ABSTRACT

Objective: To explore the hypothesis that idiopathic restless legs syndrome (RLS) protects or mitigates Parkinson’s disease (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 ± 13.5 for subjects with only PD (p=0.01).

The CNS iron deposition and iron deposition is greater in RLS/PD (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 = 0.02) 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 statistical 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).

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). Patients with idiopathic RLS that later develop PD have increased 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, 18 female, 18 positive family history of RLS, 6 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.

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.

Studies of predominantly Caucasian Parkinson’s disease (PD) populations consistently show that about 20% of PD patients meet criteria for Restless Leg Syndrome (RLS). Patients with idiopathic RLS that later develop PD have increased iron deposition whereas RLS has reduced CNS iron. It is therefore possible that idiopathic RLS could actually protect against 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. PD also has increased CNS iron deposition whereas RLS has reduced CNS iron, which is in fact the most robust and consistent pathological finding in RLS. 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 neuretrodegradation are at least partially based on reducing non-enzymatic dopamine turnover in order to reduce this free radical formation. Ragasline, a MAO-B inhibitor, is the only medication to date that can possibly be used to neutralize dopamine, spinal iron levels.15-16 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.1 Thy-1 activity is reduced in PD,10 possibly for increased iron in PD may be simply too complex for the reduced available endogenous dopamine, increasing the efficiency of release. To our knowledge this possibility has never been examined. Once there, however, the iron could activate 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 consumption could 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 significant derangement in the PD scoring. Finding only 31 subjects who had RLS prior to PD, in a database of more than 10,000 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.

REFERENCES