Clinical Characteristics and Frequency of the Hereditary Restless Legs Syndrome in a Population of 300 Patients

Juliane Winkelmann* MD; Thomas C. Wetter* MD; Victor Collado-Seidel* MD; Thomas Gasser# MD; Martin Dichgans# MD; Alexander Yassouridis PhD*; Claudia Trenkwalder* MD

**Max Planck Institute of Psychiatry, Section of Neurology, Section of Biostatistics, Munich, Germany; #Department of Neurology, Klinikum Grosshadern, Ludwig Maximilian University of Munich, Munich, Germany*

Abstract: There is a genetic contribution to the idiopathic restless legs syndrome (iRLS). An autosomal dominant mode of inheritance is suspected, but as yet no gene has been identified. To assess the frequency and characteristics of the hereditary restless legs syndrome (RLS) in comparison to those of non-hereditary RLS, we analysed the clinical data of 300 RLS patients. All 300 patients diagnosed as RLS according to the criteria of the International RLS Study Group were examined using a standard questionnaire covering demographic data, family history, clinical symptoms, subjective sleep disturbances and course of the disease. In all patients a complete neurological examination was performed, and in selected cases electrophysiological examinations and polysomnographic studies. Family history was rated as definitely positive when at least one first-degree relative was examined and classified as RLS according to the criteria by one of the authors. If it proved impossible to contact family members to verify reports of a family history, the patients were classified as only having a "possible positive family history." 232 of the 300 patients had iRLS and 68 secondary RLS due to uremia (uRLS). 42.3% of the patients with iRLS and 11.7% of those with uRLS were classified as having "definite positive" hereditary RLS, with a further 12.6% of iRLS patients and 5.8% of uRLS patients as having "possible positive" hereditary RLS. Patients with definite hereditary RLS were significantly younger at the age of onset than those with a negative family history (35.45 vs. 47.17 years, $p < 0.05$). The clinical characteristics of the disease were similar in both groups, except that women with hereditary RLS experienced a worsening of symptoms during pregnancy (19.1% vs. 2.6%, $p < 0.05$). Our study shows that patients with hereditary RLS may experience an earlier onset of the disease. Hereditary and non-hereditary RLS present with similiar clinical signs and symptoms.

Key words: Restless legs syndrome; genetics; periodic limb movements; sleep

Abbrevations: RLS= Restless Legs Syndrome, PLM= Periodic Limb Movements

INTRODUCTION

IN 1995, THE INTERNATIONAL RLS STUDY GROUP DEFINED CRITERIA FOR DIAGNOSING THE "RESTLESS LEGS SYNDROME"[1]. This consensus of the definition criteria was a prerequisite for describing an RLS population and comparing different studies, as well as forming the basis for genetic studies. The four minimal criteria that are obligatory in order to diagnose RLS are (a) an urge to move the limbs, usually associated with paresthesias and/or dysesthesias, (b) motor restlessness, (c) symptoms that are exclusively present or become worse during rest with a partial and temporary relief through activity, and (d) symptoms that are worse in the evening or at night. Additional symptoms that can often be present are (e) problems with initiating and maintaining sleep, (f) periodic limb movements (PLM), (g) normal neurological examination, (h) a clinical course of the disease that can either fluctuate or be continuous and finally (i) a positive family history.

Ekbom estimated the frequency of hereditary RLS compared to sporadic cases as "one third"[2]. Since then, an increasing number of families with RLS have been documented and investigated, suggesting the possibility that RLS is a hereditary disease with an autosomal dominant mode of inheritance.[3-9] High variable expression of the symptoms has been observed within single families.[7] The age of onset is usually in the second decade, but varies within families.[3-5] In some affected family members the disease can manifest itself in childhood[3] or in late adult life.[9] Initially, symptoms do not appear daily, but a progressive worsening of all RLS symptoms is observed with age.[9]

Two major forms of the disease can be distinguished: an idiopathic (iRLS) and a symptomatic form. Symptomatic forms of RLS can occur in association with renal failure or dialysis treatment (=uremic RLS; uRLS), with a prevalence of about 15%–20% in hemodialysis patients.[10,11] Rare, spo-

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Address correspondence to: Juliane Winkelmann MD, Max Planck Institute of Psychiatry, Section of Neurology, Kraepelinstr.10, D-80804 Munich, Germany, Tel: +49-89-30622-1, Fax: +49-89-30622-605, E-mail: janew@mpipsykl.mpg.de

radic cases have been described in connection with rheumatoid arthritis,[12] amyloidosis,[13] iron deficiency[14] or folate and B12 deficiency.[15]

The primary aim of the present study was to assess the frequency of hereditary RLS in a large population of patients diagnosed according to the RLS Study Group criteria.[1] Secondly, we wanted to assess the clinical characteristics of definitive hereditary iRLS patients in comparison to those of non-hereditary RLS.

