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Brief Report

EPIDEMIOLOGY OF FAMILIAL AND SPORADIC RESTLESS LEGS SYNDROME IN IRAN

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Restless legs syndrome is one of the most common sleep and movement disorders. For lack of sufficient information on this syndrome in Iran, this study was conducted at Alzahra Hospital, Isfahan, Central Iran, to determine the epidemiology of idiopathic, familial and sporadic forms of the syndrome. From September 1999 to April 2003, 61 patients in two groups were selected. A questionnaire with emphasis on sleep history and neurological history was completed and a thorough physical examination was performed for each patient. Familial and sporadic groups had mean ± SD ages of 22 ± 2.1 and 41 ± 3.2 years, respectively (*P* < 0.05). Female to male ratio was 2:1. The mean ± SD ages for women and men were 31 ± 5.3 and 42 ± 6.1 years (*P* < 0.05), respectively. Our findings support the current opinion that restless legs syndrome should be divided into the early-onset disease with a clear genetic component and the late-onset disease with an unclear etiology.

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Introduction

Restless legs syndrome (RLS) was first described in 1672 and given its name in 1945.[1] RLS is idiopathic in most patients. However, it may result from conditions such as iron deficiency, uremia, or polyneuropathy. The hallmarks of the idiopathic or primary RLS are intense disagreeable creeping sensations (paresthesia or dysesthesia) of legs. The symptoms are described as uncomfortable, tingling, crawling, burning, and prickling. Some patients are unable to describe the discomfort verbally. The symptoms become worse when the patients are lying down in bed in the evening. The symptoms occur more frequently at sleep onset. The prevalence of RLS has been estimated to be about 10% to 15% for the general adult population, particularly those of European descent.[1, 2] In some surveys from Asia, nonetheless, the prevalence of RLS is extremely low, suggesting the possible role of ethnicity on the prevalence of RLS.[3] RLS is a life-long condition that may begin at any age. However, it becomes severe in middle-aged and elderly patients, in whom it gets a chronic progressive course.[3]

Probably, there is a genetic component for RSL; the inheritance follows an apparently autosomal dominant pattern in one-third of patients,[4] and those with at least one affected family member account for up to 60% to 65% of patients.[5] Nevertheless, many familial cases have no obvious inheritance pattern.

So far a number of studies have compared the clinical features between the familial and sporadic forms of RLS. It has been shown that those with a family history of RLS, have a younger age at onset.[6] Previous studies have used the term "early-onset" for those patients presenting the symptoms before the age of 45 years. It has been shown that RLS has a slower progression in these patients.[7] "Late-onset" RLS, as defined by onset of the symptoms after the age of 45 years, has a more rapid progression.[7]

For lack of sufficient information on RLS in Iran, the characteristics of patients with idiopathic

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RLS were investigated in this study. In addition, a comparison of familial and sporadic types of RLS regarding age of onset, gender, and severity features was made.

Patients and Methods

This study was conducted over a 5-year period (1999 – 2003) in Alzahra Medical Center, an educational and referral center for neurological patients affiliated to Isfahan University of Medical Sciences, Isfahan, Central Iran. After taking informed consents, those with RLS were evaluated using an approved protocol established by the Iranian Neurological Society. Those included in the study had clinical signs of idiopathic or primary RLS consisting of the following four criteria established by the International Restless Legs Syndrome Study Group (IRLSSG).[8]

- The subjects must have an urge to move the legs, usually accompanied by an unpleasant sensation in the legs.
- Symptoms must be aggravated by rest.
- Symptoms must be alleviated by movement (walking).
- RLS symptoms must have been worse in the evening at some point during the course.

Patients were enrolled into the study if they had all of the above-mentioned four criteria.[8] Anyone with a history or signs of RLS secondary to other illnesses, or those who had concurrent illnesses, including peripheral vascular disease, peripheral neuropathy due to diabetes, myelopathies, etc, or those with Parkinson's disease, were excluded from the study.

A questionnaire with emphasis on neurological history was completed and a thorough physical examination was performed for each patient.

In addition to family history, gender, and age at onset, subjects were assessed for RLS severity symptoms based on the IRLSSG severity scale (very severe: 30 – 39; severe: 20 – 29; moderate: 10 – 19; mild: 1 – 9). Family history was considered "present," if the subject reported another family member with two degrees of relation who also had RLS.

All questions from the RLS questionnaire were analyzed with Chi-square test.

Results

Between September 1999 and April 2003, 61 patients in two separate groups were selected.

Fourteen patients were excluded from analysis due to either incomplete history or the presence of a possible secondary cause as mentioned earlier.

Analysis showed difference between the mean age of patients with familial and sporadic forms of RLS. Patients with familial form had an age at onset of 20 – 25 (mean ± SD: 22 ± 2.1) years whereas those with sporadic form of RLS had an age at onset of 38 – 44 (mean ± SD: 41 ± 3.2) years ($P < 0.05$).

The most important finding in this study was a significant effect of gender and family history on predicting the age at onset; those with a positive family history had a significantly earlier age at onset of symptoms. Females in our series were more likely to be affected than males (40 females vs. 21 males) with a female/male ratio of 2:1.

The mean ± SD age for women and men, was 31 ± 5.3 and 42 ± 6.1 years ($P < 0.05$), respectively. Therefore, the female gender was associated with an earlier age of onset of RLS.

We found that there was a relationship between age at onset of RLS and the severity of clinical features. The higher the total severity score, the earlier was the age at onset ($P < 0.05$).

Discussion

The association of age at onset with familial and sporadic forms of RLS supports the current opinion that RLS should be divided into the early-onset disease with a clear genetic component and the late-onset disease with an unclear etiology. This finding is consistent with the fact that there is a tendency in diseases such as Alzheimer and Parkinson to occur at earlier ages if they have a Mendelian inherited pattern.[9] Although, we cannot rule out any biases in data collection, we also found a female/male ratio similar to previous reports.[4 – 10] There are several possible explanations for this finding, such as the role of environmental and hormonal factors. However, the role of iron status in RLS, though unexplained, has been established.[10] It is interesting to speculate what effect the menstruation and the resulting relative iron load in menstruating females might have on these findings. This was not a population-based study, and thus, these findings may suffer from ascertainment bias, as women in our society may be more likely to seek medical attention, or to enroll in studies than are men. Additionally, we

interviewed only the proband rather than family members in this study. Because the symptoms of RLS may go unmentioned to family members if they were mild, or they may be easily mistaken for other disorders by the lay persons as well as by healthcare providers, interviewing the relatives, themselves, would have enhanced the reliability of the methods used. Further studies are needed to redefine the early- and late-onset groups and to determine the cut-off age. Finally, the cause of RLS still remains unknown; however, our data and those of others allow the disorder to be roughly categorized into the early-onset severe Mendelian disease and the late-onset less severe and less clearly inheritable disease. As it has been for other neurological disorders,[3] identifying a gene responsible for development of the early-onset familial form of RLS will help us in better understanding of the biology of the disease.

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