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The usefulness of accelerometric registration with assessment of tremor parameters and their symmetry in differential diagnosis of parkinsonian, essential and cerebellar tremor

Przydatność rejestracji akcelerometrycznej z oceną parametrów drżenia i ich symetrii w diagnostyce różnicowej drżenia parkinsonowskiego, samoistnego i móżdżkowego

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Abstract

Background and purpose: The aim of the study was to perform an analysis of the recorded tremor using accelerometry and select those parameters that are the most useful in differentiation of tremor types.
Material and methods: We examined 45 patients with parkinsonian tremor (PT), 39 patients with essential tremor (ET) and 35 patients with cerebellar tremor (CT). The control group consisted of 52 healthy persons. The analysis included tremor intensity, frequency of spectral peaks, centre frequency, standard deviation of the centre frequency, and harmonic index. Parameters of tremor were compared between particular groups of patients with pathological tremor and with the control group. The side-to-side symmetry of these parameters was also analysed.
Results: Tremor intensity was significantly higher in patients than in controls. There was a significant side-to-side asymmetry of intensity in all patient groups. Significantly lower peak frequency, centre frequency and standard deviation of centre frequency were found in patients compared to the control group. The frequency was symmetric in ET and in controls, but asymmetric in other subjects. The differences bet-

Streszczenie

Wstęp i cel pracy: Celem pracy była analiza drżenia zarejestrowanego za pomocą akcelerometru z wyodrębnieniem tych parametrów, które są najbardziej przydatne w różnicowaniu drżeń.
Materiał i metody: Zbadano 45 pacjentów z drżeniem parkinsonowskim, 39 pacjentów z drżeniem samoistnym oraz 35 pacjentów z drżeniem móżdżkowym. Grupa kontrolna składała się z 52 zdrowych neurologicznie osób. Oceniono: intensywność drżenia, częstotliwość pików w widmie, częstotliwość środkową, odchylenie standardowe od częstotliwości środkowej i indeks harmoniczny. Porównano parametry drżenia między grupami pacjentów i grupą kontrolną oraz grupy pacjentów między sobą. Analizowano symetrię badanych parametrów pomiędzy rękami.
Wyniki: Intensywność drżenia w grupach chorych była znamiennie większa w porównaniu z grupą kontrolną. W grupach chorych znamienna była asymetria intensywności pomiędzy rękami. Częstotliwość pików w widmie, częstotliwość środkowa oraz odchylenie standardowe od częstotliwości środkowej były znamiennie niższe w grupach chorych w porównaniu z grupą kontrolną. Częstotliwość była symetryczna

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ween hands regarding the standard deviation of centre frequency were significantly greater in all patient groups than in controls, who revealed no difference of this parameter between sides. Harmonic index was significantly greater and asymmetric in all groups of patients when compared to the control group.

Conclusions: Standard deviation of centre frequency and harmonic index are the most valuable variables in differentiation of tremor. The assessment of symmetry of tremor parameters is useful in discrimination of various types of pathological tremor.

Key words: tremor, differential diagnosis, quantitative analysis, tremor parameters, power spectrum.

w obu rękach u osób z drżeniem samoistnym i grupie kontrolnej, asymetryczna w pozostałych grupach. Różnice odchylenia standardowego od częstotliwości środkowej pomiędzy rękami były znamiennie większe we wszystkich grupach chorych w porównaniu z grupą kontrolną, w której nie stwierdzało się istotnych różnic pomiędzy stronami. Znamiennie wyższy był indeks harmoniczny, który był asymetryczny w obu rękach w grupach chorych w porównaniu z grupą kontrolną.

Wnioski: Największą wartość w różnicowaniu drżenia mają odchylenie standardowe od częstotliwości środkowej i indeks harmoniczny. W różnicowaniu typów drżenia chorobowego przydatna jest ocena symetrii badanych wskaźników.

Słowa kluczowe: drżenie, diagnostyka różnicowa, analiza ilościowa, parametry drżenia, widmo mocy.

Introduction

Differentiation between tremor and other involuntary movements is usually simple due to the oscillatory and rhythmic characteristics of the tremor. Differential diagnosis of various forms of tremor can be quite challenging, however, and difficulties encountered might result in inappropriate therapeutic decisions.

Differentiation between essential tremor (ET) and parkinsonian tremor (PT) is often problematic because of the high prevalence of both disorders. Essential tremor is more common than Parkinson disease (PD), and the prevalence of both disorders increases with age of the studied population. It seems therefore that the proper diagnosis of tremor, especially among elderly subjects, requires considerable insight.

Essential tremor is one of the most common neurological disorders but its diagnosis may still pose some difficulties. According to Schrag *et al.* [1] only 50% of patients diagnosed earlier with ET fulfilled the diagnostic criteria. The definition of ET in that particular study was narrow and included a positive family history as a diagnostic criterion. Jain and colleagues verified the diagnosis of ET in 71 patients and estimated that the diagnosis was inappropriate in 37% of patients [2]. Repeated evaluation revealed that the most common proper diagnosis was PD (15%). The authors used the criteria proposed by the Movement Disorders Society, which do not consider a positive family history as a prerequisite of ET diagnosis; thus, other factors established during history-taking and neurological examination influenced the changes in diagnosis.

