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RESEARCH ON CHARACTERISTICS OF ESSENTIAL TREMOR IN THE LATVIAN POPULATION

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Essential tremor (ET) is a common movement disorder, characterised by symptoms such as bilateral postural and kinetic tremor with prevalent manifestation in hands. The disease has chronic progressive development. In the case of continuous severe form it may resemble Parkinson's disease (PD) and sometimes comorbidity with PD is possible. Although both diseases have different pathogenesis and treatment, some tremor characteristics for both are similar, thus causing difficulties and mistakes in diagnosing. The aim of the research was to determine ET characteristics within the Latvian population to identify possible causes for making mistakes.

Key words: *essential tremor, Parkinson's disease, postural, action/intention, rest tremor.*

INTRODUCTION

Data on essential tremor (ET) prevalence in the world varies from 0.008–22% (Louis, 2005). There are no data on prevalence and incidence in Latvia, but in Finland the disease prevalence after the age of 40 is 5.6%, and after 60 years — 9% (Fahn *et al.*, 2005). The pooled prevalence is 0.9%, and 4.6% after 50 years of age (Fahn *et al.*, 2005; Louis and Ferreira, 2010).

The first author of the article has accumulated experience in the field during a ten-year period by clinically consulting patients with movement disorders, especially with essential tremor, and participating in ET genetic research projects in cooperation with the Latvian Biomedical Research and Study Centre. Patients came from all over Latvia, and at the beginning it seemed that the disease was difficult to be recognised, in addition to its faulty interpretation as Parkinson's disease. Being aware of existing possible clinical characteristics, an objective was set to identify these within the framework of research.

The Consensus Statement of the Movement Disorder Society (MDS) of 1997 still defined ET as a monosymptomatic illness, describing it as symmetrical, postural and/ or kinetic tremor with an intentional component, frequency 4–12 Hz, stronger manifestation of it in hands and forearms and not associated with any other neurological deficit. However, during the last 15 years, extensive research has shown other deficits — mild gait ataxia, mild cognitive impairment, reduced speech fluency, mental shifting and verbal working memory, as well as anxiety and depression (Chandran and Pal, 2012). The disease might also have neurodegenerative character (Louis *et al.*, 2007). Undoubtedly, tremor is the most conspicuous symptom and depending on its manifestation the clinical diagnosis is made. Irrespective that there are additional diagnostic tests, though expensive, for example, DaTSCAN and electrophysiological examination, diagnosis for both the diseases is made clinically.

According to the MDS diagnostic criteria, tremor is bilateral and mostly symmetrical (Lyons and Pahwa, 2005, p. 81). Literature mentions that about 20% of ET patients are diagnosed with rest tremor and it is a late sign of the disease (Rajput *et al.*, 1993; Cohen *et al.*, 2003). Comorbidity of ET and Parkinson's disease (PD) is stated in 3% of the cases as benign tremulous Parkinsonism (Benito-Leon *et al.*, 2009). Some scholars believe that association between these two diseases is possible, moreover, that ET is a possible risk factor of PD development (Fekete and Jankovic, 2011).

The initial stage of PD and late stage of ET might seem misleadingly similar and there is a possibility for erroneous diagnosis as 20–35% (Elbe, 2011). However, careful and detailed evaluation of the symptoms, taking into account the diagnostic criteria of both diseases, making additional examinations and following the disease process over time (at least five years), allow a qualified neurologist to make an accurate correct final diagnosis. In the cases when ET is erroneously diagnosed as PD, there are grounds to believe that medication for treating the disease is not appropriate. A sample of the Latvian population was investigated to test this assumption.

