Psychiatr. Pol. 2015; 49(5): 921–930
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: http://dx.doi.org/10.12740/PP/35395

Frequent difficulties in the treatment of restless legs syndrome – case report and literature review

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Summary

Restless legs syndrome (RLS) is one of the most common sleep disorders. The purpose of this paper is a case description of the patient suffering from RLS, concurrent with numerous clinical problems. In our patient, during long-term therapy with a dopamine agonist (ropinirole), the phenomenon of the augmentation, defined as an increase in the severity of the RLS symptoms, was observed. The quality of life of the patient was significantly deteriorated. Due to the augmentation of RLS symptoms the dopaminergic drug was gradually withdrawn, and the gabapentin as a second-line drug for the treatment of RLS was introduced. Because of the large increase of both insomnia and RLS symptoms during the reduction of ropinirole dose, clonazepam was temporarily introduced. In addition, in the neurological assessment of the distal parts of the lower limb sensory disturbances of vibration were found. The neurographic study confirmed axonal neuropathy of the sural nerves, which explained an incomplete response to dopaminergic medications. However, gabapentin treatment in the dose recommended in neuropathies was impossible due to bothersome side effects. Another important issue in the treatment of the patient were depressive symptoms and the fact that the majority of used antidepressants (mirtazapine, mianserin, tricyclic antidepressants) increase the severity of RLS. Among antidepressants recommended for the treatment of depression in patients with RLS (such as bupropion, moclobemide, reboxetine, tianeptine and agomelatine) only agomelatine exhibits promoting sleep properties. Because of the concomitant insomnia, this drug was applied in our patient.

Key words: depression, restless leg syndrome, augmentation

The study was not sponsored

Introduction

Restless legs syndrome (Willis-Ekbom syndrome, lat. asthenia crurum paraesthetica, anxietas tibiarum, according to the ICD-10 classified as "Other specified extrapyramidal and movement disorders" (G.25.8)) is a neurological disorder characterised by a feeling of discomfort and uneasiness in the legs that occurs at rest and disappears during motion. The disease can appear at any age. The typical age of onset is the second, or the third decade of life with the gradual worsening of the symptoms of the disease with age. The first medical visit due to the symptoms of RLS is most common 20–30 years from the beginning of the disease. Symptoms occur mainly in the evening after going to sleep. The patients experience the compulsion to perform continuous movements of the lower limbs. Very rarely similar symptoms relate to the upper limbs. The course of the disease is usually chronic with rare periods of remission [1, 2].

Epidemiological studies have shown substantial RLS prevalence in the general population, which is 13% for Germany, 8% for France and 4.6% for the United Kingdom [3]. The discrepancies in the results of epidemiological studies are related largely to the fact that the diagnosis is based mainly on a subjective description of symptoms by the patient without objective confirmation with the use of more specialised tests (such as polysomnography, actigraphy). RLS is often misdiagnosed and confused with other diseases such as gout, blood circulation abnormalities or mental disorders such as conversion [3]. In addition, idiopathic RLS should be differentiated from the secondary forms of this syndrome. For each patient with RLS, iron deficiency should be ruled out, manifested both as anaemia, and latent, which can be identified only after the determination of serum ferritin. Other diseases, which should be differentiated from RLS are: renal failure, pharmacological treatment-induced akathisia, neuropathies and polyneuropathies (for example in the course of diabetes), iron deficiency during pregnancy, radiculopathies, Parkinson's disease, arterial or venous circulatory insufficiency, rheumatoid arthritis, fibromyalgia, osteoarthritis, epilepsy, dystonia, multiple sclerosis, tics, paraneoplastic syndrome, ADHD, other primary sleep disorders such as sleep apnea, delayed sleep phase syndrome [4].

