CLINICAL NEUROSCIENCES

Neurophysiological Characteristics Of Restless Legs Syndrome In Parkinson's Disease

Alenikova O.A. [1], Likhachev S.A. [1], Svinkouskaya T.V. [1]

ABSTRACT

AIM OF THE STUDY: To investigate the neurophysiological features of restless legs syndrome (RLS) in Parkinson's disease (PD).

METHODS: We used International RLS Severity Scale and investigated somatosensory evoked potentials (SEPs), blink reflex (BR) and sympathetic skin response (SSR). 75 patients with PD were examined at the age of 40-70 years: 36 with RLS and 39 without RLS. 30 healthy individuals were included in the control group.

RESULTS: SEPs study revealed that in the RLS+, the inter-peak intervals (IPI) N9–N13, N11–N13 were significantly shorter and the IPI N13-N20 was longer as compared with the RLS- group. A significant increase in the amplitudes N20-P23 and N13-P18 was observed in the RLS+, which reflects sensitization processes in patients with RLS. A trend to hyperexcitability responses of BR was observed, which can reflect insufficiency of the inhibitory mechanisms at the segmental level and deficiency of supraspinal descending control in PD patients with RLS. SSR study revealed prolonged latency and an increase in the amplitude in the RLS+ group and positive correlation between the severity of RLS (according to International RLS Severity Scale) and SSR latency.

CONCLUSION: A change in the complex interaction between the peripheral, spinal, and cerebral divisions of the nervous system was revealed in RLS. Identified somatosensory disturbances and changes in the brainstem and spinal reflexes probably determine the clinical features of RLS in PD.

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(1) *Republican Scientific and Practical Centre of Neurology and Neurosurgery*, Minsk, Belarus

INTRODUCTION

Restless legs syndrome (RLS) is a chronic sensory-motor disorder characterized by sensory discomfort in legs, appearing or worsening during rest in the evening or night-time, evoking the urge to move. This syndrome can be a primary disorder, likely caused by a genetic predisposition, or secondary to other medical conditions and can occur with such diseases as neuropathy, endocrine pathology, iron deficiency anaemia, or Parkinson`s disease (PD) (Rothdach *et al.*, 2000, Earley *et al.*, 2005). The pathogenetic mechanisms underlying the primary and secondary RLS are common and closely related to dopaminergic insufficiency and iron metabolism disturbances in the structure of the extrapyramidal system. This fact likely explains why RLS in patients with PD occurs more frequently than in general population (Sun *et al.*, 1998).

Clinically, RLS is represented by two main groups of symptoms: subjective pathological sensations (sensory component) and excessive motor activity (motor component). Sensory component is described by patients as unpleasant feelings in their limbs such as creeping, pulling, itching, tingling, burning, or aching. Paresthesias or dysesthesias predominantly involve the legs, but many patients also have symptoms in the arms or trunk (Allen *et al.*, 2005). Symptoms are usually bilateral and occur simultaneously. The severity of unpleasant sensations depends on the motor activity and posture of the patient. The stereotypical movements carried out by the patient tend to be voluntary and help to reduce paresthesias or dysesthesias in the legs, but it was found that some movements do not depend on sensory symptoms and are performed involuntarily. During the development of the disease the representation of involuntary component of RLS increases (Ondo and Jankovic, 1996).

A change in the functional state of the subcortical-brainstem-spinal systems is a neurophysiological basis of the RLS. In particular, it may be caused by hypofunction of diencephalic-spinal dopaminergic tracts (Clemens *et al.*, 2006). The source of this tract is a group of dopaminergic neurons A11 located in the caudal hypothalamus and periaqueductal gray of the midbrain. The descending pathways target preganglionic sympathetic neurons in the tractus intermediolateral (IML), dorsal horn regions responsible for afferent nerve processing, interneurons, and somatic motor neurons of the spinal cord are involved in the RLS mechanisms (Earley *et al.*, 2005, Allen *et al.*, 2005, Clemens *et al.*, 2006). Along with central disturbances, peripheral deafferentation in PD can also be important in the occurrence of RLS. Earlier performed electrophysiological studies and biopsy of peripheral nerves revealed signs of axonal polyneuropathy in patients with PD (Nolano *et al.*, 2008, Abbruzzese *et al.*, 2004), which can contribute to clinical signs of RLS. Consequently, disorders of the sensory system at different levels in patients with RLS lead to changes of spinal and brainstem reflexes and can be objectified by neurophysiological methods.

