The Association Between Restless Legs Syndrome and Essential Tremor

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Abstract

OBJECTIVE: To explore the relationship between restless legs syndrome (RLS) and essential tremor (ET). **BACKGROUND:** We have observed that several families with ET clinical co-segregated with RLS. Often the RLS was not diagnosed despite being present in many family members. **METHODS:** We prospectively evaluated for the presence of RLS in 100 patients presenting to the Baylor College of Medicine with ET, and prospectively examined all patients presenting with RLS for the presence of tremor during the same time frame. **RESULTS:** Of 100 consecutive ET patients (60 female, and 75 with a family history of ET) seen over 19 weeks, the age was 65.2±16.3 years, and the age at tremor onset was 37.8±19.9 years. Thirty-three met all criteria for RLS, of which 25 had never been previously diagnosed. A family history of RLS was reported in 57.6% of these 33 patients and was the only significant predictor of RLS in the ET population. Their IRLSRS was 16.6±8.1. Over 19 weeks we also examined 68 consecutively seen RLS patients (63.2% female and 54.4% with a family history of RLS) for the presence of tremor. Their age was 55.8±14.4 years and the age at RLS onset was 33.7±19.5 years. No patient who presented for RLS had any rest tremor or any postural tremor greater than 1 of 4. A single patient had a 2 of 4 kinetic arm tremor. Trace tremor; however, was very common. **DISCUSSION:** Overall, we found a very high rate of undiagnosed RLS in patients presenting for tremor, but unlike other "secondary" forms of RLS, this was also associated with a high familial history of RLS, suggesting that they share some genetic similarities. In contrast, trace tremor was frequent in patients presenting with RLS but overtly pathological postural tremor was uncommon.

Introduction

Restless legs syndrome (RLS) and essential tremor (ET) are arguably the two most common adult movement disorders.(1) Despite this abundant epidemiology, our understanding of their CNS pathophysiologies is relatively poor, especially in ET. Both of these movement disorders have strong genetic components (2-5) and may be worsened by serotonin reuptake inhibitors.(6,7) Both also show increased activity in the same sub-cortical structures (cerebellum, thalamus, and probably the inferior olive).(8-10) Additionally, one large family identified at our center, on which the chromosome 2 ET was linked, also demonstrated RLS that largely co-segregated with the ET.(2) A single published case also reports the association of the two conditions.(11) We therefore prospectively evaluated for RLS in patients presenting with ET and also looked for ET in patients presenting with RLS.

Methods

All patients (new and follow-up) were seen in the Baylor College of Medicine Movement Disorders Clinic. ET was diagnosed based upon established criteria.(12) Our inclusion into the survey was necessarily "possible ET" since any other neurological disease following the onset of tremor, including RLS, excludes the diagnosis of "classical ET". RLS was diagnosed based on the NIH criteria.(13) Two patients referred to us for both ET and RLS were a priori excluded to minimize the referral bias towards more complicated cases in a tertiary referral center.

In patients presenting with ET, we queried their current age, age of onset of tremor, sex, clinic status (new or follow-up), the presence of any dystonia, for a family history of tremor, for a family history of RSL, and for well characterized periodic limb movements of sleep (PLMS), usually from a bed partner if present. We also included a basic scale of tremor severity based on postural arm tremor (0-4). We did not feel a more detailed assessment would give more meaningful data because the results were mitigated by current pharmacological treatment. If DBS had been implanted the rating was done while stimulation was disengaged. If they were diagnosed with RLS, we scored the RLS with the international restless legs rating scale (IRLSRS).(14) We also codified them into those previously diagnosed with RLS by us or elsewhere. Patients presenting to us for both RLS and ET were excluded but we did not exclude patients who may have been self-diagnosed or physician diagnosed with RLS but did not mention it at intake.

In patients presenting with RLS, we examined for arm tremor (rest, postural, and kinetic) to make the diagnosis of ET. We rated arm and other tremor anatomy modified from the Tremor Study Group scale: <0.5 cm was trace, 0.5cm-1.0cm =1, 1cm-3cm =2, 3cm-10cm =3, >10cm =4. A simple formula was used to assess factors which might predict ET in the RLS population. This combined the worse arm scores (rest, posture, kinetic), and any other observed tremor (head, voice, face, worse leg), which were also rated 0-4. Additional information including age, sex, clinic status (new or follow-up), family history of RLS, a family history of tremor, the age of RLS onset, and secondary causes of RLS including serum ferritin, and electromyography. We also compiled medications taken by the patients that could either augment or improve tremor.