The diagnosis is not difficult if you take into account the medical history of RLS diagnostic criteria (Table 1)

Table 1. **Diagnostic criteria for Restless Legs Syndrome (according to National Institute of Health, 2003)**

The constant urge to move the lower limbs accompanyied by the uncomfortable sensations and discomfort in the legs (sometimes the forced movements are not accompanied by uncomfortable sensations) and sometimes in addition to the lower limbs, the upper limbs or other body parts are included in physical movements.
The urge to move or unpleasant sensations occur during periods of rest or physical inactivity such as lying or sitting.
The urge to move or unpleasant sensations are alleviated or completely disappear during the movement, at least for a period of physical activity.
The urge to move or unpleasant sensations are more pronounced in the evening or at night than during the day or the symptoms occur in the evening or at night (when symptoms are very severe, worsening at night may be imperceptible, but before that must be present).

It is particularly important to pay attention to the circadian rhythm of the symptoms (i.e. worsening in the evening and early in the night) and to distinguish if the symptoms disappear during motion. Simple single screening question: "Does it happen that when you are trying to relax in the evening or to sleep at night, you experience the uncomfortable feeling of restlessness legs that passes away while moving legs or walking?" allows to identify the RLS patients with 100% sensitivity and 96.8% specificity [5].

Approximately in 50% of patients, the severity of RLS symptoms is so large that it significantly interferes with and extends the period of falling asleep. It causes a significant shortage of sleep and prevents the patient from getting rest for a long time during the subsequent day. The therapy can be divided into symptomatic and causal. The causal treatment, usually applied in the secondary forms of RLS, is based on solving the clinical problems underlying the symptoms of RLS. Treatment of RLS can also be divided into pharmacological and non-pharmacological (e.g. cooling compresses for the lower limbs, exercises that involve tensing the muscles of the lower limbs). American experts distinguished three forms of RLS: periodic, daily and resistant RLS. For that reason the short-term and long-term type of pharmacotherapy were distinguished. According to data from 2012 European scientific societies involved in neurological and sleep disorders recommend the use of dopamine agonists (rotigotine, ropinirole, pramiprexol) and alpha-2delta receptor ligands (gabapentin, gabapentin enacarbil, pregabalin) for the short-term treatment of RLS [6]. According to data from 2013 an international group of researchers of RLS, recommended dopamine agonists and alpha-2-delta receptor ligands for the long-term treatment of choice. The selection of a particular drug of the above groups should be based on the individual characteristics of a particular clinical case. In Poland, low dose of ropinirole (0.25–2 mg/d) are most commonly used in the treatment of RLS, probably due to the availability of that drug. If the monotherapy fails, the change for the other class of drugs is recommended. The subsequent kind of treatment involve the combination therapy with the dopamine receptor agonist and alpha-2-delta receptor ligands [7, 8]. In the case of severe iron deficiency (e.g. in pregnant women), besides of the oral iron supplementation, parenteral iron administration may be considered.

Aim

The purpose of this paper is a case presentation of the RLS patient. The therapy was difficult due to the complications of dopaminergic therapy, coexisting diseases and pharmacological psychiatric treatment.

Case report

The patient was a 72 years old woman, for the first time hospitalised for psychiatric reasons. She was admitted to the hospital due to severe restless legs syndrome and the accompanying sleeplessness. The disease was first diagnosed four years before the

admission, the mild symptoms of RLS were present from about 30 years of age. Previous treatment with ropinirole 5.5 mg daily (taken in divided doses at 13:00 p.m., 21:00 p.m. and after waking at night) did not provide adequate improvement despite relatively high doses of the drug. The patient described the toes' pain in both feet and a warm feeling in the feet, which forced her to get up out of bed. In addition, she described "a burst of heat radiating from the legs to the head" consisting of a very unpleasant numbness of legs and flushing the skin of the lower limbs. The patient reported that for the preceding several weeks, the symptoms interfered not only with her sleep but also with her daily activities. Sometimes the anxiety was also present in the upper limbs and trunk. Any kind of movement brought relief in such situations. The patient added that both her sister and mother suffered from the restless legs syndrome. The patient denied the use of psychoactive substances. Among the comorbidities she mentioned glaucoma, degenerative changes in the cervical and lumbar spine, varicose veins of the lower extremities, joint pain and the stress urinary incontinence.

