Restless Legs Syndrome Among the Elderly

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SUMMARY

Restless legs syndrome is a sleep and movement disorder that affects 5–15% of the general population, with an increased prevalence among the elderly population. It not only affects quality of life but also increases risk of mortality among older adults. The diagnosis is based on clinical symptoms of the patient by four minimal essential criteria. Restless legs syndrome can be divided into primary or secondary causes. Examination should be performed to rule out potentially treatable illnesses, such as iron deficiency, renal failure or peripheral neuropathy, especially among elderly patients. The initial approach to restless legs syndrome should be nonpharmacologic management, such as good sleep hygiene, regular exercise, cognitive behavioral therapy and avoidance of certain aggravating drugs. An algorithm based on scientific evidence and expert opinion was developed for guidance of treatment. Combination or change of medication can be applied to resistant or difficult cases. Since elderly patients are prone to treatment-related side effects, the best strategy is to start medication cautiously and at the lowest recommended dosage. [International Journal of Gerontology 2009; 3(4): 197–203]

Key Words: anticonvulsants, diagnosis, dopamine agents, opioid, treatment

Introduction

Restless legs syndrome (RLS) is a neurologic sleep and movement disorder characterized by an irresistible urge to move, with unpleasant limb sensations occurring at rest and during the evening or night. It is one of the leading causes of insomnia and possibly the commonest movement disorder known, but remains underrecognized and undertreated. RLS affects 5–15% of the general population, with a female preponderance of almost 2:1[1]. It may start at any age, but there is a demonstrated increase in RLS among the elderly, with an estimated prevalence of 10–35% among those older than 65 years[2]. RLS symptoms may lead to anxiety, depression, insomnia, and excessive daytime somnolence that sometimes requires lifelong treatment. The severity of RLS symptoms in older adults affects not only sleep quality but also many aspects of quality of life, including social functioning, daily functioning, and emotional well-being[3]. In a 20-year follow-up study of Swedish women, RLS resulting in excessive daytime sleepiness was associated with increased mortality risk[4]. Therefore, accurate diagnosis and therapy of the disorders may substantially improve the quality of sleep and life in this patient population. We summarize the recent knowledge on diagnosis, epidemiology and treatment of RLS, especially among elderly adults.

Diagnosis of RLS

The diagnosis of RLS is based on the history of the patient, with input from the patient's sleeping partner. In 2003, the National Institutes of Health consensually agreed to define RLS by four cardinal features[5]: (1) an urge to move the limbs with or without sensation, (2) a worsening urge to move at rest, (3) an improvement with activity, and (4) a worsening urge to move in the evening or nighttime.

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One study showed that it was possible to screen for RLS with good sensitivity and specificity by asking one single question, "When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement[6]?" An interview with a trained physician is necessary for the correct diagnosis of RLS. If only questionnaires with the RLS criteria are given to patients, this results in approximately 10–25% false positives due to RLS mimicry[7]. The ability to verbally express experienced limb sensations may be diminished in the elderly by the impact of comorbid conditions, such as cognitive impairment, speech disorders or aphasic syndromes. Allen and colleagues[5], therefore, developed new criteria for the diagnosis of RLS among cognitively impaired elderly adults (Table). Observation of the restless leg movement behavior is helpful for the diagnosis. For example, rubbing the legs or excessive motor activity at night could indicate that the patient experiences sensations and the urge to move. A detailed history of restless leg movement given by family members and caregivers is considered very important for diagnosing RLS among these patients.

Several RLS rating scales were used to assess severity in medical studies. The International RLS Study Group rating scale, validated in 2003, is currently considered the standard scale by most RLS specialists. The scale is used to quantify the degree of RLS and monitor the patient longitudinally. This measure comprises 10 questions, each rated on a scale of 0–4, with a maximum disability score of 40.

