Restless Legs Syndrome in 2004

Šonka K., Kemlink D.
Department of neurology of the First Faculty of Medicine,
Charles University in Prague, Czech Republic

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Abstract: The restless legs syndrome (RLS) is a sensorimotor disorder characterised by an intense urge to move the legs and sometimes also other parts of the body, and accompanied by a marked sense of discomfort or pain in the affected body parts. This urge has a circadian pattern – it is most pronounced in the evening or during the night. RLS symptoms are relieved by movement. The pathophysiology of RLS is related to dopamine transmission insufficiency, low iron storage in substantia nigra neurons, and spinal cord dysfunction. RLS is idiopathic or secondary (usually associated with iron deficiency, end-stage renal failure, pregnancy and spinal lesions). One half of the patients with idiopathic RLS have positive family history of RLS. RLS is curable, though the choice of therapy and proper dosage titration may take a long time, and though the therapy may sometimes have to be changed owing to augmentation. The most important pharmacologic treatment used in RLS includes L-DOPA, dopamine agonists, opiates, anticonvulsants and benzodiazepines. Therapy improves significantly the condition in long-term at least in 80% of RLS patients.

Key words: Restless legs syndrome (RLS) – Dopamine – Iron – L-DOPA – Opiates – Periodic limb movements in sleep (PLMS) – Genetics.

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Mailing address: Department of neurology of the First Faculty of Medicine, Charles University, Kateřinská 30, 120 00 Prague 2, Czech Republic,
Phone +420 224 965 568 (18), Fax +420 224 965 518, e-mail: ksonka@lf1.cuni.cz

Milestones of restless legs syndrome research

To the best of our awareness, the history of the knowledge about the restless legs syndrome (RLS) can be traced back to the 17th century when Sir Thomas Willis, an English physician and anatomist, cogently described its manifestations [1]. While symptoms of RLS were scrutinised by many great personalities of medicine and neurology in particular, the modern history of RLS study started with a basic work published in 1945 by Swedish neurologist Karl Ekbom, who gave the disease its name – restless legs syndrome [2]. In 1953, British physician Symonds described nocturnal myoclonus (to use present-day terminology – periodic limb movements in sleep – PLMS) [3]. In 1965, Lugaresi and coworkers from Bologna noted an association between PLMS and RLS [4]. Dopaminergic treatment for RLS was first reported by Akpinar in 1982 [5]. In 1995, the International RLS Study Group devised precise diagnostic criteria [6] to upgrade them later on [7].

Prevalence and impact on the quality of life

The significance of RLS is highlighted by two facts – a surprisingly high prevalence (in Europe and Northern America) and impact on the patients´ quality of life.

As early as 1945, Ekbom expected 5% prevalence in the population [2]. The results of prevalence research in recent years, with the existing RLS criteria already applied, show RLS prevalence in the two regions as ranging between 5 and 12%. Having contacted by phone a total of 18,980 persons aged 15 – 100 years in Britain, Spain Germany and Italy, Ohayon and Roth [8] found an RLS prevalence of 5.5 %. Another large European prevalence study was undertaken in Germany. 4,310 persons aged 20 – 79 years were addressed face to face and found to show an overall prevalence of 10.6 % with the figure rising with age [9]. A recent study by Hening et al. of 23,052 patients and their primary care physicians in the United States, Canada, Italy, France and Spain found RLS in 11.1% of the respondents with 9.6% of them experiencing weekly symptoms [10]. Ulfberg et al [11], who found RLS in 5.8% out of 4000 Swedish men approached by way of a questionnaire, also noted RLS prevalence as increasing with advancing age. RLS patients reported more sleep-related complaints, headache, bad temper, lowered libido, hypertension, and heart problems. Recent studies point to a higher RLS prevalence in women [8, 9, 10, 11]. A substantially lower prevalence of RLS was found in pilot studies undertaken in Asia – 1.5% in Japan [12], less than 1% in Singapore [13], thus indicating geoethnical differences in the occurrence of RLS. A comparison between the SF-36 scores in patients with RLS and the normative general population suggests that this disorder has a significant impact on patient QOL [14]. Patients often fail to get adequate treatment [10].