Several months earlier the patient consulted a psychiatrist because of depressed mood. The response to prescribed medication from the group of serotonin reuptake inhibitors (sertraline) was poor and the severity of lower limbs symptoms increased. After discontinuation of drug treatment the patient remained under the care of a psychologist.

At admission to the hospital the patient was conscious and correctly oriented. Cognitive functions at the screening evaluation remained unchanged when compared to the age norm. The speech remained comprehensive and the course of thinking – coherent, delusions absent, hallucinations denied. Mood was moderately depressed, but the appetite and the psycho-motor functions remained unchanged. She reported the severe sleep disorder. Suicidal thoughts were absent.

Physical examination showed the following abnormalities: mild oedema of the lower limbs localised around the ankles, trophic changes in the skin of legs, varicose veins of the lower extremities. Romberg test was unstable. Strength of the lower limbs was symmetrically weakened – with difficulty in standing on tiptoe. Disturbances of the sensory vibration of the lower limbs were present (right lateral ankle 2/8, toe 4/8, left medial ankle 4/8, toe 4/8. Results of laboratory tests are shown in Table 2.

Table 2. **Results of the laboratory tests**

Fasting glucose	102.6 mg/dl
Potassium in serum	4.46 mmol/l
Sodium in serum	143.9 mmol/
OB	17 mm/h
ALT	14.5 U/l
AST	

table continued on the next page

A complete blood count	WBC: 4.12 K/uL; RBC: 4.35 M/uL; HCT: 40.2% HGB: 13.0 g/dL; MCV: 92.4 fL; MCHC: 32.3 g/dL; MCH: 29.9 pg; PLT: 206 K/uL
HBs antigen	absent
HCV antibodies	absent
Serum urea	24.57 mg/dl
Urea nitrogen	11.48 mg/dl
Serum creatinine	0.64 mg/dl
EGFR	>= 60 ml/min/1.73
Serum iron	72: ug/dl
Ferritine (L05)	100: ng/ml
Serum magnesium	2.33 mg/dl
CRP	0.7 mg/l
Urinalysis	specific gravity 1.015; the color yellow; transparency – cloudy; pH 5.0; protein – negative; glucose – negative; urobilinogen – normal; bilirubin – negative; ketones 15 mg / dL; erythrocytes – negative; nitrites – negative; leukocytes – negative

Due to the lack of the satisfactory response to treatment with ropinirole and the worsening of the symptoms of restless legs syndrome (probably in the course of the phenomenon called augmentation), we decided for the gradual withdrawal of the dopaminergic medications. Gabapentin at a dose of 900 mg per day was used, but at the time of increasing the dose of gabapentin, the patient reported dizziness and balance disorders. Due to the significant worsening of symptoms caused by the dose reduction and discontinuation of ropinirole, clonazepam was introduced, which was administered for a period of two weeks after withdrawal of ropinirole. The diagnosis of the RLS was also performed with the use of clinical rating scales and actigraphy. In addition, due to the abnormal neurological examination and abnormal vibration perception and the presence of the symptoms uncharacteristic for RLS (e. g. disturbed pain detection, changes in skin colour of the legs, localisation of the symptoms rather at the level of the fingers and feet than in the calves, weakness of lower extremities), neurography was performed (Table 3).

Table 3. **Results of the clinical scales and the additional tests**

Actigraphy	Increased physical activity at night hours. PLMS index left leg 47.7/h, right leg 49.9/h. The results: Severe form of RLS
Neurography	Advanced axonal neuropathy of both sural nerves with more severe changes on the left.

table continued on the next page

RLS Severity Scale	36/40 points
Epworth Somnolence Scale	8/ 24 points
Beck Depression Scale	15/ 63 points
Athens Insomnia Scale	21/24 points
Sheehan Disability Scale	10/30 points

After the two weeks period without the use of the dopaminergic drugs, combination therapy with gabapentin 900 mg per day and ropinirole 0.5 mg per day was introduced. Unfortunately, due to developing symptoms of depression, the patient required the introduction of antidepressant. Considering the poor tolerance of the serotonergic antidepressants in the past, the drug acting through the different mechanism, agomelatine 25 mg/day, was selected. The patient was discharged from the hospital, with the relative improvement in the field of RLS symptoms and her mental state remained stable. The patient was diagnosed with the restless legs syndrome and concomitant axonal neuropathy of both sural nerves. Pharmacological therapy with gabapentin 900 mg per day and ropinirole 0.5 mg per day, further neurological diagnostics towards the polyneuropathy and the fasting glucose control were recommended.

