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Family history study of the restless legs syndrome

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Abstract

Background: Although there is a relatively high rate of occurrence of sporadic cases of restless legs syndrome (RLS), the systematic study of family history of RLS in populations of RLS patients has been very limited. The objective of the present study was to determine the risk of RLS for first- and second-degree relatives of a population of primary RLS patients not selected for the number of affected relatives in their families and to obtain an estimate of the degree of genetic involvement in RLS.

Methods: Consecutively consenting patients from two different sites who met the criteria for RLS completed a worksheet that asked them to indicate their current age, the date of their earliest RLS symptoms, and the names and RLS status of all of their first- and second-degree relatives. Controls with no clinical history of RLS also completed the worksheet.

Results: First- and second-degree relatives of patients with RLS had a significantly greater risk of RLS than the first- ($P < 0.001$) and second-degree relatives ($P < 0.003$) of controls. The risk of RLS was found to be greater for first-degree relatives of early-onset, rather than late-onset, RLS probands ($P < 0.001$).

Conclusions: This study provides a complete systematic examination of the risk of RLS among relatives of RLS probands and controls using the same assessment methodology. Although the results are consistent with a genetic etiology for RLS, they do not support the presence of one simple, Mendelian-inherited major gene in most RLS families.

Keywords: Restless legs syndrome; Family history

1. Introduction

Ever since the restless legs syndrome (RLS) was well described by Ekbom in 1945 [1], it has been noted to be fairly common to have a variable age of onset [2] and to occur in several members of the same family. Although Ekbom originally estimated the prevalence to be 5% of the population [1], some limited population surveys found prevalence of only 1.2% among Italians [3] and 2.5% among Australians [4]. In more recent population-based studies, the prevalence of those with RLS symptoms has been estimated to range from about 8 to 15% [5–9]. These were all from European or predominantly European descendant populations. Two Asian population surveys have, however, reported much lower prevalences of 3% and less than 1% [10,11].

Despite the common claim that this is a genetic disorder frequently occurring in several members of a family [12], most case series report both sporadic (only one member of the family affected) and familial cases. In four separate studies, 40–60% of all cases were identified as familial, and the risk to first-degree relatives of the affected patient was approximately 25–40% [2,13–15]. In one study of a family with five generations of affected individuals, there was both a suggestion of anticipation and a risk factor close to 50%, consistent with an autosomal dominant genetic disorder with nearly full penetrance [16]. A subsequent review of five families with many affected individuals, however, failed to show any consistent pattern of anticipation [17]. Gene identification studies using these and similar families have been generally unsuccessful, except for one recent study that found a significant linkage on chromosome 12q apparently occurring in some, but not most, RLS families [18]. Despite the relatively high rate of occurrence of sporadic cases, the systematic study of family history of RLS in populations of RLS patients has been very limited. To date, only one very limited unblended twin study has been published [19], and no adoption studies or complete segregation analyses have been performed. There is no good estimate of the magnitude of the genetic contribution to RLS due to the lack of a reasonable set of standard evaluations. Without this information, it is hard to determine whether or

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not evaluation of families with several affected members provides enough power to reasonably expect detection of the genetic basis for RLS. Moreover, it has been suggested that there may be two phenotypes based on age-of-onset of symptoms that may relate to family prevalence, but there have been only limited data to support this view [13,20]. The current study is designed to provide a complete family history of RLS to determine the risk of RLS for first- and second-degree relatives of a population of primary RLS patients not selected for the number of affected relatives in their families. The study also compares this risk to that in control probands, yielding an estimate of the degree of genetic involvement in RLS.

2. Methods

The participants in this study were each given the same standard worksheet that first asked them to list all of their first- and second-degree relatives. The participants were then asked to indicate the RLS status for each relative as (1) probably having RLS, (2) having no indication of RLS, or (3) having inadequate information to determine RLS status ('uncertain' or 'unknown'). The worksheet also asked each participant to indicate his or her current age and the earliest date of RLS symptoms. In a separate study of 25 consecutive RLS patients, this self-reported age-of-symptom-onset correlated well with that reported in a clinical interview ($r = 0.98$, $P < 0.001$, absolute difference between the two reported ages-of-symptom-onset = 2.1, standard error = 0.73).

