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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

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GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

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Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

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In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

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1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

კარდიოპროტექტორულ ეფექტს. აერობული ფიზიკური აქტივობა სადღეისოდ წარმოადგენს კარგად შესწავლილ მოდელობას პროგნოზზე დადებითი ეფექტით, რეკომენდებულია ყველა ზრდასრული ჯამრთელი პირებისათვის, ასევე სუბიექტებისათვის კორონა-რული რისკის ფაქტორებით, პაციენტებისათვის გულის ქრონიკული დაავადებით. კარდიორესპირაციულ ფიტნესის დონის გამოკვლევის მიზნით რეკომენდებულია კარდიოპულმონული დატვირთვის ტესტის ჩატარება VO_2max-ის გაზომვით რისკების შეფასების, ვარჯიშების დანიშვნის მიზნით. ფიზიკური აქტივობის და მკურნალობის გაუმჯობესების მიზნით მიზანშეწონილია კონსულტაციების ჩატარება.

THE RESTLESS LEGS SYNDROME (REVIEW)

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Restless legs syndrome (RLS), also known as Willis-Ekbom disease is a neurological sensorimotor disorder often profoundly disturbing sleep and quality of life. RLS is primarily characterized by an urge to move the legs, usually accompanied by sensations that are described as unpleasant or even extremely unpleasant. Symptoms occur or increase when the patient is at rest i.e. sitting or lying down. Typically, the patients move or rub their legs or walk around to alleviate the sensations; in the case of very pronounced complaints, calm sitting, lying down is almost impossible and sleep is severely impaired. At the beginning, the symptoms typically occur in the evening or at night whereas later in the course of the disease, this circadian component may not be present and a spread of the complaints on previously unaffected limbs can be observed [1].

Diagnosis

The diagnosis is based on the criteria of the International RLS Study Group summarized in Table 1.

In clinical practice, the application of the criteria may be problematic because the symptoms are primarily subjective and based almost exclusively on the information provided by the patients [1]. Affected persons may have difficulties to describe the sensations as well as the urge to move appropriately. The symptoms are hardly comparable with other sensations, which is one of the main causes of the under- and misdiagnosis of RLS. The patients often do not perceive their complaints as symptoms of a disease and are more likely to describe the consequences such as sleep disorders, fatigue, or exhaustion. The symptoms usually occur bilaterally between the ankle and knee, and may alternate between both legs. In addition, they often show a variable expression and vary from day to day.

RLS symptoms may already occur in children and adolescents and can be misdiagnosed as a “hyperactivity syndrome” or “growing pains”. The diagnosis may be difficult, because the diagnostic criteria require that the description of the symptoms should be given in own words. Therefore, it may also be difficult to diagnose RLS in patients with dementia [1].

In addition to the essential criteria, the IRLSSG identified clinical features supporting the RLS diagnosis:

- periodic leg movements;
- dopaminergic treatment response;
- family history of RLS among first-degree relatives;
- lack of profound daytime sleepiness.

As an objective feature, periodic leg movements (PLM) can occur during sleep (PLMS) or relaxed wakefulness (PLMW), the latter in more severe forms of RLS. PLM are detected in about 80-90% of RLS patients if sleep recordings are made during several nights by polysomnography (PSG) or actigraphy. PLMS are highly regular, jerky, unilateral or bilateral movements characterized by involuntary repetitive extensions of the toe, often accompanied by flexions of the ankles, knees or hip. According

Table 1. International Restless Legs Syndrome Study Group (IRLSSG) consensus diagnostic criteria for RLS [1]

Essential diagnostic criteria (all must be met):
1. An urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs.
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying 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 the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or at night than during the day.
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

to the international criteria based on PSG, PLMS include at least four consecutive leg movements with an intermovement interval of ≥ 10 s and £ 90 s with a duration of 0.5-10 seconds [12]. It is unclear to what extent PLMS without RLS are a stand-alone syndrome, a precursor of RLS or an endophenotype of the RLS genotype [37]. PLMS can be associated with EEG arousals and a short-term increase in heart rate, heart rate variability or blood pressure.