PATIENTS AND METHODS

Patients undergoing investigation were selected from those who were consulted by L. Smeltere at the Neurology Outpatient Centre at Pauls Stradiņš Clinical University Hospital and at the Consultation for Parkinson's Disease and Other Movement Disorders at Health Centre 4. A total of 40 ET patients underwent investigation. Only patients with clear ET diagnosis were involved. The ET diagnosis was made on the basis of anamnesis data for tremor for at least five years, neurological investigation according to the Fahn, Tolosa, Marin Tremor Rating Scale and the MDS diagnostic criteria for ET. The patients were undergoing magnetic resonance imaging of the brain and clinical analysis to exclude other phenotypically similar diseases. The patients for investigation were those L. Smeltere had consulted repeatedly (2–10 times during a ten-year period) and the dynamics of neurological symptoms were assessed. These included also patients with previous erroneous PD diagnosis and who had undergone dopaminergic therapy. Consequently, the neurological condition of these patients was examined several times according to the Unified Parkinson's Disease Rating Scale (UPDRS) (MDS PD rater certificate possessed by L. Smeltere) and the Fahn, Tolosa, Marin rating scale, as well as the diagnostic criteria for both diseases while using the medication and up to six months after discontinuation. Only patients with a clear ET final diagnosis underwent the investigation. Patients with comorbid ET-PD diseases were not included in the studied group. Participants signed informed written consent and research was approved by the Ethics Committee.

Statistical analysis. Statistical data processing was conducted using the SPSS software (IBM SPSS Statistics Version 22). The quantitative variables were estimated by arithmetic mean (M) and standard deviation (SD). In the cases when the distribution sharply differed from a normal distribution, the median and the interquartile range were calculated. The qualitative variables were characterised as the number and percentage ratio. The materiality level was chosen to be 0.05, thus, a p value smaller than 0.05 indicated statistical significance. Comparison of normally distributed quantitative variables was done by using the paired samples t-test and the independent samples t-test between two groups or the analysis of variance (ANOVA) method between three or more groups; eta squared was used to calculate the statistical effect size. To determine group differences the ANOVA Post-hoc Tukey correction was applied. The Kruskal-Wallis test and the Wilcoxon signed-rank test were used for variables that did not correspond to a normal distribution. Depending on data distribution, association between two variables was tested by applying the Pearson's r or Spearman's r_s correlation. Qualitative variables were tested by using a Pearson's chi square test. Cronbach's alpha and the Intraclass correlation coefficient (ICC) were estimated to determine internal reliability. The area under the curve (AUC) of receiver operating characteristic (ROC) was used for calculating the statistical effect

RESULTS

The age group of the ET patients was 19–93 years (M = 52.05; SD = 20.18 years). Prior to visiting the specialised consultation, 67.5% of the patients had not been diagnosed, although the anamnesis data had shown symptoms already for some years. 30.0% of the patients had an erroneous diagnosis, namely, Parkinson's disease (see Fig. 1) and 25.0% of all the ET patients had undergone continuous dopaminergic therapy, although it had been a non-effective treatment (see Fig. 2).

The situation was different with PD patients — according to the PD diagnostic criteria 80% had an appropriate diagnosis, 5.7% had an erroneous diagnosis and in 14.3% cases no diagnosis had been made.

Taking into account the high ratio of erroneous diagnosis of ET patients in the sample of Latvian population, its impact on the patients' psyche was investigated to attempt to find out whether it causes depression. For this reason they were asked to participate in the Beck Depression Inventory

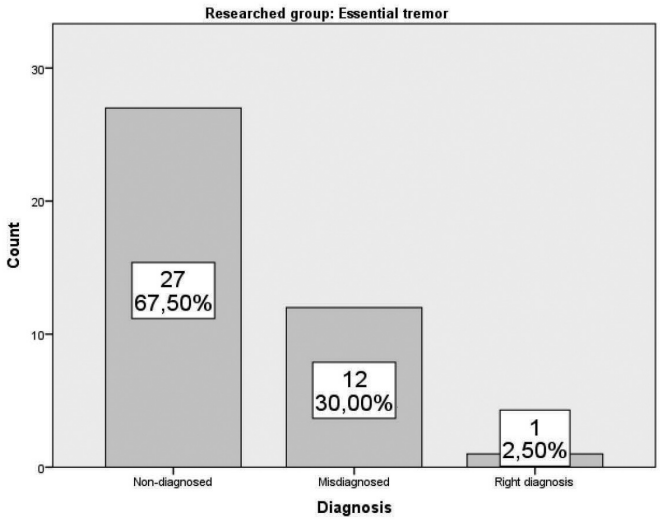

Fig. 1. Essential tremor diagnostics.