Diagnostic errors may also occur in the reverse situation, when ET is diagnosed and treated as PD. One of the early epidemiological studies on PD estimated that tremor was not parkinsonian but essential in 26% of patients diagnosed with PD [3]. Meara *et al.* [4] studied 404 patients diagnosed with PD and found ET in 12% of those patients. Other studies also confirmed quite common errors in diagnosis of both these disorders based on the type of the tremor [5-10].

Diagnosis of the tremor according to the clinical characteristics is sometimes insufficient to establish the appropriate diagnosis. Methods enabling the quantitative assessment of various tremor parameters and supporting the diagnostic process are therefore important.

Accelerometric registration of tremor provides objective data on tremor features. We have previously determined the parameters that are the most useful in differentiation of tremor [11]. The discriminative features included the standard deviation of centre frequency and harmonic index; they attested to the rhythmicity and regularity of tremor.

The aim of the present study was to establish the usefulness of spectral analysis parameters along with the assessment of their symmetry between sides in differential diagnosis of tremor in patients with clinically diagnosed ET, PT or cerebellar tremor (CT).

Material and methods

Patients

Our study comprised 119 patients with tremor of more than 1 year duration diagnosed according to the Consensus Statement of the Movement Disorders Society on Tremor [12]. The study group comprised 45 patients with PT, 39 subjects with ET and 35 patients with CT.

Exclusion criteria consisted of diagnosed endocrine dysfunction, use of any medication that might evoke tremor, use of psychoactive substances, and psychiatric disorders.

The subgroup of patients with PT comprised 45 patients (age range 42-81 years; mean 64.2 ± 10.2), including 17 women (age range 49-81 years; mean 67 ± 10), and 28 men (age range 42-77 years; mean 62.4 ± 10.2). The duration of the disease ranged between 1 and 12 years (mean disease duration 5 ± 3 years). The study involved patients with clinically diagnosed tremor-dominant or mixed form of idiopathic PD, in whom uni- or bilateral rest tremor or rest and postural/kinetic tremor was present. Parkinson disease was diagnosed according to the specific diagnostic criteria [13].

Tremor severity was assessed in the 'off' stage on a five-point scale (0-4 pts) according to the third part of the Unified Parkinson's Disease Rating Scale (UPDRS-III), items 20 (rest tremor) and 21 (kinetic or postural tremor) [14]. Tremor of the first type was diagnosed in 42 patients, and tremor of the second type was noted in 3 other patients. Among patients with tremor of the first type, 15 subjects had an isolated rest tremor. Rest tremor (UPDRS-III, item 20) had the range of 1-4 pts (mean: 2.3 ± 0.75 pts) in the hand with more severe tremor and 0-2 pts (mean: 1.0 ± 1.0 pts) in the hand with less severe tremor. Postural/kinetic tremor (UPDRS-III, item 21) had the range of 1-4 pts (mean: 1.2 ± 1.1 pts) in the hand with more severe tremor and 0-3 pts (mean: 0.4 ± 0.78 pts) in the hand with less severe tremor.

The subgroup of patients with ET comprised 39 patients (age range 16-74 years, mean 48.2 ± 17.5) including 19 women (age range 16-74 years, mean 53.1 ± 18.4) and 20 men (age range 17-69 years, mean 43.6 ± 16). The duration of disease ranged from 2 to 39 years (mean 7.2 ± 7). Essential tremor was diagnosed according to the clinical evaluation that revealed bilateral, more or less symmetrical upper limb tremor of postural and/or kinetic quality (without rest tremor) with or without accompanying head tremor, without any abnormal posturing of the head.

The severity of tremor among patients with ET was assessed with the scale used in the WHIGET study (Washington Heights-Inwood Genetic Study of Essential Tremor) [15]. Thirty-seven patients had postural and kinetic tremor, while two other subjects had postural tremor only. The severity of tremor assessed on the WHIGET scale ranged from 4 to 34 pts (mean 19.66 ± 5.65 pts). SevPostural tremor ranged from 1 to 3 pts; the mean severity of tremor in the hand with more severe tremor was 1.46 ± 0.64 pts; the mean severity of tremor in the hand with less severe tremor was 1.46 ± 0.64 pts; the mean score in both hands was 1.46 ± 0.64 pts.

The severity of kinetic tremor ranged from 0 to 3 pts; the mean severity of tremor in the hand with more severe tremor was 1.69 ± 0.74 pts; the mean severity of tremor in the hand with less severe tremor was 1.65 ± 0.73 pts; the mean score in both hands was 1.67 ± 0.74 pts.

The subgroup of patients with CT comprised 35 patients (age range 21-76 years; mean 48 ± 14), including 19 women (age range 21-69 years; mean 43.8 ± 15.5), and 16 men (age range 37-76 years; mean 52.2 ± 12.1). The duration of disease ranged from 1 to 37 years (mean 6 ± 7). Cerebellar tremor was diagnosed according to the clinical evaluation and confirmed with the presence of a cerebellar lesion in neuroimaging (computed tomography and/or magnetic resonance imaging). Patients were qualified for the study if they had isolated or predominant uni- or bilateral intentional tremor with possible associated postural tremor and without rest tremor.

