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Review

Restless Legs Syndrome

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A B S T R A C T

Being of the most frequent causes of insomnia, which in the end leads to chronic fatigue, inadequate performance of daily activities, and serious disruption of quality of living, restless legs syndrome (RLS) is nowadays not only a serious medical problem but a socio-economical one as well. Prevalence of the disorder in general population is estimated at 5 to 15%. Family history is positive in over 50% of idiopathic RLS patients which points to genetic basis of the disorder. The characteristics of the secondary or acquired form of RLS are symptoms that start later in life as well as a rapid progression of the disease. On the other hand, idiopathic RLS more often starts at a younger age and the prognoses are better. Over twenty disorders and conditions are brought in connection with secondary RLS. Although the cause of primary RLS is still unknown, there is a strong connection between central metabolism of iron as well as dopamine levels and RLS manifestation. A differential diagnosis of RLS includes a wide specter of motor and sensory disorders. Diagnosis is based on clinical features and the history of disease. To correctly diagnose idiopathic RLS one must first eliminate secondary causes of RLS and then also exclude any disorders with clinical features that mimic those of RLS. It has been estimated that some 20 to 25% of patients need pharmacological therapy. Best initial therapy is the application of nonergot dopamine agonists. Anticonvulsants, benzodiazepines and opioides can be given to patients who are refractory to dopaminergic therapy, those suffering from RLS with emphasized painful sensory component and those with RLS connected with insomnia

Key words: *Restless legs syndrome, epidemiology, clinical feature, diagnosis, treatment*

Introduction

Restless legs syndrome (RLS) is the central nervous system disorder characterized by an irresistible need to move one's legs or arms, less commonly. Such need is accompanied or caused by unpleasant sensations in the extremities, which mostly manifest themselves at rest. Moving the extremities eases or removes the unpleasant sensations altogether. It is common for the symptoms to get worse in the evening, before going to sleep and during the night, which has a direct negative influence on the ability to fall asleep or to stay asleep.

For the first time in 1672 Thomas Willis, M.D., described as a separate clinical entity a patient who would today be diagnosed as suffering from RLS. Willis wrote in the London Practice of Physick (1685): »...Wherefore to some, when being in bed they betake themselves to sleep, presently in the arms and legs. Leaping and contractions of the tendons and so great a restlessness and tossing of the members ensure, that the diseased are no more able to sleep, than if they were in the place of the greatest torture...«. It was not until 1945 that a Swedish doctor Karl-Axel Ekbom identified and described the syndrome and presented it on eight different cases in his book »Restless Legs«[1]. The syndrome is also known as the »Ekbom syndrome«. Another important year in the history of RLS was 1982 when dopaminergics (DA) were introduced as a form of therapy[2], which is still a gold standard for treatment. The syndrome has been called different names – »Asthenia Crurum Paraesthetica«, »Irritable Legs«, »Anxietas Tibiarum« – the most widely accepted term today is the »Restless Legs Syndrome«.

Epidemiology

In spite of great discrepancies in the results of epidemiological studies conducted so far, RLS is considered the most common movement disorder and among the most frequent of all known disorders. It is also one of the most common causes of insomnia which can lead to chronic fatigue and reduced ability in performing daily

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activities. These are the reasons why RLS is no longer considered to be only an important medical issue but a socio-economical issue as well. The prevalence of RLS is controversial. The data differ from one study to another, and according to some research the prevalence is as high as 30%. In many epidemiological studies making a diagnose of RLS was mostly based on fulfilling the four essential diagnostic features without taking into account the differential diagnosis of RLS mimics, thus probably explaining high prevalence in some studies. Recently, Cambridge-Hopkins diagnostic questionnaire for RLS (CH-RLSq) was developed with sensitivity and specificity of 87.2% and 94.4%[3]. It is the first validated self-completed questionnaire that includes questions designed to exclude conditions that imitate RLS, making the true prevalence lower than previously reported. In support to this observation is finding that 16% of patients with other disorders fulfilled four essential RLS features[4]. The largest studies have suggested that the prevalence of RLS is 5–12% in general population with prevalence of the clinically significant RLS being between 1–3%[5,6].

According to our observational study, performed in outpatient clinic of Department of Neurology, Zagreb School of Medicine and University Hospital Center Zagreb, the prevalence of RLS in Croatian population is high[7]. Questionnaire based on diagnostic criteria developed by the International Restless Legs Study Group was used[8]. A survey included 500 subjects with various neurological symptoms aged 21 to 71 years. A total of 79 (15.8%) examines answered positively, fulfilling criteria for RLS. Idiopathic form of RLS was found in 74 (93%) of them, while secondary form of RLS due to anemia, diabetes mellitus and uremia was found in 5 (7%) subjects. High percentage of newly diagnosed could be imputable to specific population included in study, although our results do not differ from some other studies conducted worldwide neither from our underway investigation in general population.

