Restless legs syndrome

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Summary
Restless legs syndrome (RLS) is characterised by an uncontrollable urge to move, in particular the lower limbs, often accompanied by discomfort or a painful sensation that occurs typically at night. It is categorized under the ICD-Classification of extrapyramidal and movement disorders. As patients often suffer from insomnia due to the involuntary nocturnal leg movements and irritable sensations in the legs, RLS is also classified as a sleep-related movement disorder. The incidence of a mild form of RLS is frequent, although it often remains undiagnosed. After the exclusion of other diseases by differential diagnosis, RLS is diagnosed on the basis of a clinical test administering a single dose of levodopa. There are two forms of RLS: idiopathic and secondary. The secondary form is encountered in an astonishing number of diseases, including renal insufficiency, diabetes, chronic obstructive pulmonary disease (COPD) and iron deficiency. The treatment of RLS is complex and the benefits and risks of pharmacotherapy should be considered carefully. Non-ergoline dopamine agonists (e.g. ropinirole, pramipexole) are the first-line treatment in severe cases of RLS. Transdermal rotigotine is also a promising treatment option. Opioids in combination with naloxone are recommended for patients suffering from severe pain. In mild cases of RLS, patients benefit from a balanced lifestyle with gentle physical activity and avoiding the excessive consumption of caffeine or alcohol.

Zusammenfassung
Das Syndrom der unruhigen Beine oder restless legs syndrome (RLS) charakterisiert sich durch einen ungewollten Bewegungsdrang, vor allem der Beine, häufig assoziiert mit einem unangenehmen, teils schmerzenden Gefühl in den Beinen. Die Symptome zeigen typischerweise einen zirkadianen Rhythmus, mit vermehrtem nächtlichen Auftreten. Das RLS wird zu den extrapyramidalen Krankheiten gerechnet, bleibt aber oft unerkannt (1, 5). Es ist deshalb wichtig, die Diagnose zu stellen und die möglichen Folgen zu beachten.

Schlüsselwörter
RLS, Restless-Legs-Syndrom, Beinbewegungen, PLMD

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Restless legs syndrome (RLS) and the associated periodic limb movement disorder (PLMD) are classed as extrapyramidal hyperkinesias. RLS is common, mildly affecting some 10% of the population and causing troublesome symptoms in about 2.7% (1, 2). The condition is characterised by sensory disturbances and an uncontrollable urge to move when at rest (>90% of affected patients) as well as spontaneous movements and twitching at rest (about 50% of patients). In more than 90% of those affected, restless legs syndrome causes considerable problems with sleep (3). The International Classification of Sleep Disorders (ICSD-2) therefore includes the condition under sleep-related movement disorders (4).

On the one hand, many patients with RLS remain undiagnosed (1, 5), while, on the other hand, the discovery of effective treatment has led to increased medication of the disease and more advertisement of the therapeutic options by the pharmaceutical industry, leading to better informed patients, who, in turn, put more pressure on doctors’ prescription practices. This is referred to as “disease mongering” in the literature (6, 7). It is therefore important for doctors to make the diagnosis and
treat severely affected persons, while at the same time protecting healthy people and those with only mild symptoms from excessive treatment with all its associated adverse reactions.

Clinical presentation

Patients with restless legs syndrome report on dragging sensations and tension as well as on tingling and even considerable pain in the legs at rest, resulting in an uncontrollable urge to move and to activate or stretch the muscles. The symptoms are usually more severe at night than in the daytime (circadian rhythm with increased activity between 10.00 pm and 4.00 am). Immediate relief of pain by muscular activity (moving around, stretching, doing exercises or cycling) is very characteristic. However, muscle activity only brings temporary relief and the symptoms recur almost as soon as it is stopped (8, 9).

Patients with severe RLS usually also have problems in getting to sleep (sleep-onset insomnia) and in staying asleep (sleep-maintenance insomnia) and thus suffer from lack of sleep, loss of drive and chronic daytime sleepiness, which may, in turn, lead to loss of concentration, exhaustion and depressiveness (10). In isolated cases, the condition progresses to a chronic pain syndrome.

The diagnosis depends on the typical clinical picture and the successful alleviation of the symptoms by a single dose of levodopa or sublingual apomorphine (ex juvantibus testing) (11). In cases that are not straightforward, further diagnostic clarification in a sleep laboratory (polysomnography) is necessary for the definitive diagnosis. The phenomenon of periodic limb movements can be particularly well observed and monitored in a sleep laboratory (12). About 20% of all patients investigated for a sleep disorder in a sleep laboratory have a previously undiagnosed restless legs syndrome.

