

Epidemiology, impact, and treatment options of restless legs syndrome in end-stage renal disease patients: an evidence-based review

Christoforos D. Giannaki^{1,2}, Georgios M. Hadjigeorgiou³, Christina Karatzaferi^{2,4}, Marios C. Pantzaris⁵, Ioannis Stefanidis⁶ and Giorgos K. Sakkas^{2,4,6}

¹Department of Life and Health Sciences, University of Nicosia, Nicosia, Cyprus; ²Institute of Research and Technology Thessaly, Centre for Research and Technology Hellas, LIVE Lab, Thessaly, Greece; ³Department of Neurology, Faculty of Medicine, University of Thessaly, Larissa, Greece; ⁴Department of PE and Sport Science, University of Thessaly, Trikala, Greece; ⁵The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus and ⁶Department of Nephrology, Faculty of Medicine, University of Thessaly, Larissa, Greece

Restless legs syndrome (RLS) (or Willis-Ekbom disease) is a neurological disorder with high prevalence among the end-stage renal disease population. This is one of the most predominant types of secondary RLS, and it is called uremic RLS. Despite the fact that uremic RLS has been less studied compared to idiopathic RLS, recent studies now shed light in many aspects of the syndrome including clinical characteristics, impact, epidemiology, and treatment options. The current review discusses the above topics with special emphasis given on the management of uremic RLS, including the management of symptoms that often appear during a hemodialysis session. Uremic RLS symptoms may be ameliorated by using pharmacological and nonpharmacological treatments. Evidence so far shows that both approaches may be effective in terms of reducing the RLS symptom's severity; nevertheless, more research is needed on the efficiency of treatments for uremic RLS.

Kidney International advance online publication, 9 October 2013;
doi:10.1038/ki.2013.394

KEYWORDS: dopamine agonists; exercise; hemodialysis; quality of life; secondary RLS; sleep disorders

During the past two decades, the scientific interest regarding restless legs syndrome (RLS) has significantly grown while, continuously, new evidence related to the clinical significance of this syndrome is coming to light. RLS is very common among the end-stage renal disease (ESRD) population.¹ This type of secondary RLS, called uremic RLS, appears to provoke further impairments in the already diminished quality of life (QoL) and health status of the uremic patients.²

WHAT IS UREMIC RLS?

Terminology

RLS (also known as Willis-Ekbom disease) is a sensorimotor neurological disorder characterized by an urgent need to move the limbs, which is usually accompanied by unpleasant sensations. This disorder mainly affects the lower body, but there are cases where patients also complained of upper body discomfort.³ The symptoms begin or worsen during periods of rest and inactivity (usually at night), resulting in a significant sleep disturbance. RLS is a disorder with both primary (idiopathic) and secondary causation, with the latter including ESRD, resulting in the diagnosis of uremic RLS.

Prevalence

The prevalence of uremic RLS in the ESRD population is significantly higher than in the general population. When the International RLS Study Group (IRLSSG) questionnaire was used as the main diagnostic tool, the prevalence reached approximately 30% of the ESRD population (range 7–45%).^{1,2,4}

Pathophysiology of uremic RLS

The precise pathogenic mechanisms responsible for uremic RLS are still unknown. According to the most widely accepted hypothesis for idiopathic RLS, a dysfunction of the dopaminergic system and reduced iron stores in specific regions in the brain are implicated.^{5,6} Studies reporting that treatment with dopamine agonists have been beneficial to uremic RLS patients⁷ indicated that dopaminergic dysfunction may be implicated in the pathophysiology of uremic

Correspondence: Giorgos K. Sakkas, Institute of Research and Technology Thessaly, Centre for Research and Technology Hellas, LIVE Lab, Trikala, Thessaly, Greece. E-mail: gsakkas@med.uth.gr

Received 20 May 2013; revised 30 July 2013; accepted 15 August 2013

RLS as well. Moreover, calcium/phosphate imbalance is also reported to be involved in the pathophysiology of uremic RLS.^{8,9} Finally, in a recent study by Marconi and co-workers,¹⁰ subclinical peripheral nerve abnormalities were present in the majority of the uremic RLS patients, in contrast to the idiopathic ones, indicating a potential role of damaged peripheral nerves in the pathophysiology of uremic RLS. However, we should note that other studies did not confirm the association between peripheral neuropathy and uremic RLS.¹¹ Still, it is noteworthy to mention that for the majority of uremic RLS sufferers the symptoms disappear after kidney transplantation,¹² a fact that points to an involvement of uremic toxicity in the pathogenesis of RLS in the ESRD patients.

