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RESEARCH ON ROPINIROLE TREATMENT OF RESTLESS LEG SYNDROME

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Summary

Introduction. The restless leg syndrome is a clinical syndrome which frequently remains unrecognized. It belongs to a group of sleep-dependent movement disorders. It is the second most common reason for chronic sleep deficiency and hypersomnia during the day. In accordance with the international recommendations, its treatment is to be started with a dopamine agonist, the most favourable of them being (due to their efficiency and few side effects) the new selective D2/D3 agonists.

Aim. The aims of the study were to explore whether ropinirol remained effective with time, whether the dose of the drug escalated, and whether side effects affected therapy.

Material and methods. In this paper, the effectiveness of a D2/D3 agonist, ropinirole, was tested in patients with restless leg syndrome. 51 patients suffering from idiopathic restless leg syndrome received ropinirole in monotherapy in a dosage of 0.25-1.5 mg/day. The efficiency of the medicine has been verified in three ways: with tracking surveys, actigraph testing and the Forced Immobilization Test.

Results. 80% of our patients responded weel to the therapy. There was a considerable improvement based on the tracking surveys after ropinirole treatment. Time without movement of the limbs measured by actigraph testing, as well as the time spent in bed, were significantly longer. Also, the FIT index was lower after than before the treatment.

Conclusions. Based on our results, it can be stated that the restless leg syndrome can be effectively treated with ropinirole monotherapy.

Keywords: restless leg syndrome, ropinirol, augmentation

INTRODUCTION

Restless Leg Syndrome (RLS) has been already known by the 17th century (1). In 1940s, public medical attention was brought to this disease by Ekbom, a Swedish neurologist (2). However, nowadays it still remains underdiagnosed, as surveys show that up to 5-15% of the population suffer from this disease (3).

In the international classification of sleep-wakefulness disorders, the restless leg syndrome is classified as a sleep-related movement disorder.

Symptoms of RLS show a circadian rhythm and they worsen in an inactive awaken state, thus, the symptoms frequently appear while falling asleep. The symptoms include a disturbing, tense feeling (dysaesthesia), mainly in the lower limbs, that occur in an inactive awaken state, often directly after going to bed. The symptoms can be relieved only by performing pedalling or kicking motion or getting up and walking. The resulting chronic disruptions in circadian rhythm may lead to mental and affective disorders and autoagression.

Based on the above described clinical features, a patomechanism including both peripheral and central nervous system that relates to the sleep and wakefulness regulation was proposed. Motor system may also

be involved. Recent research suggest multiple elements that may contribute to the development of the disease, including the hypofunction of post-synaptic dopamine (DA) receptors in the motor-related areas of striatum, the role of opioid receptors in the modulation of DA release, the importance of iron metabolism to the central nervous system (4-5).

The first successful treatment for this disease was already described more than 300 years ago by Willis, who treated a patient with serious symptoms with a an opioid. Ekbom also observed the beneficial effects of opioids and other sedatives and hypnotics.

The beneficial effect of levodopa became well-known in the 1980s. It was verified in several papers, including the placebo controlled double-blinded trials (6-7). The consequences of the long-term levodopa treatment, which include the need for augumentation of the dosis and the rebound phenomenon, resulted in the decrease of use of this substance, especially after the appearance of the modern dopamine agonists. Based on the current clinical experience, dopamine agonists with longer half-life are less likely to result in the need for augumentation of the dosis and in the rebound phenomenon, but are still effective in reducing the symptoms of restless leg syndrome. Currently, they are recommended as the first-line treatment for RLS (8).

The recommendations of the American Academy of Sleep Medicine (AASM) of the 1999 remain the most commonly applied ones. They are acknowledged as having good scientific evidence (9, 10). The updated version of these recommendations was published in 2004, making it possible to include the results of the newest papers on dopamine agonists (11, 12).

In our laboratory, we examined the effectiveness of ropinirole in patients suffering from restless leg syndrome.

Ropinirole is a non-ergotamine derivative dopamine agonists as it mainly binds with D3 receptors and, to lesser extent, with D2 receptors. Its plasma half-life accounts for about 5 to 6 hours. Renal elimination prevails. It is reported to be effective in treatment of RLS (13, 14), even in patients resistant to other forms of therapy (15, 16). Long-term use causes only a slight need for augumentation of the dosis which is easily manageable (17).

AIM

The aims of the study were to explore whether ropinirol remained effective with time, whether the dose of the drug escalated, and whether side effects affected therapy.