The purpose of this study was to investigate the neurophysiological features of RLS in PD.

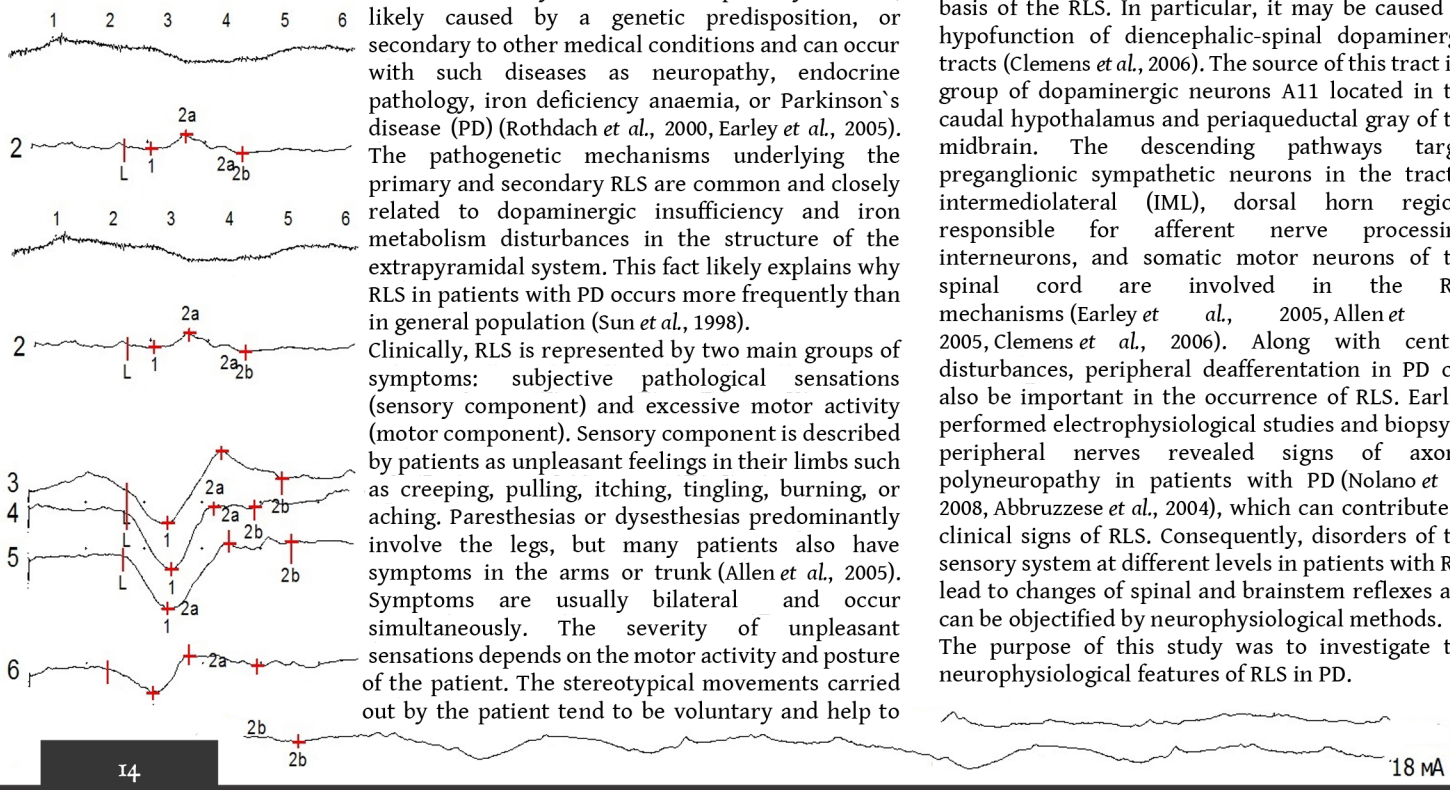


TABLE 1. Comparison of PD patients with and without RLS

Parameters	RLS+ Me (Q1, Q3)	RLS- Me (Q1, Q3)
Age	59 (55; 65)	57 (52; 64)
Duration of PD	8 (5; 13) *	4 (3; 7)
UPDRS scale	49 (40; 59)	47 (41; 60)
PDQ-39	75 (56; 95) *	44 (25; 63)

