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Turns-amplitude analysis of interferential electromyography as a diagnostic method for restless leg syndrome in patients with diabetic polyneuropathy

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Abstract
The effectiveness of pramipexole use in patients with restless leg syndrome due to diabetic polyneuropathy has been studied by means of immobilization test. The study involved 123 patients with type II diabetes mellitus, complicated by diabetic polyneuropathy. 32 patients were diagnosed with restless leg syndrome on the basis of principal diagnostic criteria as well as prior ineffective treatment with gabapentin. Patients were interviewed according to the international scale of restless leg syndrome. Immobilization test advanced with turns-amplitude analysis was used to objectivate the manifestations and define the severity of the disease. The study of the dynamics of movement indices revealed that on the 4th week of treatment the number of movements decreased and was 16.51±0.34 versus 44.63±0.45 before treatment ($p<0.05$). Conducting turns-amplitude analysis made it possible to differentiate the causes of pathologic afferentation of lower limbs in patients with restless leg syndrome comorbid with diabetic polyneuropathy.

Keywords: restless leg syndrome, diabetic polyneuropathy, immobilization test, turns-amplitude analysis, pramipexole

Introduction
Restless leg syndrome (RLS) is a sensory-motor disorder characterized by motor anxiety mainly at rest due to unpleasant sensation in lower limbs [3].

RLS is considered the most common motor disorder, and its prevalence among general population is 5-15%. However, until recently it has been rarely diagnosed [1, 2]. It is considered that this is due to poor knowledge of physicians about this disorder as they often misinterpret patients' complaints of tingling, feeling of fullness, itching, tightening, creeping sensation, pain in lower limbs forcing the patient to perform annoying movements, to disorders of peripheral nerves, vessels, joints or complications caused by osteochondrosis [9].

RLS may be either primary (idiopathic) or secondary. Primary RLS usually develops in the first decades of patient's life and in 60-90% of cases it is hereditary [14]. Secondary RLS often occurs in later life and is characterized by rapid progression of symptoms. The most common causes of secondary RLS are: iron deficiency, terminal stage of renal failure, pregnancy, neuropathies, Parkinson's disease, radiculopathy, obesity, use of tricyclic antidepressants, antiepilepsy drugs, caffeine abuse [3, 4].

Coexistence of RLS and diabetes mellitus (DM) in one patient is rather controversial. Modern foreign studies have found that the prevalence of Ekbom's syndrome in diabetic patients makes up 17-25% as opposed to 7-15% among the general population [7]. Their findings confirmed that diabetic polyneuropathy (DPN) is a risk factor for RLS, though; it only partly explains the high prevalence of the disease in diabetic patients, in terms of coexisting central dopaminergic dysfunction caused by metabolic disorders in type II diabetes mellitus [14]. It also explains higher prevalence of RLS among patients with type II diabetes mellitus as compared to those suffering from type I diabetes mellitus. However, the hypothesis that DM without polyneuropathy can cause RLS was not confirmed in the studied research works [7].

The diagnosis of RLS is made on the basis of patient's case history. In patients with typical symptoms, diagnosis is not difficult, but with existing atypical signs and comorbid diseases, the diagnosis cannot be made at once.

There are 4 main diagnostic criteria for RLS that were proposed by the international RLS study group (IRLSSG) in 2003: 1) symptomatic urge to move legs usually accompanied by or caused by uncomfortable sensations in the legs; 2) symptom complex occurs or worsens at rest

or during the period of reduced physical activity (lying down or sitting); 3) complaints are completely or partially relieved when moving; 4) the described symptoms aggravate or occur usually in the evening or at night, that is they are of circadian character.

The severity of symptoms of this disease is evaluated by various scales: international restless legs scale (IRLS), RLS severity rating scale, RLS-6 rating scale [10, 15]. Although they are all easy to use, their duration is limited, since they rely exclusively on the patient's subjective assessments and reference over the recent 7 days. In addition, the result based on the rating scale significantly depends on the patient's physical activity. Consequently, the objective evaluation of RLS symptoms requires examination in more controlled conditions.