RLS symptoms – clinical diagnosis

Though Ekbom's pioneering work of the 1940s gave an exhausting description of RLS symptoms, a modern unification of diagnostic criteria only came with the set

of criteria put out by the International RLS Study Group in 1995 [6]. In the year 2002, these criteria were specified and extended to comprise also children and persons with cognitive disorders [7]. At the same time, the RLS rating scale was developed and validated [7, 15] (Tab. 1).

The diagnostic criteria are classified in three groups:
1. Essential criteria defining RLS which must be present if the diagnosis is to be made. 2. Supportive clinical features of RLS; their presence can help resolve any

Table 1 – Restless Legs Syndrome Rating Scale (RLSRS)

Have the patient rate his/her symptoms for the following ten questions. The patient and not the examiner should make the ratings, but the examiner should be available to clarify any misunderstandings the patient may have about the questions. The examiner should mark the patient's answers on the form.
In the past week ...
1. Overall, how would you rate the RLS discomfort in your legs or arms?
Very severe.
Severe.
Moderate.
Mild.
None.
2. Overall, how would you rate the need to move around because of your RLS symptoms?
Very severe.
Severe.
Moderate.
Mild.
None.
3. Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?
No relief.
Mild relief.
Moderate relief.
Either complete or almost complete relief.
No RLS symptoms to be relieved.
4. How severe was your sleep disturbance due to your RLS symptoms?
Very severe.
Severe.
Moderate.
Mild.
None.
5. How severe was your tiredness or sleepiness during the day due to your RLS symptoms?
Very severe.
Severe.
Moderate.
Mild.
None.

diagnostic uncertainty. 3. Associated features of RLS. The diagnosis of RLS in adults is based on the patient's clinical history. If typical features are present, the diagnosis is easy to establish. However, it could be more difficult in patients with atypical symptoms and comorbidity, especially with sleep and movement disorders.

The RLS essential criteria include: 1. An urge to move the limbs, mainly the legs. This urge is usually associated with paresthesias and dysesthesias; such sensations may well be reported as a trigger of that urge. Their presence in the extremities of RLS patients is described in a variety of ways – burning, tickling, pinching, pain, prickling, titillation, pressure, getting cold, feeling warm, feeling

Table 1 – Restless Legs Syndrome Rating Scale (RLSRS)

6. How severe was your RLS as a whole?
Very severe.
Severe.
Moderate.
Mild.
None.
7. How often did you get RLS symptoms?
Very often (6–7 days in 1 week).
Often (4–5 days in 1 week).
Sometimes (2–3 days in 1 week).
Occasionally (1 day in 1 week).
Never.
8. When you had RLS symptoms, how severe were they on an average?
Very severe (8 h or more per 24 h).
Severe (3–8 h per 24 h).
Moderate (1–3 h per 24 h).
Mild (less than 1 h per 24 h).
None.
9. Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs, for example, carrying out a satisfactory family, home, social, school or work life?
Very severe.
Severe.
Moderate.
Mild.
None.
10. How severe was your mood disturbance due to your RLS symptoms – for example, angry, depressed, sad, anxious or irritable?
Very severe.
Severe.
Moderate.
Mild.
None

Answers for this IRLS are scored from 4 for the first (top) answer (usually 'very severe') to 0 for the last answer (usually none). All items are scored. The sum of the item scores serves as the scale score.

as if soda water were circulating in one's veins, etc. The sensory symptoms may occur bilaterally or unilaterally (the sides may take turns or only one side is permanently affected). 2. The urge to move and unpleasant sensations are exclusively present or are at least worst at rest or inactivity. Typically, the patient complains of the symptoms appearing while lying in bed, sitting while watching TV, in the theatre or at a concert, or also during long journeys. 3. The urge to move or unpleasant sensations are partially or totally relieved by movement at least as long as the activity continues. Hence, patients perform all sorts of useless movements – stretching, flexing, stamping their legs, rubbing one leg against the other, standing up, standing, pussyfooting and, in particular, walking about. The intensity of movements is more or less dependent on the intensity of RLS. 4. The urge-to-move intensity is marked by circadian variation with clearly defined nocturnal and evening maxima. Yet the nocturnal peak is independent of sleep.

Supportive clinical features of RLS comprise: 1. a positive response to dopaminergic medication, 2. periodic limb movements – PLM (Fig 1 – 5) and, 3. a family history of RLS. PLM are seen, according to Montplaisir et al. [16], in 80% of RLS patients.

