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No Evidence for Cognitive Dysfunction or Depression in Patients with Mild Restless Legs Syndrome

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Abstract

Restless legs syndrome is a common disoder that may interrupt sleep and has been reported to produce daytime fatigue and/or mood changes. This study assessed whether patients with RLS have more cognitive dysfunction and depression than individuals of the same age and education who do not have RLS. The study showed that older individuals with mild RLS for at least 1 year do not have cognitive dysfunction and are not depressed compared with a control group of similar age and education.

Keywords

restless legs syndrome; cognitive dysfunction

Restless legs syndrome (RLS) affects up to 25% of the adult population.1 RLS is characterized by uncomfortable sensations in the legs, which are relieved by movement but commonly worsen at night. This often interrupts sleep and may cause daytime fatigue. It has been reported that patients with RLS suffer from increased rates of irritability, anxiety, and depression.2–5 However, almost all previous studies (both population-based and clinic-based) have used

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varying RLS diagnostic criteria and various depression scales and have not completely assessed the associated cognitive function.5 This study assessed whether patients with RLS have more cognitive dysfunction and depression than individuals of the same age and education who do not have RLS.

SUBJECTS AND METHODS

The Sun Health Research Institute Brain and Body Donation Program (BBDP) database was reviewed for subjects with and without RLS. All subjects had received annual movement disorder and neuropsychological evaluations. Subjects with Parkinson's disease, parkinsonism, essential tremor, other tremor disorders, progressive supranuclear palsy, dystonia, peripheral neuropathy, fibromyalgia, or dementia were excluded from this analysis. The diagnosis of RLS was made by a movement disorder specialist using the IRLSSG criteria.[6] Neuropsychological testing included Rey-AVLT, Trails A and B, stroop, controlled oral word association, animal fluency, judgment of line orientation, digit span, Folstein mini-mental status examination (MMSE), and clock drawing. The 30-item Geriatric Depression Scale (GDS) was used to assess depression.

Data were compiled from the subject's most recent visit that had both movement and cognitive testing. The mean level of each measure in the RLS group was compared with that of the control group and the statistical significance was calculated by using the two-sample *t* test.

RESULTS

After exclusion criteria were applied there were 26 subjects with RLS, 208 without RLS (control group), and 79 subjects were excluded. There was no difference in mean age (RLS, 77 years; control, 78 years) (Table 1). The 95% CI for the difference in mean age (95% CI = −5.0 to 2.3) indicates that the mean age is equivalent within 5 years. The mean duration of education was 15 years in both groups. The mean duration of education was equivalent within 1 year (95% CI = −0.9 to 1.3).

The mean RLS rating scale score for the RLS group was 11.0 (SD = 7.6, N = 25) and the mean duration of RLS was 11.0 years (range, 1–51 years). Ten RLS subjects had a family history of RLS and one had a family history of Parkinson's disease.

Twelve of the 26 subjects had been or were being treated for RLS (6-gabapentin, 1-ropinirole, 1-pramipexole, 3-narcotics, 1-quinine), 9 had been or were on antidepressants, and 8 had been or were using benzodiazepines. Only 4 patients were using an antidepressant or benzodiazepine at the time of cognitive testing. There were no significant differences in neuropsychometric testing between these two groups of RLS patients. Therefore, they were combined into one group for comparison with controls. Also, no significant difference was found in cognitive testing between the RLS patients on medications for RLS and those who were not on treatment medications. Therefore, these subjects were not separated from the RLS group in the comparative analysis. Medications for the control subjects were not recorded.

None of the mean cognitive scores differed by more than half of the standard deviation of the group without RLS (Table 1). All of the mean cognitive scores were equivalent within one standard deviation of the group without RLS. The mean GDS scores differed by less than 1 point on a 30-point scale. The percentage of subjects with GDS ≥ 10 was 6% (n = 3/208) among controls and 4% (n = 1/26) among RLS cases (Δ = −0.02, 95% CI = −0.08 to 0.13, $P > 0.99$). The sample was too small to assess for a correlation between the GDS score and severity of RLS.

DISCUSSION

These findings suggest that older individuals with mild RLS for at least 1 year do not have cognitive dysfunction and are not depressed compared with a control group of similar age and education. Previous epidemiological studies have reported that patients with RLS have more anxiety and depression.2–5 Whether this is secondary to the actual RLS symptoms, insomnia or another sleep disorder, or other factors is unclear. These prior reports varied significantly in their methodology, including study design (population to random sampling), sample size (range, seven subjects to over 3,000), the RLS diagnostic criteria (the IRLSSG was not normally used), the exclusion or inclusion of patients with a known history of depression, and various assessment scales for evaluation of depression.2–5 Furthermore, cognitive dysfunction in this population has not been systematically or extensively evaluated. In two previous conflicting reports, untreated RLS patients showed cognitive deficits similar to that seen in sleep-deprived patients, yet the follow-up study found untreated RLS patients to perform better than sleep-deprived controls.7,8 These studies were limited by a small sample size (n = 16), the RLS cases being withdrawn from treatment, and no correlation with RLS severity.[7] These factors make it difficult to assess for medication-withdrawal effects and RLS severity on the cognitive dysfunction found.

The current study used the International RLS Study Group criteria assessed by a movement disorder specialist, the RLS rating scale for quantifying the symptoms, and prospective neuropsychological testing to objectively assess cognitive function. Additionally, patients with depression were not prospectively excluded. Limitations of this study included the cases having relatively mild RLS, no treatment withdrawal for RLS medications (n = 12), no controlling for the use of antidepressants or benzodiazepines (n = 4), and no measurement for sleep disturbances in either group. Further prospectively designed studies of RLS and control populations are needed to determine if cognitive or neuropsychiatric symptoms occur in more severe cases of RLS and what factors may be correlated with these disorders.