All 35 patients had some cerebellar signs other than the tremor. Twelve patients had unilateral cerebellar syndrome, while another 23 patients had bilateral symptoms and signs.

The severity of tremor among those patients was assessed with items 11 and 12 of the second part of the International Cooperative Ataxia Rating Scale (ICARS) [16]. The severity of intentional tremor in the more affected limb ranged from 2 to 4 pts (mean 2.7 ± 0.64 pts), and from 0 to 4 pts (mean 1.1 ± 1.07 pts) in the contralateral limb. The severity of tremor associated with voluntary muscle contraction in the more affected limb ranged from 0 to 4 pts (mean 2.1 ± 1.14 pts), and from 0 to 4 pts (mean 0.94 ± 1.08 pts) in the less affected limb.

The control group consisted of 52 healthy subjects (age range 16-82 years; mean 52 ± 16.3), including 27 women (age range 16-78 years; mean 50 ± 18) and 25 men (age range 27-82; mean 54 ± 14.5).

Methods

Examinations were performed using a biaxial accelerometer from Analog Devices with the registration software from CrossBow. The accelerometer was mounted at the dorsal surface of the patient's hand. Measurements were carried out for the right and left hand separately and consecutively in three positions: (1) at rest, when the hand and forearm were fully

supported; (2) in the writing position; and (3) when the upper limb was held outstretched and extended in pronation.

The registration took 3 minutes (one minute for each position of the limb). The signal was sampled with the frequency of 50 Hz per channel and recorded on a computer hard disk. Spectral analysis was done with Matlab software. The initial signal processing included the restoration of the acceleration vector in the registration plane and bandpass filtration from 1 to 15 Hz using a fourth-order Butterworth filter. The distribution of the spectral density estimator was established through the calculation of 512-point fast Fourier transformation (FFT). A Hanning window was used to reduce the spectral leakage. The spectrum was averaged for 10.2 second-wide time epochs of the registered signal.

The analysed parameters included:

- tremor intensity – calculated as the root-mean-square of acceleration [m/s^2]; the acceleration is the second derivative of position with respect to time (m),
- the frequency of peaks within the spectrum [Hz],
- centre frequency – the frequency below which lies 50% of the power in the spectrum and above which lies the other 50% [Hz],
- standard deviation of centre frequency or dispersion about median frequency – the frequency width of an interval around the centre frequency that contains 68% of the total power in the spectrum; it reflects the degree of discoordination of the tremor; a very rhythmic tremor has a small value of that variable, indicating that most of the energy is produced within a narrow frequency band [Hz],
- harmonic index (HI) or the index of harmonic contents in the spectrum. It defines the distance of the spectrum to the single narrow peak; that value is normalized to the highest peak.

The obtained results were statistically analysed using STATISTICA v.7.1 software.

The basic statistical measures, including mean, median, maximum, minimum, standard deviation, skewness, and kurtosis, were calculated for all interval variables. The distribution of the variables and its compatibility with normal distribution was tested with the Shapiro-Wilk test. The association of tremor parameters with age in patients was tested with Spearman rank correlation coefficient. The differences in tremor parameters among patient subgroups were tested with Kruskal-Wallis rank analysis of variance, supplemented with post-hoc analysis with the Tukey test. The Tukey test (in contrast to the Mann-Whitney *U*-test) takes into account the 'cumulative alpha effect' due to the multiple comparisons.

Analysis of variance was performed for the variables standardized according to age. The results of that analysis account for the differences in age among studied groups (the impact of age was reduced due to the standardization). The Wilcoxon signed-rank test was used to compare the tremor parameters between hands with greater and smaller intensity of tremor. This test was used instead of Student's *t*-test for paired samples because of non-normal distribution and high absolute values of skewness and kurtosis for multiple variables.

The relationship between intensity and frequency of tremor was verified with linear regression. *P*-values < 0.05 were considered statistically significant.

Tremor parameters were compared between groups with pathological tremor and the control group as well as among subgroups with particular tremor. The following variables were analysed: (a) mean values from both hands; (b) data grouped according to the accelerometry results from the hand with greater and smaller intensity of tremor; (c) differences in values of particular parameters between sides. The values of studied parameters were also compared between hands with greater and smaller intensity of tremor. The relationship between intensity and frequency of tremor was also analysed.

Results

Tremor intensity

Analysis of data derived from the more affected hand and from the mean values of both hands revealed that the tremor intensity was significantly greater in any type of pathological tremor than in controls ($p < 0.001$ for each difference between ET, PT or CT subgroups and controls). Tremor intensity was greater in ET than in PT or CT ($p < 0.001$). Tremor intensity was similar in patients with PT and CT.

Patients with ET ($p < 0.001$) or CT ($p = 0.04$) had greater tremor intensity than controls also in the less affected hand. In patients with PT, tremor intensity in the less affected hand was similar to healthy controls.

The difference of tremor intensity between sides was also significantly greater in patients than in controls (PT vs. controls, $p = 0.005$; ET vs. controls, $p < 0.001$, CT vs. controls, $p = 0.02$); it was also greater in ET patients when compared with other patients ($p < 0.001$). Tremor intensity in the hand with more severe tremor was greater than in the hand with less severe tremor ($p < 0.001$). There was no difference between the hand

with greater and that with lesser tremor intensity in the control group (Tables 1 and 2).