Because primary (idiopathic) and secondary (comorbid) RLS do not generally differ in clinical terms, further investigations may be necessary to exclude underlying treatable causes such as iron deficiency and to differentiate RLS from similar disorders that may mimic RLS. The clinical testing for RLS is summarized in Table 2.

Table 2. Clinical testing for RLS [43]

Tests considered mandatory
Hemoglobin
Urea
Creatinine and electrolytes
Serum ferritin and total iron binding capacity
Tests occasional helpful if clinical pointers
Thyroid function tests
Glucose
B12 and folate levels
Nerve conduction studies

Polysomnography

PSG often reveals significant abnormalities in patients with RLS. Sleep latency is typically increased whereas sleep efficiency and total sleep time is decreased and sleep continuity may be impaired by frequent awakenings and PLMS associated EEG arousals. In addition, there are alterations of sleep architecture such as an increase in light sleep and a decrease in sleep stage 3 (SWS) and REM sleep. Because RLS is a clinical diagnosis, PSG is not mandatory in most cases. However, possible indications for PSG may be the following [19]:

- persistent RLS complaints or severe sleep disorders under treatment;
- daytime sleepiness as the main symptom;
- before starting treatment with dopaminergic drugs or opiates in young patients with severe RLS;
- to rule out comorbid sleep-related breathing disorders.

Epidemiology

The prevalence varies depending on the population studied and the criteria used. If solely the diagnostic criteria are used, RLS complaints may be determined in up to 10% of the Caucasian population [18]. If the frequency of complaints is additionally assessed, the proportion of "RLS sufferers" (complaints at least 2 times/week) or RLS patients in need of treatment is between 1.5 and 2.7% [2]. In two prospective studies in Germany, a cumulative incidence of 9.1% and 7%, respectively (observation period: 5.2 and 2 years, respectively) was found [35]. RLS mostly affects middle-aged and older people. Women are significantly more affected than men (ratio between 1: 1.5 and 1: 2.0) [13] due to parity (the risk of developing RLS increases with increasing numbers of births). According to the epidemiological studies, RLS affects approximately 15 to 25% of pregnant women in Western countries. Some reports suggest marked ethnic and geographic differences in the prevalence of RLS with a lower proportion in most Asian countries. The prevalence of RLS in a Georgian primary healthcare setting is 11.3% [24].

Development and course

The onset of RLS ranges from childhood to elderly people, with a higher familial occurrence at early onset [3]. RLS is usually a chronic disease with a variable course. According to recent studies, the complaints persist in nearly 50% of cases in follow-up periods of 2 to 5.2 years [35]. It is distinguished between "chronic persistent RLS" i.e. symptoms when not treated occur on average at least twice weekly for the past year and "intermittent RLS" i.e. symptoms when not treated occur on average < 2/week for the past year, with at least five lifetime events [1]. The course of the disease is also determined by the age of the first manifestation. In patients with a manifestation of symptoms before the age of 45 ("early onset RLS") the course is usually characterized by longer periods of remission, whereas in those with an onset after the age of 45 years («late onset RLS») more unfavorable courses have been described [3].

Quality of life

The symptoms of RLS cause significant distress or impairment in social, occupational, educational or other important areas of functioning by their impact on sleep, vitality, daily activities, cognition or mood. The impact of an RLS on the quality of life is therefore far-reaching. RLS patients may suffer from a diminished ability to concentrate, psychomotor restlessness, anxiety and depressive disorders [overview in 44]. In severe forms of RLS, the quality of life is considered comparable to other chronic diseases (e.g. diabetes mellitus, polyneuropathy) or even worse.