Three associated clinical features may provide additional information about the patient's diagnosis. 1. Natural clinical course: while RLS is essentially a

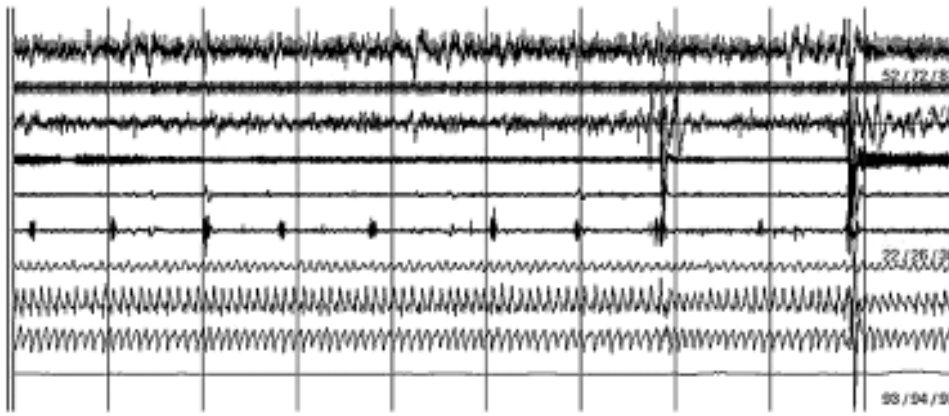

Figure 1 – PLMS of the left leg during sleep 2 NREM. Duration of represented period is 5 min. Polysomnography of 56 years old man suffering from RLS and periodic limb movements in sleep (PLMS). Channels are represented in all figures in the same order:
1. EEG (C3-A2); 2. ECG (M2-M5); 3. Electrooculogram; 4. Surface electromyogram of mental muscles; 5. Surface electromyogram of right tibialis anterior muscle; 6. Surface electromyogram of left tibialis anterior muscle; 7. Respiration flow in front of mouth and nose; 8. Respiratory movements of the chest; 9. Respiratory movements of the abdomen; 10. Saturation (pulse oxymetry)
Numbers concerning channels 2, 7 and 10 indicate the minimal, average and maximal values.

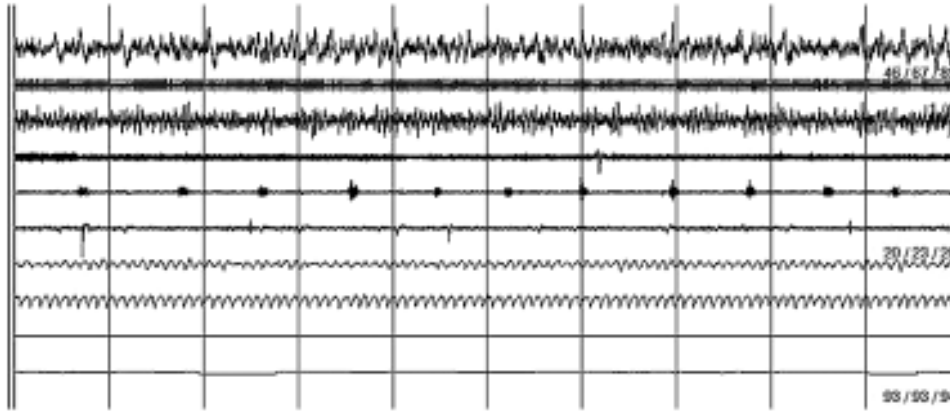

Figure 2 – PLMS of the right leg during sleep 3 NREM. Duration of represented period is 5 min. Polysomnography of 56 years old man suffering from RLS and periodic limb movements in sleep (PLMS). Channels are represented in all figures in the same order:
1. EEG (C3-A2); 2. ECG (M2-M5); 3. Electrooculogram; 4. Surface electromyogram of mental muscles; 5. Surface electromyogram of right tibialis anterior muscle; 6. Surface electromyogram of left tibialis anterior muscle; 7. Respiration flow in front of mouth and nose; 8. Respiratory movements of the chest; 9. Respiratory movements of the abdomen; 10. Saturation (pulse oxymetry)
Numbers concerning channels 2, 7 and 10 indicate the minimal, average and maximal values.