Discussion

The above described case reports frequent problems that psychiatrists may encounter in the course of the pharmacotherapy of insomnia in patients suffering from RLS. The first problem is the phenomenon of the augmentation. Augmentation of RLS symptoms is defined as an increase in the severity of RLS symptoms in the course of long-term pharmacotherapy. Currently, a basic class of drugs that is used for the treatment of RLS are dopaminergic drugs: levodopa and dopamine agonists (pramipexole, ropinirole and rotigotine). Unfortunately dopaminergic drugs used in long-term treatment of RLS can cause the phenomenon of the augmentation on the average of 2.7 +/ – 2.4 years of continuous pharmacotherapy [9]. This problem is observed in at least 20% of the patients treated with the dopamine receptor agonists and in up to 80% of patients treated with levodopa. For these reasons, the current guidelines recommended levodopa only for the periodically occurring forms of RLS. Daily form of RLS should be treated with dopamine receptor agonists [6]. In the described patient, in the period of reducing the dose of the dopaminergic drug, a short-term clonazepam therapy was introduced due to significant worsening of symptoms (insomnia, RLS symptoms). Benzodiazepines, due to their addictive properties, negative influence on the cognitive functions and the increase in a risk of falls – especially in elderly people, are not recommended for the long-term RLS therapy [3]. Clonazepam is the most commonly used drug within this group in RLS therapy with concurrent insomnia [5].

Diagnostic criteria for augmentation of RLS symptoms are:
Criterion 1
a) occurrence of symptoms of RLS two hours earlier than usual;
Criterion 2:
a) worsening of the symptoms' severity at the time of the increasing the dose of the drug or the reduction of the symptoms after the dose reduction;
b) reducing the time delay of the occurrence of RLS symptoms despite the use of the same drug at the same dose;
c) occurrence of the symptoms spreading to other parts of the body;
d) shorter persistence of the effect of treatment than at the beginning of treatment;
e) emergence of new or the increase in intensity of pre-existing periodic limb movements during wakefulness.

To diagnose the phenomenon of augmentation it is needed to meet criterion 1 and two or more sub-criterion of Criterion 2.

NIH (National Institutes of Health) introduced one more condition for the diagnostic criteria of RLS augmentation concerning the time of the occurrence of the symptoms described above – i.e. the presence of symptoms in the last week, and their occurrence by 5–7 days per week [9]. For the above presented patient, both the basic criteria necessary for diagnosis of RLS and criteria for the augmentation of the symptoms of restless legs syndrome were fulfilled. Symptoms of circadian nature were present in our patient as well as the significant symptoms' improvement during physical activity. For that reason she experienced a constant need to move. As in the idiopathic form of RLS, in our patient the long term course of the treatment as well as the occurrence of the RLS symptoms in the family members was present. Laboratory tests excluded the RLS in the course of the iron deficiency. Determining the level of iron itself is very important in the diagnosis of RLS, for the reason that the iron is involved in the synthesis of dopamine in the substantia nigra. While the low ferritin levels correlate with the severity of RLS symptoms. Recent studies suggest that ferritin could be a marker of the developing RLS augmentation in the course of RLS pharmacotherapy [7, 9]. Therefore, according to a recent recommendations of International Restless Legs Syndrome Study Group (IRLSSG) for patients suffering from RLS, in which the level of the serum ferritin is less than 75 ng/ml oral iron supplementation should be used (if there are no contraindications, and the oral tolerance of iron is good) [7]. Determination of ferritin in women complaining of RLS in the course of the pregnancy is particularly important.