METHODS

Patients

250 consecutive in- and out-patients of the Movement Disorder Clinic, Klinikum Grosshadern, Munich, and the Max Planck Institute of Psychiatry, Section of Neurology, Munich, who were diagnosed with RLS according to the definition criteria of the International RLS Study Group,[1] entered the study. A further 50 relatives from 16 families with RLS, who suffered from RLS and who fulfilled the criteria, were added to our patient population and counted as "affected relatives of RLS index cases." Patients with a history of neuroleptic exposure were not included in the study. The study period covered four and a half years. One of the authors (C. T.) is a member of the RLS Study Group, and the diagnosis criteria were therefore available to us prior to their publication in 1995.

Study Design and Protocol

The following study protocol was implemented: 1) All patients underwent a complete physical and neurological examination . 2) The patients were assessed with the help of a standardized questionnaire that was filled out by the physician interviewing the patient. The questionnaire covered the following topics: a) demographic data, b) age of onset (taken by history: the first symptoms the patients remembered), c) a listing of the qualities of their motor and sensory symptoms—patients were allowed to list several qualities for each symptom, d) course of the disease, e) localization of symptoms, f) subjective sleep disturbances, such as difficulties with initiating and maintaining sleep, and number and duration of awakenings, g) changes of medication at follow-up visits. 3) A polysomnography (after one night spent adapting to the laboratory environment) was performed in 120 patients before treatment was started. The presence of PLM was assessed by recording a surface electromyogram (EMG) of both tibialis anterior muscles in addition to standard polysomnographic parameters in accordance with standardized guidelines.[16] Scoring of PLM was based on the criteria established by the American Sleep Disorders Association.[17] The number of PLM per hour of sleep (PLMS index) was calculated. A PLMS index greater than 5 was regarded as abnormal, whereas an index less than 5 was regarded as a benign sleep-associated phenomenon.[18] 4). Blood chemistry (including full blood count, creatinine, urea, ferritin, vitamin B12, and folate) was analyzed in the 250 patients who visited the movement disorder clinic in order to rule out treatable secondary forms of RLS. 5). Nerve conduction studies were performed in 119 patients.

Evaluation of the Family History

During the first interview all patients were asked about the possible occurrence of RLS symptoms in their family. If any positive family history was reported by the patient, we attempted to contact and, if possible, to visit the affected family members in order to find out whether they fulfilled the definition criteria. These family members then underwent the same procedure as listed in the study protocol. Patients who did not report a positive family history were requested to contact all their family members and inquire about possible RLS symptoms. If these were reported by the patients, we tried to contact the relatives. Depending on their "family history status," the patients were divided into the following four subgroups:

1. "Definite positive family history": if at least one first-degree relative had been examined by one of the authors and classified as an RLS positive according to the criteria.
2. "Possible positive family history": if the patient reported a family history, but contacting the family members was impossible for various reasons.
3. "Negative family history": if the patients were not aware of any RLS symptoms in their family even after they had asked relatives about possible symptoms.
4. "Unknown family history": if no information about the family history could be obtained.

To clearly distinguish between "idiopathic hereditary" and "idiopathic non-hereditary RLS," all statistical analyses were only performed on iRLS-patients with a "definite positive" or a "negative" family history. Patients with a "possible positive family history" or a "unknown family history" as well as the "affected relatives of RLS index cases" were excluded from statistical analysis.

Furthermore, we differentiated between patients with iRLS who had no signs of any disease associated with RLS, and patients with secondary RLS associated with uremia and dialysis treatment.