MATERIAL AND METHODS

51 patients suffering from idiopathic restless leg syndrome were included in the study. At the beginning of the treatment and after 12 weeks of ropinorole monotherapy, they were asked to fill in a tracking survey. The efficacy of the medicine was examined in three ways: with tracking surveys, actigraph testing and the Forced Immobilization Test (FIT test).

Tracking survey with self-report subjective measurement scale

We used a survey which was developed by the International Restless Leg Study Group and is widely accepted in the international literature. The survey covers the characteristic symptoms of the disease dividing them into 12 items. To assess each item, the severity of each symptom is assessed on a scale from 1 to 5. This enables a subjective self-estimation of the patient's state. The reliability of the survey is sufficient, as it had been validated (Annex 1). Therapeutic efficacy was monitored with the Epworth Sleepiness Scale as well as the Insomnia Severity Index (ISI) (Annexes 2-3).

Actigraph testing during sleep

The efficacy of the therapy was also verified by actigraph testing. For this purpose, the Actiwatch (Mini Mitter®) tool was used (fig. 1 and 2).

In the actigraph testing, a small-sized motion sensor (accelometer) detects limbs and torso movements. It enables continuous registration for a time ranging from few hours to many weeks and data storage. It is fastened on the ankle or on the wrist of the patient. Thanks to the software, RLS events can be filtered out of the physiological movements with a high degree of certainty. Also, the intensity and timing of these movements is registered. There are many practical applications of this device. It can also measure the range of motion (18). The ciclicity of the movements can be verified. In this research, we calculated the change of the quotient of time spent without limb movements to total time spent

Fig. 1. Actiwatch actigraphy devices

Fig. 2. Actigraphy test

in bed – the increase of this quotient represents the improvement of the symptoms.

Forced Immobilization Test (FIT Test)

This test is used to verify the intensity of the main RLS symptom – the movement incentive. It is carried out during the daytime. During the test, the patient sits still on the bed with his legs upright. During the test, the limbs are to be relaxed, but motionless. EMG electrodes are placed bilaterally in the musculus tibialis anterior and the musculus quadriceps femoris. Involuntary leg movements are registered. The test takes 60 minutes. An event is recorded when a myoclonic activity is detected in EMG. FIT index is calculated by dividing the number of events by the time of recording them (in minutes) and multiplying it by sixty. The test is positive when the FIT index is higher than 10.

Statistical methods

Changes that occurred during the therapy are depicted in the "box-and whiskers" diagrams. A one-sample t-test was applied to compare the groups. This test can be used with coherent samples only. The analysis and the diagrams were created with the STATISTICA 7.0 software.

RESULTS

We examined 106 patients with RLS and qualified 60 of them, who presented with idiopathic RLS, into our research. Dopamine$_2$ agonist (ropinirole) monotherapy was prescribed for 51 of these patients. The dose ranged from 0.25 to 1.5 mg/day. Eight patients received the 1.5 mg dose. More than 80% of patients responded well to the therapy. The therapy was continued for over a year with no signs of the need for augumentation present. The average age of the patients was 55.2 ± 15.1 years of age in men (n = 18) and 55.9 ± 13.3 years of age in women (n = 33). The effects of the therapy were measured with tracking surveys, the actigraph testing and the FIT test.

Therapeutic effectiveness was monitored at the beginning of the treatment and after 12 weeks of the treatment with the International RLS Study Group Rating Scale (IRLS), the Epworth sleepiness scale and the Insomnia Severity Index (ISI). The change in IRLS score after ropinirole treatment suggests a substantial improvement. Daytime sleepiness measured with Epworth Sleepiness Scale decreased following treatment with ropinirole. Treatment with ropinirole was associated with an improvement of the Insomnia Severity Index (ISI) (tab. 1).

The quotient of time spent without limb movement to total time spent in bed measured with actigraph testing improved considerably following the ropinirole treatment (fig. 3). The change was statistically significant (analysed with one-sample-Student's t-test; p=0.01).

The results of the Forced Immobilized Test also improved considerably after the treatment (fig. 4). The change was statistically significant (analysed with one-sample-Student's t-test; p=0.01).

