Does Idiopathic Restless Legs Syndrome Delay Onset and Reduce Severity of Parkinson's Disease

William G Ondo MD, Elizabeth M Dragan MD

Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas

ABSTRACT

Objective: To explore the hypothesis that idiopathic restless legs syndrome (RLS) protects or mitigates Parkinson's disease onset and severity.

Background: Studies of PD populations show that about 20% of PD patients meet criteria for RLS, however, the vast majority of patients present with PD first. No study has yet evaluated patients who have idiopathic RLS and later develop PD. Despite similar treatments, PD has reduced dopamine whereas RLS has increased dopamine turnover. PD has increased CNS iron deposition whereas RLS has reduced CNS iron. It is therefore possible that idiopathic RLS could actually protect against PD.

Methods: Patients with idiopathic RLS preceding PD onset, as defined by onset of RLS greater than 5 years before motor symptoms of PD, or a family history of RLS in a first degree relative and onset of RLS anytime before PD, were collected and compared to a control group of PD for demographics, age of onset, motor progression, appearance of dyskinesia, L-dopa equivalent dose, and basic PD phenotype at onset.

Results: The RLS/PD group: N=31, 13 female, 18 positive family history of RLS, 6 with family history of PD. PD group: N=31, 9 females, 1 with family history of RLS, 9 with family history of PD. Age at onset of RLS/PD was older (65.1 ± 6.5yr vs. 56.7 ± 11.5) than for patients with idiopathic PD ($p<0.01$). Patients in idiopathic PD developed dyskinesia more (14/31) than RLS/PD (2/21) at last follow-up ($p<0.01$). PD phenotype and L-dopa dose were similar in both groups.

Conclusion: Idiopathic RLS may delay the onset of PD, reduce dyskinesias, and possibly reduce progression of PD.

INTRODUCTION

Studies of predominantly Caucasian Parkinson's disease (PD) populations consistently show that about 20% of PD patients meet criteria for Restless Leg Syndrome (RLS). [1-3] Studies in Asian populations, where RLS is less common, show lower rates. [4, 5] However, when queried, the vast majority of patients present with PD prior to RLS. No study has yet evaluated patients who have idiopathic RLS that later develop PD.

Despite similar treatments, the pathology of PD and RLS are contradictory in two major regards. PD has reduced dopamine and dopamine cells whereas RLS has increased dopamine turnover and possibly increased dopamine cells. [6, 7] PD also has increased CNS iron deposition [8-10] whereas RLS has reduced CNS iron, which is in fact the most robust and consistent pathological finding in RLS. [6, 11] Iron has been proposed to cause or at least potentiate PD via the formation of free radicals via the Fenton reaction, which is catalyzed by iron. In fact, theories on MAO-B neuroprotection are at least partially based on reducing non-enzymatic dopamine turnover in order to reduce this free radical formation. Rasagiline, a MAO-B inhibitor, is the only medication to date that can possibly claim neuroprotection based on clinical trials in PD. [12] Other direct toxic effects of iron are also postulated. [8] Given the reduced iron in RLS and the demonstrated increased dopamine turnover, we hypothesized that idiopathic RLS may actually protect against the development and progression of PD.

METHODS

Charts of 31 patients with idiopathic RLS preceding the development of PD, as defined by onset of RLS greater than 5 years before motor symptoms of PD, or a family history of RLS in a first degree relative and the onset of RLS anytime before PD, were reviewed from the Baylor College of Medicine Parkinson's Disease Center (BCMPDC) database. They were compared to a group of 31 consecutively seen patients with idiopathic PD seen over two weeks in clinic. We compared demographics, age of onset, Unified Parkinson's Disease Rating Scale (UPDRS) in the "on" and "off" states at first visit and final visit, appearance of dyskinesia, L-dopa equivalent dose, duration of illness, and basic PD phenotype at onset.

L-dopa dose equivalent dose was calculated using the formula ((L-dopa + L-dopaCR(.7)*(1.1 if on entacapone or tolcapone)) + pramipexole(100) + pergolide(100) + ropinirole(25)). Analysis of data was carried out using chi squared test to statistical significance of dyskinesia and surgery between the two groups. T-tests for independent samples were used to calculate all other data.

RESULTS

The RLS/PD group had 31 subjects (13 female), 18 had a positive family history of RLS, and 5 had a family history of PD, 3 of which had a family history of both PD and RLS. Only 1 patient in the RLS/PD group was referred for only RLS, however demonstrated signs and symptoms of PD at the initial visit. All other patients were referred for PD. 10/31 RLS/PD did not have any follow-up visits. The PD group had 31 subjects, 9 of which were females, 1 with family history of RLS, and 9 with family history of PD. PD motor phenotype (relative amount of tremor, bradykinesia, rigidity, and gait disorder) was similar in both groups. The age at onset of PD was 65.1 ± 6.5 years in the RLS/PD group vs. 56.7 ± 11.5 for subjects with only PD ($p<0.01$).

The initial Hoehn and Yahr stage was greater in the RLS/PD group (2.08 ± 0.87) than the PD group (1.8 ± 0.6), $p = 0.02$. The UPDRS motor "on" (25.5 ± 15 vs. 20.1 ± 8.6, $p = 0.03$), UPDRS ADL "off" (15.5 ± 8.4 vs. 8.7 ± 6.8) and UPDRS average ADL scores (13.5 ± 7.9 vs. 8.3 ± 4.4, $p = 0.002$) were significantly lower in the idiopathic PD group compared to the PD/RLS group. All differences disappeared at the final follow-up visit, suggesting more rapid progression in the idiopathic PD group. There also was no statical difference in L-dopa dose equivalent or duration of PD between the two groups ($p= 0.14, 0.42$) at final follow-up. The number of patients with idiopathic PD with dyskinesia at final follow-up was 14/31 vs. 2/21 RLS/PD patients ($p=0.015$).

