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Essential tremor – assessment of tremor accelerometric parameters' symmetry and the relationship between hand dominance and severity of tremor

Drżenie samoistne – ocena symetrii wskaźników akcelerometrycznych i związku dominacji ręki z nasileniem drżenia

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Abstract

Background and purpose: Essential tremor (ET) is likely the most common movement disorder. The aim of the study was to carry out spectral analysis of the essential tremor recorded by an accelerometer and assess the symmetry of tremor parameters between the two hands.
Material and methods: We examined 39 patients with ET diagnosed clinically using the criteria of the Movement Disorder Society. The control group consisted of 52 healthy persons. A biaxial accelerometer mounted at the dorsal side of the hand was used. Spectral analysis was performed. Tremor intensity, frequency of spectral peaks, centre frequency, standard deviation of the centre frequency, and harmonic index were measured. The side-to-side symmetry of these parameters was analysed. The relationship of hand dominance and severity of tremor was also analysed.
Results: There was significant side-to-side asymmetry of intensity in ET. The intensity in the more affected hand was over two times higher than that in the less affected one. The tremor was more severe in the nondominant hand in 62% of patients. In spite of significant difference in tremor intensity between the two sides, tremor frequency was similar in both hands. The standard deviation of centre frequency was significantly lower and the harmonic index was significantly higher in the more trembling hand.

Streszczenie

Wstęp i cel pracy: Drżenie samoistne (DS) jest prawdopodobnie najczęściej występującym zaburzeniem ruchowym. Celem pracy była analiza widmowa zarejestrowanego drżenia samoistnego za pomocą akcelerometru z oceną symetrii badanych wskaźników pomiędzy rękami.
Materiał i metody: Zbadano 39 chorych na DS rozpoznane na podstawie kryteriów Movement Disorders Society. Grupa kontrolna liczyła 52 zdrowe osoby. Użyto dwuosiowego akcelerometru, który umieszczano na części grzbietowej ręki. Dokonano analizy widmowej zapisu, oceniając: intensywność drżenia, częstotliwość wartości szczytowych w widmie, częstotliwość środkową, odchylenie standardowe od częstotliwości środkowej i indeks harmoniczny. Porównano wartości badanych parametrów z ręki o większej i mniejszej intensywności drżenia. Analizowano również związek dominacji ręki z nasileniem drżenia.
Wyniki: U chorych na DS stwierdzono znamienną asymetrię intensywności pomiędzy obiema rękami. W ręce z bardziej nasilonym drżeniem intensywność była ponaddwukrotnie większa niż w drugiej ręce. U 62% chorych większą intensywność drżenia stwierdzono w ręce niedominującej. Pomimo znamiennych różnic w intensywności drżenia, częstotliwość była porównywalna w obu rękach. Odchylenie standardowe od częstotliwości środkowej było istotnie mniejsze, a indeks

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Conclusions: Accelerometric registration revealed that asymmetry of intensity and symmetry of frequency are characteristic features of ET. The remaining two coefficients reflecting the rhythmicity and regularity of tremor also differed considerably between the hands.

Key words: essential tremor, quantitative analysis, tremor parameters, power spectrum.

harmoniczny znamiennie większy w ręce o większym nasileniu drżenia.

Wnioski: Badanie akcelerometryczne wykazało, że asymetria intensywności i symetria częstotliwości są charakterystycznymi cechami DS. Pozostałe dwa wskaźniki, które świadczą o rytmiczności i regularności drżenia, także różniły się znamiennie pomiędzy rękami.

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

Introduction

Essential tremor (ET) is most likely the most common movement disorder but its cause is still unclear. The definition of ET is constantly being modified [1,2].

There are different opinions concerning the symmetry of ET. Some authors consider ET a symmetric disorder [3,4], while others suggest that asymmetry of tremor is often experienced [5-8].

The aim of the study was to perform a spectral analysis of the essential tremor recorded by an accelerometer and to assess the symmetry of tremor parameters between the two hands. We also investigated the relationship between tremor severity and handedness.

Material and methods

The study group comprised 39 patients with ET (19 women and 20 men) at the mean age of 48.4 ± 17.4 years (range: 16-74 years). The duration of the disease ranged from 2 to 39 years (mean: 7.2 ± 7 years). Essential termor was diagnosed clinically according to the criteria proposed by the Movement Disorder Society (Consensus Statement of the Movement Disorder Society on Tremor) [9].

The control group consisted of 52 healthy persons (27 women and 25 men) at the mean age of 52 ± 16.3 years (range: 16-82 years).