All consecutively consenting patients who met the criteria for RLS were included in this study, except that patients who were either pregnant or had end-stage renal disease were excluded to minimize occurrence of clearly secondary RLS. Patients were recruited independently at two separate sites: the Sleep Disorders Center at both the Johns Hopkins University Bayview Medical Center and the University of Texas Southwestern Medical Center. Eighty-three patients at Johns Hopkins were sent the family history questionnaire, and 64 (77%) returned the questionnaire. Thirty-two RLS patients at the University of Texas consented to the study, and all completed the questionnaire. A sample of 15 controls were selected from consenting patients and staff at the Johns Hopkins University who were determined by clinical history to have no symptoms of RLS. This sample of normals permitted comparison of familial rates between RLS patients and nonpatients using the same techniques.

2.1. Statistical analyses

Degree of familiality was determined for each proband as the percentage of relatives thought to have RLS. The standard Pearson correlation was used to evaluate the relation between age-of-symptom-onset and the degree of familiality. The familial rates for patient conditions were compared to the controls using the Fisher exact test. The risk of RLS for relatives was defined as the percentage of proband relatives with RLS.

3. Results

Patient probands reported an average of 6.2 first-degree relatives and 15.8 second-degree relatives. There were no significant gender differences between clinic sites or degrees of familiality, and therefore data were combined from both sexes. The combined patient data showed that risk of RLS was significantly greater for RLS probands than for controls (19.9 vs. 3.5%, $P < 0.001$ for first-degree relatives; 4.1 vs. 0.5%, $P = 0.003$ for second-degree relatives) (see Table 1).

As shown in Table 1, data from the sites differed with a greater familial risk in the Texas than in the Hopkins sample (28.4 vs. 16.5%, $P = 0.001$ for first-degree relatives; 5.8 vs. 3.5% for second-degree relatives). The Texas compared to the Hopkins sample were slightly younger (average age of 52.9 vs. 65.0 years) and had on average a significantly younger age-of-symptom-onset (27.0 vs. 40.7, $P < 0.001$). The significant difference in the age-of-symptom-onset suggested the need to examine this factor more carefully. The degree of familiality (defined as percentage of relatives with RLS) correlated significantly with age of onset for the Hopkins sample ($r = -0.36$, $P = 0.38$), but not the Texas sample ($r = -0.07$, $P = 0.74$). On further inspection of the distribution of the age-of-symptom-onset, it was noted that the distribution for the Hopkins sample was bimodal (see Fig. 1), with a 7-year period between the modes when no probands reported onset of symptoms. This relative low point between the modes centered on age 45.

Table 1
Family size and risk to relatives for RLS in patient and control samples

Source	Site	Sample Size (n)			Risk for RLS in:	
		Probands	First-degree relatives	Second-degree relatives	First-degree relatives	Second-degree relatives
Patients	Johns Hopkins	64	423	1101	16.5%	3.5%
	Texas	32	169	417	28.4%	5.8%
	Total	96	592	1518	19.9%	4.1%
Controls	Johns Hopkins	15	85	202	3.5%	0.5%

