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CLINICAL STUDY

Restless legs syndrome in Parkinson's disease: relationship with quality of life and medication

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ABSTRACT

OBJECTIVES: We aimed to disclose the relationship between restless leg syndrome (RLS) and antiparkinsonian treatment, and its effect on quality of life (QoL) in patients with Parkinson's disease (PD).
BACKGROUND: Previous studies documented the prevalence of RLS among patients with PD to be higher than in the general population, but conclusions regarding the aetiology and impact were contradictory.
METHODS: We examined 101 patients with idiopathic PD. All participants completed the five-dimension/five-level-EuroQoL questionnaire (EQ-5D-5L) and the International Restless-Legs-syndrome-study-group rating Scale (IRLS).
RESULTS: The prevalence of RLS was 22.77 %. There were no statistically significant differences in levodopa or dopamine agonists (DA) doses between RLS-positive and negative participants. However, the use of levodopa as the last night-time medication was connected with a higher risk of RLS (OR=2.049, p=0.041). There was significantly lower prevalence of RLS in patients after surgical treatment for PD (p=0.024). Participants with RLS were at a greater risk for sleep disturbances (OR=3.866, p=0.023) and excessive daytime sleepiness (OR=7.202, p<0.001). Greater RLS symptoms were associated with worse QoL (higher IRLS score predicted higher EQ5D5L score, p=0.023).
CONCLUSION: RLS is prevalent among PD patients and night-time dopaminergic over-excitation with levodopa plays an important role in its pathogenesis. Since the symptoms of RLS are associated with decreased QoL, early accurate diagnosis and appropriate adjustment of dopaminergic therapy can lead to immediate relief from RLS symptoms and to QoL improvement *(Tab. 4, Fig. 1, Ref. 34)*. Text in PDF *www.elis.sk*
KEY WORDS: restless legs syndrome, Parkinson's disease, quality of life, aetiology, medication.

Introduction

The prevalence of restless legs syndrome (RLS) in the general population is approximately 7 %, and it increases with age (Allen et al, 2005). Studies have documented the prevalence of RLS among patients with Parkinson's disease (PD) is higher than the general population, ranging between 9.7 % and 24 %, depending on methodology; however, the authors reached contradictory conclusions regarding the aetiology and pathogenesis of RLS in patients with PD[2–] (Qu et al, 2019).

Some authors consider PD and idiopathic RLS to be separate entities (Zhu et al, 2015, Möller et al, 2010), while others found an association between RLS and dopaminergic or non-dopaminergic (Verbaan et al, 2010) features of PD, as well as antiparkinsonian treatment (Peralta et al, 2009a). However, the association between RLS and PD is still not fully understood. According to Ylikoski et al the prevalence of early onset RLS (before the age of 45) in patients with PD was not higher than observed in general population (Ylikoski et al, 2015). Similarly, Moccia et al (2016) revealed that the prevalence of RLS in patients with PD is comparable to the general population at the time of diagnosis, but increases over the course of PD. Thus, some factors connected with PD progression, including neurodegeneration or increasing amounts of antiparkinsonian treatment, may contribute to the rising incidence of RLS during the course of PD.

According to the results of Qu et al (2019), RLS severity among patients with PD was associated with PD duration but also with daily levodopa equivalent dose. Peralta et al (2009a) found a link between RLS symptoms and motor fluctuations, a complication of PD treatment. This suggests that dopaminergic medication may play a main role in the development of RLS in PD. Up to now, only total levodopa equivalent daily dose (LEDD) was taken into consideration. Previous studies documented contradictory results also in the field of the impact of deep brain stimulation (DBS) on RLS symptoms (Marques et al, 2015a, Zuzuárregui and Ostrem,

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2020). To our knowledge, there are no studies which have included patients with levodopa/carbidopa intestinal gel (LCIG).

The primary aim of our work was to examine the therapeutic regimen in PD more specifically as it relates to RLS, including the class of medication (levodopa versus dopamine agonists) and the timing of dosages. Additionally, we included patients treated with deep brain stimulation (DBS) and levodopa/carbidopa intestinal gel (LCIG).

The second aim was to characterize the impact of RLS severity on quality of life among patients with PD using five-dimension/ /five-level version of EuroQoL questionnaire (EQ-5D-5L) – a less PD-specific questionnaire assessing not only PD but also general health including comorbidities.