Frequency of peaks within the spectrum

The frequency of peaks was significantly lower in patients than in controls ($p < 0.001$) when mean values from both hands in particular subgroups of patients were analysed. This frequency was lower in PT than in ET but it was the lowest in CT. Results in particular groups were significant ($p < 0.001$). The frequency of peaks in all three studied subgroups of patients was lower than in controls, both in the hand with greater tremor intensity and in the hand with smaller tremor intensity.

The frequencies of peaks in the more affected hand were also significantly different among groups (CT < PT < ET) ($p < 0.001$), while in the less affected hand the frequency of peaks was similar in PT and ET, but lower in CT than in other patient subgroups ($p < 0.001$).

The difference in frequency of peaks between sides was significantly greater in PT than in controls or other subgroups of patients ($p < 0.001$); the two other patient

Table 1. Results of accelerometry – tremor parameters in patients with parkinsonian tremor (PT), essential tremor (ET), cerebellar tremor (CT) and control group

Tremor parameters	More trembling hand; median (range)	Less trembling hand; median (range)	Both hands (median)	Odds of values between hands; median (range)
Tremor intensity [m/s^2]				
PT	0.32 (0.07-3.17)^{a,b}	0.11 (0.04-1.33)^{b}	0.16^{a,b}	0.19 (0.01-2.02)^{a,b}
ET	1.33 (0.14-9.42)^{a,c,d}	0.52 (0.08-3.61)^{a,c,d}	0.88^{a,c,d}	0.79 (0.01-5.81)^{a,c,d}
CT	0.32 (0.06-4.08)^{a,b}	0.14 (0.05-1.67)^{a,b}	0.22^{a,b}	0.16 (0.0-2.93)^{a,b}
Controls	0.095 (0.017-0.213)^{c,b,d}	0.088 (0.016-0.204)^{b,d}	0.091^{c,b,d}	0.006 (0.0-0.19)^{c,b,d}
Frequency of peak [Hz]				
PT	5.18 (4.10-6.64)^{a,b,d}	5.97 (4.10-9.77)^{a,d}	5.57^{a,b,d}	0.78 (0.09-4.29)^{a,b,d}
ET	6.54 (4.20-11.70)^{a,c,d}	6.64 (4.10-11.10)^{a,d}	6.64^{a,c,d}	0.30 (0.0-1.23)^{c}
CT	3.13 (1.96-5.01)^{a,c,b}	3.52 (1.95-4.92)^{a,b,c}	3.40^{a,c,b}	0.32 (0.0-2.20)^{c}
Controls	8.69 (4.79-12.01)^{c,b,d}	8.89 (4.93-11.70)^{c,b,d}	8.80^{c,b,d}	0.471 (0.02-1.66)^{c}
Centre frequency [Hz]				
PT	5.60 (4.19-6.80)^{a,b,d}	6.50 (4.59-8.70)^{a,d}	5.93^{a,b,d}	0.87 (0.02-2.76)^{a,b,d}
ET	6.64 (4.36-11.10)^{a,c,d}	6.65 (4.31-10.60)^{a,d}	6.65^{a,c,d}	0.25 (0.01-0.92)^{c}
CT	3.18 (1.94-4.89)^{a,c,b}	3.61 (1.96-4.50)^{a,b,c}	3.36^{a,c,b}	0.21 (0.01-1.99)^{c}
Controls	8.37 (7.11-10.54)^{c,b,d}	8.39 (7.18-10.74)^{c,b,d}	8.37^{c,b,d}	0.198 (0.0-0.72)^{c}
SD of centre frequency [Hz]				
PT	1.17 (0.10-3.71)^{a,d}	2.54 (0.10-4.98)^{a,d}	1.95^{a,d}	0.88 (0.0-2.74)^{a,b,d}
ET	1.76 (0.20-3.61)^{a,d}	2.35 (0.78-3.67)^{a,d}	2.05^{a,d}	0.47 (0.0-1.66)^{a,c}
CT	0.98 (0.10-1.66)^{a,c,b}	1.37 (0.29-2.44)^{a,b,c}	1.17^{a,c,b}	0.49 (0.10-1.95)^{c}
Controls	4.54 (3.42-5.18)^{c,b,d}	4.64 (3.22-5.27)^{c,b,d}	4.59^{c,b,d}	0.195 (0.0-1.08)^{c,b}
Harmonic index [Hz]				
PT	0.95 (0.90-0.99)^{a}	0.90 (0.81-0.99)^{a}	0.94^{a}	0.03 (0.0-0.15)^{b,d}
ET	0.95 (0.88-0.98)^{a}	0.93 (0.89-0.98)^{a}	0.94^{a}	0.02 (0.0-0.6)^{c}
CT	0.95 (0.9-0.99)^{a}	0.93 (0.88-0.98)^{a}	0.94^{a}	0.02 (0.0-0.07)^{c}
Controls	0.751 (0.62-0.88)^{c,b,d}	0.732 (0.634-0.86)^{c,b,d}	0.746^{c,b,d}	0.030 (0.0-0.134)

SD – standard deviation; [a]significant difference between patients and control group; [b]significant difference in comparison with ET; [c]significant difference in comparison with PT; [d]significant difference in comparison with CT; ($p < 0.05$, Kruskal-Wallis one-way analysis of variance)