Statistical Analysis

Besides the analysis of contingency tables for examining any association between nominal and categorial variables, a discriminant analysis was also performed to identify those symptoms that discriminated well between hereditary and non-hereditary iRLS. The non-metric variables used in the discriminant analysis were scaled accordingly (marginal normalization) before the analysis. To compare

proportions of symptom occurrence between the two groups, Fishers exact test was applied, whereas the significance levels of group means of continuous variables were tested with an analysis of variance (ANOVA).

RESULTS

Patients: Demographic Data, Primary and Secondary RLS

232 out of 300 German subjects had iRLS (55.1%, n= 128 female and 44.8%, n=104 male), and 68 had uRLS (33.8%, n=23 female and 66.1%, n=45 male). The mean age at the time of the evaluation was 57.31 years (SEM: ± 0.87) in patients with iRLS and 54.88 years (SEM: ± 1.41) in patients with uRLS.

Frequency of Hereditary RLS in iRLS Patients (n=232)

For the evaluation of the frequency of hereditary iRLS (n= 232) the 50 relatives (affected relatives of index cases) with RLS were not included. Of the remaining 182 iRLS patients, 42.3% (n= 77) revealed a "definite positive family history" (index cases), 12.6% (n= 23) revealed a "possible positive family history" and in 43.9% (n= 80) the family history was negative. Two patients were categorized as having an "unknown family history" (see Table 1).

Frequency of Hereditary RLS in uRLS Patients (n= 68)

In patients with secondary RLS due to uremia (n=68), 11.7% (n= 8) had a "positive family history" and 5.8% (n= 4) had a "possible positive family history." In 82.3% (n= 56) family history was negative (see Table 1).

Comparison between iRLS patients with a "definite positive" (n=77) and a "negative" (n=80) family history

Demographic data

The mean age at the time of the evaluation was 57.75 years (SEM: ±1.48) in patients with a "definite positive family history", and 59.6 years (SEM: ±1.25) in patients with a "negative family history". There was no significant age difference between the two groups of patients (ANOVA).

Age of Onset

Patients with a "definite positive family history" were significantly younger when they experienced their first symptoms compared with patients with a "negative family history." (35.45 years, SEM: ± 1.83, n=77 vs. 47.17 years, SEM: ± 1.7, n=79; $p<0.05$, univariate F-Test in ANOVA).

Demographic Data and "Age of Onset" of the "Affected Relatives" (n= 50) of the Index Cases

The mean age at the time of the evaluation was 51.26 years (SEM: ±2.27) in the group of the "affected relatives of index cases." There were 58% (n=29) females and 42.0 % (n=21) males. They experienced their first symptoms at the age of 29.07 years (SEM±1.62).

Clinical Symptoms of the Disease

By performing a discriminant analysis with the demographic and clinical variants we found that the two groups of patients (hereditary iRLS and non-hereditary iRLS) could be fairly reliably identified (percent of cases correctly classified >69%). Among the variables considered, only the variables "pain," "influence of alcohol," and "worsening during pregnancy," contributed significantly to identifying the type of RLS. The variables in Table 2 that show significant frequency differences between the two groups are included in the set of the significant discriminance variables.

In the group with a negative family history, patients more often described their symptoms as painful (61.0% vs. 85.0%, Fisher exact test, $p< 0.05$). In the group with a positive family history, patients more often described an influence of alcohol on their symptoms (21.6% vs. 3.8%, Fisher exact test, $p< 0.05$) while more patients experienced a worsening as a consequence of alcohol ingestion (17.5% vs. 1.25%, Fisher exact test, $p<0.05$).

Women with a positive family history experienced significantly more often a worsening of their symptoms during pregnancy: 19.1% (n=9) with a positive family history vs. 2.6% (n=1) with a negative family history.

The results of the questionnaire on the clinical characteristics, including course of the disease, coping mecha-

Table 1—Frequency of hereditary RLS among 250 patients with iRLS

	Idiopathic RLS (iRLS) n= 182		Uremic RLS (uRLS) n= 68	
	%	n	%	n
Definite positive family history	42.3	77	11.7	8
Possible positive family history	12.6	23	5.8	4
Negative family history	43.9	80	82.5	56
Unknown family history	1.2	2	0	0