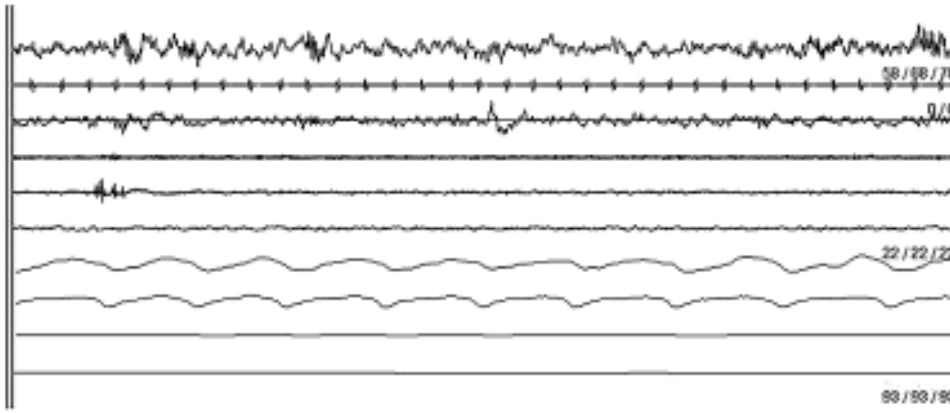

Figure 3 – PLMS of the right leg during sleep 2 NREM without arousal. Duration of represented period is 30 sec. Polysomnography of 56 years old man suffering from RLS and periodic limb movements in sleep (PLMS). Channels are represented in all figures in the same order:
1. EEG (C3-A2); 2. ECG (M2-M5); 3. Electrooculogram; 4. Surface electromyogram of mental muscles; 5. Surface electromyogram of right tibialis anterior muscle; 6. Surface electromyogram of left tibialis anterior muscle; 7. Respiration flow in front of mouth and nose; 8. Respiratory movements of the chest; 9. Respiratory movements of the abdomen; 10. Saturation (pulse oxymetry)
Numbers concerning channels 2, 7 and 10 indicate the minimal, average and maximal values.

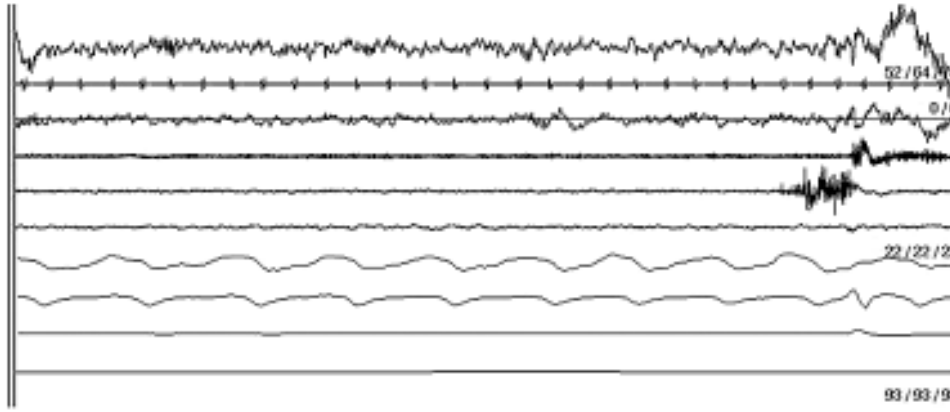

Figure 4 – PLMS of the right leg during sleep 2 NREM producing arousal. Duration of represented period is 30 sec. Polysomnography of 56 years old man suffering from RLS and periodic limb movements in sleep (PLMS). Channels are represented in all figures in the same order:
1. EEG (C3-A2); 2. ECG (M2-M5); 3. Electrooculogram; 4. Surface electromyogram of mental muscles; 5. Surface electromyogram of right tibialis anterior muscle; 6. Surface electromyogram of left tibialis anterior muscle; 7. Respiration flow in front of mouth and nose; 8. Respiratory movements of the chest; 9. Respiratory movements of the abdomen; 10. Saturation (pulse oxymetry)
Numbers concerning channels 2, 7 and 10 indicate the minimal, average and maximal values.