The RLS is closely related to a sleeping disorder called Periodic Limb Movement in Sleep (PLMS), condition characterized by rhythmic extensions of a toe thumb and the dorsiflexion of the ankle joint with periodic flexions in a hip or knee. Approximately 85% of RLS patients have PLMS[9]. Whether RLS and PLMS are separate clinical entities or just two forms of the same disease remains to be revealed.

Etiology and Pathophysiology

RLS can etiologically be divided into idiopathic (familial, hereditary) and secondary (acquired). The latter manifests itself as a consequence of other pathological activities. The main causes of the secondary RLS are kidney failure/uremia, iron deficiency, neuropathy, pregnancy, folic acid deficiency, drugs (antipsychotics/neuroleptics, tricyclic antidepressants, calcium channel antagonists, antihypertensive, selective serotonin reuptake inhibitors/SSRIs, lithium, antiemetics with central effect, antihistamines), injuries and diseases of the spinal cord and the Parkinson's disease (PD). According to the Winkelmann's study conducted on 300 RLS patients, 77% of them suffered from the idiopathic form of the disorder[10]. The characteristics of the secondary-acquired form of RLS are that the symptoms appear at an older age and faster progression in contrast to idiopathic form. Family history tested positive in over 50% of the cases with the idiopathic form of RLS, but also in 10 to 15% of those with a secondary/acquired form, suggesting a genetic basis underlying the disorder. The real cause behind the RLS is still unknown. Peripheral localization of symptoms had indicated that the origin of the syndrome might have been peripheral. However, recent studies have shown a central dysfunction to be a more plausible solution. Akpinar's finding of the dramatic amelioration of RLS symptoms[11] on DA replacement therapy led to general conclusion that RLS was hypodopaminergic condition, similar to PD. That postulate has recently been disallowed.

Most research on the RLS pathophysiology has focused on the DA and iron system. Several functional neuroimaging studies, using SPECT (single photon emission computer tomography) and PET (positron emission tomography) techniques, have been conducted in order to understand the role of the DA system. Two of the studies have shown a reduction of presynaptic DA function[12] as well as reduced reuptake of DA within nucleus caudatus and putamen[13]. However, other studies did not confirm these findings. The studies which focused on postsynaptic DA function came up with more consistent results. There is evidence for reduced binding potential of postsynaptic striatal D2 receptors[14,15]. Recent study that evaluated dopamine transporter (DAT) binding potential using PET techniques showed reduction of membrane-bound striatal DAT, but not total cellular DAT in RLS patients[16].

The main shortcoming of the studies conducted so far is their focus primarily on nigrostriatal DA pathway while disregarding the mesolimbic and diencephalo-spinal DA systems that could, hypothetically speaking, be a location for the primary disorder as well. The occurrence of RLS following spinal anesthesia, or injuries and diseases of the spinal cord, has been established in the literature[17]. A possible explanation could be found in the loss of the supraspinal inhibition resulting in the facilitation of spinal flexor responses.

Iron and DA metabolism exhibit daily oscillations marked with higher levels of elementary iron in serum at noon and lower levels at midnight. That, and the fact that iron deficiency is among the most frequent causes of secondary RLS, creates fertile ground for new ideas and research on the possible role of iron in RLS pathophysiology. The role of iron in the disorder was further emphasized when it became apparent that the levels of ferritin in serum and the severity of clinical features in RLS patients are inversely proportional. Low amounts of ferritin are the best indicators of reduced iron reserves. Normal levels of ferritin are not always indicators of required iron reserves since ferritin is known as a reactant of the acute phase. It has been observed that people who experienced the first symptoms of the disease later in life

