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Higher prevalence of restless legs syndrome/Willis-Ekbom disease in multiple sclerosis patients is related to spinal cord lesions

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ABSTRACT

Background: Multiple sclerosis (MS) is connected with higher prevalence of secondary restless legs syndrome/Willis-Ekbom disease (RLS/WED). Aim of this study was to determine risk factor for developing symptoms of RLS in MS patients.
Methods: In cross-sectional study we examined 200 random MS patients. After obtaining informed consents, patients undervent a structured interview based on RLS and MS symptoms and characteristics, demographic, and health-related data. Than we collected results of brain/spinal cord magnetic resonance imaging (MRI). Blood samples were examined for blood count and biochemistry.
Results: From all 200 subjects, 26% were RLS-positives (95% CI: 20–32%). From positive patients, 44% had negative family history for RLS, and developed secondary RLS after onset of MS. Compared to RLS-negatives, the positives had significantly higher prevalence of spinal cord lesions (p=0.01). Presence of spinal pathology was connected with higher risk of RLS development (OR=3.846, 95%CI:1.304-11.346). There were no statistically significant differences in the levels of red blood cells, iron metabolism parameters, or levels of B or D vitamins.
Conclusion: Risk of RLS/WED in MS increases with presence of lesions in spinal cord. The role of decreased dopamine delivery to lower spinal regions as the pathological background must be proved by more detailed research.

1. Introduction

Multiple sclerosis (MS) is known to be a chronic disabling neuroinflammatory and neurodegenerative disease affecting mostly persons in their productive age. Quality of life is decreased both by motor impairment and non-motor features, including also symptoms of restless legs syndrome/Willis-Ekbom disease (RLS/WED). It presents with (I) an urge to move the legs usually accompanied by unpleasant sensations in the legs; (II) these feelings begin or worsen during periods of rest or inactivity; (III) these feelings are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues, and (IV) only occur or are worse in the evening or night than during the day. The occurrence of the above features (criterion V) is not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping). With unpleasant character and nocturnal occurrence, RLS/WED can severely disturb sleep and quality of life. Prevalence of this syndrome is reported to be approximately 7% in general population (Allen et al., 2014).

According to the recent scientific data, combinations of genetic and environmental factors contribute to RLS/WED onset. The main role might have any condition leading to:

- iron deficiency - anemia, pregnancy, chronic renal disease, etc.;
- spinal hyperexcitability - serotoninergic antidepressants, thyrotoxicosis, neuropathy; and
- spinal hypodopaminergic state - dopamine-depleting agents, anatomical or functional damage to the spinal cord (Ondo, 2014; Allen, 2015).

When RLS/WED is not connected with any above-mentioned condition, we consider it idiopathic - mainly with genetic background. The others rank among secondary forms, including RLS in MS. Research dealing with prevalence and probable etiology and pathogenesis of RLS in MS has relieved contradictory results.

According to the recent studies, prevalence varies between 14.4 and 32.1 per cent (Deriu et al., 2009; Douay et al., 2009; Manconi et al.,

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2008a; Miri et al., 2013; Vavrova et al., 2012; Aydar et al., 2011). It is the fact that patients with MS are at higher risk of developing RLS, compared to general population. Gender and body mass index were not connected with RLS (Douay et al., 2009; Miri et al., 2013). Manconi et al. (2008a) independently with Aydar et al. Aydar et al., (2011) confirmed higher age in RLS subgroup; what was not observed by Douay et al. Douay et al., (2009) and Miri et al. Miri et al., (2013) Type of MS course varies among studies - with preponderance of relapse-remitting (Douay et al., 2009) or primary progressive (Manconi et al., 2008a) course; or with no influence (Miri et al., 2013). Regarding MS duration, three studies revealed connection with RLS occurrence (Manconi et al., 2008a; Vavrova et al., 2012; Aydar et al., 2011), two had no link between MS duration and development of RLS symptoms (Douay et al., 2009; Miri et al., 2013). Severity of MS (according to signs dissemination, EDSS, MRI findings) was higher in RLS positives in vast majority of studies (Manconi et al.,2008a; Miri et al., 2013; Vavrova et al., 2012; Aydar et al., 2011). Probably "load" of disease rather than its duration is connected with RLS. Vávrová et al. Vavrova et al., (2012) even looked at genetic factors in a huge sample of MS patients - there was a trend for association with the MAP2K5/SCOR1 gene, and no significant association with MEIS 1, BTBD9, and PTPRD gene variants.

Based on these data, we decided to disclose the prevalence and to identify possible causes of RLS/WED in our cohort of MS patients.

2. Subjects and methods

2.1. Subjects

We examined 200 random consecutive patients of specialized MS outpatient center of Second department of Neurology, Comenius University Bratislava, Slovakia. Patient must have been at least 18 years old, diagnosed with MS according to revised 2010 McDonald criteria.