Materials and methods

Patients

We examined 101 consecutive patients who were diagnosed with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank criteria. The mean age of the sample was 66.88 ± 8.42 years (min 42.00, max 86.00) and 40 % of the participants were female. Mean PD duration was 9.21 ± 6.44 years (min 0.25, max 30.00) and median of Hoehn & Yahr (H&Y) stage was 3.0 (min 2.0, max 5.0, average 3.08 ± 0.72). A total of 28 participants previously underwent bilateral DBS (24 in subthalamic nucleus and 4 in internal pallidum), and 21 patients were on stable dose of levodopa/carbidopa intestinal gel LCIG.

Procedures

Informed consent was obtained in accordance with the Declaration of Helsinki and the local Ethics Committee (Derer´s University Hospital, Bratislava, Slovakia) approved the study protocol. Participants with mild cognitive impairment were included, provided informed written consent could be obtained, and they were able to complete questionnaires alone or with the help of their caregiver. We collected demographic and clinical data including age, gender, weight, PD duration, Hoehn & Yahr staging, and a current list of all medications. Levodopa equivalent daily dose (LEDD) was calculated according to previously established standards(Tomlinson et al, 2010).

Participants underwent an interview based on official RLS diagnostic criteria(Allen et al, 2014). Participants fulfilling all five criteria were categorized as RLS positive, and they continued with International Restless Legs Syndrome Study Group rating scale (IRLS) (Walters et al, 2003). It consists of 10 domains: legs discomfort, need to move, relief with moving, sleep disturbance, tiredness or sleepiness, overall severity, symptoms frequency, average day severity, daily affairs, and mood disturbance. Possible scoring for each domain is (4) very severe, (3) severe, (2) moderate, (1) mild, and (0) none. The clinical descriptions for IRLS scores include very severe (31–40 points), severe (21–30 points), moderate (11–20 points), mild (1–10 points), and none (0 points).

All of the participants completed the five-dimension/five-level version of EuroQoL questionnaire (EQ-5D-5L) (Herdman et al, 2011) to assess their QoL. The first part of the EQ-5D-5L includes five domains: mobility, self-care, usual activities, pain/ /discomfort, and anxiety/depression. Each domain score ranges between 0 and 4 points, and the total score ranges between 0 and 20 points. Higher numbers represent poorer QoL. The second part represents visual analogue scale (VAS) representing actual health state from 0 ('the worst health you can imagine') to 100 points ('the best health you can imagine').

Statistical analysis

The data were analysed with the IBM® SPSS Statistics 23 software. Descriptive statistics were used to evaluate demographic and clinical data. To compare RLS positive and RLS negative participants, individual variables were first tested with the Lilliefors test (modification of the Kolmogorov-Smirnov test). Data were compared by the Mann-Whitney U-test for non-parametric variables. For the Mann-Whitney test, effect size was given by the rank biserial correlation (0.0–0.3 – small effect, 0.3–0.5 – moderate effect, 0.5–1.0 – large effect). For correlation statistics, Spearman correlation coefficient for non-parametric variables was used. In the cross-sectional analysis, a binary logistic or linear regression model was used to estimate probability and 95 % confidence intervals (CI) for the risk factors potentially related to RLS.

Results

Prevalence of RLS

Among 101 participants with PD, 22.77 % (n = 23) reported current symptoms of RLS or being treated for RLS – these participants were categorized as RLS positive. Among the RLS positive participants, the average IRLS total score was 16.30 ± 11.94 (min 0.00, max 33.00). The mean intensity score was 1.95 ± 0.97 (min 0, max 3) and mean frequency score was 2.37 ± 1.42 (min 0, max 4) out of 4 possible points in both cases.

Fourteen participants (60.9 % of RLS positives) developed RLS after PD onset. There were no statistically significant differences in age, gender or PD duration between RLS positive and RLS negative participants (Tab. 1). Only one of the RLS positive participants (4.3 %) reported a family history of RLS. Hoehn & Yahr staging was significantly higher in RLS positive participants compared to RLS negative participants (3.3703 ± 0.786 versus 2.994 ± 0.677, p = 0.041). Patients with higher H&Y had a higher risk for RLS development (B = 0.130, 95 % CI: 0.026–0.308, p = 0.026).