The onset of RLS is typically between the ages of 30 and 40 and the condition tends to progress with age (13). It is not, however, a degenerative neurological disease.

Differential diagnosis

The neurological work-up has to differentiate restless legs syndrome from a peripheral polyneuropathy, funicular myelosis (vitamin B12 deficiency), radiculopathy and akathisia (14).

From the vascular point of view, the differential diagnosis includes peripheral arterial occlusive disease and chronic venous insufficiency, but these two conditions are relatively easy to distinguish.

Furthermore, simple sleep-onset myoclonic movements and nocturnal cramps in the calf have to be differentiated from restless legs syndrome, in order to save these patients from unnecessary medication (14).

Most RLS patients suffer from the primary (idiopathic) form. Secondary RLS may be found in severe iron deficiency (15), pernicious anaemia (vitamin B12 deficiency), renal insufficiency (16), as an adverse reaction to certain drugs (dopamine antagonists or antidepressants) and in Parkinson’s disease (17). Pregnancy may also cause RLS for a while (18).

Pathophysiology

Even though neurological studies and imaging over the past twenty years have drawn pathophysiological parallels with Parkinson’s disease, there is no direct relationship between the two conditions. Patients with RLS do not develop Parkinson’s more often than the average control population (17).

Positron emission tomography (PET) in functional magnetic resonance imaging (fMRI) as well as single photon emission computed tomography (SPECT) can be used to show dysfunctional processes in the central dopaminergic system (substantia nigra), as well as in the red nucleus, the reticular formation in the vicinity of the thalamus, and in the area of the brain stem. The interpretation of these results is still controversial (19).

Treatment of restless legs syndromes

The treatment of severe restless legs syndrome with dopamine agonists was discovered about 20 years ago.

Transient forms of RLS can be treated effectively with levodopa (a precursor of dopamine). Long-term administration of levodopa is not recommended, however, as it leads to exacerbation of the symptoms (20).

There are two types of dopamine agonists: ergoline (derived from ergot alkaloids) and non-ergoline agents. The current gold standard of treatment for severe RLS is to give a non-ergoline dopamine agonist (ropinirole, pramipexole). Applying rotigotine as transdermal patches is also very promising. These medicines can be used indefinitely, as long as they do not cause any serious adverse reactions. In principle, the same applies to the ergoline dopamine agonists, pergolide, cabergoline, bromocriptine and lisuride (15).

A whole range of medicinal products, such as antihistamines, dopamine antagonists, antiemetics, anxiolytics, antidepressants (e.g. mirtazapine, escitalopram, fluoxetine and mianserin), neuroleptic agents (e.g. olanzapine), beta-blockers, anticonvulsants, L-thyroxine and lithium should be avoided (21).

If the restless legs syndrome is associated with severe pain, opioids such as morphine, methadone and oxycodone can be combined with naltrexone for effective treatment. Besides their well-known analgesic effects, these medicines have a welcome dopaminergic action. Nevertheless, tachyphylaxis with a ceiling effect may develop if opioids are given in the treatment of RLS. For this reason, their use should be delayed for as long as patients can manage without them. The tachyphylactic effect is seen far less frequently with methadone and the combination of oxycodone with naloxone than with codeine or oxycodone alone (22).

In general, it can be said that patients with mild RLS can be treated with milder forms of therapy. Muscle-stimulating physiotherapy such as yoga, tai chi, qi gong or Pilates may provide very effective relief. Patients should be advised against relax-
Conclusions

Restless legs syndrome, which is associated in about 50% of cases with periodic limb movement disorder, is a common phenomenon affecting possibly up to 10% of the population. Nevertheless, only one in four persons affected requires treatment. Sleep disorders, which often lead to chronic tiredness and loss of concentration, are typical of the condition.

The doctor's task is to diagnose RLS and to differentiate between mild and severe forms. Patients with severe RLS can today benefit from effective treatment, which is based on the prescription of dopaminergic agents. Muscle-stimulating exercises reinforce treatment success. Patients with mild RLS should, on the contrary, not be given unnecessary medication.

Further treatment options

At the present time, the use of intravenous iron is disputed; a Swedish study showed that intravenous iron dramatically reduced RSL symptoms, but this could not be confirmed by other studies (15, 24). Alternatively, the use of gabapentin, pregabalin and anticonvulsants (clonidine, valproic acid or dronabinol) for RLS patients with pain is open to discussion (23).

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical guidelines

For this review article no studies on humans or animals were conducted.

References