and whose family history is negative, had significantly lower levels of ferritin in serum then those with a positive family history and those who experienced first onset of symptoms at an earlier age[18]. Recent discoveries strongly suggest that there are abnormalities of iron metabolism in the brain of the RLS patients. Reduced amounts of ferritin and elevated levels of transferring were found in cerebrospinal fluid[19]. On the other hand, the magnetic resonance imaging showed a reduced iron concentration in putamen and substantia nigra in RLS patients[20,21]. In their pioneer work, Allen and the coworkers examined the brains of the deceased who suffered from RLS during lifetime and compared their observations with healthy control samples. They realized that the subjects who had RLS while they were alive had lower levels of ferritin and higher levels of transferrin. They also noticed that the transferrin receptors expression on neuromelanin cells was lowered in the above mentioned subjects[22]. The latter is interesting because the lower levels of iron should in fact result in the increase of transferrin receptors expression. Whether the low levels of intracellular iron are regulates the uptake athe cause for the impaired homeostatic mechanism whichnd outlet of iron, has yet to be answered. However, a strong connection between iron metabolism and DA system has been established. Iron is a cofactor for tyrosine hydroxylase (TH), an enzyme crucial for the synthesis of DA. Being an integral part of the DA receptors iron deficit alter DA transporter functioning and causes up to 50% reduction of D1 and D2 receptors (as tested on mice)[23,24]. Moreover, iron has a role in regulating Thy1 protein, which is present as a cell adhesion molecule on DA neurons in high degree. Thy1 protein regulates vesicular release of monoamines, DA included[25]. Animal models with iron deficiency have shown a reduced expression of Thy1 molecule on DA neurons. It can be assumed that the reduced levels of iron cause a reduction of DA transporters and DA receptors which, as a consequence, results in the increase of DA production and in the disruption of circadian DA rhythm. This leads to an assumption that postsynaptic receptors cannot adjust adequately to such extreme variations in the circadian rhythm, thus causing a considerable reduction of DA stimulation during the phase of lower concentration of DA, which in high degree coincides with the development of symptoms of RLS[26].

Two recent studies turned the new page in understanding the pathophysiology of RLS, both disallowing the thesis of RLS being hypodopaminergic condition. Autopsy study of RLS patients found increased TH activity in the substantia nigra and decreased D2 receptors in the putamen[27], while abnormally increased CFS 3-O-methyldopa (3-OMD) in untreated RLS patients was found in the second study[28]. Both results are indicative for abnormally increased DA synthesis in contrast to previous thinking. Taken together, RLS is now considered to be hyperdopaminergic condition (increased TH and 3-OMD) consequently leading to postsynaptic desensitization (decreased D2 receptors) that overcompensates during evening and night (circadian low DA activity).

The theory of genetic basis of the origin of RLS, which arose due to epidemiological findings on familial frequency of the disorder's occurrence, is still being investigated. The assumption is that inheritance is autosomal dominant with high penetration, although there are some exceptions. Six suspected loci on chromosomes have been described so far. These are loci on the chromosomes 12q22-23.3 (RLS1), 14q13-21 (RLS2), 9p24-22 (RLS3), 2q33 (RLS4), 20p13 (RLS5) and 19p, with a recessive inheritance form in the first and the autosomal dominant form in the rest of the cases. Desaultes and the associates were the first to identify a potential locus for RLS on a 12q chromosome of a French-Canadian family[29]. It has been assumed that the genetic product is neurotensin, a neuropeptide functioning as a neuromodulator of DA neurotransmission. The inheritance form is autosomal recessive in this case. Bonati and the associates found a potential locus on the chromosome 14q13-21 of the Italian family with a three generation history of RLS and PLMS[30]. That is the first locus with an autosomal dominant inheritance form. Third described locus for RLS was the one on chromosome 9p24-22[31]. RLS4 locus was located on a 2q chromosome and was identified in an isolated population of southern Tyrol[32]. The fifth locus was detected on the 20p13 chromosome of a French-Canadian family[33]. The last suspected locus that was detected is the one on the 19p chromosome[34]. Two recently published genetic studies showed that there was a significant connection between RLS and the intron variants of MEIS 1 gene on the 2p chromosome[35], mitogen-activated protein kinases MAP2K5 and the transcription factor LBXCOR1 on the 15q chromosome as well as BTBD9 gene on 6p chromosome[36]. The risks of manifestation of RLS in patients with variation of BTBD9 gene is 50%. More recently, novel RLS susceptibility loci on 2p14 and 16q12.1 have been identified, but their involvement in pathogenesis of RLS remains to be elucidated[37]. In addition, variants within the NOS1 (nitric oxide synthase) gene were suggested to have a role in the pathogenesis of RLS[38]. Whether these observations can be linked to the fact that the prevalence of cardiovascular diseases is higher in the individuals with RLS symptoms[39] is yet to be seen. Further research of NO modulating agents and their possible therapeutic effects represent a major challenge.