Connection with PD treatment

There were no statistically significant differences in the dose of levodopa, dose of dopamine agonists (DA) or total levodopa equivalent daily dose (LEDD) between RLS positive and negative participants (Tab. 1). RLS positive participants were more likely to report levodopa as the last daily dose before bedtime (95.7 % versus 71.8 %, p = 0.017), whereas RLS negatives were prescribed dopamine agonists as the last medication of the day (28.2 % versus 4.3 %, p = 0.057). The use of levodopa as a last medication was connected with higher risk of RLS (OR = 2.049, 95% CI: 0.093–4.220, p = 0.041).

There was significantly lower prevalence of RLS in the STN-DBS group compared to patients with PD managed by medica-

Tab. 1. Clinical characteristics of participants with and without restless leg syndrome.

	RLS + (n=23)	RLS – (n=78)	*p*	effect size d
Gender (% female)	39.1	39.7	0.962	0.006
Age (years)	64.22 (8.99)	67.67 (8.14)	0.096	0.229
PD duration (years)	8.96 (5.66)	9.28 (6.68)	0.994	0.002
Hoehn & Yahr (average)	3.37 (0.79)	2.99 (0.68)	**0.041**	0.264
L-DOPA LEDD (mg)	1288.61 (776.95)	1003.73 (541.09)	0.104	0.224
DA LEDD (mg)	208.00 (192.81)	168.57 (182.07)	0.486	0.094
total LEDD (mg)	1579.48 (855.31)	1313.44 (616.21)	0.281	0.149

RLS – Restless legs syndrome, PD – Parkinson's disease, LEDD – levodopa equivalent daily dose, DA – dopamine agonists

Tab. 2. Clinical characteristics of participants with and without deep brain stimulation of the subthalamic nucleus.

	DBS + (n=24)	DBS – (n=21)	*p*	effect size d
RLS prevalence (%)	12.5	42.9	**0.024**	0.304
L-DOPA LEDD (mg)	707.25 (438.97)	1467.62 (563.40)	**<.001**	0.722
DA LEDD (mg)	215.41 (145.77)	117.76 (176.13)	**0.019**	0.401
total LEDD (mg)	1001.66 (532.79)	1680.38 (645.78)	**<.001**	0.601

RLS – Restless legs syndrome, PD – Parkinson's disease, LEDD – levodopa equivalent daily dose, DA – dopamine agonists

Tab. 3. Clinical characteristics of patients with and without Levodopa/Carbidopa Intestinal Gel.

	LCIG+ (n=21)	LCIG – (n=41)	*p*	effect size d
RLS prevalence (%)	38.1	14.6	**0.039**	0.235
L-DOPA LEDD (mg)	1558.52 (509.79)	957.93 (621.45)	**<.001**	0.584
DA LEDD (mg)	64.05 (134.38)	182.95 (174.46)	**0.004**	0.426
total LEDD (mg)	1657.38 (577.70)	1300.12 (719.85)	**0.040**	0.322

RLS – Restless legs syndrome, PD – Parkinson's disease, LEDD – levodopa equivalent daily dose, DA – dopamine agonists

Tab. 4. Health-related quality of life among patients with and without RLS.

	RLS + (n=23)	RLS – (n=78)	*p*	effect size d
Sleep disturbances (%)	82.6	55.1	0.018	–0.275
EDTS prevalence (%)	82.6	39.7	p<0.001	–0.429
EQ5D Total	8.57 (4.21)	5.96 (3.49)	**0.006**	–0.375
Mobility	2.13 (0.82)	1.68 (1.03)	0.060	–0.249
Self-care	1.74 (1.10)	1.03 (1.09)	**0.005**	–0.373
Activities	1.78 (1.17)	1.24 (1.10)	**0.041**	–0.268
Pain/Discomfort	1.70 (1.02)	1.26 (1.07)	0.064	–0.246
Anxiety/Depression	1.22 (1.00)	0.77 (0.76)	**0.050**	–0.254
EQ5D5L Health Status	58.70 (18.66)	64.99 (18.67)	0.172	0.185

RLS – Restless legs syndrome, EDTS – excessive daytime sleepiness, EQ5D – five dimension/five-level version of the EUROQoL questionnaire

tions when groups were matched by age, gender and PD-duration (12.5 % versus 42.9 %, p = 0.024). Patients with STN-DBS had significantly lower total and levodopa LEDD, and higher LEDD of dopamine agonists (Tab. 2). Patients with STN-DBS had a lower risk of developing RLS compared to matched patients with PD without this intervention (OR = 0.190, 95% CI 0.043–0.842, p = 0.029).