In contrast to idiopathic RLS, the familial component is significantly lower in uremic RLS. Winkelmann *et al.*¹³ classify cases as being 'definite positive' hereditary in 42.3% of the idiopathic RLS patients, but only in 11.7% of the uremic RLS patients.¹³ In a more recent study by members of this and our groups,⁴ the *BTBD9* gene was found to be significantly associated with RLS in ESRD patients from Germany and Greece, showing a genetic contribution to susceptibility in ESRD. It is evident that more studies covering various regions worldwide are needed in order to explore in more depth the issue of genetic influence on uremic RLS.

RLS symptoms during the hemodialysis session

Uremic RLS patients may experience both sensory^{11,14} and motor¹⁵ symptoms during a hemodialysis (HD) session. Because of that, approximately 20% of HD patients reported a premature discontinuation of their therapy owing to the presence of RLS symptoms.¹⁶ A possible explanation for the above phenomenon may lie in the procedure of the HD therapy itself, during which patients are instructed to avoid movement for 3–4 h. As RLS symptoms begin or worsen during inactivity periods such as lying down or sitting, the HD procedure *per se* provides one of the main triggers of RLS, that is, inactivity.

FACTORS AFFECTING RLS STATUS AND SEVERITY

Factors affecting RLS status and severity include hypertension,¹⁴ female gender,^{11,14,17} increased body weight, and dialysis vintage.¹⁸ In addition, age and diabetes mellitus were associated with the severity of RLS symptoms in an epidemiological study by Unruh and co-workers¹⁹ in a sample of 894 HD patients.¹⁹

The association between HD modality, adequacy, time of delivery of the HD session, and RLS severity remains controversial. In a recent multicenter study by Jabera and co-workers,²⁰ short home-HD sessions (six sessions per week) resulted both in significant improvements in RLS symptoms' severity score and reductions of sleep disturbances. However, we should note that the percentage of patients who were prescribed RLS-related medication did not significantly change. Inadequate dialysis has been reported to be related to the presence and the severity of uremic RLS.²¹ However, we

should note that no significant differences in dialysis adequacy were noted in studies comparing uremic RLS HD patients with RLS-free HD patients.^{2,11,17} Moreover, in the same or other studies, no associations were reported between RLS and biochemical indices of dialysis adequacy, such as urea and creatinine levels.^{2,8,9} Interestingly, receiving the HD treatment later during the day was independently associated with an increased risk of reporting RLS symptoms.²² Merlino *et al.*,¹¹ in a perhaps inadequately powered study comparing HD and continuous ambulatory peritoneal dialysis, observed that both the frequency (3.0 ± 0.0 vs. 2.8 ± 0.3 sessions per week) and the duration (4.0 ± 0.5 vs. 3.8 ± 0.4 h per session) of HD sessions were significantly higher in the uremic RLS patients compared with their RLS-free counterparts.¹¹ Finally, in a very recent multicenter study by Lin and co-workers,²³ longer duration of HD dependence (i.e. years in HD) was associated with RLS prevalence and correlated with its severity, confirming previous data by Gigli *et al.*²⁴

DIAGNOSIS OF UREMIC RLS

For idiopathic and secondary forms of RLS alike, the four essential diagnostic criteria of RLS, developed by the IRLSSG,³ are considered the gold standard diagnostic tool for the diagnosis of the syndrome (see Table 1). The diagnosis is mainly based on an interview with the patient that includes various questions based on the four diagnostic criteria (Table 2). The clinician should be aware that RLS is positively

Table 1 | Diagnostic criteria of RLS according to the International Restless Legs Syndrome Study Group³

Essential criteria

Restless legs syndrome is defined by the presence of the following four essential clinical criteria

1. An urge to move the legs, usually accompanied or caused by uncomfortable or unpleasant sensations in the legs
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
3. The urge to move or unpleasant sensations are partially or totally relieved by movement such as walking or stretching, at least as long as the activity continues
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or occur only in the evening or night

Note: The occurrence of the RLS symptoms should not be solely accounted for by another condition

Supportive criteria

Supportive clinical features that can help resolve any diagnostic uncertainty

1. Positive family history of restless legs syndrome
2. Response to dopaminergic drugs
3. Periodic limb movements during sleep or wakefulness

Associated features of RLS

Significant clinical features that have been identified as being associated with the restless legs syndrome

1. The natural clinical course of the disorder is in general chronic and progressive
2. Significant sleep disturbance induced by restless legs syndrome
3. Medical evaluation and physical examination (mainly used for idiopathic patients and not for secondary restless legs syndrome patients)

Download English Version:

<https://daneshyari.com/en/article/6163583>

Download Persian Version:

<https://daneshyari.com/article/6163583>

[Daneshyari.com](https://daneshyari.com)