Making a correct analogy between different medical conditions and the manifestation of the RLS is a substantial problem since RLS pathophysiology is still unclear. More than 20 different disorders are linked to secondary RLS. The connection between iron deficiency and the manifestation of RLS has already been discussed. Kidney failure/uremia is among the most common causes of secondary RLS with prevalence of RLS in patients undergoing dialysis of 20 to 57%. The studies regarding the possible differences between patients undergoing a hemodialysis and those undergoing peritoneal dialysis have not been conducted. Pathogenesis of the uremic RLS is unknown. An important clinical feature of kidney failure is anemia, which occurs due to endocrinal insufficiency of kidneys (reduced erythropoietin synthesis), reduced

iron absorption, increased iron loss via digestive system, and shorter life cycle of erythrocytes. The results of most of the studies did not make a connection between any of the markers (urea, creatinine) of renal function and RLS. In study conducted on 490 patients undergoing hemodialysis, Takaki specified stress and hyperphosphataemia as possible signs of RLS in dialysis patients[40]. Dialysis patients, whose therapy includes Ca^{++} antagonists, have a higher chance to develop RLS[41]. In some patient with renal failure and concomitant RLS, renal transplantation showed great improvement of RLS symptoms[42]. It has been estimated that 15 to 30% of RLS patients suffer from a mild to moderately severe neurophatic abnormality which can be proven with standard electrophysiological testing or nerve biopsy. The RLS patients with confirmed neuropathic disturbances usually have an inconspicuous family history. Their first RLS symptoms begin at an older age and reach their top intensity rapidly, which separates their symptoms from those associated with the idiopathic form of the disease. It has been noticed that two forms of Hereditary Motor and Sensory Neuropathy (HMSN), Charcot-Marie-Tooth (CMT) type 1 and type 2 show different inclinations toward the development of RLS. 37% of patients with CMT type 2 exhibited symptoms of RLS while none of the patients suffering from CMT type1 demyelinating neuropathy showed symptoms similar to those of RLS[43]. Prevalence study of different neuropathic diseases accompanying diabetes mellitus (DM), conducted on 800 DM patients, showed statistically insignificant difference in RLS prevalence between the healthy control group and the group with DM. However, the same study showed a significantly higher percentage of RLS in patients with DM type II then in those with DM type I[44]. Traumatic injuries of spinal cord, spinal anesthesia, neoplastic processes which spread to the spinal cord, demyelinating or postinfectious lesions can enhance one's chances to develop RLS. Transient form of RLS was recorded in 8.7% cases immediately after the spinal anesthesia had been performed[45]. Symptoms of RLS are common in multiple sclerosis (MS) patients as well. In prospective study by Italian authors, the prevalence of RLS in MS patients stood at 37% and patients with severe damage to cervical part of their spinal cord had significantly higher risks of developing RLS[46]. Pregnancy is a predisposing factor for RLS development and RLS is thought to affect more than 20% of pregnant women. Furthermore, women who developed RLS during pregnancy had a 4-fold increased risk of developing chronic RLS compared with women who did not have RLS when pregnant[47]. Symptoms most frequently occurred in the third trimester. There were no significant differences in age of the pregnant women, their body mass index, the duration of pregnancy, tobacco consumption, way of delivery, and the weight of the baby in those who developed RLS symptoms and in those that did not. However, it has been noted that the levels of elementary iron and hemoglobin in serum were significantly lower in pregnant women who had developed clinical features of RLS[48]. Lee and the coworkers monitored 45 healthy women prior to conception, during pregnancy and after the delivery. The prevalence of RLS grew from 0% prior to conception to 23% in the third trimester. It was noted that pregnant women with developed clinical features of RLS had low ferritin in serum prior to conception, as well as significantly lowered amounts of folates during pregnancy. Since the symptoms persisted in only one pregnant woman after the delivery, this too is the case, just like after the spinal anesthesia, of a transient form of RLS[49]. Folates are necessary for synthesis of DA in CNS. 5-methylenetetrahydrofolate increases the production of tetrahydrobiopterine which is a cofactor in TH synthesis. An interesting fact is that tetrahydrobiopterine has a circadian pattern of concentration in serum with higher amounts in the morning and lower in the evening. The connection between RLS and *PD* has been established long ago. Both RLS and PD have a positive reaction to application of DA. Abnormalities of DA system through neuroimaging studies were established in both disorders and they were both closely connected to PLMS[12,13,50]. It is important to mention that the patients suffering from RLS developed augmentation after levodopa treatment[51]. Augmentation is a phenomenon similar to manifestation of motor fluctuations in PD patients who were treated with levodopa as well. It is hard to evaluate the prevalence of RLS in PD patients because the symptoms of RLS in PD patients are mostly short-lived and passing and they can be easily mistaken for symptoms such as dystonia, akathisia, tremors and nocturnal motor fluctuations. Approximately 20.8% of PD patients have symptoms of RLS[52]. Of all predisposing factors for the development of RLS in PD population, the role of low levels of ferritin in serum is the only one that has been confirmed. Frequent manifestation of RLS in patients suffering from spinocerebellar ataxia (SCA) was observed by Abel[53]. Even though the results of some studies say that the prevalence of RLS among rheumatoid arthritis patients is 30%, nothing apart from severely lower levels of ferritin in serum could explain the connection between these conditions. Different drugs can cause RLS directly or can exacerbate the already existent RLS. The most commonly described drugs in this context are those from the group of antipsychotics (neuroleptics) due to D2 DA receptors blockage. Antiemetics (except for domperidon) can also cause RLS, due to the blockage of central DA receptors. Other drugs that can provoke RLS are SSRIs, tricyclic antidepressants, lithium, antihistamines, calcium channel antagonists, antihypertensives. The latest epidemiological studies have brought RLS in connection with social habits and economic status[54,55]. Increased body mass index has been related to RLS. The few studies that examined the relations of blood pressure, smoking and alcohol consumption to RLS either found no relation or report controversial results.