In order to assess predictors of RLS in patient presenting with ET, we used simple logistic regression for the 100 ET patients with RLS as the dependent variable and both categorical variables (family history of RLS, family history of tremor, dystonia, sex) and continuous variable (tremor severity, age and age of tremor onset) as the independent variables individually. We also repeated logistic regression using a more inclusive criteria that combined RLS, near RLS (3/4 criteria), and observed PLMS (n=41) as the dependent variable.

In the 68 RLS patients, we dichotomized tremor into those with a total score of ≤0.5 and >0.5 as the dependent variable, and assessed for family history of ET, family history of RLS, sex, age, age of onset of RLS, IRLSRS, ferritin, tremor suppressing drug, and tremor augmenting drugs, via simple logistic regression. The logistic regressions were conducted using SAS procedure Logistic (SAS 8.2, Cary, NC). In the models, the interpretation of the significance of the relationship between the response variables and the continuous covariates is based on one unit change. It is worth noting that the significance depends on the unit of the covariates.

Results

It required 19 weeks to accrue 100 consecutive different patients with ET. During the same period 68 different patients with RLS were seen.

Fifty-eight of the 100 ET patients were follow-up evaluations and 42 were new consults. Sixty were female. Five were Hispanic, two Asian, and one African. The remaining 92 were Caucasian. A family history of ET was reported in 75. The mean age at inclusion was 65.2±16.3, [range: 16.8-89.1] and the age at tremor onset was 37.8±19.9, [range: 5-80]. Arm postural tremor severity was 1 (19 subjects), 2 (37 subjects), 3 (25 subjects), and 4 (19 subjects). Concurrent dystonia was seen in 19: neck (6), arm/hand (5), voice (5), cranial (3). DBS of the VIM nucleus had been performed in 24, all follow-up evaluations.

RLS was diagnosed in 33 patients who presented with ET. Two additional patients met ¾ criteria and six additional patients were reported to have PLMS. Of the 33 patients with definite RLS, 19 (57.6%) reported a family history of RLS. Only 4/67 (6.0%) of ET patients without RLS reported a family history of RLS. Of the 33 with definite RLS, 4 (12.1%) were diagnosed prior to seeing us, 4 (12.1%) were diagnosed by us at a previous visit, and the remaining 25 (75.8%) were diagnosed at this visit. The mean IRLSGS on the 33 RLS patients was 16.6±8.1, [range: 7-35]. This was significantly less severe than those presenting to us for RLS, 2-tailed t-test p<0.0001 (see below). Pharmacological treatment for RLS was started in 7/25 (28.0%) of newly diagnosed patients. Onset of ET preceded the onset of RLS in 19, RLS preceded ET in 10, and 4 reported a simultaneous onset.

RLS in the ET population was strongly associated with a family history of RLS (O.R. 21.4 (95% CI: (6.3, 72.7), p<0.001) and tended to be more common in women (p=0.09) but was otherwise not associated with patient age, tremor severity, age at tremor onset, dystonia, or family history of tremor. Results were similar when we assessed for risk factors of the more inclusive criteria of RLS, near RLS, and PLMS. Tremor severity did not significantly correlate with RLS severity (Pearson's correlation coefficient =0.25, p=0.16).

Of the 68 patients presenting with RLS, 42 (61.8%) were follow-ups and 26 (38.2%) were new consultations. Forty-three (63.2%) were female. The age at time of evaluation was 55.8±14.4 years, [range: 14.2-82.3] and the age at RLS onset was 33.7±19.5 years, [range: 5-78]. A family history of RLS was seen in 37 (54.4%), whereas 28 (41.2%) denied a family history. In three patients we could not ascertain family history because either the patient was adapted or lost contact with all genetic relatives during their childhood. Serum ferritin levels (n=65) were 75.0±65.1, [range: 5-320]. A ferritin of less than 50 was seen in 31 patients. Electromyogram / nerve conduction velocities (n=40) were normal in 26 (65%) and demonstrated some abnormality, usually mild sensory neuropathy isolated to the feet, in 14 (35%). The IRLSRS, which was assessed in all new patients and some follow-up patients (n=41) was 28.8±7.0, [range: 13-38]. Fifteen patients (22.1%) reported a family history of tremor. Thirteen RLS patients were on a single medicine and one on two medicines that could possibly worsen tremor, usually a serotonin re-uptake inhibitor. A single medicine that could possibly improve tremor (gabapentin, benzodiazepines, and beta-blockers) was taken by 17 RLS patients, whereas three patients took 2 such medicines and one took three such medicines. None of these patients were diagnosed with ET or took the medicines for tremor.

