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Restless legs syndrome

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Restless legs syndrome is common; it is characterised by an urge to move and usually, but not exclusively, affects the legs. This urge to move is typically accompanied by abnormal sensations, variably described as burning, tingling, aching, or "insects crawling under the skin." These sensations are transiently or partially relieved by movement, and there is a strong circadian influence—symptoms are worse in the evening. It may be idiopathic or secondary to iron deficiency, pregnancy, uraemia, or neurological problems.

Estimates of prevalence of the syndrome range from 1.9% to 15%, depending on case ascertainment,[1] and it affects all age groups, although prevalence increases with age. Prevalence is about twice as high in women as in men.

Restless legs syndrome is a common cause of insomnia related to problems with sleep initiation and sleep maintenance, unrefreshing sleep, and excessive daytime sleepiness, and it may signify an underlying medical condition. Recognition of the condition and appropriate treatment therefore has a large impact on morbidity and quality of life.[2]

What is it?

Restless legs syndrome, which was first described by Ekbom in 1945,[3] is mainly characterised by sensory symptoms or an urge to move. It is now recognised that, in addition to affecting the legs, the syndrome can also affect the arms and even axial segments.[4 5] The diagnosis is essentially clinical, and there are no specific biological markers. The International Restless Legs Syndrome Study Group refined diagnostic criteria for the condition in 2003.[6] The four essential criteria are: an urge to move the legs, usually accompanied by unpleasant sensations; the urge to move or the sensations worsen during periods of rest or inactivity; the urge to move or the sensations are partially or totally relieved by movement; the urge to move or the sensations are worse in the evening or during the night. Supportive criteria and associated features have also been defined (box).

The diagnosis may be problematic, because patients typically present with disturbed sleep, discomfort, pain, or a non-specific increase in motor activity. They often do not ascribe the sleep disturbance to the symptoms of restless legs syndrome. Furthermore, patients may use a variety of terms to describe the symptoms: a sensation of pulling, jittering, worms or insects moving, tingling, itching, aching, bubbling, fidgeting, electric current sensations, tightness, and throbbing.[7] In some people, pain may be the dominant symptom, and they are often misdiagnosed as having a chronic pain syndrome.

As well as the sensory features, patients may also experience motor features, in addition to the voluntary movements that they make to alleviate discomfort. These involuntary movements may occur in sleep or while awake, and they typically involve brief repetitive movements of the legs, ranging from subtle extension of the hallux to flexion of the hip, knee, and ankle. About 80% of patients with the syndrome experience periodic limb movements of sleep,[8] and these movements can result in arousals, leading to unrefreshing sleep and sleep maintenance insomnia.

Restless legs syndrome is usually a chronic disorder that worsens with time, although it does fluctuate. Periods of remission are common, especially in younger adults.[6] Many patients do not develop daily symptoms until 40-60 years of age.

Who gets it?

The prevalence of restless legs syndrome is controversial. Studies have used a variety of methods to ascertain cases, ranging from a single question such as "Do you have restless legs, or troublesome twitches of the legs?" to more stringent diagnostic criteria and subsequent case review to rule out differential diagnoses. On the basis of a single question, prevalence has been estimated at 9-15%, whereas studies that tried to rule out alternative diagnoses estimated the prevalence as 1.9-4.6%.[1] These prevalence figures are based on a review of 47 peer reviewed published studies of the syndrome in the general population between 1994 and 2010.

The age of onset varies widely, from childhood to over 80 years of age.[9] It occurs in nearly 2% of school age children,[10] and half of these cases have a positive parental history of restless legs syndrome.[11] The disorder is probably underdiagnosed in children, given that 38% of adults have reported the onset of symptoms before age 20 years and 10% before age 10 years.[8] Some children who have been diagnosed as having "growing pains" meet the diagnostic criteria for restless legs syndrome.[12] The sleep disturbance associated with this disorder in childhood can manifest

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SUMMARY POINTS

- Restless legs syndrome is common in primary and hospital care; it causes great distress and disturbance of sleep
- The syndrome may be idiopathic or secondary to other disease
- Because of its varied presentations, it is often missed or misdiagnosed; diagnostic criteria have now been defined
- Screen all affected patients for iron store status; consider iron supplementation if serum ferritin is below 112 pmol/L (50 µg/L)
- Dopamine agonists are a licensed and proved treatment but are associated with augmentation and impulse control disorders; other unlicensed agents may be efficacious

SOURCES AND SELECTION CRITERIA

We searched Medline, the Cochrane Library, and the National Institute for Health and Clinical Excellence website with the search term "restless legs syndrome". We used evidence from published articles and guidelines on the management and treatment of restless legs syndrome by the International Restless Legs Syndrome Study Group, the European Restless Legs Study Group, and the Movement Disorders Society taskforces. Priority was given to evidence obtained from well conducted systematic reviews and meta-analyses.

