Summary

Introduction: The Restless Legs Syndrome (RLS) is a frequent neurological disorder with a prevalence ranging from 5 – 10%. RLS is characterized by an urge to move the lower extremities during the night, thus RLS causes sleep disturbance. It presents as both idiopathic and secondary form. Idiopathic RLS is associated with common genetic variants in *MEIS1, BTBD9, PTPRD* and *MAP2K5/SCOR1*. Recently, multiple sclerosis (MS) was identified as a common cause for secondary RLS, the prevalence of RLS in patients with MS ranges from 13.3 to 37.5%.

The aim of our study was to analyse the clinical and genetic aspects of this disorder, especially in patients with multiple sclerosis.

In the clinical part, we evaluated the prevalence of RLS among Czech patients with MS and we compared the extent of brain damage between patients with and without RLS using magnetic resonance imaging (MRI). In the genetic part, we further analysed the impact of known genetic variants (*MEIS1, BTBD9, MAP2K5/SCOR1, PTPRD)* for RLS in other European populations and in patients with MS.

Methods: Clinical part: Each patient with MS underwent a semi-structured interview. A patient was considered to be affected by RLS if he/she met all four standard criteria at life-long interval. Lesion load (LL – T2), brain atrophy – T1 and brain parenchymal fraction (BPF) were assessed in some patients.

Genetic part included two genetic association studies. In the first study, we investigated these variants in 649 RLS patients and 1230 controls from the Czech Republic, Austria and Finland. Ten SNPs (single nucleotide polymorphisms) within the three genomic regions (*MEIS1, BTBD9* a *MAP2K5/SCOR1)* were selected. In the second study, 203 MS patients with RLS were compared to 438 MS patients without RLS. In total 12 SNPs within the four genomic regions (*MEIS1, BTBD9* a *MAP2K5/SCOR1, PTPRD*) were genotyped.

Results: Clinical part: A total of 765 subjects (553 females, mean age 36.54, ±SD 9.5) with MS were included in the study. The diagnosis of RLS was confirmed in 245 subjects (32.1%, 95% CI 28.7 – 35.4%) with MS. Patients suffering from both MS and RLS were significantly older (38.6 vs. 35.6 years), had longer durations of MS symptoms (11.0 vs. 8.2 years) and had higher EDSS score (2.9 vs. 2.3).

Quantitative MRI data were obtained in 385 patients without RLS and 215 patients with RLS. We found no difference between the two groups in the whole brain LL, brain atrophy and BPF, despite the fact that we were able to replicate the correlation of these data with clinical parameters of MS.

Genetic part: We replicated associations for all loci in the combined samples set (*MEIS1*, P = $1.26x10^{-5}$, odds ratio (OR) = 1.47, *BTBD9*, P = $4.11x10^{-5}$, OR = 1.58 and *MAP2K5/SCOR1*, P = 0.04764, OR = 1.27).

No significant association with *MEIS 1*, *BTBD9* and *PTPRD* was found in patients with MS despite sufficient statistical power for the first two loci. There was a trend for association with *MAP2K5/SCOR1* – the best model for the risk allele was the recessive model (p nominal = 0.0029, p corrected for four loci and allelic + recessive model = 0.023, odds ratio = 1.60 – 95% CI 1.17 – 2.18).

Conclusion: RLS is a common comorbidity of multiple sclerosis and MS should be considered among causes of secondary RLS forms. RLS is more prevalent in advanced stages of MS, but does not correlate with MRI markers of brain damage.

Our study confirmed that variants in these three loci (*MEIS1*, *BTBD9*, and *MAP2K5/SCOR1)* confer consistent disease risks in patients of European descent. On the contrary, RLS in MS patients shares only few genetic determinants with the idiopathic form, the gene variant *SCOR1* can partially contribute the phenotype (max. 50%).