Prevalence of RLS

In the Restless Legs Syndrome Prevalence and Impact Study[8], 7.2% of the general population reported RLS symptoms, but symptoms were moderately or severely distressing in only 2.7%. The prevalence of RLS symptoms increased at least until the seventh or eighth decade of life. The increasing prevalence of RLS with age is partially due to the fact that, although RLS can develop at any age, it rarely resolves on its own. The prevalence may be lower in Asian populations than that reported in Caucasian populations. In a recently published Japanese population study of RLS[9], the

Table. *Diagnostic criteria for the diagnosis of probable restless legs syndrome in the cognitively impaired elderly (all five are necessary for diagnosis)*

Essential criteria

1. Signs of leg discomfort, such as rubbing or kneading the legs and groaning while holding the lower extremities
2. Excessive motor activity in the lower extremities, such as pacing, fidgeting, repetitive kicking, tossing and turning in bed, slapping the legs on the mattress, cycling movements of the lower limbs, repetitive foot tapping, rubbing the feet together, and the inability to remain seated
3. Signs of leg discomfort are exclusively present or worsen during periods of rest or inactivity
4. Signs of leg discomfort are diminished with activity
5. Criteria 1 and 2 occur only in the evening or at night, or are worse at those times than during the day

Supportive criteria

1. Dopaminergic responsiveness
2. Patient's past history as reported by a family member, caregiver or friend is suggestive of restless legs syndrome
3. A first degree, biologic relative (sibling, child or parent) has restless legs syndrome
4. Observed periodic limb movements while awake or during sleep
5. Periodic limb movements of sleep recorded by polysomnography or actigraphy
6. Significant sleep-onset problems
7. Better quality sleep in the day than at night
8. The use of restraints at night (for institutionalized patients)
9. Low serum ferritin level
10. End-stage renal disease
11. Diabetes
12. Clinical, electromyographic or nerve-conduction evidence of peripheral neuropathy or radiculopathy

Modified from Allen et al.[5] with permission.

prevalence among inhabitants of Ajimu aged > 65 years was 0.96%. The distribution of age at onset in a large cohort study showed that early- and late-onset RLS could be separated with a cut-off at 36 years of age, clearly differentiating patients with a primary RLS (early onset) from those with secondary RLS[10].

Comorbidity and Secondary Forms of RLS

Among the elderly population, RLS is associated with other diseases such as iron deficiency, renal failure, diabetes mellitus, peripheral neuropathy, and various other conditions such as rheumatoid arthritis, lumbosacral radiculopathy, and fibromyalgia. Several neurodegenerative disorders, such as Parkinson disease (PD) and multiple system atrophy, usually occurring among elderly patients can also be the cause of RLS[11]. Nonetheless, the higher prevalence of RLS in patients with PD is possibly attributable to the long-term antiparkinsonism therapy, rather than PD itself[12].

Clinical and neurophysiologic examinations should be performed to rule out potentially treatable illnesses that may cause or exacerbate secondary RLS. These examinations should be directed towards seeking evidence of peripheral nerve or spinal dysfunction. Blood tests are done primarily to screen for anemia, iron storage dysfunction, diabetes, and renal insufficiency. More than two-thirds of people who develop RLS for the first time after 64 years of age have an underlying cause such as iron deficiency[13]. Interestingly, iron deficiency can be present in the absence of anemia. Thus, iron status, as indicated by serum ferritin levels and iron saturation, should be assessed, because patients may benefit from iron supplementation when the serum ferritin level is < 50 ng/mL. There is some evidence that oral iron supplementation is effective in low–normal ferritin patients with RLS[14].