Clinical Features

Based on clinical features, the symptoms of RLS can be divided into sensory and motor. The patients commonly complain to their doctor about uncomfortable sen-

sory sensations in legs, accompanied with a need to move, although in some cases the first signs of RLS can be sleep disorders. Upper extremities are involved in 50% of cases but the most common location of sensory sensations is the area between the knee and the ankle joint. The changes in the quality of sensations can be manifested as paresthesia and dysesthesia. Patients use different expression to describe their sensory symptoms: crawling, creeping, itching, pins and needles, painful, »antsy«, electrical, or uncomfortable. Some of the most creative descriptions are a »toothache in legs« and »Elvis legs«. Another major symptom of RLS is motor discomfort. People who cannot stop moving their legs while sitting do not necessarily have RLS. One of the main characteristics of RLS is that moving results in easing or in complete disappearance of uncomfortable sensations. Such movements are rich in their diversity and they can manifest as jerking and turning of legs and arms, stretching and flexing, rubbing the legs against each other, walking up and down. This is why patients with RLS either avoid or handle poorly the »activities« that include staying still, such as long plane journeys, trips to a theater or similar activities. A characteristic of RLS is worsening of symptoms at rest, especially in the evening, prior to bedtime or during the night. In typical cases, the symptoms reach their peak between midnight and 4 am, and the biggest relief comes between 6 am and noon. The fact that the symptoms get worse in the evening has a negative effect on falling asleep process as well as on staying asleep, which leads to chronic daytime exhaustion and fatigue. According to severity of clinical features, RLS can be divided into a mild form (symptoms occur only occasionally accompanied with mild sleep disorders), moderately severe to severe form (symptoms occur on daily basis and demand treatment) and refractory form which does not seem to respond well to daily DA therapy or it leads to progression of symptoms.

The natural course of disease is typical. RLS is a chronic condition which can occur at any age. An early occurrence is a characteristic of the idiopathic, hereditary form, while a later onset of the disease, followed by a fast progression of symptoms, points to the secondary form of the disease. The symptoms fluctuate at first but become more frequent and severe in time. Over 90% of RLS patients suffer from a sleeping disorder and RLS is itself among the most common causes of insomnia. RLS is combined with PLMS in 80% to 90% of cases. The characteristic of that disorder are periodic flexions in hips and knees and less often in wrists as well as dorsiflexions in the upper ankle joint and in toes. Polysomnographic tests are used in order to make the diagnosis. The movements occur in series of al least four in a row. One such movement lasts from 0.5 to 5 seconds while the frequency is every 5 to 90 seconds. The index (the number of PLMSs during one hour of sleep) larger then 5 during the course of the night is pathological. PLMS movements should not be confused with the so called »hypnic jerks« or irregular twitching of the whole body or just the extremities during the falling asleep process.

It is hypothesized that also cognitive impairments may occur[56]. In 60% of RLS patients the disease has a progressive course, while in 40% of the cases the disease manifests itself in a relapse-remitting form with remission phases of different longitudes. It is important to stress out that a neurological examination of RLS patients does not show any deviations from normal, except from a possible existence of neuropathy.

Diagnosis

Diagnose of RLS is based on clinical features. It is easy to diagnose a patient with typical symptoms. However, it can be hard to make a diagnosis if the symptoms are atypical or if RLS is joined with another movement disorder. The criteria in making the RLS diagnosis have been suggested by NIH (National Institute for Health) work group[8] and updated in 2003[55,57] (Table 1). They consist of four essential criteria and three supportive features, which can be used to confirm the diagnosis but are not crucial for making the diagnosis in the first place. Besides these diagnostic criteria, there are also associated features furthermore contributing the correct diagnosis.

