Parkinsonism and Related Disorders 20S1 (2014) S5–S9

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Restless legs syndrome in Parkinson's disease

Roselyne M. Rijsman *, Louise F. Schoolderman, Rob S. Rundervoort, Maartje Louter

Center of Sleep and Wake Disorders and Department of Neurology, Medical Center Haaglanden, The Hague, The Netherlands

ARTICLE INFO

Keywords:
Restless legs syndrome
RLS
Parkinson's disease
PD
prevalence
mimics
sleep
profile
impact
quality of life

SUMMARY

The Restless legs syndrome (RLS) and Parkinson's disease (PD) are two disorders that can co-exist, whether or not they share a common pathophysiology. If, and to what extent RLS and PD share the same pathophysiology, is still under debate. Sleep disturbances are prevalent in PD, and as PD progresses, nocturnal disturbances become even more evident, in association not only with motor symptoms but also with non-motor symptoms. Alertness to, and recognition of, RLS in PD patients with sleep disorders could improve customized treatment and quality of life of these patients. In this article the prevalence of RLS in PD, the clinical profile of RLS in PD, the PD profile of patients with RLS, RLS mimics specifically related to PD and impact of RLS in PD will be reviewed.

1. Introduction

Restless legs syndrome (RLS) is a common neurological disorder, with an estimated prevalence of 4–10% in the general population. Although the precise pathophysiology remains unknown, it is assumed that dopaminergic mechanisms play a central role. In the past few years, several studies have been done which suggest an association between RLS and Parkinson's disease (PD). Both RLS and PD respond to dopaminergic treatment, making the assumption of a common pathophysiology, and therefore an association between the two disorders, fairly plausible [1,2]. The RLS symptoms seem to result from an abnormal sensorimotor integration, due to dysinhibition at the spinal level which, in turn, results from reduced inhibitory mechanisms at the supraspinal level. The descending supraspinal diencephalospinal dopaminergic neurons, originating in the hypothalamus (A11), are proposed to play an important role in the pathophysiology of RLS. It is postulated that, in the course of the PD disease, these neurons degenerate, along with nigrostriatal neurons, leading to the development of RLS, and, therefore, to a higher prevalence of RLS among PD patients. But shared pathophysiology is still under debate [1,2]. Unlike in the case of PD, no neuronal degeneration or Lewy body deposition has ever been recognized in RLS post-mortem studies. Furthermore, until now, no shared disease loci have been identified. Except for the provocation of both RLS and PD by neuroleptics, and possibly lower ferritin levels in PD patients with RLS, the secondary forms of PD and RLS do not form an argument for a common pathophysiology [2].

Even though the relationship between RLS and PD is still controversial, RLS has revealed itself to be co-existing with PD. Sleep disturbances are prevalent in PD, and as PD progresses, nocturnal disturbances become even more evident, in association not only with motor symptoms but also with non-motor symptoms. Thus, alertness to, and recognition of, RLS in PD patients with sleep disorders could improve customized treatment and quality of life of these patients. That is why, in this article, we will specifically look at studies on the prevalence and on the clinical profile of RLS in PD, as well as on the impact that RLS has on PD patients.

2. Prevalence of RLS in PD

Good comparisons of the different estimates of RLS prevalence in PD studies are rather difficult due to variations in methodology, and so, definite generalisations are hard to make.

In total, 18 cross-sectional studies on the prevalence of RLS in PD, published in English, were found [3–20]. In all these studies, the international IRLSSG essential criteria for the diagnosis of RLS were used, but some studies used the criteria of 1995, whereas other (more recent) studies used the revised IRLSG diagnostic criteria of 2003. The methodology, however, for the assessment of these criteria in the subjects was not identical in all studies. In addition, the background of the interviewers varied from study to study, which might influence, of course, the focus, the wording and the interpretation of the RLS histories that were collected. In most studies, the definite diagnosis of RLS was based only on the constellation of the four minimal IRLSSG criteria, but in some other studies, thresholds on severity, frequency, and on the impact on quality of life were included. From a purely epidemiological and pathophysiological point of view, the former procedure may be

* Corresponding author. Medical Center Haaglanden, Center for Sleep and Wake Disorders, Lijnbaan 32, 2501 CK The Hague, The Netherlands

1353-8020/$ – see front matter

regarded defensible and thoughtful, but from a clinical point of view, inclusion of the threshold criteria could obviously help to better define PD patients who actually need treatment for RLS.

The appearance of secondary RLS is usually related with a late onset of RLS (above 45 years of age). As a result, there may be more secondary forms of RLS in PD cohorts, besides purely PD-related RLS, simply because PD is also a disease that becomes more frequent with age. Some studies, therefore, deliberately excluded these secondary forms of RLS from their data [3,16], to avoid confusion with this age-related variable in their assessment of the true relation between RLS and PD. From a clinical point of view, one may question whether such an exclusion of these 'secondary' forms of RLS from the investigation of the co-morbidity of any sort of RLS in PD is appropriate, because, in doing this, we can obviously not assess their impact and, by implication, also not their possible implications for therapeutic intervention.

There was also variation in the size and composition of the PD cohorts, and in the way they were treated. And last but not least, a few studies excluded PD-specific RLS mimics, such as motor symptoms, akathisia, non-motor symptoms, as pain, and other sensory symptoms, motor fluctuation, such as dystonia, and non-motor fluctuation symptoms, even though the possible overlap of these symptoms with 'true' RLS has been discussed explicitly by some authors.