Pathophysiological aspects

The etiology of RLS is still not fully understood. Current hypotheses on the pathophysiology of primary RLS favor a heterogeneously genetically determined, complex disorder of the cerebral iron stores with subsequent dysregulation of the dopaminergic system. Studies on large family pedigrees showed that RLS follows a pattern of autosomal-dominant inheritance. Family linkage analysis identified several associated loci with RLS (chromosomes 12q, 14q, 9p, 2q, 16p, 4q, 17p, 19p and 20p). In genome-wide association studies, single nucleotide polymorphisms (SNPs) were found in a number of genes, which are associated with an increased risk of RLS (*MEIS1, BTBD9, MAP2K5, PTPRD, SKOR1, TOX3, LBXCOR1*) [reviewed in 21]. The exact function of these genes often remains unclear, but seems to play an important role in embryonic development [31]. In addition, an involvement in the development of the basal ganglia was described for *MEIS1* [34]. Autopsy material from RLS patients revealed that the *MEIS1* gene is associated with an increase in the expression of H-ferritin, L-ferritin and divalent metal transporter-1 RNA in the thalamus [9]. This may be an indication that *MEIS1* gene mutations predispose to iron deficiency.

The serum iron is often normal in RLS patients; however, a state of low iron in the brain has been shown in a small sample by using magnetic resonance imaging (MRI) studies. These areas included the substantia nigra and, to a lesser extent the putamen and caudate nucleus. In addition, a significant decrease of ferritin and an increase of transferrin in the cerebrospinal fluid (CSF) were found in RLS patients compared with healthy controls [for review 11].

Positron emission tomography (PET) and single positron emission computed tomography (SPECT) findings support a dysfunction of dopaminergic pathways involving not only the nigrostriatal but also mesolimbic pathways. It is suggested that a reduction of brain iron may cause a dysfunction of mesolimbic and nigrostriatal dopaminergic pathways and in turn a dysregulation of limbic and sensorimotor networks [29].

Clinical observations of RLS in the context of myelopathies or following spinal anesthesia as well as neurophysiological studies demonstrating a spinal hyperexcitability favor a central role of the spinal cord in RLS. A dysfunction of the dopaminergic hypothalamo-spinal inhibitory descending pathways is suggested [25].

Differential diagnoses and "RLS mimics"

Leg muscle cramps and leg-associated pain syndromes are often the cause of misinterpretations, especially if they occur at rest or at night. Therefore, the term "RLS mimics" was introduced. If only the first 4 essential criteria are taken into consideration, a false positive diagnosis will be made in 16% of the cases [17]. The most common differential diagnoses of RLS are summarized in Table 3.

In contrast to RLS, nocturnal leg muscle cramps are usually not associated with an urge to move or movements of the extremities. A particularly important differential diagnosis is neuroleptic-induced akathisia, which may be induced by typical (and rarely atypical) neuroleptics.

Other disorders that should be distinguished from RLS include myelopathy, symptomatic venous insufficiency, peripheral arterial disease, orthopedic disorders and anxiety-induced restlessness or agitated depression. If the diagnosis of RLS is uncertain, the assessment of supportive characteristics of RLS, in particular PLMS or a positive family history, may be helpful, as well as the clinical response to treatment with dopaminergic substances.

Comorbidities

Diseases associated with an increased incidence of RLS are summarized in Table 4.

An association between iron deficiency and the occurrence of an RLS is sufficiently proven. It has been demonstrated that in patients with iron deficiency anemia, the RLS prevalence is about 6 times higher than in the general population [4]. For an indicator of the cerebral iron storage, the serum ferritin level is used. Even low normal levels of ferritin (<50 μg/l) may be associated with more severe RLS symptoms. Ferritin is also an acute phase protein and an increase in inflammation may indicate false high values. Therefore, transferrin saturation is often included as an additional parameter of the iron metabolism.

A 2 to 3-fold increase in RLS prevalence has been reported in patients with chronic renal insufficiency, with changes in iron metabolism as well as uremia [4]. In dialysis patients with RLS, symptoms usually remit after successful kidney transplantation [45].

Other comorbid internal disorders include hypertension and other cardiovascular diseases, diabetes mellitus, fibromyalgia and thyroid disorders. RLS has been associated with cardiovascular disease in both cross-sectional and prospective studies, although the latter are limited in number yielding conflicting results [22]. However, further studies are necessary to clarify this complex interaction.