Table 2. Comparison of tremor intensity, frequency of peaks, centre frequency, standard deviation of centre frequency, and harmonic index between more and less trembling hand (Wilcoxon signed-rank test)

	More trembling hand vs. less trembling hand				
	Tremor intensity	**Frequency of peak**	**Centre frequency**	**SD of centre frequency**	**Harmonic index**
PT	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
ET	$p < 0.001$	NS	NS	$p < 0.001$	$p < 0.001$
CT	$p < 0.001$	$p < 0.003$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Controls	NS	NS	NS	NS	$p < 0.003$

PT – parkinsonian tremor; ET – essential tremor, CT – cerebellar tremor; SD – standard deviation; NS – non-significant

subgroups did not differ between each other or in comparison with controls.

The frequency of peaks was similar in both hands in patients with ET and in controls. The frequency of peaks was greater in the less affected hand than in the more affected hand in PT ($p < 0.001$) and in CT ($p < 0.003$) (Tables 1 and 2).

Centre frequency

Centre frequency was also significantly lower in patients than in controls, both in the less or more affected hand and in terms of mean values ($p < 0.001$).

The differences in centre frequency were also significant among subgroups of patients when more affected hands or mean values were analysed (CT < PT < ET) ($p < 0.001$). Centre frequency in the less affected hand was similar in patients with PT and ET but was lower in CT ($p < 0.001$). The difference in centre frequency between sides was significantly greater in PT than in controls or other patient subgroups ($p < 0.001$); the two other patient subgroups did not differ between each other or in comparison with controls.

Centre frequency was symmetrical in both hands in patients with ET and in healthy controls.

Lower values of centre frequency were noted in the hand with greater tremor intensity in patients with CT and PT ($p < 0.001$) (Tables 1 and 2).

Standard deviation of centre frequency

Standard deviation of centre frequency was significantly smaller in patients than in controls ($p < 0.001$). This difference was found between values from the less and more affected hand as well as between mean values from both hands.

Standard deviation of centre frequency in the hand with more or less severe tremor and regarding the mean values from both hands was similar in patients with PT and ET; it was lower in patients with CT than in other patient subgroups ($p < 0.001$).

The differences between hands in standard deviation of centre frequency were greater in PT ($p < 0.001$) and ET ($p = 0.03$) than in controls. They were also greater in PT than in other patient subgroups (PT vs. ET, $p = 0.02$; PT vs. CT, $p = 0.006$). The differences were similar between patients with CT and controls as well as between ET and CT.

Standard deviation of centre frequency was similar in both hands in controls but it was significantly lower in the hand with greater severity of tremor than in the hand with lesser severity of tremor in each subgroup of patients ($p < 0.001$) (Tables 1 and 2).

Harmonic index

The harmonic index was higher in all subgroups of patients than in controls ($p < 0.001$) regardless of whether data were derived from the hand with smaller or greater tremor intensity or from the mean value for both hands. Those values were similar among subgroups of patients.

The difference of harmonic index between sides in all subgroups of patients was comparable with the same difference noted in controls but it was significantly greater in PT than in patients with other types of tremor ($p = 0.02$); the difference between the two other groups of patients was not significant.

Significant asymmetry of the harmonic index between the hand with greater and lesser tremor intensity was noted in all studied groups, including controls (PT, ET or CT: $p < 0.001$, controls, $p < 0.003$). The harmonic index was greater in the hand with greater tremor intensity (Tables 1 and 2).

The relationship between tremor intensity and frequency of peaks, as well as centre frequency, in patients with pathological tremor and in controls

Linear regression showed an inverse relationship between tremor intensity and centre frequency in patients with ET ($p < 0.001$) and in controls ($p = 0.03$ and $p = 0.006$) both in the hand with less and that with more severe tremor. In patients with PT, this relationship was only significant for the hand with greater tremor intensity ($p = 0.01$), and was close to significance in the other hand ($p = 0.06$). An inverse relationship between tremor intensity and frequency of peak was found only in patients with ET and in controls, both in the hand with greater and that with lesser severity of tremor ($p < 0.001$). No significant inverse relationship was observed in CT regarding tremor intensity and centre frequency or tremor intensity and frequency of peak.

Discussion

Most of the studies did not assess the relationship between asymmetry of tremor intensity and asymmetry of frequency. Some authors did not address symmetry at all; they registered and analysed amplitudes and frequencies in one hand only. Papers that included registration of tremor from both hands most often analysed merged data from both hands or mean values from the right and left hand or compared data from the dominant and non-dominant hand. The first paper dealing with asymmetry of tremor intensity and frequency in patients with PT and ET was published in 2006; the authors identified a relationship between those two features, comparing data from the less and more affected hand [17].

When data from the hand with greater and lesser severity of tremor were analysed, greater tremor intensity was noted in both hands of patients with ET and CT than in controls but only in the more affected hand in patients with PT. Tremor intensity in the less affected hand in patients with PT was similar to the values obtained in controls.

The greatest tremor intensity was found in patients with ET. Tremor intensity was similar in patients with PT and CT.