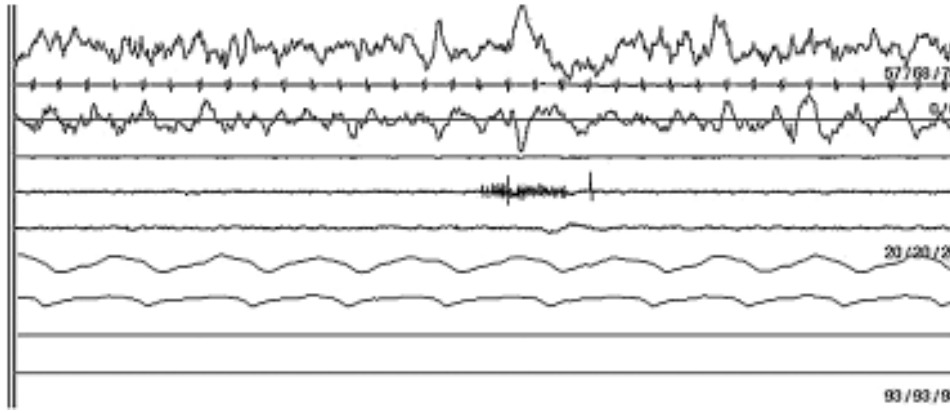

Figure 5 – PLMS of the right leg during slep 3 NREM without arousal. Duration of represented period is 30 sec. Polysomnography of 56 years old man suffering from RLS and periodic limb movements in sleep (PLMS). Channels are represented in all figures in the same order:
1. EEG (C3-A2); 2. ECG (M2-M5); 3. Electrooculogram; 4. Surface electromyogram of mental muscles; 5. Surface electromyogram of right tibialis anterior muscle; 6. Surface electromyogram of left tibialis anterior muscle; 7. Respiration flow in front of mouth and nose; 8. Respiratory movements of the chest; 9. Respiratory movements of the abdomen; 10. Saturation (pulse oxymetry)
Numbers concerning channels 2, 7 and 10 indicate the minimal, average and maximal values.

chronic affection, it is marked by particular types of development. At the appearance of symptoms in young age it takes a slow course with periods of remission. In later age the symptoms set in relatively suddenly and tend to be more pronounced. Cases of secondary RLS may show major improvement once the underlying disease has responded to therapy (e.g., after kidney transplantation in cases of renal failure). 2. Sleep disturbance is very frequent in RLS and also the actual reason, which makes the patient seek medical advice. 3. Medical evaluation/physical examination. The outcome of physical examination is generally normal. It contributes to the differentiation of idiopathic RLS and secondary RLS. In the case of the secondary RLS an underlying condition is considered to cause RLS.

Genetics

Studies of the type of heredity in RLS seem to advance two hypotheses. The predominant view is that the familial forms of the syndrome are due to an autosomal dominant mode of inheritance [17]. Findings in German and Czech populations suggest that monogenic heritability is more likely in patients who were younger than 30 at the onset of symptoms [18, 19].

The first linkage study to have successfully discovered the area of the genome significantly related to the disease was conducted in a large family of French-speaking Canadians. This suggested the candidate gene to be located on the short arm of chromosome 12 with rather an autosomal recessive type of inheritance and a large proportion of heterozygotes in the population [20]. The next locus identified on chromosome 14 is consistent with the autosomal dominant mode of inheritance. It was found in an Italian family by way of a two-point linkage analysis with phenotype scoring used as an important input [21]. Recently, a third locus was published as significantly correlated with RLS heritability using a free inheritance model. This time, non-parametric two – and multipoint statistical LOD scoring helped to identify the chromosomal region in 15 families with 134 affected members in the USA [22].

Pathophysiology

RLS pathophysiology knowledge is based on empirical data relating mainly to treatment and coincidence with other diseases as well as on specific molecular biology research of the past few years. The pathophysiology of RLS is localized in the CNS rather than in peripheral nerves for a number of reasons, the most relevant of which is the fact that drugs of central action affect the intensity of RLS manifestations. Spinal cord involvement is suspected from clinical experience and from observations of PLM as a concomitant feature of spinal cord lesions [23, 24], though they are not accompanied by RLS symptoms and though they obviously show a different body distribution or responsiveness to dopaminergic therapy.