Criteria for a diagnosis of restless legs syndrome

Essential diagnostic criteria

An urge to move the legs, usually accompanied or caused by uncomfortable or unpleasant sensations in the legs

Unpleasant sensations or urge to move begin or worsen during periods of rest or inactivity, such as lying or sitting

Unpleasant sensations or urge to move are partially or totally relieved by movement, at least for as long as the activity continues

Unpleasant sensations or urge to move are worse during the evening or night than during the day, or they occur only during the evening or night

Supportive criteria

Positive response to dopaminergic agents

Periodic limb movements of sleep or during wakefulness

Positive family history of restless legs syndrome

Associated features

Onset can be at any age, but patients are usually middle aged or older at presentation

Leg discomfort or the need to move results in insomnia

Low serum ferritin (112 pmol/L; <50 µg/L)

TIPS FOR NON-SPECIALISTS

Online algorithms are available for the diagnosis of restless legs syndrome

Ensure that exacerbators—such as poor sleep hygiene, caffeine, alcohol, smoking, and drugs such as antidepressants, neuroleptics, and other dopamine blocking agents—have been withdrawn or minimised if possible

Always use the minimum dose of dopamine agonist in an effort to avoid augmentation and impulse control disorders

Consider avoiding dopamine agonists in patients with a history of impulsive or compulsive behaviour and counsel all patients on the risks of pathological gambling, compulsive shopping, hypersexuality, and compulsive eating

as difficulty falling asleep, bedtime resistance, or nighttime awakenings, and symptoms are often associated with attention-deficit/hyperactivity disorder.[13] Diagnostic classifications that require children to describe the sensations in their own words can prove difficult to apply in practice, and other supporting information often needs to be taken into account.[6] Because specialist input is needed in children, this review focuses mainly on adults.

Extensive review of the published literature suggests that prevalence is about two times higher in women than in men and increases with age. It is the most common movement disorder in pregnancy, affecting 13.5-26.6% of pregnant women, and it tends to become more severe and more prevalent over the duration of the pregnancy.[1] Women who experience transient restless legs syndrome in pregnancy have a fourfold increased risk of developing the disorder later in life.[14] Most studies suggest that there is a higher prevalence in Northern Europeans and North Americans than in African, Middle Eastern, Asian, Hispanic, or south eastern Europeans.[15]

Restless legs syndrome may be idiopathic or symptomatic. Idiopathic disease seems to have a strong genetic component, with a family history in 18.5-59.6% of patients.[16 17] Restless legs syndrome has been associated with a wide variety of conditions, most often iron deficiency and uraemia. Other disease associations include cardiovascular disease, obesity, diabetes, rheumatological disorders, peripheral neuropathy, radiculopathy, Parkinson's disease, multiple sclerosis, Charcot-Marie-Tooth disease, and spinal cord lesions. However, many of these described associations were not seen in all studies, and the strengths of these associations are unclear.

What causes restless legs syndrome?

Clinical observation has informed our understanding of the pathophysiology of the syndrome. Dopaminergic drugs alleviate the symptoms and dopamine antagonists can trigger or exacerbate them. However, despite a clear indication of dopamine being implicated in the pathophysiology, its role remains uncertain. Studies in animal models and patients have shown increased tyrosine hydroxylase (the rate limiting enzyme in dopamine synthesis) concentrations in the substantia nigra, decreased numbers of D2 dopamine receptors in the putamen, and increased concentrations of 3-O-methyldopa in the cerebrospinal fluid,[18] which implies that the syndrome is characterised by upregulation of dopaminergic transmission, with postsynaptic desensitisation. Dopaminergic activity shows natural circadian fluctuations, and this is thought to be the underlying mechanism for the characteristic circadian pattern of the symptoms.

Iron deficiency has also been implicated. Although iron deficiency alone is not sufficient to cause restless legs syndrome—and neither is it necessary—precipitation or exacerbation of symptoms with venesection is well described, and serum ferritin correlates inversely with symptom severity. Magnetic resonance imaging and studies of cerebrospinal fluid and autopsy specimens of substantia nigra have shown that brain iron stores are reduced in patients with restless legs syndrome.[19 20] Iron is an essential cofactor for tyrosine hydroxylase and seems to have a crucial role in dopamine metabolism.