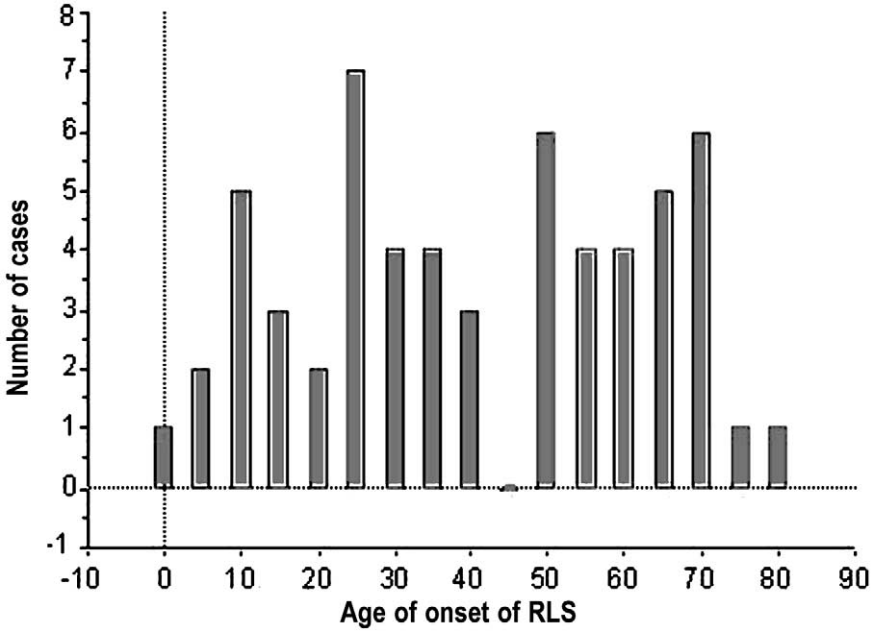

Fig. 1. Number of probands with age of onset in each 5-year period from age 0–85: Johns Hopkins University sample.

Based on these analyses, the Hopkins and Texas samples were divided into those who reported initial onset of RLS symptoms before age 45 (early-onset RLS) and those who reported initial onset of RLS symptoms at age 45 or older (late onset RLS). For the early-onset RLS patients, the Hopkins compared to the Texas samples showed no significant differences in age or age-of-symptom-onset. Both showed approximately the same risk of RLS for first- and second-degree relatives (23.6 vs. 20.3% for first-degree relatives, 4.3 vs. 4.3% for second-degree relatives; see Table 2).

The Texas sample included only three RLS probands with late-onset of RLS symptoms, prohibiting further analysis of that group. The Hopkins group, however, included 38 early-onset and 26 late-onset RLS patients, permitting a direct statistical test of whether or not this division by age-of-symptom-onset related to familial patterns of RLS. As shown in Table 2, the risk of RLS was significantly greater in the Hopkins group for first-degree relatives of early- rather than late-onset RLS probands (23.6 vs. 10.1%, $P < 0.001$), but only marginally significantly greater for second-degree relatives (4.3 vs. 2.8%, $P = 0.091$). Compared to the control sample, RLS risk in first-degree relatives was 6.7 times greater for the early-onset Hopkins group, but only 2.9 times greater for the late-onset group.

4. Discussion

Although this is a limited study, it is the first published family study that provides the complete systematic examination of occurrence risk among relatives of RLS probands, compared to controls using the same assessment methodology. The same techniques were used to establish risks to all proband relatives, both for normal controls without RLS and for all patients with RLS, excluding only those on dialysis or who were pregnant. Despite a lack of evidence, literature in the field often cites an autosomal dominant mode of transmission for RLS, although the only positive-linkage analysis reported a genetic association following a recessive, not

Table 2
Evidence supporting differential etiology in early- versus late-onset RLS[a]

Sample	Correlation between age of onset and familiality	Risk to 1st-degree relatives	Risk to 2nd-degree relatives
Texas[b], full sample	-0.07, $P = 0.74$	28.4%	5.8%
Texas, early-onset	-0.09, $P = 0.67$	20.3%	4.3%
Johns Hopkins, full sample	-0.36, $P = 0.01$	16.5%	3.5%
Johns Hopkins, early onset	-0.16, $P = 0.38$	23.6%	4.3%
Johns Hopkins, late onset	-0.16, $P = 0.38$	10.1%	2.8%

[a] Early onset is defined as onset < 45 years of age. Late onset is defined as onset > 45 years of age. Note that familiality is defined for each proband as the percentage of relatives reported to have RLS.