In all three subgroups of patients, significant asymmetry of tremor intensity was noted between hands. The grade of asymmetry was different in different subgroups. In patients with PT, the tremor intensity in the more affected hand was more than three times greater than in the less affected hand; in patients with ET or CT, the corresponding value was more than two times greater than in the less affected hand. Due to the significantly greater tremor intensity in patients with ET, the difference between hands regarding the tremor intensity was the greatest in that particular subgroup of patients.

In healthy controls, the measurements of tremor intensity revealed similar values in both hands. It may be assumed, therefore, that physiological tremor is characterized by symmetry of the registered tremor intensity, while the occurrence of various grades of asymmetry suggests pathological tremor. These observations are in agreement with the results obtained by Farkas *et al.* [17].

The asymmetry of symptoms and signs is highlighted as a clinical feature of PD. Tremor of one limb is the first motor symptom in 75% of patients with PD. As the disease progresses, the tremor spreads and becomes bilateral but it is commonly more severe in the limb where it occurred at the onset of disease [18-23]. Essential tremor is commonly thought to be symmetrical but the opinions of experts are contradictory. Some authors believe that the symptoms of ET are symmetrical, while others think that asymmetry of tremor intensity is common [24]. In CT, the symmetry depends on the cause of the damage to the cerebellum. Tremor is bilateral and more or less symmetrical in neurodegenerative or toxic disorders of the cerebellum, while unilateral tremor occurs in hemispheric cerebellar damage, e.g. due to stroke or tumour.

The quantitative method used in the present study has helped to reveal the difference in tremor intensity between hands, confirming thereby the common opinion that asymmetry, included in the additional diagnostic criteria, is a characteristic feature of PD. The asymmetry of the tremor intensity observed in our study among patients with ET contradicts the opinion that ET is usually symmetrical [25]. Louis *et al.* [24] reported similar findings and showed that the asymmetry was a typical feature of ET. The authors believe, however, that the occurrence of asymmetry depends on the accepted definition and 'norm' of asymmetry. They showed that any asymmetry between hands regarding severity of tremor was present in 89% of patients with ET. If a greater value of difference was assumed as suggestive for asymmetry, the percentage of patients with asymmetric tremor was lower. Biary and Koller found asymmetry greater than 25% in 62% of patients with ET [26]. The differences in reported prevalence of tremor asymmetry also result from various measures of tremor, i.e. scales or quantitative methods. As the new

research methods are applied, it is believed more and more often that ET is a disease with common asymmetry of symptoms and signs.

Farkas *et al.* [17] used accelerometric registration of tremor and found marked difference in tremor intensity between hands (defined as mean + 1 standard deviation of the value obtained in the control group) in 68% of patients with ET, and in 44% of patients with PD. Asymmetry of ET was also noted in half of the patients studied by Whaley *et al.* [27].

In the present study, the greatest difference between hands was also noted among patients with ET but the grade of asymmetry as measured by the ratio of the intensity in the more affected hand to the less affected hand was greatest in patients with PD.

The explanation of the surprisingly high asymmetry of ET among our patients may take into account the duration of the disease. It is believed that the duration of the disease is the most important factor influencing the asymmetry of symptoms and signs. A shorter duration of symptoms is related to a greater degree of asymmetry, similarly to the earlier onset of symptoms.

Duration of symptoms in studied patients with ET was relatively short (7.2 ± 7 years) and the mean age was also lower (48.2 ± 17.5 years) in comparison to the populations studied by the other authors. These factors might therefore have affected our results. The mean duration of symptoms among other subgroups of our patients was also short but more similar to the duration reported in previous papers. The different degree of asymmetry may also be related to the different rate of disease progression in studied groups of patients.

The observations made by us and by other authors indicate that patients with pathological tremor may have normal or almost normal values of tremor intensity, so it cannot be the criterion of differentiation. Tremor intensity should be analysed along with other indices and with the assessment of symmetry between sides.

The greatest percentage of patients with tremor intensity similar to that noted in controls was found in patients with PD (11% in the more affected hand and 66.7% in the other hand) and a smaller percentage of such patients was noted in CT (8.6% in the more affected hand and 42.9% in the other hand). In patients with ET, however, such small values of tremor intensity were not found at all in the more affected hand and were observed in 10% of patients in the less affected hand. Other authors also observed low-amplitude tremor in patients with PD or in ET [17,28-30].

Farkas *et al.* reported greater percentages of patients with small tremor intensity: 46% of patients with PD and 15% of patients with ET had tremor intensity in the more affected hand ≤ 0.2 m/s^2, which was equivalent to the mean + 1 standard deviation in controls [17].

The discussed disorders are characterized by a specific frequency range. Similarly to other authors, we found some patients with frequencies that departed from the most typical frequencies reported for the specific type of tremor [17,31-33]. The registered frequencies differed significantly among studied subgroups of patients. The frequency of tremor in PD was significantly lower when compared with ET, and the frequency of tremor in CT was significantly lower than in the other two subgroups, regarding the values from the more affected hand and the mean value from both hands. We did not find a significant difference in tremor frequency between patients with PT and ET, when the less affected hand was taken into account. Tremor in patients with PT had significantly lower frequency than tremor in controls, including in hands with the tremor intensity not different from that noted in healthy controls. It may be suggested that the generators of pathological tremor are active in the early stages of disease already.