The mechanism by which pregnancy worsens or triggers restless legs syndrome has not been elucidated. The symptoms often disappear or dramatically improve after delivery, strongly suggesting a hormonal influence, perhaps through the action of oestradiol or prolactin on dopaminergic transmission.[21] However, iron deficiency in pregnancy may also be important.

Because a family history is common and twin studies have shown hereditability estimates of 54-83%, efforts have been made to identify genetic factors involved in the pathophysiology of restless legs syndrome. Genome-wide association studies have shown associations with variants in four genes, *MEIS1*, *BTBD9*, *MAP2K5/SKOR1*, and *PTPRD*, but the findings have been inconsistent and the roles of these genes remain unclear.[w1-w5] *BTBD9* has also been associated with periodic limb movement of sleep.[w6]

What else could it be?

Several conditions can mimic restless legs syndrome. These include the sensory symptoms associated with peripheral neuropathy, cramps, positional discomfort, akathisia (a feeling of motor restlessness associated with dopamine receptor blocking neuroleptic agents), parkinsonism with sensory symptoms or drug induced dyskinesias, arthritis, hypnic jerks, fibromyalgia, and varicose veins.[7] Careful history taking and a general neurological examination can rule out these differential diagnoses. A diagnosis of restless leg syndrome can then be made if all four essential diagnostic criteria are met (see box).

What impact does restless legs syndrome have on health?

Restless legs syndrome has a large impact on quality of life, similar to that of type 2 diabetes and osteoarthritis.[22 23] Increased symptom severity is associated with serious psycho-logical impairment in multiple psychological domains.[w7] Patients with the disorder have longer adjusted sleep latencies and a higher arousal index than controls,[2] and they report difficulty initiating sleep, difficulty maintaining sleep, and un-refreshing sleep two to three times more often than controls.[1]

Emerging evidence also suggests that restless legs syndrome is associated with metabolic dysregulation, autonomic dysfunction, and risk of cardiovascular disease. A recent extensive systematic review of 629 sources concluded that the syndrome is strongly and positively related to cardiovascular disease, is probably associated with diabetes and impaired glucose tolerance, and may be modestly associated with body mass index and dyslipidaemia.[24] However, the direction of the association is unclear. The syndrome may lead to increased risk for these disorders, perhaps via chronic activation of the sympathetic nervous system and the hypothalalmic-pituitary-adrenal axis; these conditions may increase the risk for the syndrome; or restless legs syndrome may be linked to these conditions through shared risk factors.

How is restless legs syndrome managed?

The treatment of restless legs syndrome in children requires specialist expertise so we will focus on the management of adults. In the past few years, evidence based guidelines have been published by taskforces for the Movement Disorders Society,[25] the European Federation of Neurological Sciences,[26] and the European Restless Legs Syndrome Study Group (EURLSSG),[7] with the last of these focusing on algorithms for treatment in primary care.

Management comprises the recognition and reversal of causes or exacerbators and symptom control. For patients with mild or infrequent symptoms, non-drug based options may be sufficient to provide symptom relief.

Measure serum ferritin in all patients with symptoms of restless legs syndrome. Anaemia is not sufficiently sensitive a marker for iron deficiency. Patients with a serum ferritin of less than 112 pmol/L (50 µg/L) should be started on iron supplements. Take a drug history to screen for exacerbating agents, such as antipsychotics, antidepressants (especially selective serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors), antihistamines, dopamine receptor blocking agents such as metoclopramide and prochlorperazine, and diphenhydramine.[27]

Not all patients need treatment, and only about 20% require drugs.[28] Non-drug based measures include avoidance of alcohol, caffeine, and smoking; good sleep hygiene; moderate regular exercise; avoidance of overexertion, stress, or sleep deprivation; and brief walking or other motor activities, hot baths, or leg massage before bedtime.[w8]

Consider drugs in patients with symptoms that seriously impair quality of life, sleep, or daytime functioning despite reversal of iron deficiency, removal of possible exacerbators, and exclusion of secondary restless legs syndrome. Choice of agent should be guided by the nature of the symptoms,[7] but the dopamine agonists—ropinirole, pramipexole, and rotigotine—are the only agents licensed in the United Kingdom, although in the United States the Food and Drug Administration recently approved a slow release preparation of gabapentin enacarbil, a prodrug of gabapentin.

What problems are associated with dopamine agonists?