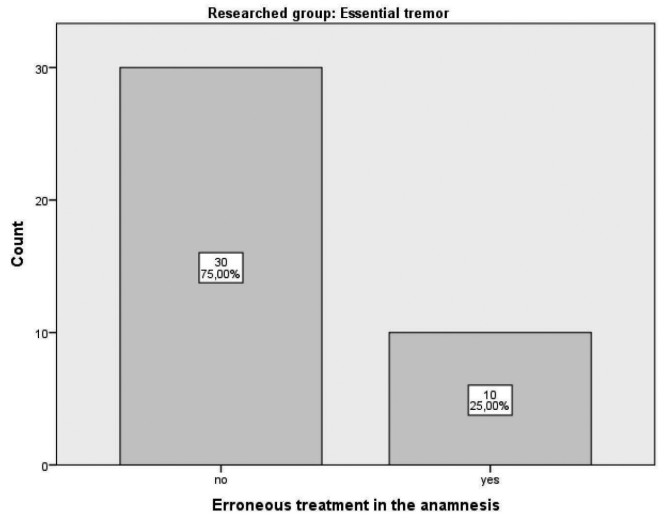

Fig. 2. Erroneous essential tremor treatment.

(BDI). The independent samples t-test revealed that the median BDI score for not diagnosed patients (M = 14.42; SD = 12.74) and erroneous diagnosis (M = 16.67; SD = 8.95) differed by 2.24 points, but was not statistically significant ($p < 0.05$). Thus, depression indicators are slightly greater in the cases of erroneous diagnosis. As 25.0% of the ET patients had previously received erroneous treatment, its impact on the depression level was tested by an independent samples t-test. It revealed that the median BDI score for the ET patients without therapy errors in the anamnesis (M = 12.93; SD = 11.43) was statistically significant ($p < 0.05$) and lower by 7.56 points than in the group with therapy errors (M = 20.50; SD = 10.53). The statistical effect calculated by the ROC curve was shown to be poor (AUC = 0.73; $p < 0.05$).

45.0% of the ET patients have a positive family anamnesis with a sign of autosomal dominant (A-D) inheritance.

The clinical assessment of the ET patients according to the Fahn, Tolosa, Marin rating scale gave a score between 8–112 with a maximum score of 144 (M = 28.98, SD = 20.14) (see Fig. 3).

More detailed analysis (see Figs. 4, 5) revealed the following: the right hand postural tremor was mild with 16 patients (40.0%); 21 patients (52.5%) had moderate tremor; only one patient (2.5%) had marked amplitude tremor and two patients (5.0%) — severe amplitude tremor. The left hand postural tremor was mild in 21 patients (52.5%); 17 patients (42.5%) had moderate tremor; one patient (2.5%) had marked tremor and one patient (2.5%) — severe amplitude tremor. 22.5% of the patients had slight asymmetrical postural tremor.

The paired samples t-tests showed that the assessment of the right hand and the left hand postural tremor was significantly ($p = 0.01$) higher for the right hand with a mean difference of 0.18 points. There was also a significant difference between the assessment of the right and left hand postural tremor ($p < 0.05$; non-parametric Wilcoxon Signed Ranks Test).

The Intraclass correlation coefficient showed significant positive correlation of postural tremor between the hands (ICC = 0.805; $p < 0.001$) in ET patients. Spearman's correlation coefficient for postural tremor severity between the hands was positive ($r_s = 0.72$; $p < 0.005$).

Action/intention tremor in the ET patients was as follows: in the right hand — no tremor with seven patients (17.5%), 19 patients (47.5%) had mild tremor; 11 patients (27.5%) had moderate tremor, two patients (5.0%) had marked amplitude tremor and one patient (2.5%) — severe amplitude tremor (Fig. 6). In the left hand there was no tremor in three patients (7.5%), 24 patients (60%) had mild tremor; 10 patients (25.0%) had moderate tremor, two patients (5.0%) had marked tremor and one patient (2.5%) — severe amplitude tremor. 22.5% of the patients had slight asymmetrical tremor, manifesting more in the left hand (Fig. 7).