Polysomnography is also a known method used for RLS diagnosis, involving continuous monitoring of a large number of biologic changes during the nocturnal sleep. The study includes the following techniques: electroencephalogram – used to measure and evaluate cerebral activity; electromyography (EMG) – the study of muscle activity, namely: jerking, teeth grinding, periodic limbs movements; electrooculography – used for eye movement recording, which plays an important role in identification of various sleep stages, including REM-phase; electrocardiogram – heart rate and rhythm recording; nasal sensors – used to record the air flow; microphone – used to record patient's snore [8, 16]. This diagnostic method is multifunctional, though, it requires the use of special diagnostic equipment, room (sleep laboratory) and special skills. That's why it is hardly accessible for a wide range of doctors and patients.

According to the literature, about 55% of patients with moderate and severe RLS experience symptoms during the day. Patients increase physical activity in order to relieve RLS symptoms. Consequently, day-time symptoms of RLS should also be taken into account and evaluated.

Immobilization test (IT) using the EMG registration system is the most significant and reliable method of RLS diagnosis which is chosen as a prototype, especially used to identify the severity of the disease. Since the RLS symptoms occur mainly due to prolonged immobilization and rest, the purpose of IT is to detect RLS signs not during patient's sleep, but during waking hours. Since the sensitive symptoms due to their subjectivity are difficult to assess, the efforts of this method are focused on the detection of motor symptoms. IT is an informative and less expensive diagnostic method for determining the severity of RLS [11].

The goal of our investigation was to determine the effectiveness of pramipexole use in patients with restless leg syndrome due to diabetic polyneuropathy with the help of immobilization test advanced with turns-amplitude analysis.

Materials and methods

123 patients with type II diabetes mellitus complicated by DPN of symptomatic stage were examined on the base of endocrinology unit of Ivano-Frankivsk regional clinical hospital using P.J. Dyck and Thomas classification (1999). The average age of patients was 51.13±0.73 years. The DM decompensation stage was determined by the glycosylated hemoglobin level (9.51±0.62%). 32 patients (26.01%) were diagnosed with RLS using the main diagnostic criteria. All the patients received routine treatment for DPN (glycemia and dyslipidemia management, α-lipoic acid, benfotiamine) and pramipexole at a dose of 0.75 mg per day for 30 days.

The control group involved 11 patients of the corresponding age without any manifestations of DM and RLS, which made up the group of apparently healthy individuals (AHI).

The patients were interviewed on the international RLS rating scale, which consists of 10 questions and includes an assessment of the following criteria: 1) discomfort in legs (score 0-4); 2) need to move (score 0-4); 3) relief of discomfort in legs due to moving (score 0-4); 4) sleep disturbance (score 0-4); 5) tiredness and sleepiness (score 0-4); 6) frequency of RLS symptoms (score 0-4); 7) assessment of RLS severity by the patient himself (score 0-4); 8) the average duration of RLS symptoms during the day (score 0-4); 9) impact of RLS symptoms on the ability to carry out daily affairs like family, house, social, study or work (score 0-4); 10) mood disturbance: anger, depression, sadness, anxiety or irritability (score 0-4). The sum of the item scores serves as the scale score assessing the RLS severity: very severe (31-40 points); severe (21-30 points); moderate (11-20 points); mild (1-10 points); none – 0 points. A re-interview was carried out 30 days after the treatment.