There was significantly higher prevalence of RLS in LCIG group compared to patients with PD matched by age, gender and PD-duration (38.1 % versus 16.7 %, p = 0.039). Patients with LCIG had significantly higher total and levodopa LEDD, and lower LEDD of dopamine agonists (Tab. 3). Patients with LCIG had higher risk for RLS development compared to matched patients with PD without a pump (OR = 3.590, 95% CI 1.004–12.345, p = 0.043).

Impact on sleep and quality of life

Participants with RLS had significantly higher prevalence of sleep disturbances (82.6 % versus 55.1 %, p = 0.018), excessive day-time sleepiness (82.6 % versus 39.7 %, p < 0.001), and higher total EQ-5D-5L score (8.57 ± 4.21 versus 5.96 ± 3.49, p = 0.006) than RLS negative participants. Furthermore, EQ-5D-5L sub-scores "self-care, activities of daily living and anxiety/depression were also significantly higher in RLS positive participants than RLS negative participants (Tab. 4).

Participants with RLS had higher risk for sleep disturbances (OR = 3.866, 95% CI: 1.204–12.414, p = 0.023) and EDTS (OR = 7.202, 95% CI: 2.236 – 23.197, p < 0.001) than participants without RLS. Among RLS positive participants, EQ-5D-5L total score and EQ-5D-5L health state were correlated with total IRLS score. Higher IRLS total score predicted poorer QoL, as measured by a higher EQ5D5L total score (B = 0.167, 95% CI: 0.026 – 0.308, p = 0.023), and worse health status (B = –0.766, 95% CI: –1.384–(–0.147), p = 0.018).

Discussion

Prevalence of RLS

Restless legs syndrome (RLS) is a disorder with a high prevalence accepted to be about 7 % in the general population(Allen et al, 2005). Its incidence increases with age, particularly after age 60, what is also the age of the highest prevalence of PD. Therefore, the co-occurrence of RLS and PD may be coincidental. Nevertheless, we disclosed the prevalence of RLS among patients with PD to be almost 23 % what is higher compared even to age-matched general population (Verbaan et al, 2010).

Impact on sleep and quality of life

There is some evidence of a connection between RLS and sleep dysfunction among patients with PD(Verbaan et al, 2010). In contrast, other studies have not revealed a higher prevalence of sleep disturbances (Loo and Tan, 2008) or diurnal hypersomnia(Gómez-Esteban et al, 2007) between PD patients with and without RLS. We disclosed significant impact of RLS on sleep in patients with PD. RLS positive participants were at

an almost four-times higher risk of sleep disturbances and more than seven-times higher risk of excessive daytime sleepiness than RLS negative participants.

Studies using PDQ-39 scale for quality of life (QoL) documented contradictory results (Gómez-Esteban et al, 2007, Zhang et al, 2020). We used EQ-5D-5L, which is less PD-specific questionnaire assessing also general health and comorbidities. In our cohort, participants with RLS reported significantly worse QoL, compared to those without RLS. Additionally, QoL impairment was associated with higher severity of RLS (according to the total IRLS score).

Connection with medication

We did not find a significant connection with RLS symptoms and daily equivalent dose of dopaminergic medication; however, the night-time use of levodopa was connected with a higher risk of RLS symptoms which are known to have circadian pattern with maximum intensity during evening and night. The timing and class of medication appear to play a role in RLS symptoms among patients with PD. Our findings are consistent with previous research that has shown the effects of dopaminergic treatment on RLS symptoms in PD (Marchesi et al, 2016, Peralta et al, 2009b). In terms of medication, low doses of dopaminergic treatment are used in the treatment of RLS symptoms. On the other hand, increasing the dosage of dopaminergic medication leads to augmentation, a well-known phenomenon of typical worsening and spreading of symptoms in RLS patients treated with high doses of dopaminergics. Whether dopaminergic medication leads to excitation or inhibition, depends on activation of either D1-like or D2-like dopaminergic receptors. This is dependent on concentration (Trantham-Davidson et al, 2004) and pulsatility of delivery (Dreyer et al, 2010) – lower doses of long-acting DA preferably stimulate D2-subtype (inhibition of RLS symptoms), and higher doses of short-acting levodopa have higher affinity to D1-subtype (excitation, worsening of the symptoms). As a result, night-time dopaminergic overload (hyperexcitation) by levodopa might lead to RLS development in these patients with PD.