TABLE 1
DIAGNOSTIC CRITERIA FOR RESTLESS LEGS SYNDROME

Essential criteria	• An urge to move the legs, usually accompanied or caused by uncomfortable or unpleasant sensations in the legs • The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting • The urge to move or unpleasant sensations are partially or totally relieved by movement such as walking or stretching, at least as long as the activity continues • The urge to move or unpleasant sensations are worse in the evening or at night than during the day, or only occur in the evening or night
Associated features	• Positive family history of RLS • Positive response to dopaminergic drugs • Periodic limb movements during wakefulness or sleep as assessed with polysomnography or leg activity devices
Supportive clinical features	• Positive family history of RLS • Positive response to dopaminergic drugs • Periodic limb movements during wakefulness or sleep as assessed

Clinical, laboratory and electro-physical tests are required in order to eliminate the secondary causes of RLS. The presence of neuropathies can be confirmed by an electromyography (EMG) or by an electroneurography (ENG). In case of positive findings, thyroid function must be tested, and the levels of folates, vitamin B12 and sugar in blood must be determined. Electrolytic status, urea, creatinine are the determinants of renal function and are involved in the testing algorithm. Radiological tests and neuroimaging tests have more of a scientific-researching value than diagnostic value. Other tests that can be helpful in RLS diagnostics are polysomnography, actigraphy and the immobilization test. Polysomnography (PSG) is an exceptionally important diagnostic method defined as simultaneous recording of several physiological functions that occur during sleep. EEG, surface EMG are electroculogram are recorded simultaneously. It is possible to perform a cardio-respiratory monitoring as well. PSG is indispensable in differentiating PLMS from other sleeping disorders (sleep apnea, nocturnal myoclony, delayed sleep-phase syndrome, and other). Actigraphy is used to detect muscular activity with an actigraph unit tied around the ankle joint. The main use of actigraphy is to evaluate the effectiveness of therapy. The immobilization test is used in diagnosing and evaluating the severity of clinical features. It is performed 90 minutes prior to bedtime and it lasts for an hour. During that time, the patient lies awake in the bed under the angle of 45°. The leg activity is measured with standard bilateral electromyography (EMG) while electroencephalogram (EEG) is recorded at the same time. Every five minutes the patient rates the intensity of discomfort on a visual analogous scale.

Differential Diagnosis

Differential diagnosis of RLS includes a wide specter of motor and sensory disorders. In order to make a correct idiopathic RLS diagnosis, first the secondary causes of RLS must be excluded and then any other disorders who clinical features can imitate those of RLS. RLS is most commonly confused with neuropathies, especially if they occur simultaneously. The characteristics of both disorders are paresthesias and dysesthesias and the difference is in daily rhythm of symptoms and the effect of movements on sensory sensations. Symptoms in RLS patients get worse at rest and in the evening while movement ameliorates them, which is not the case in neuropathy patients. Polysomnographic testing can be helpful because if PLMS is detected, it can be used to confirm RLS diagnosis. Akathisia is a drug-induced movement disorder which is characterized with inability to either stand or sit still. Akathisia can be caused by medications which block central DA receptors (neuroleptics, anti--emetics affecting the central nervous system). When compared with RLS, symptoms of akathisia do not seem to have a daily rhythm – motor discomfort lasts throughout the day and can attack any body parts whereas sensory sensations do not exist. Nocturnal cramping in legs is characterized by painful sensations in legs and can imitate RLS clinical features with dysesthesias. RLS can also be confused with myoclonus. They are unconscious, involuntary, rapid twitches of one or a group of muscles which can but do not have to cause movements. Targeted case history and clinical examination are enough to differentiate these to disorders. Diseases of blood vessels like varicose veins or peripheral arterial stenosis can be characterized by painful sensory sensations. Main differences in regards to RLS are worsening of symptoms while moving and easing of the symptoms while resting. Hyperpigmentation and trophic skin changes can also be there. Numerous other syndromes (painful leg and moving toe syndrome, causalgia-dystonia syndrome, hypotensive akathisia, arthritis) can partially overlap with RLS clinical characteristics. Being familiar with essential criteria and supportive features can alleviate the discerning and recognizing of RLS and enable correct treatment, which can subsequently help make the everyday life of patients less uncomfortable and restless.