	PD Group	PD/RLS Group	P-value
Age onset PD	56.67 ± 11.47	65.1 ± 6.5	0.001*
Duration of PD at initial visit	4 ± 3.89	4.7 ± 3.63	0.352
Age at first dopaminergic medication	59.64 ± 11.38	65.96 ± 5.78	0.0003*
Initial H and Y	1.77 ± 0.63	2.08 ± 0.87	0.02*
Initial Schwab	86.94 ± 10.62	81.72 ± 13.91	0.08
Initial UPDRS motor "on"	20.07 ± 8.55	25.46 ± 15	0.03*
Initial UPDRS motor "off"	22.16 ± 12.36	26.9 ± 16.37	0.12
Initial ADL "on"	8.2 ± 5.43	11 ± 6.1	0.33
Initial ADL "off"	8.65 ± 6.84	15.45 ± 8.39	0.01*
Average ADL	8.34 ± 4.42	13.48 ± 7.87	0.002*
L-dopa dose equivalent	267.1 ± 330.66	324.35 ± 355.97	0.51
Final H and Y	2.31 ± 0.71	1.86 ± 0.87	0.23
Final Schwab	82.86 ± 11.13	90 ± 7.07	0.18
Final UPDRS motor "on"	20.24 ± 15.28	23.75 ± 18.2	0.3
Final motor UPDRS "off"	27.3 ± 15.89	22.17 ± 8.73	0.09
Final ADL UPDRS "on"	11.15 ± 9.05	8.73 ± 13.63	0.73
Final ADL UPDRS "off"	17.33 ± 5.82	20 ± 5.32	0.34
Average ADL UPDRS	13.54 ± 7.97	14.89 ± 4.56	0.19
Final L-dopa dose equivalent at f/u	794.74 ± 383.42	733.9 ± 5.94	0.16
Total disease duration at last visit	11.38 ± 5.54	7.31 ± 5.77	0.42
First PD symptom	19 trem, 6 dext, 6 gait	18 trem, 8 dext, 3 gait	$X^2 = 1.25$, 0.535
Final Dyskinesia	14/31	2/21	$X^2 = 5.88$, 0.015*
Rate of change in H&Y	0.19 ± 0.36	0.12 ± 0.15	0.008*
Rate of change in UPDRS motor "on"	-0.910 ± 2.836	0.71 ± 4.27	0.077
Rate of change in UPDRS ADL average	0.270 ± 5.628	1.11 ± 0.76	<.0001*

DISCUSSION

We found that patients with idiopathic RLS who subsequently developed PD did so at a later age than patients with idiopathic PD. They were less likely to develop dyskinesia and possibly had slower motor progression during the time they were followed by us.

While both RLS and PD initially respond to treatment with dopamine agonists, RLS pathology shows no evidence of neurodegeneration, and there is evidence for increased dopamine turnover.[7] This in itself could explain resistance to the development of clinical parkinsonism. Reduced brain iron is the major identified pathology in RLS, although the mechanism by which it is reduced, and its exact relationship to the robust clinical benefit of dopaminergics is not known. Iron is part of the D2 receptor, and iron reduction will down regulate striatal D2 receptors in rodents [13], but not in spinal dopamine receptors, postulated to be involved with RLS symptoms.[14] Interestingly destruction of diencephalic-spinal dopamine neurons will reduce spinal iron levels[15], so iron and dopamine may be inter-related in a complex manner.

The mechanism or reason for which iron is increased in PD, and a number of other neurodegenerative diseases, has not been explored. Iron is necessary for activation of the synaptic protein Thy-1, which is involved in both synaptogenesis and release of monoamines such as dopamine.[16] Thy-1 activity is reduced in RLS. [16] One possibility for increased iron in PD may be simply to compensate for the reduced available endogenous dopamine, by increasing the efficiency of release. To our knowledge this possibility has never been examined. Once there, however, the iron could accelerate cell death via its role in free radical formation or other toxic effects. Given what we know about the pathology of both disease processes, reduced iron concentration would seem to play the most likely role in possible neuro-protection in the RLS/PD population, however neither the pathophysiology of RLS or PD is fully elucidated, so unknown factors may be involved.

Our study is limited due to the nature of a retrospective chart review. Not all patients had UPDRS score or H&Y stage at every follow-up. In addition, several patients with RLS and PD did not follow-up after the initial visit so progression could not be determined. One could speculate that they did not follow-up because their disease was readily managed by a local neurologist and the patients did not feel they needed a movement disorder specialist, possibly suggesting the development of fewer complications. Finding only 31 subjects who had RLS prior to PD, in a database of more than 10,000 PD subjects is of course less than would be expected; however we suspect many cases were not ascertained so this statistic is probably not valid. Importantly, we have not yet compared brain iron content in the two groups. Therefore it is possible that the PD/RLS group does not actually have reduced CNS iron. Nevertheless, we feel this is an interesting and potentially useful observation for understanding the development and progression of both PD and RLS.

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