To objectify the manifestations and assess the severity of RLS all patients underwent immobilization test (IT) on admission and 30 days after the treatment. This test was performed within one hour after the patient's immobilization who lay on the couch with legs stretched out and moved as little as possible. The EMG registration system consists of electrodes that dispel the potentials of the muscle, the amplifier of these signals and the recording device. Bipolar leads with surface electrodes are used in EMG registration. The electrodes were fixed on the skin above the muscle motor point (m. tibialis anterior) on both sides. Grounding electrode was placed on the patient's skin above the ankle joint. Potential difference between electrodes is transmitted to the amplifier input. Upper bandpass of the amplifier makes up 10000 Hz, and the lower one – 2-10 Hz. The recording speed rate is 2 ms/cm. The large size and distance from the muscle tissue of the surface electrodes allows to record the total muscle activity, that is, the interference of the action potentials of many muscle fibers. Each contraction on the interference curve, corresponding to posterior flexion of toes, was considered as one periodic limb movement (PLM). In the presence of 10 to 20 PLM per hour the patient was diagnosed with mild RLS, 20-50 PLM – moderate RLS; >50 PLM – severe form (patent 108040 U IPC A61B5/0488). In addition to the RLS severity, the analysis of movement index (MI) made it possible to study other parameters, namely: lateralization index (LI) – (right leg movements + left leg movements)/MI (LI); number of leg movements during the first 30 minutes of recording (MIF30); number of leg movements during the last 30 minutes of recording (MIL30); mean interval between movements in seconds (MIM).

However, valid interpretation of the results of normal interference curve of EMG is quite cumbersome in time due to "manual" counting of PLM number.

Therefore, for the improvement of the technique, all the patients underwent turns-amplitude analysis of interference surface EMG, based on the correlation of number of turns of interference EMG and mean amplitude of the interference curve, the points of their dependence on the graph form a turns-amplitude "cloud" that may change its value depending on the number of limbs movements. Points of amplitude and turns frequency dependence form turns-amplitude «cloud» that may change its value according to the number of limbs movements and shift on the reference plane depending on the

pathology, namely: in case of motoneuron damage the group of points on the «cloud» shifts towards the larger amplitude and smaller frequency (upper left corner of the graph); in case of primary muscular damage the points shift towards high frequency but low amplitude (lower right corner). Normally these points are located in the left segment of the graph, closer to the lower corner. Each point of the turns-amplitude «cloud» corresponded to the limb movement over a particular period of time (3,5sec).

Statistical processing was carried out with the help of variation statistics methods using "StatSoft\STATISTICA 6" software.

Results of the investigation and their discussion

Detailed history taking in 123 patients with DPN showed that practically all of them were previously administered gabapentin at a dose of 900 to 2400 mg a day to reduce pain, heartburn, paresthesia, which typically occurred in the evening or at night and disturbed sleep. The above-described symptoms have significantly decreased in some patients; however, 32 patients indicated no effect of gabapentin use or its inadequate efficacy that served as an additional criterion to confirm their RLS.

Patients' survey on the international RLS rating scale revealed the following: 7 (21.9%) patients were diagnosed with mild RLS before treatment that made up 6.52±0.34 points. 19 (59.4%) patients were diagnosed with moderate RLS that corresponded to 17.11±0.53 points. 5 (15.6%) patients had severe RLS; 24.24±0.21 points. 1 (3.1%) patient was diagnosed with very severe RLS, 33 points. 30 days after the performed treatment 3 (9.4%) patients indicated the absence of the disease symptoms and were recorded 0 points by the international RLS rating scale. Mild RLS was diagnosed in 17 (53.1%) patients (7.23±0.33 points), moderate RLS – in 11 (34.4%) patients (15.12±0.21 points), and 1 (3.1%) patient was diagnosed with severe RLS, that corresponded to 24 points. The above mentioned findings show that the treatment had significant positive influence on the RLS symptoms in patients with DPN, as the indices of RLS differed considerably before and after treatment ($p<0.05$).