Treatment

The decision to start therapy is based on the severity of symptoms and their influence on the general condition of the patient. The assumption is that 20% to 25% of RLS patients require pharmacological treatment[58] (Table 2). Nonpharmacological measures are favored in case of mild RLS symptoms. Effective ones seem to include avoiding drinking coffee, tea or alcohol prior to bedtime, quitting cigarette-smoking, proper sleep hygiene with regular going to sleep pattern, relaxation and concentration techniques, yoga, light to moderate physical activity and warm or cold baths. Secondary RLS needs to be treated etiologically. The most common causes of secondary RLS are uremia, anemia and pregnancy. In most of the pregnancies the symptoms improve after delivery[59]. Unlike kidney transplantation, dialysis does not remove

TABLE 2
PHARMACOLOGIC TREATMENT OF RESTLESS LEGS SYNDROME

Intermittent RLS symptoms	• Dopamine agonists: ropinirole, pramipexole (low dose if tolerated) • Levodopa with decarboxylase inhibitor • Mild to moderate strength opioid (codeine, tramadol) • Sedative – hypnotics
Daily RLS symptoms	• Dopamine agonists • Anticonvulsants (gabapentin) • Opioids • Benzodiazepines (clonazepam)
Refractory RLS symptoms	• Change to a different dopamine agonist • Switch to an opioid or anticonvulsant • Add a second medication, possibly with reduced agonist dose • High potency opioids for severe and resistant case (methadone)

RLS in patients with chronic renal failure[60]. Levels of ferritin in serum which are bellow 50 ng/ml call for compensation. Intravenous iron application proved to be far more efficient then oral preparations. Early and the associates achieved almost 60% symptom regression in RLS patients after intravenous application of 1000 mg of iron[61].

Four groups of medications have proved to be effective in relieving RLS symptoms[60,62] (Table 3).

a) DA drugs: Akpinar's discovery regarding the positive effects of levodopa, led to a new era in treating and understanding RLS. DA are the best studied group of medications and they represent a first choice therapy. Still, there are certain differences in characteristics among different subcategories of DA. Levodopa with dopa-decarboxylase inhibitor: one evening application of levodopa/benserazid (100+25) has proven to successfully eliminate nocturnal symptoms (PLMS reduction, sleep quality improvement) of the idiopathic and of the secondary RLS as well. The disadvantages are the short half-life of levodopa (1 to 3 hours). Due to side-effects, the treatment principle can best be described with »start low, go slow« phrase. Complications due to long-term use of all DA are augmentation, rebound phenomenon and wide spectrum of impulse control disorder including binge eating, compulsive shopping, pathological gambling, punding and hypersexuality[63]. Augmentation phenomenon was recorded in 80% of patients who had been on levodopa for periods longer than two months[51]. Augmentation is clinically manifested by an increase in severity of symptoms beyond the level at baseline. Latest diagnostic standards for determining the augmentation phenomenon date from 2007 and the severity of augmentation itself can be assessed with the assistance of ASRS scale (Augmentation Severity Rating Scale)[64,65]. It is a progressive condition that requires a change in treatment regimen in severe cases. When augmentation occurs the dosage should be lowered and applied in several intervals. There is also a possibility of introducing non-DA drugs in therapy[58]. Having no specifically designed trials to measure augmentation it is hard to evaluate true rate of this complication[66]. In addition, it remains to be explored whether genetic predisposition for developing augmentation or protective haplotype exist. The rebound phenomenon has first been described in 1993[67]. It denotes the apparition of RLS symptoms in second half of the night and before morning, once the applied dose looses its effect. It appears less often than augmentation and poses a less severe clinical problem. The augmentation and rebound phenomena are quite similar to motor fluctuations that occur in PD patients who have been on levodopa for years. Side-effects seem to be less frequent when controlled-release form of levodopa is applied. DA agonists are considered to be best initial therapy. Bromocriptine was the first DA used in RLS treatment. Compared to levodopa, bromocriptine has shown a similar effectiveness and more frequent side-effects. The drug that has been tested for longest time is pergolide, a long-lasting ergotine-based DA receptor agonist. In a two year study 45% of patients on pergolide did not exhibit any symptoms and 50% of them experienced a moderate relief of symptoms. The most frequent side-effects are those that occur in the very beginnings of treatment (in 60% of patients) such as nausea, vomiting, insomnia and constipation. Augmentation manifested in 27% of patients and mostly mildly disturbed clinical condition[68]. After reports of the fibrous changes of heart valves induced by ergots these drugs are avoided[69,70]. Based on clinical evidence, estimation of treatment efficiency, severity and frequency of side-effects, nonergot DA pramipexole and ropinirole are considered to be the best possible initial therapy. When a dose of 0.375 to 0.75 mg of pramipexole is applied, the symptoms of RLS are alleviated and those of PLMS reduced[71]. The drug did not seem to affect certain parameters of sleep quality (overall time spent sleeping, the number of awakenings). Side-effects when the treatment began (nausea, dizziness) are milder and transient. Around 5 to 10% of patients who use pramipexole for at least six months develop augmentation. It develops more often in patients with secondary RLS. But pramipexole is effective in patients who have developed augmentation and levodopa tolerance. Ropinirole has the same effect on RLS and PLMS symptoms as pramipexole. The advantages of pramipexole and ropinirole are reduction of daytime sleepiness and improvement in sleeping quality as well as quantity. Other DA mentioned are apomorphine, rotigotine[72] and lisuride[73].

