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Original Article

Age-at-onset in restless legs syndrome: A clinical and polysomnographic study

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Abstract

Objective: To determine the distribution of age-at-onset in a large cohort of patients with restless legs syndrome (RLS) and to compare clinical and polysomnographic characteristics of patients with early and late age-at-onset of RLS.

Methods: Two hundred and fifty patients with RLS were studied. Information on age-at-onset, etiology, familial history and symptoms severity of RLS was obtained. Age-at-onset density functions were determined from bootstrap methods and kernel density estimators.

Results: Age-at-onset showed a significant bimodal distribution with a large peak occurring at 20 years of age and a smaller peak in the mid-40s. Early- and late-onset RLS could be separated with a cut-off at 36 years of age. Distributions of age-at-onset differed as a function of presence/absence of a familial history and etiology of RLS. Age-at-onset clearly differentiated patients with a primary RLS (early onset) from those with secondary RLS. Finally, early-onset RLS was associated with increased RLS severity with higher indices of periodic leg movements in sleep (PLMS) associated with microarousals and periodic leg movements during wakefulness (PLMW).

Conclusions: Early- and late-onset RLS could be distinguished depending on familial history and etiology of RLS. Our data suggest that different pathological processes are involved in these two groups, the early-onset group being highly genetically determined.

Keywords: RLS; PLMS; PLMW; Age; Heritability; Gender differences

1. Introduction

Restless legs syndrome (RLS), is a sensorimotor disorder characterized by an urge to move the legs, associated with unpleasant leg sensations described as itching, crawling, even pain in the legs, triggering the need to move [1]. Typically symptoms worsen at rest, are relieved by activity and increase in severity in the evening or during the night [1]. In the most severe cases, the sensations can be present in the arms [2]. The prevalence of RLS is approximately 5–15% in the Caucasian population [3,4]. Other characteristics that support the diagnosis include an elevated index (number per hour)

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of periodic limb movements during sleep (PLMS) and during wakefulness (PLMW), as well as a positive family history of RLS [1].

RLS was considered for a long time to be a condition of middle-aged individuals, but several studies revealed that in a significant number of patients RLS symptoms appear before the age of 20 years and even during early childhood [5,6]. Recently, studies have reported that early age-at-onset may be related to increased disease severity and a slower progression of the condition [7–9]. In addition, three independent studies reported an association between an early age-at-onset and the presence of a positive family history of RLS [9–11].

Several conditions were shown to be associated with RLS, especially anemia [12,13], renal failure [14], rheumatoid arthritis [15], fibromyalgia [16] and peripheral neuropathy [7]. These are considered secondary forms of RLS. In absence of those medical disorders, RLS is called "primary" or "idiopathic" RLS, the most frequent form of this condition.

Overall, only a few studies have focused on age-at-onset in RLS and have defined cut-off values to separate early- and late-onset groups; in these studies, the cut-off values were defined empirically [10,11]. The range of reported cut-off values varied from 30 to 45 years. These studies that separated RLS patients on the basis of either age-at-onset did not report between-group differences for PLMS and PLMW indices or detailed polysomnographic data.

The aims of the present study were to determine the distribution of age-at-onset in a large cohort of patients with RLS using a mathematical model, to study age-at-onset distribution separately for idiopathic and secondary RLS and for familial and non-familial forms of RLS, and to compare the clinical and polysomnographic characteristics of RLS patients with early and late age-at-onset of symptoms.

2. Methods

Two hundred and fifty (151 females and 99 males) unrelated patients affected with RLS entered the study. All patients were studied in the sleep laboratory between 1993 and 2005 and gave written informed consent before the beginning of their respective protocol. Most subjects ($n = 184$) were untreated for RLS at the time of their participation since this visit also serve as their diagnostic evaluation. Some subjects, who had been treated for RLS had undergone a withdrawal of more than five half-lives ($n = 39$). However, some subjects ($n = 27$) were taking a dopaminergic agent at the time of the study. Diagnosis of RLS was made by a sleep specialist on the basis of the four standard criteria clinical criteria [1] defined by the last consensus of National Institutes of Health (NIH): (1) an urge to move (mainly the legs), usually accompanied or caused by uncomfortable and unpleasant sensations in the limbs; (2) these symptoms begin or worsen during periods of rest or inactivity; (3) symptoms are partially or totally relieved by movement (at least as long as the activity continues); and (4) symptoms are worse or only occur in the evening or night [1]. The age-at-onset of RLS was determined in all patients at the initial visit by clinical interview. In addition, all patients filled out a standard questionnaire including demographic data, presence or not of RLS in first-degree relatives and the presence of symptoms in the arms.

The presence of associated conditions (secondary RLS) was determined by clinical interviews, complete physical and neurological examinations, and blood chemistry and electromyogram when clinically recommended. Two hundred and eighteen (218 or 87.2%) patients received a diagnosis of primary RLS and 32 received a diagnosis of secondary RLS, including 10 patients with a diagnosis of anemia (with evidence of iron deficiency in 6), 7 patients with peripheral neuropathy, 6 patients with a type 1 or 2 diabetes mellitus, 6 patients with fibromyalgia, 2 patients with a rheumatoid arthritis and 1 patient who had received a diagnosis of a major depression and was treated with antidepressants before the onset of symptoms. Overall, 19 patients were diagnosed with depression, but in 18 patients RLS symptoms occurred before the onset of the mood disorder. Those 18 patients were, therefore, classified as primary RLS sufferers.

All patients underwent one night of polysomnographic recording in the sleep laboratory. Sleep was recorded and scored according to the standard method [17]. Electromyogram from both anterior tibialis muscles were recorded to score PLM (during sleep and wakefulness). PLMS were scored according to Coleman's criteria [18]. Only movements lasting 0.5–5 s, separated by intervals of 4–90 s and occurring in series of at least four consecutive movements, were counted. PLM were also calculated in the nighttime epochs scored as wakefulness (PLMW) with the same criteria as those for PLMS, except for the duration of movements, which could last from 0.5 to 10 s [18]. The amplitude criterion for both PLMS and PLMW was at least 25% of the EMG potential recorded at the time of a voluntary movement performed prior to nocturnal polysomnographic recording. Microarousals were scored according to the criteria developed by a task force of the ASDA (American Sleep Disorders Association, 1992) [19]. A leg movement was considered associated with a microarousal if the microarousal started within 2 s before or after the onset of PLMS.

Two hundred and forty-three patients underwent the suggested immobilization test (SIT) performed for 1 h before bedtime, during which patients lay down at a 45° angle with their legs outstretched and were instructed to avoid moving their legs [20]. Leg movements (PLMW) and the degree of leg discomfort were