A functional MRI study showed activation of the thalamus and cerebellum during sensory events without movements and of the pons and red nucleus during sensory events accompanied by movement [25]. SPECT and PET studies found a mild decrease of the dopamine D2-receptor in the striatum [26, 27]. F-DOPA uptake was found reduced in the putamen [27] and in the putamen and caudate nucleus [28]. No difference in DA transporter ([123I] beta CIT) binding was seen in RLS-PLMS patients [29]. A lower binding of the striatal D2-receptor ([123I]IBZM) was found by Michaud et al. [29] but Tribl et al. [30], examining patients currently exhibiting RLS symptoms, didn't replicated it. These controversial findings prevent us from localising RLS in only one region of the central nervous system on the basis of neuroimaging.

It is the iron and dopamine that are believed to have maximum importance in the pathophysiology of RLS.

Iron

The relevance of iron deficiency for the development of RLS was noted by Ekbom as early as 1945 [2]. Repeated corroboration of this fact kept coming in subsequent reports. In the 1950s, Norlander [31] reported successful treatment for RLS with iron supplementation even in persons with normal iron levels. The iron factor appears to be related to a greater RLS incidence in blood donors, and to a greater RLS involvement of female donors than of male donors [32] and, apparently, to a greater rate of RLS involvement in pregnant women [33, 34]. Studies by O'Keefe et al [35] and later also by Sun [36] revealed a negative correlation between RLS severity and serum level of ferritin. An MRI study showed iron content diminution in the substantia nigra of RLS patients [37]. The cerebrospinal fluid level of ferritin was less than a third in RLS patients compared with healthy subjects while that of transferrin was more than thrice as high in RLS patients compared with controls although both groups had normal serum levels [38]. This last finding points to a reduction of iron supplies in the brain of patients with idiopathic RLS. Autopsy studies of brains from individuals with idiopathic RLS found decreased transferrin receptor expression in neuromelanin – containing cells in substantia nigra, suggesting the cause of insufficient neuronal iron uptake [39]. Later lower levels of iron regulatory protein 1 (IRP1) and also the lowering of its binding capacity in neuromelanin cells from RLS brains were found and it was suggested that IRP1 insufficiency promotes destabilization of the transferrin receptor mRNA, leading to cellular iron deficiency in substantia nigra in RLS [40].

Dopamine

Dopamine involvement in the pathophysiology of RLS was shown in Akpinar's reports [5, 41] on the efficacy of L-DOPA in RLS treatment. This was confirmed in a number of well-controlled studies. Later on, RLS symptoms were found to

improve also in response to dopamine agonists and, vice versa, to deteriorate under the impact of its antagonists passing through the blood-brain barrier [42]. The part played by dopamine is also corroborated by the above-mentioned brain imaging studies. However, dopamine metabolism changes in RLS are small and apparently secondary only to some other, more important pathophysiological process in RLS.

The most widely accepted explanation of the connection between iron and dopamine dysfunctions in RLS lies in the notion that in RLS iron deficiency in brain cells inhibits dopamine transmission in the CNS; this might be so, e.g., as regards tyrosine-hydroxylase (the rate-limiting enzyme in the synthesis of dopamine) requiring iron as a cofactor.

Opioids

RLS connection with opioid transmission was already noted by Willis when he described favourable effect of opiates [1]. It appears that this effect comes into the picture in connection with changes in dopaminergic transmission similarly as in the control of pain at the level of the dorsal horn of the spinal cord [43]. Normal level of such transmission may be affected by spinal anaesthesia [44] or presumably also by chronic use of non-opioid analgesics [45]. Discontinuation of such analgesics resulted in the appearance of RLS symptoms in 15 out of 120 subjects [46], which is, however, roughly the rate for prevalence in the general population.

Neurophysiology

Movements in RLS are not preceded by any readiness potential [47], which points to their extravoluntary nature. Nonetheless, Rau et al. recently did find movements characteristic of RLS to be preceded by preparatory cortical activation of the mesial central region that cannot be attributed to sensory processing or to the expectancy of movement [48].

Studies using transcranical magnetic stimulation revealed the cortical silent period in RLS patients to be shorter than in healthy controls [49]. TMS showed a significant decrease in inhibition and increase in facilitation in the abductor digiti minimi [50]. Increased need for motor-cortical inhibition in RLS patients due to an increased level of excitation by motor cortex activation and input from neigh boring, functionally interrelated cortical areas was found using the post-movement oscillations method [51].