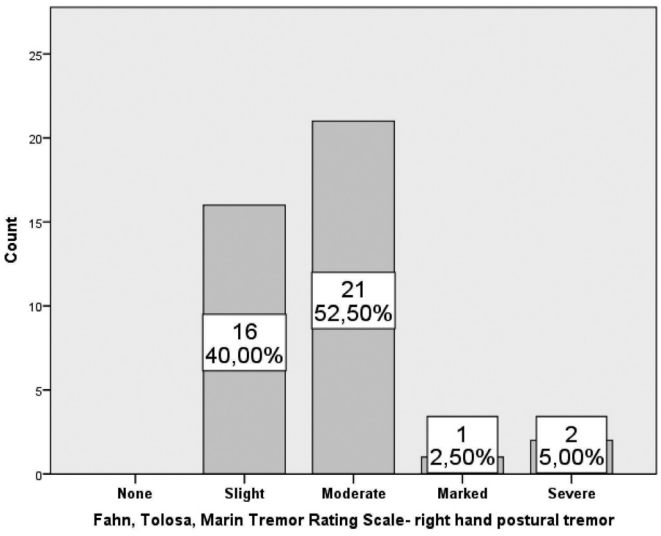

Fig. 4. Assessment of right hand postural tremor.

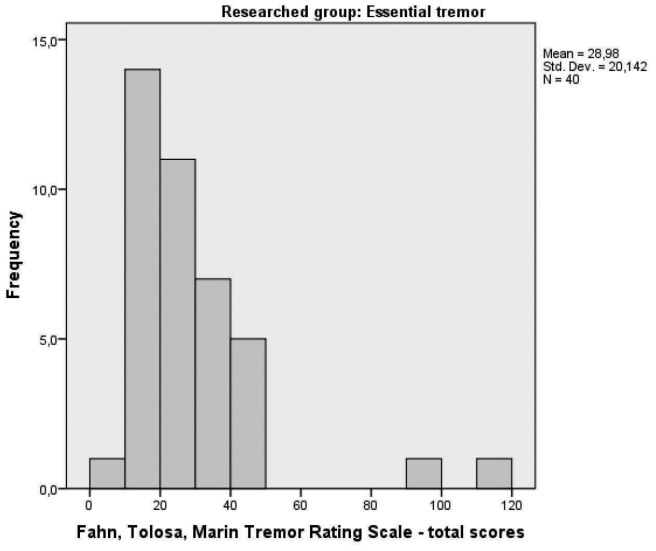

Fig. 3. Assessment of tremor in essential tremor patients.

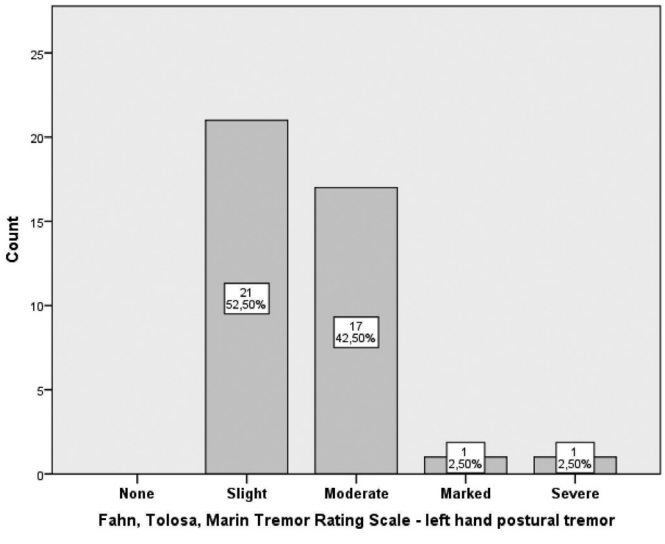

Fig. 5. Assessment of left hand postural tremor.