DISCUSSION

The restless leg syndrome is a frequent form of sleep-dependent movement disorders and the second leading cause of chronic sleep deficiency, as well as of hypersomnia during the day. The disease remains

Tab. 1. Effect of ropinirole treatment on symptoms of RLS measured with IRLS Rating Scale, Epworth Sleepiness Scale and Insomnia Insomnia Severity Index

	Before treatment			After treatment			N	t	df	p-value
	Mean	Std. error mean	Std. deviation	Mean	Std. error mean	Std. deviation				
IRLS rating scale	25	1.421	6.029	9.06	0.551	2.338	51	10.673	50	0
Epworth Sleepines Scale	13.89	0.718	3.046	6.17	0.513	2.176	51	7.965	50	0
Insomnia Severity Index	19.33	0.836	3.548	7.72	0.685	2.906	51	12.89	50	0

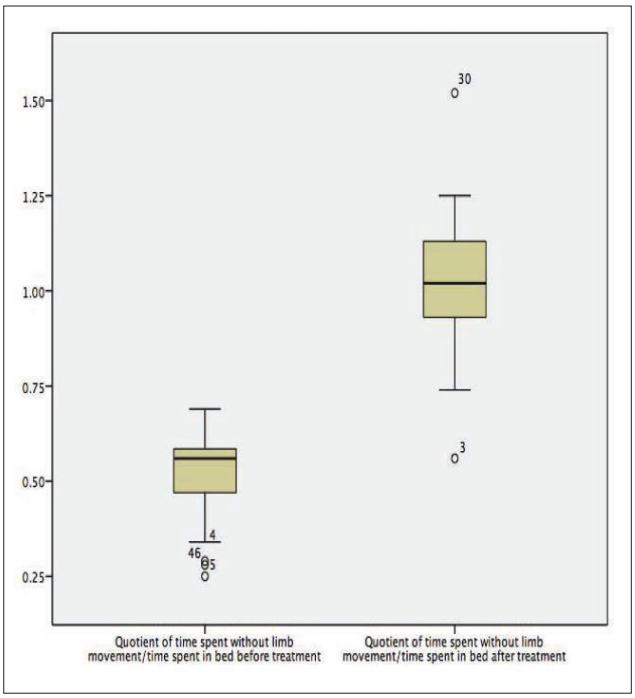

Fig. 3. The effect of ropinirole treatment on the quotient of time spent without limb movement to total time spent in bed measured by actigraph monitoring

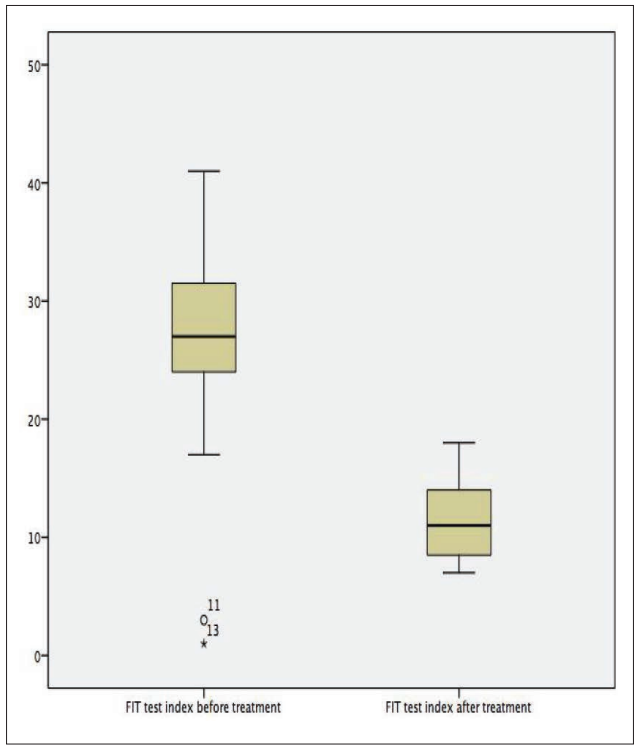

Fig. 4. FIT test results before and after ropinirole treatment

often unrecognized, and its serious symptoms can significantly reduce the patient's quality of life. What is important, these very symptoms can be considerably relieved with the current therapeutic options.

The pharmacotherapy is based on four groups of medications: dopaminergic drugs, opioids, benzodiazepines and antiepileptic drugs. The dopaminergic drugs are the most thoroughly examined and the most effective ones. The treatment algorithm recommend them as the first-line treatment, especially in cases of severe RLS. All the dopamine agonists used for treating Parkinson's syndrome were proven to be effective in the treatment of restless leg syndrome (19, 20, 21).

CONCLUSIONS

We measured the effectiveness of ropinirole monotherapy in 51 patients suffering from RLS. The medication caused significant improvement in self-assessment as well as in actigraphic testing and FIT test, both of which enable to objectivize the results. Ropinirole was well tolerated and the treatment was not interrupted in any of the patients due to the adverse effects. In some patients, however, the adverse effects, such as gastrointestinal side effects, hypotension, peripheral edema, resulted in the dose reduction.

Based on our results, it can be stated that the symptoms of restless leg syndrome can be treated effectively using ropinirole monotherapy.