* – Statistically significant difference ($p < 0.05$)
Me (Q1, Q3) – Median (lower and upper quartiles)

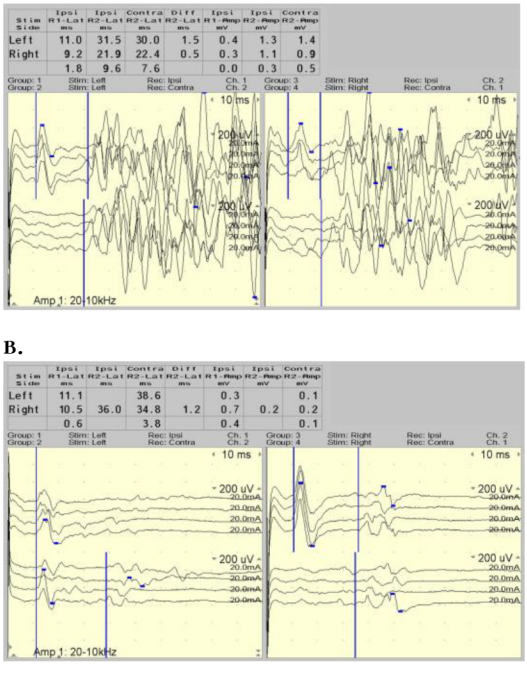


FIGURE 1. (A) Hyperexcitabe BR; (B) Hypoexcitable BR. Opposite types of blink reflex in patients with Parkinson's disease.

SUBJECTS & METHODS

To assess the functional status of the somatosensory system in PD patients with RLS we used short-latency somatosensory evoked potentials (SEPs). The SEPs responses from the upper limbs were analysed with bipolar stimulation of the median nerve at the wrist. Because the clinical symptoms of RLS primarily occur in the lower extremities, it would be logical to examine the SEPs using posterior tibial nerve stimulation. However, we preferred to examine the SEPs from the upper limbs for several reasons. Firstly, the stimulation of the median nerve provides a precise mapping, which is especially important during the examination of patients with tremor interfering with recording. Secondly, the analysis of SEPs parameters such as peak-latency (PL) and inter-peak intervals (IPI) allows us to neglect the height of patients. Thirdly, it can be useful for the detection of subclinical manifestations of RLS from the upper limbs.

Another method for evaluating sensory processes and especially the processes of sensory-motor integration in RLS is an investigation of the blink reflex (BR). BR studies provide important information about the afferent and efferent pathways and is an excellent physiological tool for the assessment the functional integrity of supraspinal structures and their descending influence on the brainstem (Pearce, 2008, Valls-Solé, 2005). BR was assessed using a two-channel system. The supraorbital branches of the trigeminal nerves were stimulated with 20 mA electric impulses on each side. We investigated the onset latency (OL) and amplitude (A) of ipsilateral R1 response and bilateral R2 (ipsilateral and contralateral) responses.

The SSR is a complex polysynaptic reflex, which courses through a common centrifugal path via sympathetic post-ganglionic unmyelinated fibres to sweat glands (Kucera et al., 2004). The posterior hypothalamus is the "generator" of the response and implements the integration between somatic and autonomic nervous systems on various stimuli. SSRs were measured at the mid-palm of both hands following electrical stimulation of the median nerve at the wrist. Active standard Ag/AG/Cl cup electrodes were attached to the mid-palm of both hands and referenced to the palmar surface of the fourth finger.

Diagnostic criteria from the International RLS Study Group and International RLS Severity Scale (Walters, 1995) were used. We also applied the Unified Parkinson's Disease Rating Scale (UPDRS) for the clinical evaluation of PD and Parkinson's Disease Questionnaire (PDQ-39) for the assessment of quality of life in PD patients (Peto et al., 1998).

81 patients with PD were examined in the age range of 40-70 years: 36 with RLS (RLS+) and 39-without RLS (RLS-). 30 age-match healthy individuals were included in the control group.