The greatest asymmetry of frequency of peaks and centre frequency was found in patients with PT. The difference in frequency between hands was greater in those patients than in controls and patients from other subgroups (those subgroups differ regarding that variable neither between each other, nor between themselves and controls). When frequencies were compared between hands, asymmetry with the lower values in the hand with greater tremor intensity was noted not only in PT, but also in CT. Centre frequency and frequency of peaks were symmetrical in both hands in patients with ET and in healthy controls.

Although the range of observed frequencies of PT in the analysed group was wide, the mean values were within the narrow range between 5.2 and 6.5 Hz. Higher frequencies were found only in the hand with less severe tremor. They were noted in patients with the lowest tremor intensity among that subgroup, which was similar to that registered in controls. Those patients also had the greatest asymmetry of tremor between sides, which was also associated with the greatest difference in frequencies (even 4.3 Hz for frequency of peak and 2.8 Hz for centre frequency).

Other authors have also noted higher frequencies of PT than those reported in the literature. Farkas *et al.* registered mean frequency of 7.32 Hz (± 1.74). The authors explained such higher frequency as being due

to the method of limb positioning during the registration, i.e. in mid-position between resting (lower frequency) and kinetic (higher frequency), and due to the fact that two-thirds of patients had the second type of parkinsonian tremor. Additionally, the frequency of tremor up to 9 Hz may occur in early stages of PD. In patients studied by the authors, mean duration of the disease was 5.33 (± 4.07) years only, and half of the patients had mild clinical symptoms and signs [17].

In our patients, mean frequencies were lower than those reported by Farkas *et al.* Ninety-three percent of patients had classic PT, i.e. tremor at rest or constant tremor with no shift of frequency at rest, while maintaining the position and during movement. Therefore, the frequency did not increase markedly with consecutive positions of the limb during registration. The vast majority of patients had tremor of moderate intensity. The mean severity of tremor at rest (according to item 20, UPDRS-III) in the more affected hand was 2.3 ± 0.75 pts, and 1.0 ± 1.0 in the other hand. The mean severity of postural/kinetic tremor (according to item 21, UPDRS-III) in the more affected hand was 1.2 ± 1.1 pts, and 0.4 ± 0.78 in the other hand.

The mean duration of the disease in studied patients with PT was 5 ± 3 years. It seems, therefore, that the higher frequencies of PT noted by Farkas *et al.* were mainly due to the higher percentage of patients with the second type of tremor, and, to a lesser extent, due to other factors, including duration of the disease and the severity of tremor itself. Those latter factors were similar in our study and in the study by Farkas *et al.*

The symmetry of frequency of peak and centre frequency between hands was significant among patients with ET. Median frequency of peak in the hand with more severe tremor was 6.54 Hz, and median of the centre frequency was 6.64 Hz. Similar values were noted in the other hand (6.64 and 6.65 Hz, respectively). Similar mean values of frequency for ET are reported by other authors, although the mean age of their patients was higher than in our study [17,29].

Studies comparing the frequency of tremor between hands with greater and lesser severity of tremor are scarce. Observations made by Farkas *et al.* related to the asymmetry of the centre frequency were similar to ours. They showed asymmetry in patients with PT but not in patients with ET [17]. The frequency of tremor in patients with ET was similar in both hands despite the significant differences in tremor intensity. Calzetti *et al.* [29] reported different findings; according to their study, patients with ET had tremor frequency lower by about 1 Hz in the hand with greater tremor frequency compared with the other hand. Burkhard *et al.* [34] found asymmetry of frequency both in patients with PT and in ET, but it was not related to the asymmetry of tremor intensity [34]. Similar divergence of frequency between hands in ET and PT was reported by O'Suilleabhain and Matsumoto, who used the term 'frequency dissociation' to describe the synchronous appearance of tremor with different frequencies in distinct muscle groups [35].

Interpretation of spectral analysis requires some caution in case of biological signals, but the phenomenon of different tremor frequencies in both hands of patients with PT suggests the complexity and some hemispheric independence of the tremor generator. Raethjen *et al.* [36] observed coherence of electromyographic activity in various muscles of the same limb but did not observe coherence between sides, suggesting the existence of distinct, not connected oscillators for each limb [36].

Symmetry of frequencies in patients with ET, observed by us and by other authors, suggests the presence of interhemispheric connections between central oscillators. Those findings are in agreement with the observations made by Hellwig *et al.* [37], who found that the tremor registered electromyographically is coherent with the EEG activity recorded from both the contralateral and ipsilateral sensorimotor cortex.

The frequency of tremor in patients with CT was significantly lower than in other groups of patients. The frequency values recorded by us in some patients were divergent from the commonly cited range. We observed cerebellar tremor with the frequency of 1.9 Hz or slightly above 5 Hz, but the median of the centre frequency was 3.18 Hz in the more affected hand and 3.61 Hz in the less affected hand. Other authors have also registered cerebellar tremor with the frequency divergent from the typical ones. The frequency of cerebellar tremor recorded by Lenz [36] was similar to that reported in the present study, while Milanov [31] and Cole *et al.* [39] observed even higher values (> 6 Hz for intentional tremor and 9-10 Hz for kinetic and postural tremor).