2.2. Data collection

Data were collected from September to December 2014. After signing informed consent, subjects filled a special questionnaire with an assistance of trained person - in order to exclude RLS mimics (myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping). The patients provided us with demographic data, comorbidities and actual medication. Than information reporting on MS characterization followed: (a) age of MS onset (in years), (b) MS duration (in years), and (c) presence of "restless legs" in first-degree relatives (yes or no).

The core of questionnaire consisted of five essential International RLS Study Group diagnostic criteria. Subjects, who responded positively for all five questions, were assessed as positive for RLS/WED (RLS+). Data on RLS symptoms onset (linked to MS onset), frequency, intensity and treatment followed. The positives were also asked about impact of MS attack and/or treatment on the severity of RLS symptoms (worsening, no change or improvement). Rest of population (with four or less positive answers) was negative for RLS/WED (RLS-).

We collected results of brain/spinal cord magnetic resonance imaging (MRI). Blood samples were examined for blood count and biochemistry, including iron metabolism parameters and levels of B and D vitamins. Accredited methods were used.

For the review of RLS in MS, a literature search was undertaken using PubMed database and relevant search terms. Articles were screened for suitability and data relevance.

2.3. Statistical analysis

Data were statistically analyzed using IBM® SPSS® Statistics version 21. We used descriptive statistical methods. To compare between groups, we used Student's *t*-test for parametric data, and Mann-Whitney *U*-test for nonparametric data (with significance at $p < 0.05$). Pearson's rank correlation coefficient (r) was used to evaluate the association between the measured parameters; Spearman's rank correlation coefficient (Rho) was used in case of nonparametric data. Significance was at p=0.01. Binary logistic regression was used to estimate the probability, with significance at $p < 0.05$.

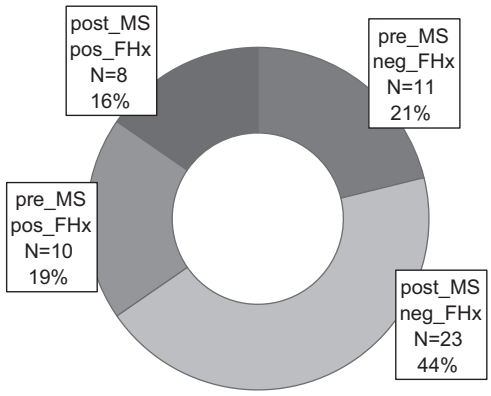

Fig. 1. Proportion of idiopathic and secondary forms of RLS (Restless Legs Syndrome) pre_MS - RLS onset before MS, post_MS - RLS onset after MS, pos_FHx - positive family history, neg_FHx - negative family history.

3. Results

From overall subjects, 26.5% were males. Mean age was 39.75 ± 9.72 years, with MS duration 7.89 ± 5.26 years. From all 200 responders, 26% (95% confidence interval 20–32%) fulfilled all essential criteria for RLS. Proportion of probably idiopathic and secondary forms are shown and explained in Fig. 1.

From all positive responders, 60% (N=31) developed RLS symptoms after MS onset. Moreover, 44% of RLS+(N=23) had negative family history, in addition. Nineteen per cent (N=10) had positive family history and onset of symptoms before MS. They represent 5% of our whole sample, what is in congruence with RLS prevalence in general population.

RLS+ had significantly higher weight compared to the negatives; all the other parameters - demographic data, MS features and results of blood tests - were not significantly different between these groups (Table 1).

Comparing RLS+ and RLS- patients, there was no difference in gender. Positive family history for RLS/WED was significantly more frequent in RLS+ group. More than 34% of RLS+ had positive family history for RLS (16.5% from all subjects). Patients with RLS/WED had significantly higher prevalence of pathological spinal cord lesions compared to RLS- patients (Table 2).

Occurrence of spinal cord lesions correlated with MS duration (rho=0.357, $p < 0.001$). Patients with spinal cord lesions were significantly older (p=0.02).

In RLS+ group, 67.31% experienced no influence of MS attack on RLS symptoms, the symptoms worsened in the rest. In 75% of RLS+, there was no effect of MS therapy, 21% experienced improvement and 4% worsening of symptoms. That differs between subgroups with RLS symptoms before and after MS onset (Fig. 2).

There was no significant difference in MS medication between groups. On the other hand, patients with RLS/WED were treated with amantadine, anticonvulsants, benzodiazepines, vitamin E, vasodilators, and thyroxin in significantly higher frequency (Table 3).

Regarding comorbidities, in RLS+ subpopulation, the prevalence of thyroid gland disease was significantly higher compared to RLS negatives ($p < 0.001$). Other comorbidities (anemia, asthma, depression, renal disease) were not significantly different (Table 4).

The onset of RLS/WED occurred after MS onset in almost 60%.