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TABLE 1

Demographic and cognitive measures of subjects with and without restless legs syndrome

	With RLS: mean (SD), N	Without RLS: mean (SD), N	Δ	95% CI	*P**
Age (yr)	76.8 (9.2), 26	78.1 (9.0), 208	−1.4	−5.0 to 2.3	0.46
Duration of education (yr)	15.3 (2.8), 26	15.1 (2.6), 208	0.2	−0.9 to 1.3	0.71
Folstein MMSE	28.2 (1.7), 25	28.7 (1.6), 204	−0.5	−1.2 to 0.2	0.15
AVLT total learning	47.7 (9.1), 26	44.7 (11.3), 205	3.0	−1.6 to 7.5	0.19
AVLT Trial 1	5.7 (1.7), 26	5.5 (2.1), 205	0.2	−0.6 to 1.0	0.64
AVLT Trial 2	8.5 (1.9), 26	8.2 (2.6), 205	0.2	−0.8 to 1.3	0.67
AVLT Trial 3	10.0 (2.5), 26	9.6 (2.7), 205	0.4	−0.7 to 1.5	0.49
AVLT Trial 4	11.4 (2.2), 26	10.3 (2.7), 205	1.1	0.01 to 2.2	0.048
AVLT Trial 5	12.1 (2.1), 26	11.0 (2.7), 205	1.1	0.01 to 2.2	0.047
AVLT intrusions (1–5)	0.6 (1.2), 25	1.5 (2.3), 200	−0.9	−1.8 to 0.0	0.06
AVLT STM (A6)	9.6 (3.4), 26	9.0 (3.3), 205	0.5	−0.8 to 1.9	0.43
AVLT intrusions (STM)	0.36 (0.70), 25	0.50 (0.96), 200	−0.14	−0.52 to 0.25	0.50
AVLT LTM (A7)	9.0 (3.5), 26	8.9 (3.7), 205	0.1	−1.4 to 1.6	0.88
AVLT LT % recall	73 (24), 26	79 (26), 205	−6	−17 to 4	0.25
AVLT List B	5.2 (2.0), 26	4.8 (2.0), 204	0.4	−0.4 to 1.2	0.33
AVLT recognition TP	13.5 (1.7), 25	13.2 (2.3), 199	0.3	−0.7 to 1.2	0.56
AVLT recognition FP	0.20 (0.41), 25	0.64 (1.25), 199	−0.44	−0.94 to 0.05	0.08
WAIS digit span - forward	8.6 (1.5), 24	9.6 (2.0), 188	−1.0	−1.8 to −0.2	0.02
WAIS digit span - backward	6.2 (1.8), 24	6.4 (2.0), 187	−0.2	−1.1 to 0.6	0.60
WAIS digit span - total	14.8 (2.6), 24	16.0 (3.3), 187	−1.2	−2.6 to 0.2	0.09
WAIS digit span - backward span	4.6 (1.2), 23	4.7 (1.2), 182	−0.1	−0.6 to 0.4	0.74
WAIS digit span - forward span	5.7 (0.9), 23	6.3 (1.2), 183	−0.6	−1.1 to −0.1	0.03
Clock drawing	9.0 (1.6), 25	9.2 (1.1), 204	−0.3	−0.8 to 0.2	0.26
STROOP word (#)	87 (15), 24	89 (16), 199	−2	−8.9 to 5.0	0.58
STROOP color (#)	63 (12), 23	63 (12), 196	0	−5 to 5	0.98
STROOP word/color (#)	32.6 (7.0), 23	33.0 (10.1), 19	−0.4	−4.6 to 3.9	0.86
STROOP uncorrected W/C errors	0.4 (1.1), 22	0.4 (1.0), 191	0.1	−0.4 to 0.5	0.72
STROOP interference	−4.0 (5.4), 23	−4.0 (7.2), 195	0.0	−3.1 to 3.0	0.99
TRAILS A/B - time (3 min limit)	37 (16), 24	38 (22), 203	−1	−10 to 78	0.79

	With RLS: mean (SD), N	Without RLS: mean (SD), N	Δ	95% CI	*P**
TRAILS A/B - A errors	0.13 (0.34), 24	0.12 (0.42), 203	0.01	−0.17 to 0.18	0.94
TRAILS A/B - B (5 min limit)	101 (43), 24	102 (53), 200	−1	−24 to 21	0.90
TRAILS A/B - B errors	0.46 (0.72), 24	0.57 (1.11), 201	−0.11	−0.57 to 0.35	0.64
COWA (CFL) total	38 (16), 26	38 (12), 205	1	−4 to 6	0.79
COWA (CFL) perseverations	2.8 (2.9), 25	2.8 (2.7), 200	0.0	−1.2 to 1.1	0.97
COWA (CFL) intrusions	0.08 (0.28), 25	0.29 (0.64), 200	−0.21	−0.46 to 0.05	0.12
Animal fluency	16.7 (5.2), 26	16.8 (5.0), 204	−0.1	−2.2 to 2.0	0.91
Animal fluency perseverations	1.0 (1.4), 25	1.0 (1.3), 199	0.0	−0.5 to 0.5	1.00
Judgment of line orientation	23.6 (3.9), 23	23.7 (4.3), 191	−0.1	−2.0 to 1.7	0.89
GDS	3.7 (3.2), 26	3.4 (3.7), 206	0.4	−1.1 to 1.8	0.63

*Two sample *t* test.