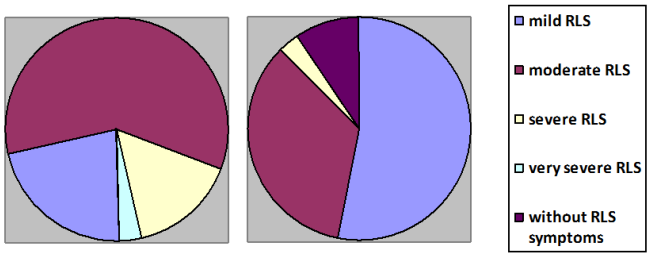

Fig 1: Dynamics of indices of international RLS rating scale before and after treatment

The interview of control group patients by the international RLS rating scale revealed that 5 women were recorded 4.82±0.34 points that might correspond to mild RLS. This may indicate a low sensitivity of the questionnaire and the dependence of the evaluation result on many other external factors and the need for more accurate diagnostic tests.

IT revealed the following data: the study of MI dynamics (RLS severity) showed that the number of movements decreased on the 4th day of treatment and was 16.51±0.34 as compared to 44.63±0.45 before treatment ($p<0.05$).

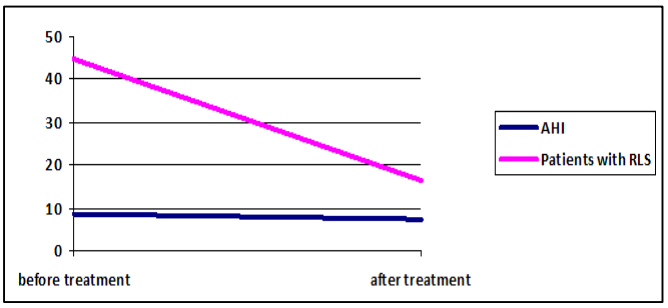

Fig 2: Dynamics of RLS severity indices according to IT data

Before treatment 3 (9.38%) patients were diagnosed with mild RLS, 6 (18.72%) patients had severe RLS and 23 (71.87%) patients were diagnosed with moderate form of RLS due to the MI. 30 days after the treatment mild RLS was revealed in 10 (31.25%) patients, moderate RLS – in 13 (40.62%) patients, and in 9 (28.13 %) patients the number of PLM in IT was less than 10 movements per hour, that was normal.

The use of IT in the control group of patients has also revealed periodic limb movements, though their number was 8.71±0.62, which essentially differed from the indices of RLS associated with DPN ($p<0.05$).

While determining the number of movements within 1 hour of IT, it was found out that PLM were observed more often during the last 30 minutes of IT. After treatment, the number of PLM (-73%) was notably reduced within the first 30 minutes of examination, as opposed to their number during the last 30 minutes (-27%). Treatment with pramipexole has increased MIM ($p<0.05$), though it hasn't influenced the value of LI ($p>0.05$) (Table 1). Even low doses of pramipexole have significantly improved subjective symptoms of RLS. Patients reported that improvement was observed even in the early days of treatment, indicating satisfactory compliance. Pramipexole has also significantly reduced the number of PLM in patients with RLS, whereas the MI hasn't normalized. This fact suggests that the response of the sensory component of RLS (and possibly the patient's impression) to treatment with pramipexole may differ from the reaction of motor component, and that PLM may be present regardless of subjective satisfaction with therapy.

Table 1: IT dynamics in patients with RLS associated with DPN under the pramipexole treatment

Indices	Before treatment	After treatment
MI	44.63±0.45	16.51±0.34*
MIF30	13.81±0.41	8.82±0.11
MIL30	35.22±1.23	9.84±0.21*
LI	0.33±0.17	0.33±0.02
MIM	28.62±0.72	59.76±0.18*

* - significant as compared to the indices before treatment ($p<0.05$)

All the patients underwent turns-amplitude analysis with the aim to improve IT findings and variance of some data with the RLS international scale, and carry out differential diagnostics of the causes of pathologic afferent activity in lower limbs resulting in leg movements. The analysis revealed that turns-amplitude «cloud» in 29 patients was locater in the left segment of the graph closer to lower corner, suggesting that excessive leg movements and discomfort were caused by RLS combined with DPN. Turns-amplitude «cloud» shifted towards higher amplitude and lower frequency (upper left corner of the graph) in 3 patients, which suggests that pathologic afferent activity in lower limbs of

these patients is probably caused by motoneuron injury, and the signs of DPN simulate RLS.