The severity of tremor was assessed by the scale used in the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) [10]. Quantitative analysis was performed using a biaxial accelerometer from Analog Devices with microcontroller interface ADXL202 EVB and software from Crossbow Inc. The sampling frequency was set at 50 Hz per channel. A sensor was mounted at the dorsal surface of the patient's hand.

Measurements were carried out for the right and left hand consecutively in three positions: (1) at rest, when the hand and forearm were fully supported, (2) in the writing position while holding a pen, and (3) in an unsupported posture, when the hand was maintained outstretched in a pronated position. The acceleration signal was recorded from each hand for 3 minutes (1 minute for each position of the hand).

Spectral analysis was done off-line in Matlab. First, the magnitude of the acceleration vector was computed from the orthogonal components. Next, the signal was bandpass-filtered from 1 to 15 Hz using a 4th order Butterworth filter. The spectral analysis was done in 10.2 second-wide time epochs, using the 512-point fast Fourier transform and the Hanning window.

The analysed parameters included:

- **tremor intensity** – calculated as the root-mean-square of acceleration [m/s^2],
- **the frequency of peaks within the spectrum** [Hz],
- **centre frequency** (the mean frequency of the accelerations) – 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** (dispersion about median frequency) is the frequency width of an interval around the centre frequency that contains 68% of the total power in the spectrum; it indicates the degree of discoordination of the tremor; a very rhythmic tremor has a small standard deviation of centre frequency, indicating that most of the energy is produced within a narrow frequency band [Hz],
- **harmonic index** (HI) defines how close the spectrum is to a single narrow peak; it is normalized to the highest peak [11,12].

The values of tremor parameters obtained from the more affected side were compared with those from the less affected one (the data were grouped according to the results of accelerometric registration). The side-to-side symmetry of parameters was analysed.

The parameters of tremor derived from patients with ET and differences between hands were compared with the data of the control group. We also investigated the relationship between hand dominance and severity of tremor.

The results were analysed using statistical software (STATISTICA). The conformity with a normal distribution was examined with the Shapiro-Wilk test. Non-normal distribution was found. Wilcoxon signed-rank test and Kruskal-Wallis one-way analysis of variance were used to establish statistically significant associations. We also investigated the relationship between tremor intensity and centre frequency and frequency of peak using linear regression analysis. A *p*-value of less than 0.05 was considered statistically significant.

Results

Both postural and kinetic tremor were observed in 37 patients; pure postural tremor was noted in 2 cases only. Thirty-seven patients with ET were right-handed and two were left-handed.

The tremor intensity was greater on the dominant side in 15 patients and on the nondominant side in 24 patients (including two left-handed persons). The mean severity of tremor assessed by the scale used in the WHIGET study was 19.66 ± 5.65 pts (range: 4-34 pts).

The postural tremor scores varied from 1 to 3 pts (mean: 1.46 ± 0.64 pts) and kinetic tremor scores ranged from 0 to 3 pts (mean: 1.67 ± 0.74 pts). Mean values obtained in particular tasks are presented in Table 1. There was no significant difference between hands in tremor scores evaluated in the WHIGET scale (Wilcoxon signed-rank test).

The mean values of the analysed parameters of tremor obtained by accelerometry in patients and controls and comparison of values between the two groups are summarized in Table 2.

Comparison of tremor parameter values between the more and less trembling hand (Wilcoxon signed-rank test) is presented in Table 3.

An inverse relationship between tremor intensity and peak and centre frequency was revealed in ET patients and the control group, in both the more and the less affected hand (Table 4).

A significant negative correlation was observed between the frequency of ET and the age of patients (Spearman's rank correlation), while there was no significant correlation between the duration of disease and the frequency in ET (Spearman's rank correlation).

Discussion

Essential tremor is commonly believed to be a disorder of symmetrical character, but there are still some disagreements on this issue. Some authors are convinced of the symmetry of symptoms in ET, while others claim that asymmetry in the intensity of tremor is a frequent occurrence.

Diagnosis of tremor is usually based on the clinical examination, which may not be thoroughly objective. It is advisable, therefore, to support the diagnostic pro-

Table 1. Tremor severity based on the WHIGET scale (mean values ± standard deviations)

Type of tremor	More trembling hand	Less trembling hand	Mean value of the two hands
Postural	1.46 ± 0.64	1.46 ± 0.64	1.46 ± 0.64
Kinetic	1.69 ± 0.74	1.65 ± 0.73	1.67 ± 0.74
pouring water between 2 cups	1.64 ± 0.81	1.62 ± 0.78	1.63 ± 0.79
drinking water from a cup	1.49 ± 0.76	1.46 ± 0.76	1.47 ± 0.75
using a spoon to drink water	2.13 ± 0.66	2.05 ± 0.69	2.09 ± 0.67
finger-to-nose movements	1.66 ± 0.62	1.64 ± 0.63	1.65 ± 0.62
drawing spirals	1.54 ± 0.71	1.51 ± 0.68	1.53 ± 0.70
Total score	9.92 ± 2.88	9.74 ± 3.04	19.66 ± 5.65