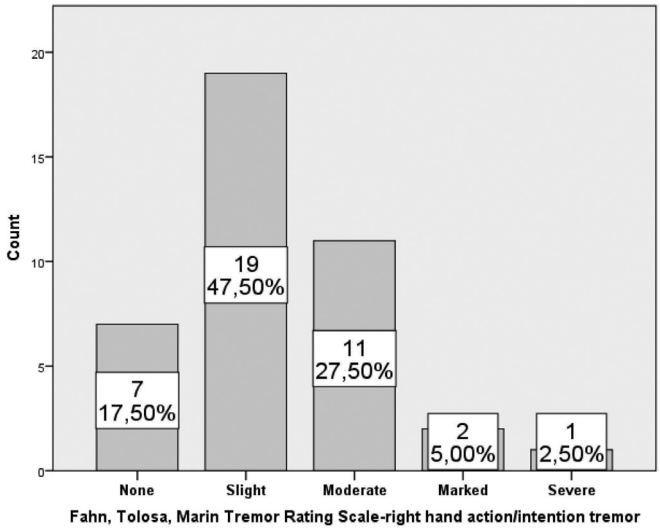

Fig. 6. Action/ intention tremor in the right hand.

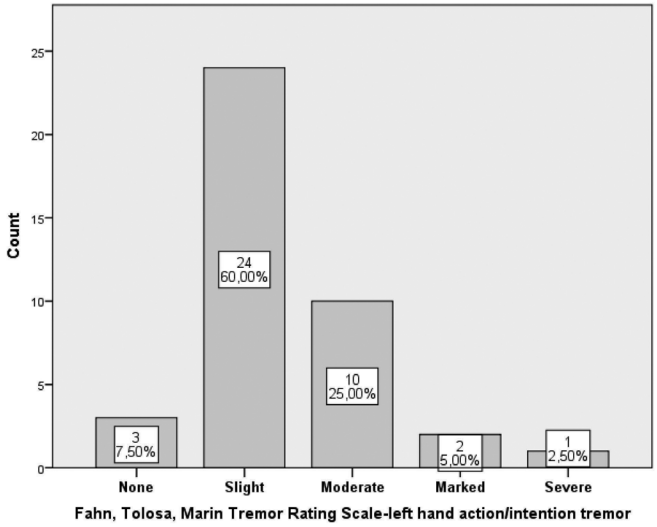

Fig. 7. Action/ intention tremor in the left hand.

Cross-section analysis of action/intention tremor with the ET patients showed that:

7.5% of the ET patients did not suffer from action tremor either in the right or the left hand; 10.0% did not have tremor in the right hand, but had mild tremor in the left hand; 45.0% had mild tremor in both hands; 2.5% had mild tremor in the right hand, but moderate in the left hand; 5.0% had moderate tremor in the right hand and mild in the left hand; 20.0% had moderate tremor in both hands; 2.5% had moderate tremor in the right hand and marked in the left hand; 2.5% had marked tremor in the right hand and moderate in the left hand; 2.5% had marked tremor in both hands; and 2.5% had severe amplitude tremor in both hands.

Thus, action/intention tremor was clinically observed in 22.5% of the patients.

However, a paired samples Wilcoxon test did not reveal significant asymmetrical action/intention tremor between both hands in the ET patients ($p < 0.05$).

The Intraclass correlation coefficient indicated significant correlation between symptoms of the right and left hand (ICC = 0.84, $p < 0.001$), thus, if one hand had mild tremor, it was mild in the other hand as well.

Spearman's correlation analysis showed moderate positive significant correlation ($r_s = 0.6$; $p < 0.001$) between the right hand action/ intention tremor and drawing of the Archimedean spiral with the right hand.

ET patients with a sustained tremor anamnesis and severe amplitude tremor had also rest tremor without the signs of hypokinesia, bradikinesia, rigidity or postural instability.

Rest tremor analysis for ET patients indicated: no rest tremor in 50.0% of patients; 37.5% had mild tremor of both hands; 5.0% had moderate tremor in the right hand and mild tremor in the left hand; 2.5% had moderate tremor in both hands; 2.5% had moderate tremor in the right hand and marked tremor in the left hand; 2.5% had severe amplitude tremor in the right hand and marked tremor in the left hand.