A recent Cochrane review showed that dopamine agonists were superior to placebo in randomised controlled trials with up to seven months' follow-up,[29] and a further meta-analysis of 35 trials also showed moderate improvements in symptom severity, self rated sleep quality, and disease specific quality of life.[30] Although these meta-analyses clearly show efficacy, treatment with these drugs has certain problems. These agents can be associated with the phenomenon of augmentation—the onset of symptoms earlier in the day; increased severity of symptoms; or the spread of symptoms to different body parts, such as the arms, trunk, or even face.[31] Augmentation should be distinguished from early morning rebound of symptoms related to declining plasma concentrations of the drug or the slow natural progression of symptoms. Augmentation rates seem to be particularly high with levodopa but are also a problem with licensed dopamine agonists. Recommendations include keeping dosages low because of the association between higher doses and augmentation; monitoring ferritin because low ferritin is associated with clinically significant augmentation[32]; and monitoring lifestyle and drug factors that might have an effect on symptom exacerbation. At present, no direct head to head trials of licensed agents have examined augmentation systematically, and most studies have not been sufficiently long in duration to evaluate augmentation fully.

The other important problem with dopamine agonists is that of impulse control disorders. Several of these disorders have been described after the use of dopamine agonists in Parkinson's disease, including pathological gambling, compulsive shopping, hypersexuality, and compulsive eating. It has recently been shown that these problems are also common in patients with restless legs syndrome treated with these drugs,[33] and that they are associated with higher dose, history of experimental drug use, female sex, and a family history of gambling disorders.[34] Impulse control disorders affect as many as one in five patients with restless legs syndrome who are taking dopamine agonists.

How do I choose between different dopamine agonists?

Currently, insufficient strong evidence is available to allow direct comparison of efficacy, safety and adverse effects such as augmentation and impulse control disorders. Evidence based guidelines do not suggest any particular dopamine agonist, although the EURLSSG taskforce recommends rotigotine, which is administered as a patch and provides therapeutic plasma levels over the entire 24 hour period for patients with severe daytime symptoms.[7] Extended release preparations of other dopamine agonists have not yet been licensed for restless legs syndrome.

Ergot derived dopamine agonists are not recommended because of the risks of cardiac valvular fibrosis and other fibrotic side effects.

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

BMJ Best Practice (http://bestpractice.bmj.com/best-practice/monograph/65.html)—BMJ Best Practice module on restless legs syndrome

European RLS Study Group (www.eurlssg.org/)—Website with an online algorithm for the diagnosis of restless legs syndrome and sleep diary templates

Resources for patients

Restless Legs Syndrome Foundation (www.rls.org)—US based charity providing information about the condition and ongoing research

RLS-UK/Ekbom Syndrome Association (www.rls-uk.org)—UK based organisation providing information and support to patients

What other drugs are available?

No other agents are licensed for restless legs syndrome. However, the Movement Disorders Society taskforce evidence based review of all published studies before 2007 found evidence that gabapentin is efficacious (at least two positive randomised controlled trials with defined outcome measures); that oxycodone, carbamazepine, sodium valproate, and clonidine are probably efficacious (one positive randomised controlled trial without contradictory evidence); but that tramadol, methadone, clonazepam, zolpidem, topiramate, and minerals and vitamins such as folate and magnesium are still under investigation (positive results from controlled clinical trials, observational controlled studies, or case series only).[25] This review also found that intravenous iron is probably efficacious in end stage renal failure but remains investigational in patients with normal renal function.

However, opioid-like drugs such as codeine and tramadol, gabapentin, and pregabalin are recommended as second line treatment by the EURLSSG taskforce,[7] although these are all off-label. Clonazepam, again off-label, is suggested as an option for intermittent symptoms that disturb sleep. These recommendations are based on consensus by European experts in restless legs syndrome and primary care practitioners.

More recently, two very short randomised double blinded placebo controlled trials found pregabalin to be helpful,[35 36] but there are inadequate data to support its long term efficacy.

Whom should I refer to a specialist?

Refer patients to a neurologist or sleep specialist if treatment is unsuccessful. The EURLSSG taskforce defines unsuccessful treatment as[7]:

- An insufficient initial response despite adequate duration and dose of treatment; adequate duration depends on the drug in question and can extend to 10 days for ropinirole
- Response to treatment becomes insufficient despite an increased dose
- The side effects are intolerable
- The maximum recommended dosage is no longer effective
- Augmentation develops.

The taskforce also recommends that children should not be treated in primary care.

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