No RLS patient demonstrated any rest tremor. No patient demonstrated a postural tremor of greater than 1, and only a single patient demonstrated a kinetic tremor of 2. Mild tremor; however, was very common. With posture, 10 patients (14.7%) were rated as 0.5 and 11 (16.2%) were rated as 1.0 in their worst hand. During finger to nose, 22 patients (32.4%) were rated as 0.5 and 18 (26.5%) were rated as 1.0 in their worst hand. Only 4 patients had any tremor anatomy aside from their hands.

Only a family history of ET was significantly associated with tremor, O.R.=6.6 (95% CI: (1.8, 24.5)), (p=0.005). Worse RLS (p=0.09) and higher ferritin (p=0.10) tended to correlate with greater probability of tremor although these associations were not statistically significant at level=0.05.

Table 1. Estimates of the Coefficients of the Predictors in the Simple Logistic Regression of RLS in Patients Presenting with Tremor

	Point estimate	p
Family History of RLS	24.05	<0.0001
Family History of Tremor	0.37	0.54
Dystonia	0.24	0.62
Sex	2.79	0.09
Tremor Severity	0.28	0.59
Current Age	0.54	0.46
Age at Tremor Onset	1.39	0.24

Table 2. Estimates of the Coefficients of the Predictors in the Simple Logistic Regression of Tremor in Patients Presenting with RLS

	Point estimate	p
Family History of Tremor	7.95	0.005
Family History of RLS	1.45	0.23
Use of Tremor Producing Drugs	0.27	0.60
Use of Tremor Suppressing Drugs	0.80	0.37
Sex	2.11	0.14
Age	0.01	0.93
RLS Severity	2.96	0.08
Ferritin	2.79	0.10
Age of RLS Onset	0.15	0.69

Discussion

We found that 1/3 of 100 consecutive patients presenting to us with ET also had RLS. The majority of these were undiagnosed despite being of moderate to severe intensity in some cases. Most of the patients with ET and RLS had family histories of both conditions and a family history of RLS predicted RLS. This contrasts with other secondary causes of RLS, such as renal failure, neuropathy or systemic iron deficiency that usually lack a family history of RLS, suggesting that ET and RLS share genetic etiologies. In contrast, patients presenting with RLS did not have clearly pathological tremor, although a large number had small amplitude tremor, which was predicted than a family history of tremor, again suggesting genetic overlap.

The diagnosis of ET variably requires minimum amplitude of postural tremor, depending on which inclusion criteria are employed.(15-17) Our clinical impression; however, was that this commonly observed mild tremor was more consistent with "enhanced physiological tremor". Furthermore, none of the RLS patients on whom we observed tremor elected to treat it. Our findings are consistent with the report of Walters et al, who only diagnosed ET in 3/56 RLS patients, based on criteria that required subjective disability and a minimum amplitude on examination.(18) They did not evaluate for low amplitude tremor. This mild tremor seen in our population could result from sleep deprivation or some intrinsic properties of RLS, or be minor form of ET, as is suggested by the high rate of familial tremor seen in our RLS population.

It is not clear why such a large number of people presenting with ET have RLS, whereas patients with RLS do not show overt ET. Some of this could reflect the prevalence. RLS is much more common than ET, and is probably diagnosed in a smaller number of people who actually have it, both before and after seeking medical attention.(19) Our center is a referral for both conditions. The severity of RLS in those referred for RLS was greater than in the RLS patients who presented for ET, so it is not surprising they were not referred for RLS. We only excluded two patients referred for both so this is unlikely to have skewed the results. Similar RLS association results have been seen in other conditions. For example, RLS is common in patients presenting with rheumatoid arthritis(20); however, patients presenting with RLS were not found to have high rates of rheumatoid arthritis.(21)

Both RLS and ET likely have multiple genetic causes so there may exist a subset of ET patients that have RLS as part of a combined ET/RLS phenotype. This is supported by the family history data in both groups, as patients with ET/RLS tended to have family histories of both conditions. Identifying specific genetic causes for both conditions will clarify this issue.

Potential problems with our report include the intrinsic problems of recall bias, especially age of onset data, the lack of objective diagnostic criteria for either diagnosis, and issues of referral bias. Family histories of both conditions also tend to be under-reported.(17, 22) Nevertheless the overwhelming data suggests that RLS is often undiagnosed in patients presenting with ET and should queried and treated if indicated. Genetic co-segregation and intriguing physiological similarities between the two conditions suggest a true relationship in at least a sub-group of patients, and should be further explored.

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