Statistical analysis was performed by using Statistica 7.0 software. The non-parametric Mann-Whitney U test was used to compare the differences between two independent groups. In order to measure the degree of association between two variables, we applied Spearman rank correlation. A p value <0.05 was considered significant.

CLINICAL QUESTIONS

Q: What is RLS?
A: Restless Leg Syndrome (RLS) is a chronic condition haracterized by sensory discomfort in legs, appearing or worsening during rest in the evening or nighttime, evoking the urge to move.

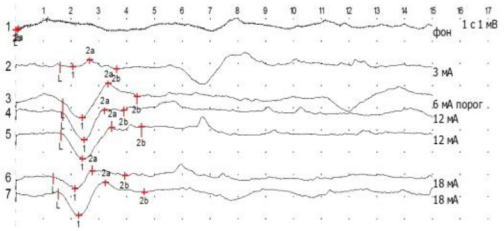
Q: What causes RLS in PD?
A: The pathophysiology is related to dopaminergic insufficiency and iron metabolism

TABLE 2. Comparative evaluation of SEPs parameters

SEP Parameters	Side	RLS+	RLS-	Control group
PL N20 (ms)	DSS	20.6 (20.1; 21.4)	20.45 (20; 20.9)	19.4 (18.8; 19.9) **
	OS	20.05 (19.7; 21.2)	20 (19.2; 20.8)	19.2 (18.5; 19.9) **
PL P 23 (ms)	DSS	23.8 (23.1; 24.65)	23.8 (23.5; 24)	22.5 (21.8; 22.8) **
	OS	23.6 (22.9; 24.5)	23.5 (22.7; 24)	22.4 (22; 22.7) **
PL N11 (ms)	DSS	11.75 (11.05; 13) *	12.6 (12; 13.1)	11.9 (11.5; 12.5)
	OS	12.2 (11.5; 13.4)	12.3 (11.8; 13.1)	11.9 (11.5; 12.6)
PL N13 (ms)	DSS	13.7 (13; 14.55)	14 (13.5; 14.6)	13.85 (13.4; 14)
	OS	13.9 (13.15; 14.8)	14.1 (13.6; 14.7)	13.6 (13.4; 13.8)
PL P8 (ms)	DSS	8.1 (7.4; 8.5)	8.46 (8.2; 8.64)	8.45 (7.84; 8.84)
	OS	7.93 (7.56; 8.57)	8.7 (8.1; 9.34)	8.3 (7.7; 8.7)
PL N9 (ms)	DSS	9.9 (9.38; 10.75)	10.3 (10.1; 10.85)	9.8 (9.1; 10.6)
	OS	10.1 (9.66; 10.7)	10.3 (9.9; 11.1)	9.7 (9.5; 10.9)
IPI N13-N20 (ms)	DSS	6.95 (6.35; 7.5) *	6.3 (5.7; 6.9)	6.1 (5.8; 6.4)
	OS	6.55 (6.05; 7.05) *	6.27 (5.58; 6.61)	6.25 (5.5; 7.3)
IPI N11-N13 (ms)	DSS	1.65 (1.35; 2) *	1.9 (1.66; 2)	1.8 (1.7; 1.9)
	OS	1.6 (1.3; 2)	1.8(1.6; 2)	1.5 (1.3; 1.8)
IPI N9-N20 (ms)	DSS	10.1 (9.53; 10.43)	10.3 (9.72; 10.7)	9.7 (9; 10.5)
	OS	10.1 (9.6; 10.8)	9.9 (9.57; 10.7)	9.75 (9; 10.4)
IPI N9-N13 (ms)	DSS	3.78 (3.42; 3.99) *	3.96 (3.8; 4.2)	4.3 (4; 4.7)
	OS	3.74 (3.4; 4.4)	3.8 (3.4; 4.3)	4 (3.7; 4.3)
A N20-P23 (mcV)	DSS	4.43 (3.32; 5.03) *	3.06 (2.4; 3.7)	3.15 (2.4; 4.3) **
	OS	4.12 (2.27; 4.87) *	2.88 (1.72; 4.3)	3.05 (1.95; 4.25)
A N13-P18 (mcV)	DSS	3.08 (2.36; 3.5) *	2.3 (1.33; 3.05)	2.35 (1.84; 3.29)
	OS	2.84 (2.36; 3.63) *	2.13 (1.63; 2.67)	2.22 (1.7; 3.15)
A P8-N9 (mcV)	DSS	4.57 (3.51; 5.87) *	3.5 (2.88; 4.6)	3.45 (2.4; 5.7)
	OS	3.87 (3.1; 5.21) *	3.13 (1.81; 4.2)	3.3 (2.8; 5.2)