TABLE 3
DOSE RANGE OF COMMON MEDICATIONS FOR RESTLESS LEGS SYNDROME

Drug class	Dose range (mg)
Dopaminergics:	
• levodopa	50–200
• pramipexole	0.125–0.75
• ropinirole	0.25–4
Opioids:	
• codeine	15–120
• tramadol	50–400
• oxycodone	5–20
• methadone	5–40
Anticonvulsants:	
• gabapentin	300–2.700
Sedative – hypnotics:	
• clonazepam	0.5–2
• flunazepam	15–60

b) Anticonvulsants: when DA therapy fails, use of anticonvulsants seems appropriate. They are also useful in treatment of RLS with emphasized painful sensory component. Compared to ropinirole, gabapentin (me-

dium applied dose of 800 mg) has a similar effect on sensomotoric RLS and PLMS symptoms[74].

c) Sedative – hypnotics: clonazepam is used most frequently. The doses from 0.5 to 2 mg significantly reduce PLMS. The drug can be an alternative to DA in treating insomnia related RLS. Wider application of benzodiazepines is limited due to numerous side-effects (daytime sleepiness, confusion, slower reactions, substance tolerance and addiction).

d) Opioids: oxycodone and propoxyphene can be useful in patients who are refractory to DA therapy as well as in treating RLS patients with pronounced sleep disorder. The efficiency of methadone in patients resistant to any other form of therapy has been noticed lately[75]. Intrathecall morphin aplication has also been investigated[76]. A wider use of opioids is limited due to numerous side-effects.

Conclusion

RLS is one of most frequent cause of insomnia leading to chronic fatigue and functional disability during the day. To diagnose idiopathic RLS one must first eliminate secondary causes of RLS and then also exclude any disorders with clinical features that mimic those of RLS. The correct diagnose is based on criteria set up by International Restless Legs Study Group which consist of four obligatory essential criteria, three supportive and three associated criteria which are used to confirm the diagnosis. Recently developed validated diagnostic questionnaire should be considered for use in future studies[3]. RLS is nowadays addressed to DA system dysfunction. This became evident when positive effect of DA therapy was observed both in primary and secondary form. Desirable objective of this review is to educate not only neurologist but general practioners as well.

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SINDROM NEMIRNIH NOGU

S A Ž E T A K

Kao jedan od najčešćih uzroka nesanice, što u konačnici uzrokuje kroničan zamor, neadekvatno obavljanje dnevnih aktivnosti te ozbiljno narušavanje kvalitete života, RLS danas predstavlja ne samo važan medicinski već i sociološko-ekonomski problem. Prevalencija se u općoj populaciji procjenjuje na 5–15%. Obiteljska anamneza pozitivna je u više od 50% oboljelih od idiopatskog RLS-a, što upućuje na genetsku podlogu ovog poremećaja. Početak simptoma u starijoj životnoj dobi i brza progresija obilježja su sekundarnog-stečenog oblika RLS-a, za razliku od idiopatskog RLS-a koji se prezentira u mlađih osoba i ima bolju prognozu. Više od 20 poremećaja i stanja dovodi se u vezu sa sekundarnim RLS-om. Iako se uzrok primarnog RLS-a ne zna, postoji veza između središnjeg metabolizma željeza i razine dopamina s pojavom RLS-a. Diferencijalna dijagnoza sindroma nemirnih nogu obuhvaća širok spektar motornih i senzornih poremećaja. Dijagnoza RLS-a se postavlja na temelju kliničke slike i povijesti bolesti pri tome zadovoljavajući esencijalne i pomoćne kriterije. Ispravno postavljanje dijagnoze idiopatskog RLS-a zahtijeva u prvom redu isključivanje sekundarnih uzroka RLS-a, a potom i poremećaja koji svojom kliničkom slikom mogu oponašati RLS. Pretpostavlja se da 20–25% oboljelih od RLS-a zahtijeva farmakološko liječenje. Najboljom početnom terapijom smatra primjena ne-ergotinskih dopaminskih antagonista. Antiepileptici, benzodiazepini i opioidi mogu se primjeniti u bolesnika refraktornih na dopaminergičku terapiju, u RLS-u s naglašenom bolnom senzornom komponentom te RLS-u povezanom s nesanicom. S obzirom na učestalost bolesti, mogućnost dijagnosticiranja te djelotvornost liječenja ne samo neurolozi i psihijatri već i liječnici primarne zdravstvene zaštite moraju biti upoznati s prepoznavanjem i liječenjem ovog sindroma.