Table 2—Results of the questionnaire in 230# patients with iRLS

Clinical symptoms	iRLS, n= 230# Definite positive family history (index cases)	Negative family history	Statistical analysis p-values*	Affected relatives of RLS index cases	Possibly positive family history n= 23
	n= 77 %	n= 80 %		n= 50 %	n= 23 %
Sensory symptoms					
Paraesthesias	85.7	85.0	n. s.	88.0	77.3
Stinging	26.0	23.8	n. s.	10.0	26.1
Pain	61.0	85.0	*	24.0	60.9
Pulling	70.1	86.3	*	52.0	65.2
Crawling	57.9	66.3	n. s.	50.0	47.8
Tearing	47.3	46.8	n. s.	42.0	30.4
Burning	18.9	15.2	n. s.	10.0	17.4
Tingling	18.9	12.7	n. s.	6.0	13.0
Motor symptoms					
Involuntary movements during wakefulness					
Cramp-like	22.1	25.0	n. s.	20.0	27.3
Myoklonus-like	48.1	43.6	n. s.	42.9	47.8
Localisation of symptoms					
Symptoms bilateral	91.7	98.8	n. s.	88.0	100
Symptoms only unilateral	13.2	1.4	*	10.9	
Symptoms in the feet	48.1	56.3	n. s.	48.0	56.5
Symptoms in the calves	75.3	90.0	*	62.0	87
Symptoms in the thights	46.8	52.5	n. s.	22.0	65.2
Symptoms in the arms	20.8	13.8	n. s.	6.0	26.1
Course of the disease					
Stable	14.3	13.8	n. s.	22.0	21.7
Intermittant progredient	79.2	82.5	n. s.	66.0	73.9
Remitting	6.5	3.8	n. s.	12.0	4.34
Coping mechanism					
Improvement of symptoms with changing temperature	44.0	38.8	n. s.	66.0	47.8
Influence of alcohol on the symptoms	21.6	3.8	*	10.0	8.7
Sleep disturbances					
RLS symptoms when falling asleep	80.5	85.0	n. s.	64.0	73.9
Difficulties maintainig sleep	90.7	93.7	n. s.	69.4	78.3
Daytime fatigue	77.3	79.7	n. s.	48.0	81.8
	Mean SEM	**Mean SEM**		**Mean SEM**	**Mean SEM**
Duration to fall asleep (min.)	82.53 10.05	73.68 7.87	n. s.	84.82 16.20	44.57 11.61
Number of awakenings (min.)	4.29 0.34	4.04 0.26	n. s.	2.56 0.36	4.09 0.56
Mean waking phase (min.)	61.23 8.19	47.25 4.46	n. s.	52.44 10.78	54.57 9.46
Mean sleeping phase (min.)	162.60 11.21	162.2 11.93	n. s.	228.80 21.40	164.4 19.31
Pregnancy (n= females)	n= 47	n= 38		n= 29	n= 11
Worsening during pregnancy	19.1	2.6	*	20.7	9.09

*= Fisher`s exact test in the analysis of contingency tables, n. s.= not significant
#= 2 patients categorized as having an "unknown family history"

nisms and sleep disturbances, are listed in detail in Table 2.

Results of Additional Investigations of All 300 Patients

In all 120 patients who were investigated with polysomnographic studies, the PLMS index was >5 and the characteristic sleep profile of RLS was seen. Assessment of nerve conduction velocity and EMG of the anterior tibial muscles led to normal results in 106 patients; 13 patients showed signs of mild to moderate axonal polyneuropathy. Of these, 3 patients had a positive family history and 10 had a negative family history, but this difference was not statistically significant.

DISCUSSION

The aim of this study was to determine the frequency of hereditary RLS in a population of RLS patients, to characterize the clinical signs and symptoms of hereditary RLS, and to compare familial and non-familial RLS.

In the survey we found that 42% of our patients with iRLS showed a "definite" and 12% a "possible" positive family history. The study demonstrated a significant difference in the age of onset between patients with a "definite" and those with a "negative" family history (35.45 years compared to 47.17 years), with few patients noting symptoms before the age of 20.