The prevalence of RLS in the 18 PD cohorts varied from 0% to 50%. Two of the studies were performed in Latin America; the one from Brazil showed a very high PD-related RLS prevalence of 50%, whereas the other one found 18.8% [5,10]. Eight of the 18 studies were performed in Asian countries, with PD-related RLS prevalence from 0.98% to 16% [4,11–14,17,19,21]. The PD-related RLS prevalence in Western countries was generally higher than those in the Asian countries, namely from 5.5% to 27% in Europe [3,6,8,9,16,18,20], and 20.8% in the USA [15]. Also, the prevalence of RLS in the 'general population' is typically lower in Asian countries than in European and North American ones, namely from 0.9% to 12.1% in Asia, against from 3.9% to 18.8% in Europe and the USA [22]. In addition, the correlation with age is clearly different in these two continents: in Asia it does not seem to go up with age, whereas in Europe and the USA, the RLS prevalence in the general population is found to double every 20 years, with a peak at the age of 65 [22]. Since the mean age of all the PD cohorts in which RLS prevalence was examined was at least 59, we may say that the factor age was probably a less confounding factor for the assessment of RLS prevalence in the Asian PD cohorts than in the non-Asian ones.

To show a real association between RLS and PD, one should find a significant increase of RLS prevalence in the PD cohorts relative to that in the general population. Seven of the 18 studies [3,6,8,13,17,19,20] did not find such a significant increase and did not support the hypothesis of a similar pathophysiology between RLS and PD. The actual percentages of RLS in these negative studies were between 0% and 5.5% in the Asian countries, and between 5.5% and 12.7% in the Western countries.

The majority of all the RLS-prevalence studies in PD were done on patient groups with relatively advanced forms of disease, treated which dopaminergic medication. So there was a serious risk of including RLS confounders and secondary forms of RLS, stemming from other causes, in the assessment. Lee and colleagues mention a prevalence of RLS, not different from that in the general population, in only one subgroup of patients who were not given dopamine medication, and who were still in an early stage of PD [12]. After multivariate analysis of the total PD cohort, only duration of dopaminergic treatment appeared to be a variable that correlated significantly with the presence of RLS. Their conclusion was that RLS in PD is associated with long-term dopaminergic treatment, rather than with PD itself. In 2011, two RLS-prevalence studies were performed in a cohort with only de novo and dopaminergic naive PD patients. Angelini and colleagues [3] found that RLS prevalence in their dopamine-free PD cohort (5.5%) was not significantly different from that in their control group (2.3%), and concluded that RLS is not really related to PD pathophysiology. The question whether an increase in risk of co-morbidity of RLS with the progression of PD is a result of dopaminergic neuron degeneration, or of dopaminergic treatment, is not answered by this study. Gjerstadt et al. [8] performed a case–control study in an early-phase and dopamine un-medicated PD cohort of 200 patients. Patients who had an urge to move their legs according to the Johns Hopkins diagnostic interview for RLS were categorized as 'true' RLS if they fulfilled the four essential IRLSSG criteria, and as 'Leg Movement Restlessness' (LMR) if they did not fulfil all four IRLSSG criteria. They found similar RLS prevalence in PD patients and controls. But they demonstrated that LMR grows to almost to a 3-fold higher risk in early PD, as weighted against controls. The authors speculated if RLS and akathisia (as one of the possible interpretations of LMR) may represent overlapping features within the same spectrum of motor restlessness in PD. Suzuki et al. [17] found significantly higher nocturnal restlessness (and not RLS), as measured by the Parkinson disease sleepiness scale (PDSS) sub-items 4 and 5, in PD compared to controls. This nocturnal restlessness was associated with the PDSS total score, but not with disease severity and treatment duration, or total levo-dopa equivalent (LDE) dose. The nocturnal restlessness was therefore interpreted as being the result of an endogenous dopamine deficit during night-time, rather than as a motor complication (i.e., wearing off phenomenon) due to dopaminergic treatment which can mimic RLS.

By contrast, however, ten studies [4,5,9–12,14–17], did find higher RLS frequencies in PD, and, thus, support the hypothesis that RLS is part of the symptomatic profile of PD, and not just an incidental co-occurrence of RLS in PD. RLS prevalence in these ten studies varied from 7.9% to 16% in the Asian countries, against from 20.8% to 27% in the European countries, and from 19.9% to 50% in the South-American countries.

3. Clinical profile of RLS in PD

3.1. Comparison of PD with and without RLS: risk factor in PD?

All but one [5] of the prevalence studies considered in this article have to some extent compared the PD profile of patients with RLS with that of patients without RLS. Several, although not necessarily consistent, significant differences between the two groups were found. Again, since the studies differ in methodology, as well as in composition of PD cohorts, it is not justified to draw definite conclusions. The following is an overview of the major results.

Onset of RLS in relation to onset of PD was evaluated in several studies [11,13–16,20]. In all of them, a clear majority of patients (76–100%) showed an onset of RLS only after, or together with the onset of PD. Ondo et al. [15] found that, for PD patients with a positive ***RLS family history***, the RLS onset preceded the PD onset more often (52%) than for PD patients without a positive RLS family history (29%). Given such a result, one might be inclined to say that RLS without a positive family history is more consistent with the 'secondary' forms of RLS in PD, but these results could not be replicated in later studies [20].

Though ***lateralization of RLS*** is found to be rather high in the PD population (range 35–70%), no correlations were found between side of PD onset and dominant side of the RLS symptoms [4,11,14] which immediately counters the suggestion, of course, that RLS in PD is related to the degeneration of the dopaminergic neurons in the substantia nigra.

The ***mean severity of RLS***, expressed in terms of the international RLS severity scale (IRLSS), varied from 11.9±6.3 to 21.3±6.3,