The negative impact of levodopa on sleep quality has been established (Junho et al, 2018). This effect can be strengthened also by the fact, that our patients on LCIG (obtaining relatively higher doses of pure levodopa) had increased prevalence and higher risk for RLS. Patients who had previously undergone STN DBS had a lower prevalence of RLS compared to matched patients with PD on conventional peroral medication. We found out that patients with DBS had significantly higher doses of dopamine agonists and lower doses of levodopa. Interestingly, some of the studies examining the effects of DBS on RLS have also found effects of change in dopaminergic medication dose in decreasing RLS symptoms (Driver-Dunckley et al, 2006, Marques et al, 2015b). Still, STN-DBS was an independent factor decreasing the risk for RLS development in our cohort. Although Zuzuárregui et al (Zuzuárregui and Ostrem, 2020) proved that STN DBS appears to help reduce RLS severity, the true impact of neurostimulation on RLS must be confirmed in prospective well-deigned studies. Our study is limited by the cross-sectional design and future studies should examine changes in RLS symptoms frequency and/or intensity before and after the invasive intervention (DBS, LCIG pump). Nevertheless, our results suggest that a considerable part of PD patients may experience RLS symptoms due to antiparkinsonian medication. In the study of Li et al (2019), RLS positive patients with PD showed functional abnormalities in sensorimotor network disrupting the lateral pain pathway, what might be an anatomical localization connected with D1-receptors overstimulation and onset of RLS symptoms in PD.

Other possible aetiologies and pathogenesis

Unlike the general population, the prevalence of RLS in our sample did not correlate with age, but rather with PD severity according to the Hoehn &Yahr (H&Y) staging. This is an important point, because H&Y staging reflects the level of neurodegeneration, overall disability (both motor and non-motor) and type and dose of antiparkinsonian medication. Individuals in more advanced stages of PD are at a higher risk of developing RLS symptoms than those in earlier stages of the disease process. This may suggest that process of neurodegeneration is somehow linked to RLS onset. However, this does not appear to involve the nigrostriatal system, as there were no significant differences in substantia nigra echogenicity between the PD patients with or without RLS (Kwon et al, 2010, Ryu et al, 2011) and no common characteristics between RLS patients and patients with early PD detectable by dopamine transporter SPECT(Linke et al, 2004). It is possible that propagation of Lewy body pathology according to the Braak's theory could involve also diencephalospinal system (A11 neurons), which is hypothesized to be responsible for RLS symptoms. Modification of Braak's theory distinguishes different ways of spreading of synuclein in the brain. One of them – brainstem type – is connected with sleep disturbances as well as vegetative dysfunction (Marras and Chaudhuri, 2016). According to Oh et al RLS is related to dysautonomia (nocturnal/supine hypertension and blood pressure fluctuations), suggesting a neuropathological association between autonomic and sleep dysfunctions in patients with PD, along with possible anatomical proximity (Oh et al, 2014).

Interestingly, previous studies have reported that there are differences between patients with idiopathic RLS and RLS co-occurring with PD. Among PD patients with RLS, they have higher age of symptoms onset, less positive family history, or more unilaterality of leg restlessness (Zhu et al, 2015). In addition, these patients have smaller periodic limb movements index measured by polysomnography (Nomura et al, 2006). According to the work of Ylikoski et al the prevalence of early onset RLS in patients with PD (before age of 45 years) was not higher than observed in general population (Ylikoski et al, 2015). As result, there could be more than one type of RLS in patients with PD – idiopathic and the one linked to PD.