An increased incidence of RLS has also been reported in peripheral neuropathies, narcolepsy, migraine, Parkinson's disease, essential tremor and multiple sclerosis [8,44]. Frequent moderate to severe RLS has also been identified recently in patients with epilepsy, in particular, localization-related temporal lobe epilepsy [16]. Recent studies suggest that the number of comorbidities is more likely to be associated with an increased risk of RLS [36].

Table 3. Differential diagnoses of RLS [27]

Common disorders	**Uncommon disorders**
Leg muscle cramps	Myelopathy
Position-related paresthesia	Myopathy
Localized leg injuries	Arterial Disease
Arthritis	Orthostatic tremor
Leg edema	Drug- induced akathisia
Venous insufficiency	Painful-legs-and-moving-toes syndrome
Peripheral neuropathy	
Radiculopathy	
Myalgia	
Anxiety disorders	
Habitual foot tapping	

Table 4. Comorbidities of RLS [37]

Comorbidity	**Comment**
Iron deficiency	RLS patients have frequently lower serum ferritin levels, especially at early onset of disease, in women and in pregnancy
Kidney disease, uremia	Depending on creatinine or glomerular filtration rate
Polyneuropathy	Increased RLS incidence in different forms of polyneuropathy, especially in small-fiber neuropathy
Syringomyelia	Patients with cross-sectional symptoms and increased PLMS have been described
Spinocerebellar ataxia	Frequent occurrence of RLS described
Coeliac disease	Association with RLS may be due to iron deficiency
Rheumatic/oncological diseases	Association with RLS may be due to iron deficiency
Pregnancy (listed here although no comorbidity)	Relatively common cause of RLS especially in the last trimester

Pregnancy is associated with an increased risk of transient RLS, which in turn is associated with an increased likelihood of developing postpartum RLS [10]. RLS prevalence dramatically decreases around the time of delivery, ranging between 5 and 6% at six months post-partum. The peak of RLS manifestation is in the third trimester, and the symptoms may persist within a few months after birth. Familial predisposition, folic acid deficiency, estrogen status and changes in iron status have been postulated as the cause of the increased occurrence of RLS in pregnancy.

Comorbid anxiety disorders and /or depressive disorders show complex interactions with RLS. With regard to the management, it is important to distinguish whether RLS precedes the psychiatric symptoms or has been developed in the course of depression. In this case, an antidepressant treatment may be an underlying cause of RLS. In a prospective study assessing the risk of RLS in second-generation antidepressants, mirtazapine has been identified as the highest-risk antidepressant [30]. Sertraline, fluoxetine, and amitriptyline appear to increase PLMS that do not disrupt sleep and are thus unlikely to be clinically significant, while bupropion may reduce restless legs symptoms, at least in the short term [for review:23].

Management

The decision to start treatment should always depend on an individual's severity and frequency of symptoms and the degree to which they interfere both with daily activities and with nocturnal sleep. RLS severity can be quantified using the International RLS Severity Scale (IRLS) validated by the International RLS Study Group (scores 1-10: low RLS severity, 11-20: moderate, 21-30: strong, 31-40: very strong [42]. If an underlying potentially treatable cause is revealed, specific therapies such as iron replacement are appropriate. Furthermore, the use of any drugs that may increase RLS symptoms, such as antidepressants, dopamine blockers and antihistamines, should be re-evaluated and if possible reduced or eventually discontinued.

Dopaminergic agents

Levodopa

Evidence-based guidelines have identified levodopa as effective in the treatment of RLS [14,20]. Levodopa plus a decarboxylase inhibitor (carbidopa or benserazide) generally results in robust initial relief with the first dose. Controlled studies have shown the efficacy of levodopa both in idiopathic and uremic RLS. In subsequent comparative studies, levodopa was found to be effective in reducing RLS, but was inferior to pramipexole and ropinirole in that respect. To avoid augmentation, a serious problem with dopaminergic treatment, the daily dosage should be lower than 300 mg/day. Adverse events may also include dry mouth, nausea, vomiting, headache or drug-induced insomnia, and sleep disruption, especially in the elderly. Thus, levodopa can be recommended for patients with intermittent but not daily RLS (Table 5).