DSS – Dominant side of symptoms in PD; OS – Opposite side.
* – Statistically significant difference ($p < 0.05$) between 1st and 2nd groups
** – Statistically significant difference ($p < 0.05$) between control and 2nd groups

A.



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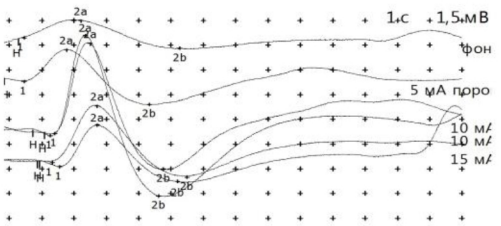

FIGURE 2. SSR recording with the main (**A**) negative component (N waveforms) and (**B**) positive (P waveforms).

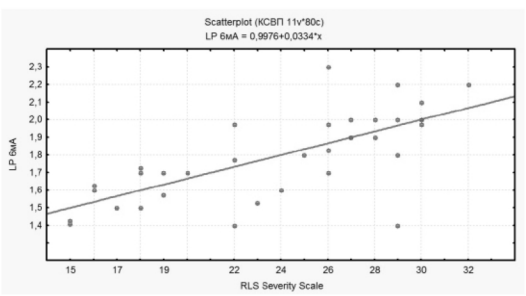

FIGURE 3. The correlation dependence between the SSR and the severity of RLS with electrical stimulation of 6mA

RESULTS

A comparison of data between PD patients with and without RLS are presented in Table 1. Based on their data, there was no significant difference in age and UPDRS scale. However, the duration of disease in group of patients with RLS was longer and their quality of life according to the PDQ-39 was significantly impaired ($p< 0.05$)

SEPS STUDY REVEALED:

In the RLS+, the PL of N11, IPI N9–N13, N11–N13 was significantly shorter and the IPI N13-N20 was longer as compared with the RLS- group.

A significant increase in the amplitudes N20-P23, N13-P18 and amplitude P8-N9 was observed in the RLS+ as compared with the RLS-, which can reflect sensitization processes at the level of spinal cord, brain stem and thalamocortical projections in patients with RLS.

Comparison between the control and the RLS- group revealed that in PD patients without RLS, PL N20, P23 was significantly longer and amplitude N20-P23 was lower than in healthy persons. SEPs findings are summarized in Table 2.

INVESTIGATION OF THE BR PARAMETERS:

Trend to hyperexcitability responses of BR was observed, which can reflect insufficiency of the inhibitory mechanisms at the segmental level and deficiency of supraspinal descending control in PD patients with RLS.

Figure 1 shows examples of hyperexitable and hypoexitable types of BR.

No significant differences were found between groups, when comparing OL and amplitude of the first BR component. In contrast, the OL of the second BR components (R2 ipsilateral and R2 contralateral) were shorter in PD patients with RLS in comparison to PD patients without RLS when stimulated DSS. The amplitudes of the second components in the RLS+ group were significantly higher than those in both the RLS- and the control groups (Table 3).

INVESTIGATION OF THE SSR:

SSR was mainly biphasic or rarely triphasic waves with different onset latency, amplitude and shape of the responses (Kucera *et al.*, 2004). Electrical stimulus with the intensity of 5 – 20 mA was applied to the median nerve. We used the amplitude and latency values of the response with the highest amplitude and shortest latency for evaluation. According to the shape and polarity of the waveform (Figure 2), the N-type of SSR with maximum negative deflection was recorded more frequently in PD patients without RLS (in 30 people (77.1%). The P-type with maximum positive deflection was revealed in 6 (15.3%). The absence of SSR to electrical stimulus with the intensity of 30 mA was observed in 3 patients (7.6%) and regarded as a sign of peripheral autonomic failure. In PD patients with RLS, P-type recording was observed in 17 (47%) cases, which is significantly more frequent than in the group of PD patients without RLS ($\chi^2 = 7.73$; $p = 0.005$).