Treatment of RLS

Not everybody with RLS requires pharmacologic therapy. In a population-based survey with 1,312 participants in Germany[15], about 20% of RLS patients requested medication to reduce their symptoms, corresponding to only 1.6% of the whole study population. Before starting pharmacologic treatment, treatment of any medical condition contributing to RLS is essential. Maintaining good sleep hygiene practices, such as stable bedtimes and rising times, a comfortable environment and avoiding daytime napping, is helpful to some degree. Regular exercise was also effective in improving RLS symptoms in one randomized controlled trial[16]. A proof-of-concept trial reported that cognitive behavioral group therapy significantly improved RLS-related quality of life and the mental health status of patients[17]. Additionally, current evidence suggests that compression stockings improve symptoms and, therefore, quality of life of some patients[18]. Certain stimulants or "aggravating" drugs (e.g., caffeine, tobacco, alcohol, sedating antihistamines, neuroleptics, tricyclic antidepressants, selective serotonin reuptake inhibitors, and lithium) should be avoided[19]. There is a strong association between RLS symptoms and *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition) (DSM-IV) major depressive disorder. Up to four of the nine symptoms listed in the DSM-IV diagnostic criteria for major depressive disorder can be attributed to sleep impairment associated with RLS, including insomnia, loss of energy, diminished concentration and psychomotor retardation[20]. To date, no recommendations exist for the treatment of depressive disorders in RLS. The problem was most pronounced with mirtazapine provoking or deteriorating RLS in 28% of patients. By contrast, no case occurred during use of reboxetine[21]. Bupropion was a possible treatment option for RLS in patients with depression. Case reports showed that a low dose of bupropion rapidly and completely ameliorated RLS symptoms within a few days of the initiation of treatment[22].

Although a variety of treatments are proposed for RLS, four identified classes of medications are commonly in use: (1) dopamine agonists and levodopa; (2) gabapentin and similar anticonvulsants; (3) opioids; and (4) benzodiazepines. An algorithm of the management of RLS product by the Medical Advisory Board of the RLS Foundation, divides RLS into three categories according to symptom severity: (1) intermittent RLS, (2) daily RLS, and (3) refractory RLS (Figure). According to evidence-based medicine criteria, dopamine agonists are currently considered to be first-line treatment for moderate to severe RLS[24]. Levodopa was the first drug approved by a government regulatory agency for treatment of RLS, but only in Germany, Switzerland, Austria, Croatia, Poland, and Brazil. It is rapidly effective with few adverse effects, except for the major problem of augmentation phenomenon. Its short-acting