Table 5. Drug therapy for RLS

Drug	Initial dose	Usual dose range	Common adverse effects	Comment
Dopaminergic substances				
Levodopa-benserazide[1]	100/25mg	100/25-200/50mg	Nausea, orthostatic hypotension, augmentation	Not used for chronic treatment because of high risk of augmentation
Pramipexole[2]	0,088 mg (Europe) or 0.125 mg (USA)	0,125-0,75 mg	Nausea, insomnia, daytime sleepiness, impulse control disorder, augmentation	Augmentation less common than with levodopa; extended release formulation not approved
Ropinirole[1]	0,25 mg	0,5-4,0 mg	Similar to pramipexole	Similar to pramipexole
Rotigotine transdermal patch[2]	1mg/24 hours	1-3 mg/24 hours	Skin irritations at application site, otherwise similar to pramipexole	Augmentation possibly less common than with dopamine agonists
Anticonvulsants (α-2-δ ligands)				
Pregabalin	25 mg	150-300 mg	Somnolence, dizziness, ataxia; addictive behaviour	No reported augmentation
Gabapentin	100-300 mg	300-1800 mg	Somnolence, dizziness	No reported augmentation
Intravenous iron formulation				
Ferrocarboxymaltose	500 mg	500-1000 mg once	Dizziness, heat sensitivity	No reported augmentation
Opioids				
Oxycodone prolonged release[2]	5 mg oxycodone /2,5mg naloxone twice daily	10-20 mg oxycodone/5-10 mg naloxone twice daily	Constipation, nausea, headache, somnolence, sleep apnea, addictive behaviour	No reported augmentation; approved as second line therapy

[1]Approved in Germany, Austria, Switzerland; [2]Approved in Europe by the European Medicines Agency;
Dopamine agonists – non-ergot derivatives

Dopamine agonists are regarded as first-line treatment for moderate to severe primary RLS, especially if daily treatment is required. This is due to their well-documented effectiveness and overall good tolerability [for review 14,20]. The available dopamine agonists differ considerably with respect to pharmacokinetics (e.g. half-life), dopamine receptor profiles, potential serious side effects, availability of long-term experience, and licensing status. If dopamine agonists are considered, there is a need to increase the dosage slowly to avoid side effects, making these drugs less suitable to use on an intermittent basis. Concerns regarding the development of "sleep attacks", following observations in Parkinson patients started on low-dose dopamine agonists, do not seem to be a major concern in RLS. However, although more common in levodopa treatment, long-term studies suggest that augmentation may also occur with most of the dopamine agonists. In addition, some patients may experience impulse control disorders, such as pathologic gambling.

Pramipexole has been shown to be effective in reducing sensory restless legs symptoms and PLM in controlled and open-label trials for time spans between one night and several months [26]. Titration of pramipexole is usually started at 0.125 mg and increased every few days. Most patients require 0.75 mg or less, and patients taking higher doses should be carefully monitored for adverse effects, especially augmentation (Table 6). Several placebo-controlled and open-label studies have shown that ropinirole is effective in significantly improving RLS. Ropinirole is usually started at 0.25 mg although most cases require around 2 mg with maximum doses in individual patients of up to 4 mg. Rotigotine is designed to be administered as a transdermal patch for 24 hours continuous dopaminergic stimulation. A multicenter controlled study has shown that rotigotine applied once a day for 6 months (dose range 1-3 mg/24 h) significantly relieved the night- and daytime symptoms of idiopathic RLS [38]. Application site reactions were the most common adverse events in comparison to oral agonists in which nausea can be a significant and limiting side effect (Table 5).