Consequently, 50.0% of the ET patients suffered from rest tremor. A greater score on the Fahn, Tolosa, Marin tremor rating scale was associated with characteristic rest tremor (see Figs. 8, 9).

While clinical assessment indicated mild asymmetrical tremor in 10.0% of the patients, a paired samples test did not show significant difference in rest tremor between the hands ($p < 0.05$).

The Intraclass correlation coefficient indicated a significant correlation for rest tremor between the hands with the ET patients (ICC = 0.96).

Pearson's correlation analysis between patient age and ET severity level according to the Fahn, Tolosa, Marin tremor scale showed a moderate, positive and significant correlation (r = 0.50; $p < 0.001$). The same was also established when applying Spearman's correlation coefficient (r_s = 0.46; $p = 0.003$).

DISCUSSION

Taking into account that 30.0% of the ET patients had prior erroneous diagnosis and 25.0% had undergone continuous dopaminergic therapy (L-DOPA, dopamine agonists), though it had been non-effective treatment, these seemed to be valid reasons for investigating the characteristics of ET within our population.

Clinically, the more frequent variant (22.5% of ET patients) was mild or moderate symmetrical postural hand tremor, but slightly asymmetrical tremor, manifesting more in the right hand. They also had mild or moderate action/intention tremor in both hands, and shaky handwriting. In the case of sustained tremor anamnesis developing moderate postural or action/ intention tremor, in 50.0% of the patients mild rest tremor in both hands was observed.

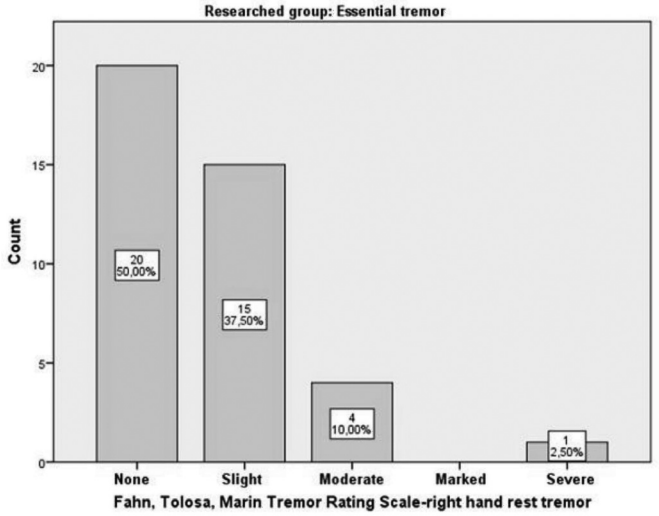

Fig. 8. Rest tremor in the right hand.

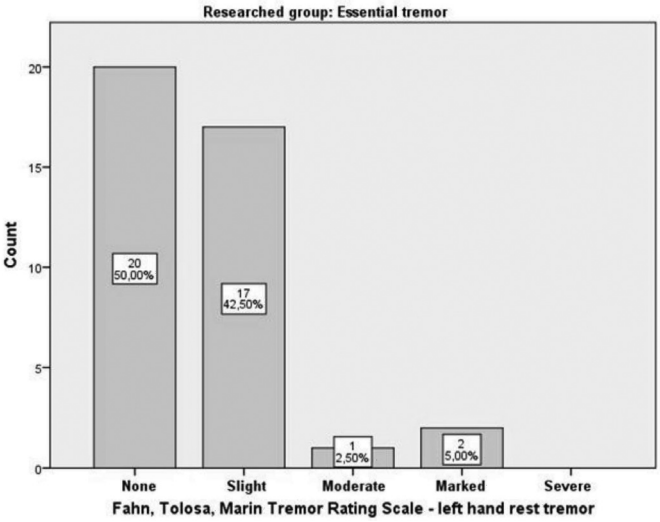

Fig. 9. Rest tremor in the left hand.

