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Review Article

Restless leg syndrome in chronic kidney disease

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ABSTRACT

Restless Leg Syndrome and Periodic Limb Movements (RLS/PLM) are a common form of sleep disturbance in Chronic Kidney Disease (CKD) patients. The pathophysiology is related to the iron deficiency, anemia of renal disease, uremic toxin accumulation resulting in encephalopathy and peripheral neuropathy. Diagnosis of the condition is made by clinical criteria and rarely polysomnography. RLS/PLM is associated with poor quality of life and increased morbidity and mortality in CKD. Therapeutic approaches include non-pharmacologic, pharmacologic and specific interventions for CKD patients.

1. Background

Chronic Kidney disease (CKD) patients often have sleep disorders, which may be under recognized. These disorders are present in all stages of CKD and include insomnia, excessive sleepiness, sleep apnea, restless legs syndrome and periodic limb movement disorder. This review focuses on restless legs syndrome (RLS) and periodic limb movement (PLM) disorder in CKD patients.

1.1. *Definition of RLS*

The criteria for the diagnosis of RLS were initially proposed by the International Restless Legs Study Group in 2003 and modified in 2012.[1,2] The five essential diagnostic criteria and three additional supportive criteria are summarized in Table 1.

1.2. *Epidemiology*

RLS has been found to be present in 14–23% of patients on maintenance hemodialysis (CKD 5HD)[3] and 20–57% among other CKD patients.[4] The prevalence of PLM is greater than 50% in the CKD 5HD and Peritoneal Dialysis (CKD 5PD) population associated with sleep onset and sleep maintenance insomnia.[5–8]

1.3. *Etiopathogenesis*

The pathophysiology of RLS/PLM in patients with CKD is not entirely understood. One of the risk factors attributed is anemia and iron deficiency. The treatment of anemia by or intravenous iron and/or erythropoietin was associated with a significant improvement in RLS and PLM. Other factors which cause RLS/PLM are the elevated serum calcium and other uremic toxins. The presence of peripheral neuropathy due to uremic polyneuropathy and the primary etiology of the CKD

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Table 1 – Diagnostic criteria for RLS.

Diagnostic criteria	1	An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. Sometimes the urge to move is present without the uncomfortable sensations, and sometimes the arms or other body parts are involved in addition to 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 only occur in the evening or night. When symptoms are severe, the worsening at night may not be noticeable but must have been previously present.
	5	Symptoms are not solely accounted for by another medical or behavioral condition, such as leg cramps or habitual foot tapping.
Supportive criteria	1	A family history of RLS.
	2	A positive response to dopaminergic drugs.
	3	Periodic limb movements during wakefulness or sleep as assessed with polysomnography or leg activity devices.

such as diabetes also contribute to RLS/PLM. The central nervous system abnormalities due to the uremic milieu and the alteration of dopamine and opioid pathways in the nervous system may result in RLS/PLM.[9]

1.4. *Clinical features*

Patients with PLM disorder have involuntary jerking movement of the legs (and occasionally the arms) during sleep.[10,11] Patients may report nocturnal awakenings associated with legs movements or, more commonly, rely on their bed partner to report them. Although both syndromes may present in the general population, RLS appears to progress more rapidly, is more severe, and is less responsive to dopaminergic medications among ESRD patients.[2]

1.5. *Diagnosis*

RLS is diagnosed based on clinical criteria as in Table 1 above. Polysomnography in a sleep laboratory is usually not necessary for the diagnosis but it may be helpful, especially when RLS is resistant to treatment, in order to exclude other causes of poor sleep.[12]

PLM disorder is often diagnosed based on the finding of periodic, involuntary movements of the legs during polysomnography. In order to determine whether PLM are responsible for complaints of sleep disruption, a trial of pharmacologic therapy may be required.[13]

1.6. *Prognosis*

RLS is associated with difficulty initiating sleep, poor sleep quality, and impaired health related quality of life.[3,4,12,14] RLS has also been associated with depression in a cohort of patients with CKD.[15] RLS and PLM are associated with increased mortality among end stage renal disease (ESRD) patients and transplant recipients.[4,12,16,17] In a carefully characterized cohort of stable kidney transplant recipients, PLM was associated with increased cardiovascular risk, assessed by the Framingham Score.[18] The mechanisms underlying the increased mortality are not known. Poor compliance with therapy, depression, and the psychological and hemodynamic consequences of recurrent sleep disruption may be the factors responsible for the increased mortality associated with RLS/PLM in CKD.[19–21]

2. Treatment

Most pharmacologic and nonpharmacologic therapies for RLS are the same among CKD patients as in the general population. Specific measures in CKD patients are described below.

2.1. *Nonpharmacologic therapy*

In patients with mild symptoms, nonpharmacologic therapies may be sufficient for symptom relief. In patients with more severe symptoms, nonpharmacologic measures are worth reviewing, as they may limit medication requirements. Use of these interventions is supported primarily on the basis of clinical experience and in some cases small randomized studies.[22,23]

- Mental alerting activities at times of rest or boredom
- Avoidance of aggravating factors:
  - ➢ Sleep deprivation is known to aggravate symptoms of RLS in many patients, and general principles of sleep hygiene should be reviewed.
  - ➢ Antidepressants, neuroleptic agents, dopamine-blocking antiemetics such as metoclopramide, or sedating antihistamines (including those found in nonprescription medications) may contribute to emergence of RLS or worsening of prior symptoms.[24] Withdrawal of these drugs however may result in patient harm. If antidepressants are necessary, the symptoms of secondary RLS can usually be treated in the same way as primary RLS. Bupropion is an alternative antidepressant that may be less likely to induce or worsen RLS.[25]
  - ➢ Tramadol, which is sometimes used to treat RLS symptoms, has also been reported to induce or exacerbate RLS symptoms in some patients.[24]