Figure 4 shows turns-amplitude analysis of patient M. (1973 year of birth), with the diagnosis of type II diabetes mellitus, insulin-dependent, moderate, decompensation stage with diabetic polyneuropathy IIA stage. On admission the patient complained of discomfort in lower limbs such as pain, creeping sensation, which were present at rest, more often in the evening and at night, and decreased when he moved his legs. In addition, the patient suffered from sleep disturbance. According to the criteria of international RLS study group the diagnosis of RLS may be considered doubtful because of the absence of involuntary movements. IT with the use of standard score of interference EMG revealed 14 PLM per hour in the patient and with well-defined RLS criteria could correspond to its mild form. IT with the use of turns-amplitude analysis made it possible to obtain the «cloud», intensity and location of which on the reference plane differed from the indices in apparently healthy individuals.

Conclusions

The findings proved the effectiveness of pramipexole treatment in patients with RLS associated with DPN, as revealed by rating scales and IT, which are considered to be reliable and valid investigation methods used to identify RLS severity and effectiveness of its treatment and may be recommended as routine examination means at suspicion on RLS.

Turns-amplitude analysis may be considered as additional method for RLS diagnostics in patients with type II diabetes mellitus, complicated with DPN, as it amplifies the suggested criteria of RLS diagnostics with the use of IT indices. The use of turns-amplitude analysis of EMG data evaluation with IT allows to diagnose RLS as soon as possible in the given cohort of patients, as well as to conduct differential diagnostics between DPN and RLS, comorbid DPN, in patients with type II diabetes mellitus. In future, this will give an opportunity to evaluate the effectiveness of treatment regimens, and improve the quality of life of patients with this pathology.

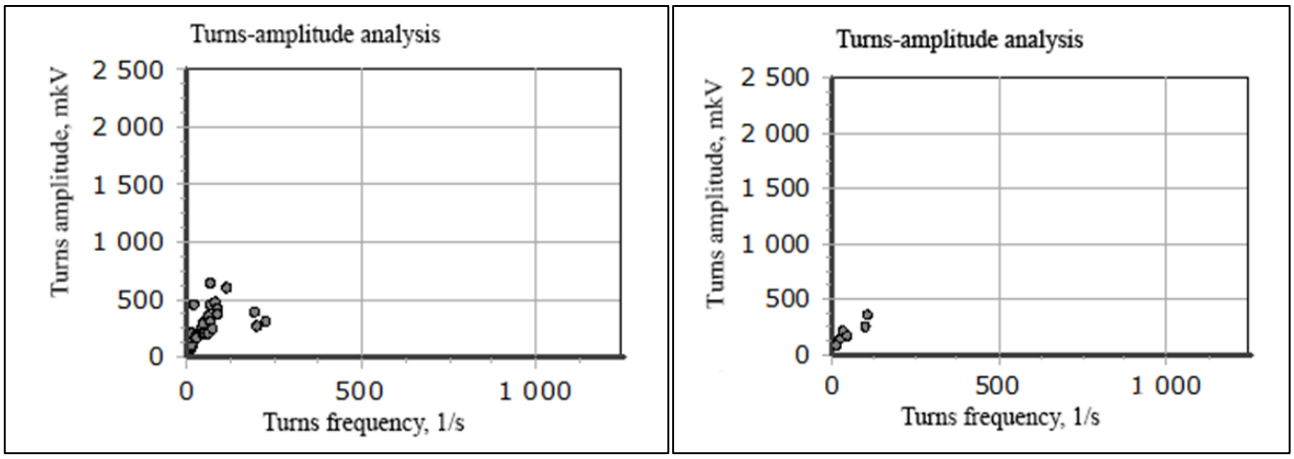

Fig 3: Turns-amplitude analysis of AHI.

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