Augmentation

All dopaminergic agents, however, have the potential for causing "augmentation" of RLS symptoms in which restlessness and associated sensory phenomena occur earlier in the day, often in a more severe form involving additional body parts such as the arms (Table 6).

Augmentation may develop as early as during the first month and in up to 82% of patients taking levodopa [5]. The occurrence typically correlates with higher daily doses (e.g. levodopa >300 mg). In terms of dopamine receptor agonists (pramipexole, ropinirole, rotigotine) augmentation may also occur, but probably less frequently compared with levodopa treatment and possibly less common with rotigotine than with other dopamine agonists, which have a shorter duration of action.

Because of augmentation, it may be necessary to discontinue levodopa and switch to dopamine agonists. If augmentation develops with dopamine agonists, it may be helpful to reduce and/or to split the dosage to an earlier time or to switch to rotigotine patch, a longer acting agonist. However, the physician should be aware that even low dose dopaminergics could cause augmentation. If augmentation still occurs, it is necessary to switch to α-2-δ-ligands or a combination therapy. In case of insufficient effects, a second-line therapy with opioids may be necessary [39].

Opioids

Opioids are recommended only in refractory RLS if symptoms fail to respond to dopaminergic medication or in cases where tolerance or augmentation are major issues [33]. In particular, a long-acting form of oxycodone may be appropriate as shown in a recent randomized controlled trial [40]. Prolonged-release oxycodone-naloxone is approved for RLS therapy in Europe. Adverse effects include nausea and constipation, dizziness, sedation, nocturnal confusion, and worsening or even the development of sleep-related breathing disorders. Screening overnight oximetry or polysomnography should be considered in case of suspected sleep apnea. Although addictive behaviour has to be carefully monitored, an escalation of dose does not seem to be a major risk in the absence of a history of substance abuse [33].

α-2-δ-*ligands: Pregabalin, gabapentin and other anticonvulsants*

Pregabalin (an analogue of γ-aminobutyric acid) or the structurally related compound gabapentin (a-2-d calcium channel ligands) may sometimes be considered as a drug of first line, particularly in patients with prominent unpleasant or frankly painful sensory symptoms. Both drugs are approved for the treatment of neuropathic pain and seizures, and pregabalin is licensed for treatment of anxiety disorders. In addition, pregabalin especially improves anxiety symptoms and sleep disturbances in RLS patients. Randomized controlled studies have shown favorable effects of gabapentin enacarbil (a prodrug of gabapentin, approved in the U.S. and Japan) and pregabalin [6]. Effective pregabalin doses are usually in the range of 150 to 300 mg/day. Adverse effects include dizziness, somnolence, and possibly addictive behavior with pregabalin treatment (Table 5).

Iron

Because iron deficiency is common in RLS, oral iron supplementation is an established treatment. Low ferritin concentra-

Table 6. Key features of augmentation [15]

A or B and C for at least 1 week and a minimum of 5 days per week
A Shifting of RLS symptoms to a period of time 2 h earlier than was the typical period of daily onset of symptoms before pharmacological intervention.
B Two or more of the following features: - An increased overall intensity of the urge to move or sensation that is temporally related to an increase in daily medication dosage. - A decreased overall intensity of the urge to move or sensation that is temporally related to a decrease in the daily medication dosage. - The latency to RLS symptoms at rest is shorter than the latency with initial therapeutic response or before treatment. - The urge to move or sensations are extended to previously unaffected limbs or body parts. - The duration of treatment effect is shorter than the duration with initial therapeutic response. - Periodic limb movements while awake either occur for the first time or are worse than with initial therapeutic response or before treatment.
C No other medical, psychiatric, behavior, or pharmacological factors explain the exacerbation of RLS.