Spinal cord

The spinal cord is involved in RLS pathophysiology because the muscles engaged in PLMS and RLS movements and receiving peripheral impulses for the sensory symptoms are controlled from the spinal part of the CNS. RLS can be induced by spinal cord lesion or spinal cord ischaemia [23, 52, 53] and also by spinal

anaesthesia [44]. Patients suffering from RLS had significantly increased spinal cord excitability [54]. Changes in dopaminergic transmission appear to be present also in the spinal cord even though its lumbar and thoracic portions are devoid of dopaminergic cell bodies. This is where dopaminergic descending pathways have their endings. As animal experiments showed, excitatory pathways from flexor reflex afferents are distinctly depressed by L-DOPA [55]. The principal source of descending dopaminergic pathways is in the periventricular posterior (A11) region of the hypothalamus [56]. There is more than one reason to see dopaminergic A11 neurons as an "RLS-generator" [43, 57]. The A11 pathway can also help explain why RLS should be so frequently associated with Parkinson's disease. Two possible mechanisms are involved here: a) a small part of descending fibres has its origin in A9, i.e. the dominant site of the lesion in Parkinson's disease, and b) Parkinson's disease is marked by a loss of dopaminergic neurons in all brain lesions including, probably, the A11 [43].

For a number of reasons, some pathophysiological analogy seems to exist between RLS and pain and flexor reflexes in the spinal cord [43]. This is where mainly the first central structure of the somatosensory pathway – the dorsal horn – appears to be involved in the pathophysiology of RLS. In RLS, there is static mechanical hyperalgesia to pinprick stimuli, but no dynamic mechanical hyperalgesia (allodynia) [58]. Other potentially significant pathophysiological factors include lack of central inhibitory stimulation and disrupted afferentation of lesions of spinal neurons.

Circadian aspect

Anecdotal reports of RLS patients on shift-work or crossing transmeridian time zones show that symptoms of RLS are related to circadian time not to sleep, tiredness or anything else. Two studies [59, 60] dealing with this problem revealed that RLS severity is determined not merely by activity but also by the circadian factor. RLS was most intense late in the circadian period – in the declining phase of the core temperature. There is no proof to show a drop in the cumulative production of melatonin in RLS patients [61], though changes in melatonin secretion are known to precede an increase in RLS patients' sensory and motor symptoms [62]. As a well-established fact, serum iron shows a marked circadian variation with the lowest level in the evening and early night [63]. The circadian iron level variation may well have an effect on dopamine metabolism, for instance, by influencing the activity of tyrosine hydroxylase.

RLS association with other diseases

Diseases and environmental, behavioral and other conditions associated with RLS include pregnancy, Parkinson's disease, peripheral neuropathy, iron deficiency, chronic renal failure, cigarette smoking, sedentary lifestyle and medication such as dopamine antagonists, antidepressants and calcium channel blockers.

Ondo et al. found symptoms of RLS in 20.8% patients with Parkinson's disease [64] and Jakoubková et al. in as many as 49% [65]. The high prevalence of RLS in Parkinson's disease comes as no surprise with regard to the significant role that dopamine plays in these two diseases.

Both neuropathy and diabetes have been reported to be associated with the development of RLS, but survey studies using full diagnostic criteria have failed to find any significant increase in the prevalence of RLS for either neuropathy [66, 67] and diabetes [68].

RLS is more frequent in spinocerebellar ataxia of type 3 (SCA3) [69], respectively in SCA1, SCA2 and SCA3 [70]. Expanded CAG repeat (mutation) does not seem to be a causative factor in the genesis of RLS in these patients [70], though Schols [69] did presume this for SCA3.

RLS was found in 37% patients with Charcot-Marie-Tooth (CMT) neuropathy – all were CMT 2 and none CMT 1, a fact possibly related to a substantially more pronounced axonal atrophy in CMT 2 than in CMT 1 [71].

PLMS were diagnosed in 5 out of 7 untreated patients with Gille de la Tourette's syndrome [72].

Rheumatoid arthritis patients were more frequently affected by RLS (25%) than controls with osteoarthritis or seronegative arthropathy (4%) [73].

Iron deficiency and correlated anaemia have already been mentioned.

RLS are encountered in the end stage of renal failure at a rate of 17 – 42% [74]; in our own study the figure was 45,6% [75].

Pregnancy often leads to RLS development or exacerbation. The risk is at its highest in the 3rd trimester and tends to be connected with anaemia, low serum folate and/or ferritin levels [33, 74].