It is possible that patients with PD may experience also coincidental *secondary* RLS related to iron deficiency, end stage renal disease, thyroid gland disorders, or neuropathies – as observed in the general population. However, Guerreiro et al did not find significant differences in levels of hemoglobin, serum iron, ferritin or creatinine between PD patients with and without RLS (Guerreiro et al, 2010). Neuropathies are not usually assessed, as patients with such conditions are excluded from epidemiological studies to avoid

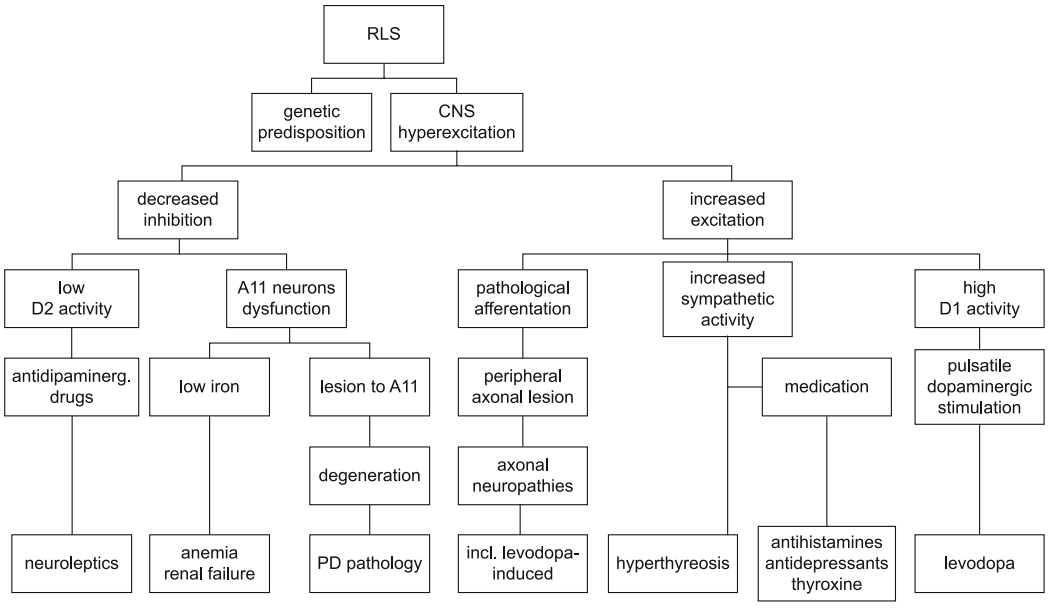

Fig. 1. Probable aetiology and pathogenesis of RLS in PD. RLS – restless legs syndrome, D1, D2 – dopamine receptors type 1 and 2, A11 – dopaminergic neurons of diencephalospinal system, PD – Parkinson's disease.

RLS mimics. But this may misrepresent the true prevalence of RLS, as any patient with neuropathy could meet all diagnostic criteria for RLS (and, thus, have this syndrome). This is further confounded by evidence that prevalence of neuropathies is higher in patients with PD, especially in those treated with levodopa (Mancini et al, 2014), what also contributes to RLS occurrence. Thyroid gland disorders have not been found to be more prevalent in PD compared to general population, but are often overlooked because the symptoms may overlap with PD symptoms (Bonuccelli et al, 1999). All these conditions could lead to RLS in predisposed patients with PD.

Previous research confirmed that use of antidepressants, neuroleptics and/or antihistamines is connected with higher risk for RLS development. In our study, we did not look at the other treatments, but having many comorbidities, patients with PD are frequent users of these medications (Hening 2003). These results suggest that a considerable part of patients with PD may experience RLS symptoms due to medication.

Conclusion

Our results demonstrated RLS is prevalent among PD patients and the symptoms of RLS are associated with a considerable decrease in QoL. However, RLS may be underdiagnosed in patients with PD due to the fact that the symptoms wane among other frequent and severe sensorimotor symptoms of PD. We documented that a remarkable part of cases is related to night-time dopaminergic excitation by levodopa. This has implications for clinical practice, as early and accurate diagnosis of RLS and appropriate adjustment of dopaminergic therapy can lead to immediate relief from RLS symptoms and better health-related quality of life. The aetiology is, however, much more complex. Restless legs syndrome is a multifactorial disease, with some level of genetic predisposition and different environmental factors. To develop symptoms, also patients with PD *must* have genetic predisposition for RLS. If this is strong enough, they will develop coincident "idiopathic" RLS, even before PD onset. In moderate genetic load for RLS, maybe only night-time dopaminergic overstimulation is enough to cause onset of RLS symptoms. Having weak predisposition, patients need to have more provoking factors – including RLS-inducing medication, neuropathy, iron deficiency, renal or thyroid gland disease. Figure 1 summarizes the proposed probable aetiology and pathogenesis of RLS.

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