tion has been associated with an increased severity of RLS and treatment has been shown to improve symptoms. In addition, very low ferritin levels increase the risk of treatment complications, specifically augmentation. Serum ferritin levels – an indirect measure of brain iron status – should be at least 50 µg/l, and transferrin saturation not less than 20%. Therefore, RLS patients with low ferritin levels should be treated with iron supplementation before starting dopaminergic therapy. A common therapeutic regimen 2 to 3 times a day is 325 mg of ferrous sulfate combined with 100 to 200 mg of vitamin C to enhance absorption. Follow-up ferritin level determinations are needed initially every 3 to 6 months.Oral iron therapy can cause constipation, nausea and abdominal discomfort. Likely efficacious are intravenous iron formulations (e.g. iron sucrose or ferrocarboxymaltose) [7,41] though not yet approved for RLS therapy (Table 5). Augmentation has not been reported. However, not all patients with iron deficiency benefit from iron supplementation. The current recommended treatment is to administer iron supplements to patients with iron deficiency and RLS, irrespective of whether they have associated anemia [39]. Potential serious anaphylactic adverse events that rarely may occur have to be considered.

Non-pharmacological treatment

Non-pharmacological treatments for mild RLS symptoms include sleep hygiene and behavioral therapy for increasing alertness (e.g., crossword puzzles, video games, increased physical activity) as well as modifications of lifestyle such as limiting alcohol and avoiding nicotine or caffeine. In idiopathic RLS, exercise was shown to improve restless legs symptoms in less severely affected patients. In hemodialysis patients, exercise may be also beneficial [32]. Autogenic training, progressive muscle relaxation or meditation have a negative effect often increasing the symptoms. Few publications report effects on restless legs symptoms in patients who were implanted or lesioned for other concurrent indications. Globus pallidus internus targets have been reported to improve RLS symptoms in patients when used to treat Parkinson`s disease and dystonia in a small number of subjects [28].

Key points

- RLS is a common and underdiagnosed disorder with a wide spectrum of severity in neurological and sleep medicine practice.
- The diagnosis is based on the history. In the diagnostic workup, it is important to search for potentially treatable causes for secondary RLS, such as iron deficiency.
- When moderate or severe, RLS is a treatable condition and dopamine agonists are regarded as first-line treatment. For patients with severe and refractory RLS opioid drugs are an option as second-line treatment.
- Augmentation is an important adverse effect of dopaminergic agents, and sometimes difficult to treat.
- Because iron deficiency is common in RLS, ferritin levels should be checked. In patients with low ferritin levels, iron supplementation should be the first-line therapy.
- Although controlled studies are lacking, there is some evidence for the efficacy of non pharmacological strategies in RLS.

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SUMMARY

THE RESTLESS LEGS SYNDROME (REVIEW)

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The restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a common sleep related neurological disorder with prevalence between 1 and 10%, increasing with age. Women are more frequently affected than men. RLS is characterized by an urge to move the legs accompanied by uncomfortable and unpleasant sensations in the legs, worsening of complaints during periods of rest, improvement by movement and an increase of symptoms in the evening or at night. In addition, affected patients may also suffer from severe sleep disorders and negative effects on daily activities. There is often a history of RLS among first-degree relatives, especially with the primary form. Among other, comorbidities or causal factors are iron deficiency, terminal renal insufficiency, pregnancy, polyneuropathy, or psychotropic drugs. The etiology of primary (idiopathic) RLS has not been clarified yet; however, genetic factors and dysfunctional dopaminergic neurotransmission as well as alterations of central iron metabolism play an important role. In addition to non-pharmacological treatment such as lifestyle modifications or behavioral strategies, levodopa, dopamine agonists, or anticonvulsants are effective. Opioids may be used in otherwise refractory forms. In the case of secondary or comorbid RLS, treatment of the underlying disease is necessary.

Keywords: Restless legs syndrome - sleep related movement disorder - differential diagnosis – comorbidity –clinical decision-making – treatment.

