and neuropathy more common in RLS patients without a positive family history [9]. Polydefkis *et al.* noted a lower rate of small fibre neuropathy in younger patients with RLS [13]. Allen and Earley reported that a family history was more common in early-onset RLS, while ferritin levels were lower in late-onset RLS [10]. However, there were only 26 patients in their study and 'late-onset' referred only to onset after 45 years. The present study extends these results to a larger and substantially older population.

The relationship between iron deficiency and a later onset of RLS was particularly strong in this study. Previous work has also suggested an important role for iron deficiency in the pathogenesis of RLS in older people. For example, in a study of 147 elderly hospital patients with insomnia, iron deficiency was present in 31% of 13 patients with RLS and 6% of 134 patients without RLS [12]. Other studies have found a moderately strong correlation (about 0.5) between serum ferritin levels and the severity of restless legs [14, 15]. Serum ferritin is accepted as the best screening test for iron deficiency and, in older hospital patients, the diagnosis of iron deficiency is almost certain in those with ferritin levels of <20 ng/ml, and is likely in those with levels <50 ng/ml [16]. Many of these patients have normal haemoglobin and MCV levels. A search for an underlying cause of iron deficiency is usually indicated [17]; in the current study, this search resulted in the detection of two new cancers. Also, oral or intravenous iron supplements can lead to considerable improvement in symptoms in iron-deficient RLS patients [14, 18].

Impaired dopaminergic neurotransmission is a major factor in the pathogenesis of RLS, and dopaminergic agonists are an effective treatment for restless legs [1–3]. Iron is an essential cofactor for tyrosine hydoxylase, the rate-limiting enzyme for dopamine synthesis, and, in animal studies, iron deficiency is associated with hypofunction of dopamine D2 receptors, which can be corrected by iron replacement [18]. Furthermore, even in idiopathic RLS without systemic iron deficiency, there is evidence to suggest that the ability of the brain to transport or store regional iron may be abnormal [19].

The relationship between peripheral neuropathy and RLS is less certain. Although RLS may be a presenting feature of sensory neuropathy [2], some studies have suggested that the frequency of RLS in neuropathic patients is similar to that in the general population [20, 21]. Recently, a detailed evaluation of RLS patients with sural nerve or skin biopsies has found a high frequency of clinically undetectable axonal and small-fibre neuropathies [13]. In the present study, there was an (non-significant) increase in the prevalence of neuropathy with increased age of onset of RLS. It is likely that the prevalence of neuropathy was underestimated in our study, since diagnosis was clinical, and electrophysiological and biopsy tests were not performed.

Of older people with RLS, some are 'graduates', perhaps presenting for the first time because of increased severity of symptoms, while others have developed RLS for the first time in later life. Allen and Earley noted a slower progression of symptom severity with age in later-onset RLS, but no difference in overall severity between early-onset and late-onset disease [10]. Our results are similar. Thus, it seems that people who develop RLS in later life progress rapidly to a severity that it may take those with earlier onset years to reach. This may reflect the role of environmental factors such as iron deficiency, perhaps acting on a background of a genetic predisposition.

This study has a number of limitations. Differentiation of the groups for analysis relied, of necessity, on patients' self-reported age at onset of symptoms. It is impossible to be certain of the accuracy of such reports, although Allen and Earley have at least confirmed that patient estimates are consistent [10]. The findings reported here from a hospital-based service with a well-established interest in RLS may not be fully applicable to RLS patients presenting to non-specialist services or to RLS sufferers in the general population. Indeed, Berger and colleagues failed to find any relationship between iron status and RLS in an elderly general population [22]. Nevertheless, our results support the utility of using age at symptom onset as a guide to the phenotype of RLS, and suggest that people presenting with RLS in later life should undergo a careful assessment for possible secondary causes of the condition.

Key points

- More than two-thirds of people who develop restless legs syndrome for the first time after 64 years have an underlying cause such as iron deficiency.
- A positive family history is relatively uncommon (<10%) in those who develop restless legs syndrome for the first time in later life.

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