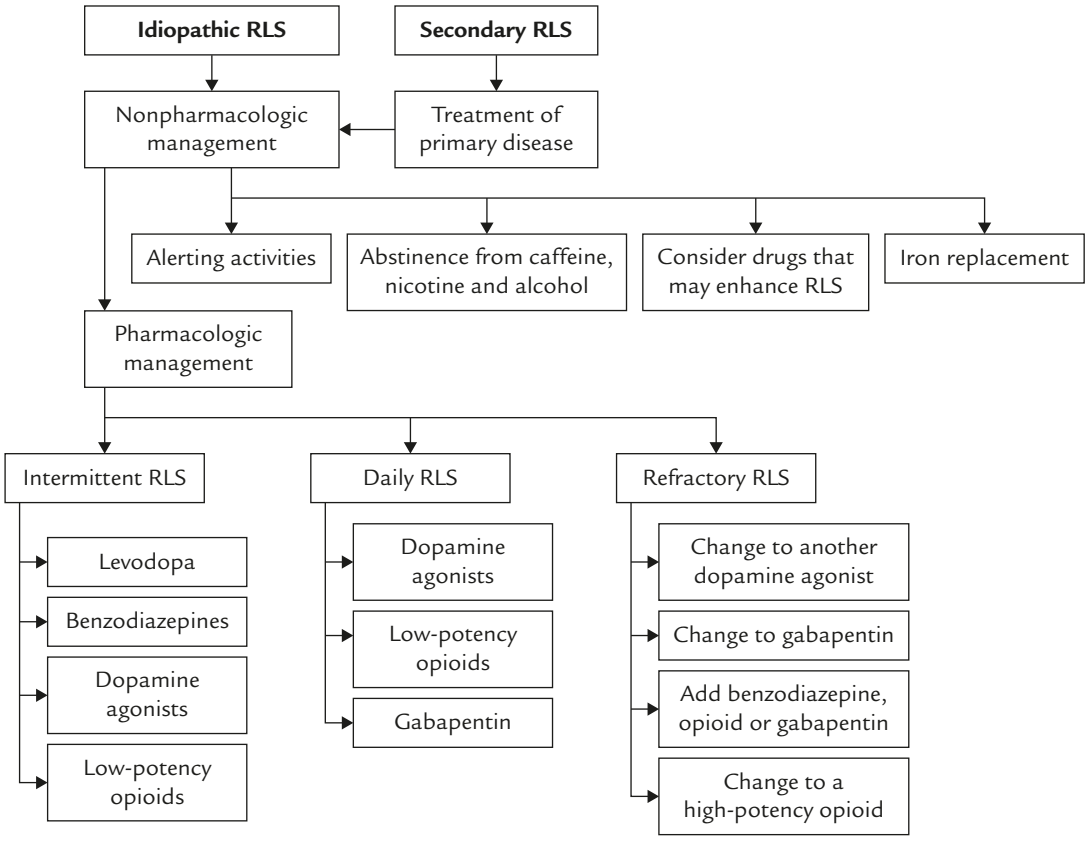

Figure. Algorithm for the management of restless legs syndrome (RLS). Modified from Silber et al.[23] with permission.

property seems to be an appropriate substance for treating mild and intermittent RLS. Currently, only ropinirole and pramipexole are approved by the US Food and Drug Administration for treatment of moderate to severe primary RLS. The two drugs can be distinguished by primarily hepatic (ropinirole) versus renal (pramipexole) excretion and by half-life (6 hours for ropinirole, 8–12 hours for pramipexole). Thus, ropinirole should be the first drug considered in uremic patients with RLS. An indirect meta-analysis confirmed the superior efficacy and tolerability of pramipexole over ropinirole. These findings should be further confirmed in a clinical trial comparing the two drugs[25]. The new dopamine agonist rotigotine, a transdermal patch, provides continuous drug delivery, benefits patients with daytime symptoms, and is generally well tolerated by the majority of RLS patients. Application site reactions were the main treatment complication. The manufacturer has filed for an indication for RLS therapy in Europe. Other dopamine agonists, such as pergolide and cabergoline, have been studied in reasonably large, double-blind, controlled studies. They cause cardiac valvular fibrosis and do not appear to have any particular advantage over other dopaminergic agents. Thus, they are not considered primary treatments for RLS. If one dopamine agonist causes side effects or does not relieve symptoms, physicians should consider prescribing another drug instead. The choice of drug depends on the patient's history, severity of the RLS, and the preference of both the patient and the physician for the drug.

Gabapentin and low-dose opioids are useful second-line drugs that can be used alone or in combination with dopaminergic agonists for dosage sparing. It seems that derangement of opioid binding and dopamine–opiate interactions play a role in the pathophysiology of RLS. It provides a rationale for use of opioids in RLS treatment[26]. Currently, only one double-blind randomized crossover trial with oxycodone (mean dosage, 15.9 mg) reduced sensory symptoms and motor restlessness at night and during daytime[27]. In controlled studies with gabapentin or its prodrug, RLS significantly improved compared with placebo[23,28]. It is probably also effective in secondary RLS and is especially helpful in treating RLS with painful symptoms or associated neuropathy. The gabapentin dosage should be reduced to

200–300 mg per day among hemodialysis patients[29]. Dialysis does not improve RLS in uremic patients, but renal transplantation does[30]. In contrast to earlier recommendations, benzodiazepines are not considered as a first choice treatment for RLS because of their limited efficacy and the development of tolerance. They should only be used when dopaminergic and opioid drugs are contraindicated. The benefits from these medications may be limited to a decrease in the number of arousals during sleep. They may have a major role to play as an add-on therapy to improve sleep.