Summarising the clinical data according to the Fahn-Tolosa-Marin tremor scale the following results were obtained: 100.0% of the patients had hand tremor, mostly postural or action/ intention tremor; 37.5% had head tremor; 25.0% had facial (mimic muscles) tremor; 77.5% had postural leg tremor; 87.5% had various level difficulties in drawing a spiral; 47.5% showed macrographic lettering, which is a sign of cerebral dysfunction and was characteristic of continuous and more severe disease process.

The data obtained from the sample of the ET patients of the Latvian population differ from those provided by Elbe (quoted in Lyons and Pahwa, 2005): in Latvia the prevalence of facial mimic muscles tremor was by 20% greater, leg tremor by 50% greater and rest tremor in hands by 30% greater. It may be assumed that the characteristics of the ET patients in Latvia are partly due to the high percentage of erroneous diagnosis, as physicians use evidence of rest tremor and asymmetry of tremor to assign Parkinson's disease. Frequency of rest tremor in the sample of the population was by 50% — greater than that reported by other authors (Rajput *et al*., 1993; Cohen *et al*., 2003). Moreover, it should be underlined that no other PD signs were observed with the patients — hypokinesia, bradikinesia, rigidity, gait problems, etc.

The MDS ET diagnosis criteria claim tremor to be largely symmetric, however, admitting slight asymmetry. Data in literature mention only 11.0% of equal postural tremor (Louis et al., 1998), however, the sample of our population produced 22.5% of assymmetry.

In clinical examination, tremor asymmetry and signs of rest tremor in ET patients should be assessed in a period longer than 10 years to exclude the development of comorbid PD. There are two publications on the observation of ET-PD patients, who had early onset of ET (earlier than 20 years of age), and who later suffered from the development of PD, with PD tremor more prominent on the side with more manifested ET (Shahed and Jankovic, 2007; Minen and Luis, 2008). Louis (cited in Lyons and Pahwa, 2005) suggested kinetic tremor as the main ET sign and different from those of PD, moreover, excluding other causes of it. Regretfully, sensitive and specific diagnostic tests are still not available for ET diagnostics (serological, diagnostic imaging, neurophysiological), and the diagnosis is clinically based. However, some researchers use electrophysiological testing to supplement the clinical criteria, but this programme is no longer available in Latvia. This may result in specific cases of of mild ET disease process being mistaken for enhanced physiological tremor.

A genetic investigation of 250 ET patients of Latvia did not identify the same genes (ETM1, HS1-BP3, DRD3) as in other populations, excepting ETM2 and LINGO1 gene A/G genotype for 1 SNPs marker in the familial ET patients (Inashkina *et al*., 2008; Radovica *et al*., 2012). Factors such as genetic heterogeneity and phenotypic variance, disease characteristics, high comorbidity with social anxiety, depression, personality traits of the patient and, possibly, physicians' qualification and unnecessary use of medication, have created a situation where ET disease is more difficult to be recognized or is interpreted erroneously. The ET frequency is by 8–10 higher than PD, therefore, when seeing a patient with tremor, the possibility of the most frequent disease should firstly be considered. Assessment of lettering is helpful in distinguishing the diseases.

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ESENCIĀLĀ TREMORA ĪPATNĪBU IZPĒTE LATVIJAS POPULĀCIJĀ

Esenciāls tremors (ET) ir bieži sastopama kustību traucējumu slimība, kuras galvenie simptomi ir bilaterāls posturāls un kinētisks tremors, prevalējoši rokās. Slimībai raksturīga hroniska progresējoša norise, ilgstošas, smagas formas gadījumā ļoti atgādinot Parkinsona slimību (PS), kā arī reizēm iespējama tās komorbiditāte ar PS. Lai gan abām slimībām raksturīga atšķirīga patoģenēze un ārstēšana, tomēr dažas tremora īpatnības abām slimībām reizēm ir līdzīgas, radot diagnostikas grūtības un kļūdas. Pētījuma mērķis bija atklāt ET īpatnības Latvijas populācijā, lai analizētu iespējamos kļūdīšanās iemeslus.