Treatment

Treatment for RLS is mostly successful bringing considerable relief and long-lasting improvement. After a follow-up of l6 months on average (ranging from 1 to 106), Clavadetscher et al. [76] found that a long-term treatment response could be

Table 2 – Dosage of dopamine agonists in RLS treatment. The single dose is given in the evening or at the time of RLS attack. This dose can be repeated if necessary

Drug	Initial treatment – single dose (mg)	Usual daily dose range (mg)
Ropinirole	0.25	0.5 – 8.0
Pramipexole	0.125	0.125 – 1.5
Pergolide	0.05	0.1 – 4.0
Cabergoline	0.25	0.25 – 4.0
Bromocryptine	1.25	1.25 – 10
Terguride	0.25	0.25 – 3.0

obtained and maintained in a clinical setting in about 80% of RLS patients. The medications should be used at the lowest effective dose. The dosage is titrated slowly upward from low single initial dose taken in the evening or at the time of RLS symptoms attempt. If necessary the dosage is slowly increased and/or repeated. The best treatment is often found empirically – that is, only by experimentation with a variety of agents.

L-DOPA and dopaminergic drugs have been the method of choice in RLS therapy since the 1980s. The effect of L-DOPA in combination with a decarboxylase inhibitor has been documented in a number of studies [77, 78, 79, 80, 81]. The usual daily dose varies between 50 and 200 mg. L-DOPA helps to improve nocturnal sleep in RLS, which is particularly true of its sustained-release form [81]. Sometimes, the application has to be repeated since the drug has a half-life of some 4 hours. No L-DOPA- induced dyskinesias have been reported in RLS patients. L-DOPA is well tolerated by RLS patients; however, its long-term application gives rise to two types of problem: rebound and augmentation. Rebound means that complaints reappear at the time of L-DOPA level drop, i.e., at night or in the morning. The nocturnal rebound can be managed by applying another dose or by switching over to the sustained-release form of the drug, though both nocturnal and early-morning manifestations of rebound can also be dealt with by a change of medication.

Augmentation is a more complex problem with the following four features: 1) earlier onset of symptoms compared with the pre-treatment state, 2) shortened latency period of the onset of symptoms at rest, 3) general worsening of symptoms and shorter therapeutic effect, and 4) symptoms proliferation to the upper extremities and trunk [82]. Simply, augmentation means a dopaminergic drug-induced increase in RLS severity. Following interruption of dopaminergic treatment in patients experiencing augmentation, therapeutic response to the same medication is usually fully restored [83]. Augmentation occurs within L-DOPA therapy in 50–80% of cases. It takes a milder course when dopaminergic agonists are applied.

The effect of dopamine agonists has been tested in many controlled studies of the efficacy of ropinirole [84, 85], pramipexole [86], pergolide [87, 88, 89] and bromocryptine [90]. Favourable properties relative to the risk of augmentation were found in cabergoline [91]. Similarly, terguride, a partial agonist of D2 receptors, proved efficacious in suppressing RLS symptoms [92]. The dosage of dopamine agonists is listed in Tab. 2.

The efficacy of opiates in RLS was described earlier by Willis himself [1]. At present, opiates are second-choice drugs for RLS. Studies are available only as regards some of the recent molecules such as oxycodone [93]. Opiates appear to be efficacious also in the long run except that the patients have to be followed up for potential signs of incipient sleep apnea [94]. Clinicians also make use of tramadol [95].

Anticonvulsants carbamazepine, gabapentine, benzodiazepines and valproate are also efficacious in RLS control. The effect of carbamazepin in low doses of 236 mg or 600 mg was documented in two controlled studies [96, 97] though the drug is seldom used in practice. Gabapentin is found efficacious in doses of 1400 – 1850 mg/day [98]; however, according to open studies a good effect was obtained even at lower doses [99]. 600 mg slow-release valproic acid was found, in a controlled study, to be more efficacious than 200 mg slow-release L-DOPA+ 50 mg benzerazide [100].

Benzodiazepines are less recommended since most of them have, owing to their long half-life, a "hang-over" sedative effect in addition to the risk of dependence. However, clinicians have had years of experience of them, supported by earlier open label studies [101, 102]. Baclofen as a central myorelaxant helps to reduce RLS symptoms [103] and contains the amplitude of movements in PLMS not, however, their number [104].

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