Refractory RLS is defined as daily RLS treated with a dopamine agonist, with one or more of the following outcomes[23]: (1) an inadequate initial response despite adequate doses; (2) a response that has become inadequate with time, despite increasing doses; (3) intolerable adverse effects; and (4) an augmentation that is not controllable with additional earlier doses of the drug.

There is no set formula for refractory RLS therapy. Referral to a specialist for RLS management should be considered, and each patient should have an individualized treatment plan based on their needs and drug tolerance. It is useful to perform a full sleep study for these patients to ensure that there is no other sleep disorder present. Sleep apnea often coexists with RLS, and its symptoms may be masked by RLS. The treatment of sleep apnea, if present, may alleviate RLS symptoms. Changing or adding a treatment to a different dopamine agonist or to gabapentin may also be helpful in such cases. In general terms, augmentation is an overall increase in symptom severity as a result of long-term dopaminergic treatment. It describes an increase in the severity of RLS, such as a time shift of the start of symptoms to earlier in the day, a shorter latency to RLS symptoms at rest, and/or a spreading of symptoms to other body parts[31]. Although augmentation initially was thought to be an exclusive problem of levodopa treatment, it develops with other dopaminergic or opioid drugs as well. Augmentation needs to be differentiated from rebound in clinical practice, particularly because the increase in daily dose typically carried out to treat rebound will inevitably lead to a worsening of augmentation. To avoid augmentation, we recommend starting treatment with low dosages and to keep them low during the course of treatment. People who develop augmentation under levodopa treatment should be treated with lower and split dosages in mild cases. In more severe cases, levodopa has to be stopped and treatment switched to a dopamine agonist. If augmentation occurs again with dopamine agonist treatment, treatment should be split into low dosages or changed to an opiate.

Treatment of RLS in the Elderly

To date, no study has specifically investigated RLS treatment for the elderly. Pooled data revealed that ropinirole provided effective relief of symptoms, regardless of age, at RLS symptom onset[32]. Older patients are prone to insomnia, daytime somnolence, orthostatic hypotension, nausea and dizziness with dopaminergic agents, and side effects that may preclude or limit their use. As side effects of all dopamine agonists are dose-related, the best strategy is to start medication cautiously and at the lowest recommended dosage. In RLS patients with dementia who wander, an empirical trial of a low-dose dopaminergic agonist should be used. The clinician must, however, bear in mind that because of possible dopamine-induced psychosis in a potentially vulnerable patient population, rapid dose escalation of such medications is ill advised. Opioids seem to have long-term efficacy in the treatment of RLS but may result in a higher risk of dependency and worsening of sleep apnea[33]. These drugs are less suited to geriatric patients because of their propensity to cause confusion, sedation, and constipation. Clinical or polysomnographic monitoring for the development of sleep apnea is recommended in patients on long-term opioid therapy. It should be kept in mind that for the dementia population, atypical antipsychotics (e.g., olanzapine, quetiapine and risperidone) that exert partial dopaminergic blocking effects may aggravate RLS.

Conclusion

A detailed history of the patient, with corroboration from the caregivers, if necessary, is important in RLS diagnosis. RLS should be considered in the differential diagnosis of any older patient with sleep disturbances and/or paresthesia of the limbs. An initial approach should examine potential exacerbating medications already in use before adding new ones. Nonpharmacologic management should be considered in all RLS patients whether they have mild or severe symptoms. Treatment with dopaminergic drugs, opioids, anticonvulsants or hypnotics is usually well tolerated by elderly

patients. However, interaction with other medications and the possibility of severe sedation due to slower metabolism among the elderly should be considered. The clinically relevant problem with dopaminergic drugs in treating RLS is the development of augmentation, which usually occurs after an initial improvement and requires a switch of medication.

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