[b] Statistics are not shown for the Texas, late-onset subsample due to the small number of cases ($n = 3$).

dominant, pattern of transmission [18]. While the results in this study are consistent with a genetic etiology for RLS, they do not support the presence of one simple, Mendelian-inherited major gene in all or even most RLS families. The data in the present study provide estimates of Risch's lambda [21]: 5.6 for all RLS, 6.7 for early-onset RLS, and 2.9 for late-onset RLS. These relatively low values reflect the common occurrence of the disorder and the relatively large number of probands with none or few affected relatives. In contrast, rare, simple Mendelian disorders such as cystic fibrosis have lambda values of 500. The lower lambda for RLS probably indicates the complex nature of the genetic factors contributing to RLS. Complex genetic factors have been determined for other disorders in which the lambda values were in the range of 4–15, including genetic susceptibility to type I diabetes and Alzheimer's disease. It seems likely that the genetics of RLS will have a similar level of complexity.

The data from the small control group in this sample showed a 3.5% prevalence of RLS for first-degree relatives. This differs little from the 5% estimate for the general population. The data for RLS among second-degree relatives is unusually low in both the control (0.5%) and patient (4.1%) populations. But the family history methods, such as those used in this study, rely upon information from the proband, in contrast with the family study method that uses direct interviews of relatives. The former notoriously provides underestimates of disease occurrence. This is particularly true for more distant relatives less known to the proband. The data in this study from second-degree relatives should therefore be viewed with some doubt. In contrast, the data from the first-degree relatives appear to correspond well with results of prior, less-complete studies. Risk to first-degree relatives from families with more than one relative with RLS was reported to be 24 and 39% in prior studies. But in these samples, about 40% of the cases are sporadic. The risk to first-degree relatives would be reduced to 14 and 24%, which is approximately the same as the 20% figure from this complete study if we add in the sporadic cases and assume equal family sizes. Thus, the data from the first-degree relatives seem likely to have provided a valid estimate, despite the limitations of the method.

The differences related to age-of-symptom-onset are particularly important. The Johns Hopkins population showed a fairly strong bimodal distribution of onset ages with a very clear low point at approximately age 45. It is important to note that it was this low point between two modes that provided the criteria for dividing the sample into early- and late-onset groups. This division was not made based on any consideration of the family history data. Nonetheless, there was a marked difference in degree of familiality between the two groups. Moreover, there was no indication of continuing relationship between age-of-symptom-onset within each group. These data suggest that there are two separate phenotypes of RLS, one with a high degree of familiality and symptoms starting early (before age 45), and another with a much lower degree of familiality and symptoms starting later (after age 45). Other studies that we reported elsewhere used this same criterion for early- and late-onset groups and found that early-onset severity correlates with age but not serum ferritin, while late-onset severity correlates with serum ferritin but not with age [20]. Small-fiber neuropathy has also been reported to occur more for late- than early-onset RLS [22]. All of these studies are consistent with this family history study and strongly suggest that early- and late-onset RLS represent two separate phenotypes with possibly different etiologies.

There have been several attempts to identify a susceptibility gene or genes for RLS based upon analyses of a small number of highly selected families that included many affected members. The results of these investigations have been generally negative with the one exception of the identification of a linkage on chromosome 12q for only a few RLS families [18]. It seems clear, however, that no convincing evidence of a vulnerability locus for RLS has been found that would apply to all or even most RLS patients. This could result from several factors. The most important factor may be the lack of the data that are needed to guide and inform the design of gene identification studies. Beyond the basic family study data typically developed to establish the familial risk for a disorder, data from complete twin or adoption studies confirm a genetic hypothesis and inform about the degree of heritability. No such data have been published for RLS, except for the limited twin study that neither provided an adequate sample nor used blinded techniques [19]. It is difficult to know the most appropriate design for further genetic studies without these data. The success of alternative designs is variable, dependent upon the true inheritance of the disorder [23]. An important next step for the study of the genetics of RLS is to conduct a basic family history study and other studies needed to define better the genetic pattern of RLS. These studies could also potentially better define the critical issue of age-of-symptom-onset for the apparently two different phenotypes of RLS suggested in this study.

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