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Conflict of interest
None

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Restless Legs Syndrome Rating Scale

The International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group Rating Scale for restless legs syndrome. *Sleep Med* 2003;4(2):121-132.

INSTRUCTIONS FOR EXAMINER

A. Patients must meet International Restless Legs Syndrome Study Group (IRLSSG) criteria for the diagnosis of Restless Legs Syndrome (RLS) before administration of the questionnaire as follows:

International RLS Study Group criteria for the diagnosis of RLS

a. Desire to move the extremities usually associated with discomfort or disagreeable sensations in the extremities.
b. Motor Restlessness-patients move to relieve the discomfort, for example walking, or to provide a counter-stimulus to relieve the discomfort, for example, rubbing the legs.
c. Symptoms are worse at rest with at least temporary relief by activity.
d. Symptoms are worse later in the day or at night.

Exception—If the patient previously met IRLSSG criteria and has undergone a spontaneous remission or is participating in a drug study with subsequent significant alteration of symptoms.

Exception—The patient at one time got relief of symptoms by activity but is now so severe that no such relief is possible.

Exception—The patient at one time was worse later in the day or at night, but is now so severe that symptoms are equal day and night.

Exception—The questionnaire may also be administered to normal controls.

B. Please fill in the following information:

Examiner Name: Patient Name:

Today's Date:_____ Sex:_____ Date of Birth:_____

Year Symptoms Began:_____

Medications: Dosage:

_____ _____

_____ _____

Annex 1. Restless Leg Syndrome Rating Scale

Restless Legs Syndrome Rating Scale

C. 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. Either the examiner or the patient may mark the answers on the form.

1. Overall, how would you rate the RLS discomfort in you legs or arms?

   (4) Very severe
   (3) Severe
   (2) Moderate
   (1) Mild
   (0) None

2. Overall, how would you rate the need to move around because of your RLS symptoms?

   (4) Very severe
   (3) Severe
   (2) Moderate
   (1) Mild
   (0) None

3. Overall, how much relief of your RLS arm or leg discomfort do you get from moving around?

   (4) No relief
   (3) Slight relief
   (2) Moderate relief
   (1) Either complete or almost complete relief
   (0) No RLS symptoms and therefore question does not apply

4. Overall, how severe is your sleep disturbance from your RLS symptoms?

   (4) Very severe
   (3) Severe
   (2) Moderate
   (1) Mild
   (0) None

5. How severe is your tiredness or sleepiness from your RLS symptoms?

   (4) Very severe
   (3) Severe
   (2) Moderate
   (1) Mild
   (0) None

Annex 1. Restless Leg Syndrome Rating Scale

Restless Legs Syndrome Rating Scale

6. Overall, how severe is your RLS as a whole?

(4) Very severe
(3) Severe
(2) Moderate
(1) Mild
(0) None

7. How often do you get RLS symptoms?

(4) Very severe (This means 6 to 7 days a week.)
(3) Severe (This means 4 to 5 days a week.)
(2) Moderate (This means 2 to 3 days a week.)
(1) Mild (This means 1 day a week or less.)
(0) None

8. When you have RLS symptoms, how severe are they on an average day?

(4) Very severe (This means 8 hours per 24 hour day or more.)
(3) Severe (This means 3 to 8 hours per 24 hour day.)
(2) Moderate (This means 1 to 3 hours per 24 hour day.)
(1) Mild (This means less than 1 hour per 24 hour day.)
(0) None

9. Overall, how severe is 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?

(4) Very severe
(3) Severe
(2) Moderate
(1) Mild
(0) None

10. How severe is your mood disturbance from your RLS symptoms–for example angry, depressed, sad, anxious, or irritable?

(4) Very severe
(3) Severe
(2) Moderate
(1) Mild
(0) None

Very severe=31-40 points
Severe=21-30 points
Moderate=11-20 points
Mild=1-10 points
None=0 points

Annex 1. Restless Leg Syndrome Rating Scale

RLS Ordinal Scale for Patients

INSTRUCTIONS FOR EXAMINER: Give the patient this piece of paper and have him or her rate their symptom severity for the preceding week overall.

1

MILD

2

3

MODERATE

4

5

SEVERE

6

7

VERY SEVERE

8

Annex 1. Restless Leg Syndrome Rating Scale

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

Annex 2. Epworth Sleepiness Scale

Insomnia Severity Index

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) = _____ your total score

Total score categories:
0–7 = No clinically significant insomnia
8–14 = Subthreshold insomnia
15–21 = Clinical insomnia (moderate severity)
22–28 = Clinical insomnia (severe)

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Annex 3. Insomnia Severity Index