Since standardized criteria were drawn up, only three studies have dealt with the frequency of family history. Data published before 1995 should be interpreted and compared with caution due to the lack of diagnostic criteria. The recent studies have displayed a positive family history in about 50%[19] to 64%[20,21] of the cases and in one study even as many as 92% (n=23) of the patients with iRLS.[20] In our opinion, this high frequency should be regarded with caution due to the small population. In a population of 133 RLS patients younger age at onset in hereditary RLS (25.9 years vs. 29.2 years) were found, but this was not significant.[21]

The frequency of familial RLS in our study is probably higher than 42% considering our finding that a further 12% of patients had a possible positive family history. It might even be higher because we did not contact the families of patients who stated that no other member of the family suffered from RLS. Therefore further studies should include investigations with non-affected family members of definite RLS patients.

In addition, there may be a variation in the prevalence of RLS and the frequency of familial cases, depending on the geographic origin of the population. As yet there have been no systematic epidemiologic studies to define the prevalence of RLS. Ekbom estimated the prevalence of RLS in the general population to be about 5%, based on a clinical review of 500 patients in his practice.[22] Limited population surveys have detected a prevalence of 1.2% among Italians[23] and 2.5% among Australians.[24] A recent survey based on a mailed questionnaire among 2000 Canadian adults showed a substantially higher prevalence of about 10–15%, with a higher occurrence for French-speaking than for English-speaking Canadians.[25] Out of 93 RLS patients, 69.8% had a positive family history, and all of these were French-speaking. The only population-based survey having been performed so far evaluated a prevalence of 9.8% in the population older than 65 years.[26] A difference in the occurrence of familial cases, however, may reflect either founder effects or the influence of local environmental factors.[27] It seems possible that the onset of the disease is recognized earlier in families with hereditary RLS because of the increased awareness of RLS symptoms. This could be one reason for the significantly younger age of onset in hereditary RLS. In our study we excluded the relatives from the statistical analysis because they may display less severe symptoms compared to the index cases. However, the clinical symptoms of the relatives cases were more similar to the index cases than to patients with a negative family history.

In our group, sporadic RLS patients with a "negative family history" described their symptoms more often as "pulling" or "painful," and in this group more patients revealed pathological findings in the nerve conduction velocity showing an additional polyneuropathy. Ondo and Jankovic found no difference between the sensory symptoms of patients with "neuropathic" and "idiopathic" RLS.[20] One reason for these different findings could be a methodological one: the patients in Ondo and Jankovics' study were asked to characterize their symptoms in their own words and were not asked directly if their symptoms were painful. Furthermore, despite similiar demographic data, a difference in patient populations cannot be excluded. The less frequent occurrence of unilateral symptoms in "negative family history" patients can not be explained. Unilaterality of symptoms is known to occur in RLS naturally. It can, however, be associated with unilateral radiculopathy. [28]

Women with a positive family history suffered statistically more often from RLS symptoms during pregnancy than women with a negative one. The occurrence of RLS symptoms during pregnancy was already described by Ekbom in 1944.[2] Godmann et al. investigated 500 pregnant women for possible RLS symptoms, and found that 19% suffered from RLS.[29] Symptoms occurred from four weeks before to four weeks after delivery, and disappeared thereafter in all but three women. This phenomenon may be due to endocrine changes during pregnancy, which could provoke RLS symptoms.

The high occurrence of sleep complaints, experienced by over 90% of the patients, underlines the importance of this symptom in diagnosing RLS, although the International RLS Study Group enumerates sleep com-

plaints only as an additional criterion.

As far as the coping mechanisms in RLS are concerned, nearly half the patients reported an improvement in their symptoms with a change of temperature. Furthermore, almost all patients who reported that alcohol had an influence on their disease experienced a worsening of their symptoms during the night after alcohol ingestion in the evening. Alcohol is known to cause significant sleep disturbances, leading to a disrupted sleep architecture, decreased REM sleep and an increase in periodic leg movements.[30] Whether the worsening of sleep in general causes the worsening of RLS after alcoholic ingestion, or whether alcohol has a specific effect on RLS cannot be inferred from our study.

In conclusion, our evaluation showed that hereditary and non-hereditary RLS present similar signs and symptoms. Genetic predisposition may lead to an earlier onset of the disease. Painful sensations tend to occur more frequently in sporadic cases with neuropathy but sleep disturbances are a frequent and major feature in all groups of RLS. A worsening during pregnancy is significantly more frequent in hereditary RLS. The overall similarity of clinical characteristics and the course of the disease in idiopathic, hereditary and non-hereditary RLS could suggest a common pathological pathway.

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