РЕЗЮМЕ

СИНДРОМ БЕСПОКОЙНЫХ НОГ (ОБЗОР)

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Синдром беспокойных ног (СБН), также болезнь Уиллиса-Экбома, является неврологическим расстройством двигательного характера с распространением от 1-10% и с превалированием среди взрослого населения женского пола. СБН характеризуется неприятными ощущуниями в конечностях, которые появляются или обостряются в состоянии покоя вечером или ночью и сопровождаются непреодолимым желанием перемещения нижних конечностей. Симптомы, которые ослабляются или исчезают после моторной активности, усложняют процесс засыпания, нарушают ночной сон и подавляют дневную активность. Семейные случаи СБН отмечаются при первичных формах. СБН часто сопутствует дефициту железа, терминальной стадии почечных болезней, беременности и полинейропатии; иногда индуцирован лекарственными средствами. В случае неизвестной этиологии значимыми патофизиологическими факторами являются генетически обусловленные дисфункции дофаминергической нейротрансмиссии и центрального метаболизма железа. Рекомендованы нефармакологические стратегии лечения; эффективными средствами являются дофаминергические и противосудорожные препараты. При резистентных формах допустимо применение опиоидергических препаратов. В случае вторичного или сопутствующего СБН необходимо лечение основного заболевания.

რეზიუმე

მოუსვენარი ფეხების სინდრომი (მიმოხილვა)

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მოუსვენარი ფეხების სინდრომი (მფს), ასევე ვილის-ეკბომის დაავადება, ძილის დარღვევით მიმდინარე ნევროლოგიური მდგომარეობაა, რომელიც აღენიშნება მოსახლების 1-დან 10%-ს, მნიშვნელოვნად უფრო ხშირია ზრდასრულებში და ქალებში. მფს ხასიათდება უსიამოვნო შეგრძნებებით კიდურებში, რომლებიც იწყება ან მწვავდება მოსვენების მდგომარეობაში, ძირითადად, საღამოს ან ღამით დაძინების წინა პერიოდში, და თან ახლავს ფეხების ამოძრავების დაუოკებელი სურვილი. სიმპტომები უკუვითარდება მოტორული აქტივობით, რაც ართულებს ჩაძინების პროცესს, არღვევს ღამის ძილს და შედეგად დაქვეითებულია დღის აქტივობა. მფს-ის ოჯახური შემთხვევები განსაკუთრებით ხშირია პირველადი ფორმებისას. მფს ხშირად თან ახლავს რკინის დეფიციტს, თირკმელების დაავადების ტერმინალურ სტადიას, ორსულობას და პოლინეიროპათიას, ზოგჯერ კი ინდუცირებულია წამლებით. უცნობი ეტიოლოგიის შემთხვევებში მნიშვნელოვან პათოფიზიოლოგიურ ფაქტორებად განიხილება გენეტიკურად განპირობებული დოფამინერგული ნეიროტრანსმისიისა და რკინის ცენტრალური მეტაბოლიზმის დისფუნქციები. მფს-ის დროს მიმართავენ არაფარმაკოლოგიურ სამკურნალო სტრატეგიებს, იყენებენ დოფამინერგულ და ანტიკონვულსიურ მედიკამენტებს, ხოლო რეზისტენტული ფორმებისას ოპიოიდერგულ პრეპარატებს. მეორადი ან თანმხლები მფს-ის შემთხვევაში აუცილებელია ძირითადი დაავადების მკურნალობა.

CLINICAL-PATHOGENETICAL ROLE OF TOLL-LIKE RECEPTOR 2 (RS 5743708) AND INTERLEUKIN-10 (RS 1800896) GENES POLYMORPHISM IN THE COURSE OF HERPES ZOSTER IN ADULTS

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Herpes zoster is one of the global problem of the present time due to rapidly increase of morbidity level. Approximately one third of patients suffer from shingles during their life. The risk of manifestation herpes zoster among the population is about 30%, with a rapid increasing of incidences in the age over 50 years. Each year in Europe and the United States there are about 4-5 new cases of herpes zoster per 1000 population [19,28]. In Ukraine, the incidence is about 12-15 cases per 100,000 population. It is known, that morbidity of herpes zoster increasing with age, and reaches 10 cases per 1000 population [17,19]. The relapsing courses rate is regularly increasing and amounting for about 14 cases per 1000 population annually [17]. Only about