In our patient, however, we observed the abnormalities in the neurological examination, which is not typical for idiopathic RLS. She also reported clinical symptoms unusual for RLS, i.e. not only anxiety and discomfort in legs, but also deep pain. In addition, the symptoms' localisation was unique and it was accompanied by the skin colour abnormalities. Physical examination showed a reduction in muscles strength and disturbed perception of vibration in legs (that was performed with the use of tuning fork). Test with the use of the tuning fork is not usually done in Poland,

although it should be routinely performed in patients with suspected RLS. Vibration perception test is an assessment of the vibration conduction in nerve fibers using a tuning fork. Oscillating tuning fork is applied on the ridge of the big toe and the fifth toe, lateral and medial ankle and on the tibial area. The average score from the three measurements is concerned as the examination result and is usually expressed as the fraction of the normal value e.g. 3/8, 6/8, 8/8. The sensitivity of this test in the detection of sensory nerve damage is high. In the case of our patient, the suspected damage to the sensory nerves of the lower extremities was subsequently confirmed in the neurography. Neuropathy of the sural nerves diagnosed during hospitalisation appeared as the second major problem in the treatment of our patient. It explained the incomplete response to the prodopaminergic medications. The necessity of the careful exclusion of polyneuropathy in any patient with RLS is supported by the results of studies using electrophysiological evaluation. Ondo and Janković [10] on the basis of the electrophysiological evaluation of 49 RLS patients (e.g. with the use of the nerve conduction study and electromyography) found the symptoms of polyneuropathy in 15 respondents (30% of the patients). At the same time, only in half of the patients with abnormal results of the neurological examination, the study found no ankle reflex, or abnormal perception of vibration, abnormal surface and proprioceptive perception. Iannaccone et al. provided another relationship between neuropathy and RLS symptoms [11]. Sural nerve biopsy performed in 8 patients with RLS revealed that the features of axonal neuropathy were present in all cases. These data indicate that in atypical forms of RLS, electrophysiological study is very valuable diagnostic test. Taking into account the fact that the prevalence of RLS symptoms and the proportion of patients who can be identified with polyneuropathy, increases with age, the electrophysiological study in patients with RLS, in whom the late onset of the symptoms was observed, should be recommended [4].

Proper diagnosis of RLS symptoms with concomitant polyneuropathy is important, since in these patients the use of alpha-2-delta receptor ligands than dopaminergic drugs is preferable [8]. Gabapentin and pregabalin are the most commonly used medications In Poland. However, gabapentin applied in the above described case was poorly tolerated.

The third important aspect complicating the treatment of this patient was the intensification of RLS symptoms by antidepressants that had to be used due to the worsening of the symptoms of depression. The epidemiological studies show, that the risk of an occurrence of a major depression episode among RLS patients is 2–4 times more common compared with healthy controls. Importantly, a large proportion of patients with concurrent RLS and depression (35%) reported suicidal thoughts as a result of their RLS symptoms. Moreover, there is a high prevalence of RLS in people with depression A few possible explanations of this phenomenon have been introduced up to now, for example: dysfunction of dopamine receptors, negative effect of chronic insomnia on mental health, shared diagnostic criteria and adverse effects of antidepressive treatment. The greatest risk of inducing RLS was reported for mirtazapine and

mianserin. In case of these two drugs, RLS symptoms may be present even in 8–28% of patients [12–14].

Drug-induced RLS has also been reported for tricyclic antidepressants, SSRI's and SNRIs. Among the monoaminergic drugs, the lowest risk of inducing symptoms of RLS is observed for reboxetine. The drugs of choice in treating patients with the symptoms of RLS are bupropion, moclobemide, tianeptine and agomelatine. And among all antidepressants recommended in RLS only agomelatine is characterised by the sleep-promoting properties. That is why this drug has been used in our patient in the course of comorbid depressive symptoms with insomnia [15].

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