This group of patients, similarly to the patients with PT, exhibited asymmetry of frequency between hands, with significantly lower frequency in the hand with greater tremor intensity. The difference between hands did not differ from the one recorded in controls and was similar to the values recorded in patients with ET. The group of patients with cerebellar tremor was aetio-

logically heterogeneous and 34% had unilateral cerebellar signs, but the frequency and other tremor parameters registered from the asymptomatic hand were within the values suggestive for pathological tremor. It comes to mind whether in this situation any connections between structures and systems responsible for tremor generation exist. If so, why does the contralateral limb show subclinical abnormalities revealed in accelerometric testing only? The available literature does not contain any reports on quantitative assessment of tremor symmetry between hands in cerebellar tremor.

The symmetry of tremor frequency between hands in healthy subjects has also been confirmed in other studies [17,40].

We also assessed the relationship between tremor intensity and frequency among studied groups. We noted an inverse correlation between tremor intensity and centre frequency or frequency of the dominant peak in patients with ET and in controls, both in the hand with greater and that with smaller tremor intensity. In patients with PT, this correlation was significant for centre frequency only, and in the hand with more severe tremor only, while in the other hand it was close to significance ($p = 0.06$). Farkas *et al.* made somewhat different observations and noted a significant inverse correlation between tremor intensity and centre frequency in both hands in patients with PT. In patients with ET, they observed such a correlation in the hand with greater tremor intensity only [17]. The results in the control group were similar in our own study and the study of the authors. Elble *et al.* [41,42] also observed the relationship between those two variables in patients with ET but it was assessed in one hand only for all studied patients.

The findings in patients with CT were different from other groups of patients. In this particular group, we did not observe any significant inverse correlation between tremor intensity and centre frequency or frequency of peak in either hand. Similar data were not presented previously for cerebellar tremor, although according to the general descriptions of two types of CT, the more severe one has lower frequency (2.5-4 Hz) and the benign one has much higher frequencies (up to 10 Hz) [43].

Only a few authors have used indices, other than amplitude and frequency, that might be more certain in differentiation of tremor. Besides those two important indices, we assessed two other features that are associated with each other and reflect the regularity and rhythmicity of tremor, i.e. standard deviation of centre frequency and harmonic index.

In all studied types of pathological tremor, we observed significantly lower values of standard deviation from centre frequency in comparison to its value in healthy subjects (about 2.4 times in PT or ET versus controls and about 3.8 times in CT versus controls). The smallest dispersion of frequency was noted in patients with CT. Values in this group were significantly smaller than in controls, but also in comparison with other patient subgroups. The difference of the obtained values between sides was markedly greater in PT than in ET or CT; the latter two did not differ between each other. The smallest, non-significant difference in comparison with the control group was noted in patients with CT.

Significant asymmetry between sides regarding the standard deviation from the centre frequency was noted in all three groups of patients. The standard deviation from the centre frequency was smaller in the hand with more severe tremor in comparison to the less affected hand. There was no difference between hands in healthy subjects.

Other authors, who used the dispersion of the frequency in assessment of tremor, also found lower values in patients with pathological tremor than in controls [17,28,32,33]. In our study, including in the hand with lower tremor intensity and even in some cases of PT or CT with clinically invisible tremor, standard deviation from centre frequency was lower than values noted in controls. Beuter *et al.* [28] made similar observations and reported that despite similar amplitude, morphological and time-related characteristics, physiological tremor can be distinguished from subclinical PT due to the other indices, e.g. dispersion of frequency, which are different in those two groups.

In papers published so far, only Farkas *et al.* [17] have also analysed the symmetry of signs between the hand with more and that with less severe signs. The asymmetry of standard deviation from the centre frequency in our study differs somewhat from the results obtained by Farkas *et al.* We obtained similar results regarding PT, but different ones regarding ET, in which the above-mentioned authors did not note an asymmetry. The available literature does not contain any data related to the dispersion of frequency in CT.

The harmonic index among studied patients was significantly higher than in controls, but the values of the harmonic index did not differ among the three studied groups of patients.

The greatest difference of the harmonic index between sides was noted in patients with PT. It was significantly greater than in other groups of patients, but sim-

ilar to controls. Differences in patients with ET and CT were similar to the values obtained in controls; they did not differ between each other, either.

We noted asymmetry of the harmonic index between hands with greater and smaller tremor intensity in all studied groups, including controls. The harmonic index was greater in the hand with greater tremor intensity. Beuter and Edwards [28,32,33] highlight the significance of the harmonic index as the important parameter in distinguishing physiological tremor from the pathological one.

The use of quantitative assessment of selected parameters along with data from history and clinical examination may also be helpful in differentiation among particular subtypes of pathological tremor. The differential diagnosis may refer to the asymmetry of the studied parameters. In case of the two most common subtypes of pathological tremor, we observed asymmetry of frequency in PT, while differences between sides in regard of frequency were small in ET. Further guidance may come from the difference in the harmonic index, which was significantly greater in PT.

Conclusions

1. Our study shows the high value of standard deviation from centre frequency and harmonic index in discrimination of PT, ET, and CT.
2. The symmetry of tremor parameters, which differs in particular subtypes of tremor, is useful in discrimination of various types of pathological tremor.
3. Parkinsonian tremor has the greatest asymmetry of the studied accelerometric indices.

Disclosure

Authors report no conflict of interest.

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