Also consider endocrine pathology or iron deficiency

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Due to the variability of the SSR amplitudes, we conducted a comparative analysis of the SSR latency that was relatively stable and less dependent on the intensity of the electrical stimulus. In PD patients with RLS, the OL was significantly longer in comparison with PD patients without RLS (1,75 (1,6; 1,98)-ms – in the 1st group and 1,5 (1,3; 1,63)-ms – in the 2nd group, p = 0,0001). A strong positive correlation between the severity of RLS and latency was found in 1st group (R *Spearman* = 0,71; p = 0,00001) (Figure3).

DISCUSSION

An increase in the IPI N13-N20 of SEPs indicates a deceleration of the signal transmission along the thalamocortical projection in PD patients as compared to healthy people, which can reflect neurophysiological features characteristic of PD in general. We observed that patients with RLS had more prolonged IPI N13-N20, but at the same time a significant shortening of the IPI N9–N13, N11–N13 was revealed as compared with PD patients without RLS. This finding as well as an increase in amplitudes N20-P23, N13-P18 and P8-N9 can be a neurophysiological sign of sensitization processes at the level of spinal cord, brain stem and thalamocortical projections in PD patients with RLS.

A decrease in latency and an increase in the amplitude of second BR components, indicate an increase in polysynaptic reflex excitability in PD patients with RLS. The tendency to hyperexcitable BR responses is explained by insufficiency of inhibition mechanisms at the level of brainstem, spinal cord segment, and deficiency of supraspinal descending control in PD patients with RLS. This is probably one of the fundamental factors predisposing to voluntary and involuntary movements in the legs.

A significant increase of the SSR latency in PD patients with RLS was found. It can reflect the synaptic delay duration at the level of the brain and superior cervical ganglion. Although, the central parts of the SSR reflex arc are still incompletely known, the mesencephalic reticular formation, posterior hypothalamus, caudate nucleus, and others are considered the most important neural structures generating the reflex. Positive correlation between the severity of RLS and SSR latency indicates that the degree of RLS depends on the severity of functional disorders in the supraspinal autonomic centres. In PD patients with RLS, P waveforms type recording was observed more often, which can point out to the predominance of sympathetic influence on the SSR. It is known that A11 dopaminergic modulatory action on sympathetic preganglionic neurons in the IML are predominantly inhibitory and its absence would favour increased basal sympathetic tone (Clemens *et al.*, 2006, Braak *et al.*, 2007, Gladwell and Coote, 1999). But in fact, most PD patients without RLS tend to give the opposite N-type recording which indicated the predominance of parasympathetic influence on the SSR. Descending pathways from the A11 region also project to the dorsal raphe nucleus (Peyron *et al.*, 1995). The serotonergic dorsal raphe promotes cardiovascular and sympathetic activity, and it has, like the dopaminergic A11, prominent projections to the IML (Robinson *et al.*, 1985). In contrast to dopamine, its actions are strongly excitatory [6]. Insufficiency in this system leading to inhibitory effects on preganglionic sympathetic neurons can explain the predominance of parasympathetic activity in PD. In the case of RLS, there is probably a tendency to sympathetic activity due to the predominance of exciting supraspinal influence on the intermediolateral nuclei of the spinal cord.

CONCLUSIONS

A change in the complex interaction between the peripheral, spinal, and cerebral divisions of the nervous system was revealed in RLS. Identified somatosensory disturbances and changes in the brainstem and spinal reflexes may determine the clinical features of RLS in PD.

LIST OF ABBREVIATIONS

PD – Parkinson`s disease
RLS – Restless legs syndrome
SEPs – Short-latency somatosensory evoked potentials
BR – Blink Reflex
SSR – Sympathetic skin response
IML – Tractus Intermediolateral
UPDRS – Unified Parkinson's Disease Rating Scale
PDQ – Parkinson's Disease Questionnaire
A – Amplitude
IPI – Interpeak intervals
OL – Onset latency
PL – Peak-latency

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Clinical features of RLS in PD may lie in the complex interaction between the peripheral, spinal and cerebral divisions of the nervous system.