WHIGET – Washington Heights-Inwood Genetic Study of Essential Tremor
There was no significant difference between hands in tremor scores evaluated in the WHIGET scale

Table 2. Results of accelerometry – tremor parameters in patients with essential tremor (ET) and control group – median and range

Tremor parameters	More trembling hand	Less trembling hand	Odds of values between hands
Tremor intensity [m/s^2], median (range)			
ET patients	1.33 (0.14-9.42)	0.52 (0.08-3.61)	0.79 (0.01-5.81)
Controls	0.095 (0.017-0.213)*	0.088 (0.016-0.204)*	0.006 (0-0.19)*
Frequency of peak [Hz], median (range)			
ET patients	6.54 (4.20-11.70)	6.64 (4.10-11.10)	0.30 (0-1.23)
Controls	8.69 (4.79-12.01)*	8.89 (4.93-11.70)*	0.471 (0.02-1.66)
Centre frequency [Hz], median (range)			
ET patients	6.64 (4.36-11.10)	6.65 (4.31-10.60)	0.25 (0.02-0.92)
Controls	8.370 (7.11-10.54)*	8.390 (7.18-10.74)*	0.198 (0-0.72)
Standard deviation of centre frequency [Hz], median (range)			
ET patients	1.76 (0.20-3.61)	2.35 (0.78-3.67)	0.47 (0-1.66)
Controls	4.54 (3.42-5.18)*	4.64 (3.22-5.27)*	0.195 (0-1.08)*
Harmonic index [Hz], median (range)			
ET patients	0.95 (0.88-0.98)	0.93 (0.89-0.98)	0.02 (0-0.6)
Controls	0.751 (0.62-0.88)*	0.732 (0.634-0.86)*	0.030 (0-0.134)

**Significant difference between ET patients versus control group ($p < 0.05$, Kruskal-Wallis one-way analysis of variance)*

Table 3. Comparison of tremor parameter values between more and less trembling hand (Wilcoxon signed-rank test)

	More trembling hand vs. less trembling hand	
	Patients with essential tremor	Control group
Tremor intensity	$p < 0.001$	NS
Frequency of peak	NS	NS
Centre frequency	NS	NS
Standard deviation of centre frequency	$p < 0.001$	NS
Harmonic index	$p < 0.001$	$p < 0.003$

NS – non-significant

cess with other methods which enable a quantitative assessment of various tremor parameters [13,14]. One of the methods of objective collection of information on the tremor is accelerometric registration, which was used for the purpose of this study.

We assessed the symmetry of the investigated tremor parameters in the hands of patients with ET as well as of the control group. In patients with ET, a significant asymmetry of the intensity of tremor in both hands was observed. The intensity rate in the more affected hand was more than twice as high as the rate recorded in the other hand. In the control group, the observed intensity rates were similar for both hands.

Table 4. Regression analysis of relationship between tremor intensity and frequency in patients with essential tremor and in control group

	Patients with essential tremor	Controls
Tremor intensity/peak frequency (in more trembling hand)	$p < 0.001$	$p < 0.001$
Tremor intensity/centre frequency (in more trembling hand)	$p < 0.001$	$p = 0.03$
Tremor intensity/peak frequency (in less trembling hand)	$p < 0.001$	$p < 0.001$
Tremor intensity/centre frequency (in less trembling hand)	$p < 0.001$	$p < 0.006$

The study shows that the asymmetry of tremor intensity in patients with ET contradicts the claim that ET has a symmetrical pattern [15]. A similar conclusion was drawn by Louis *et al*., who demonstrated that asymmetry is a characteristic feature of ET [7]. The authors claim, however, that the frequency of asymmetry occurrence depends on the adopted definition and 'standards of asymmetry'. In their study, no difference in the intensity of tremor whatsoever occurred in 89% of patients with ET. Yet, when a difference below a certain value was discarded as insignificant in asymmetry, then the proportion of patients with asymmetric tremor was smaller. Biary and Koller found asymmetry greater than 25% in 62% of patients with ET [16]. The various occurrence of asymmetry quoted in the literature may also be attributed to the fact of using different diagnostic tools in the assessment of tremor, i.e. scales or quantitative methods. With the development of new research technologies, the opinion that ET is a condition with common occurrence of asymmetry of symptoms is gaining in popularity.

Using accelerometric registration, Farkas *et al*. discovered a significant difference in intensity between the hands (determined as the average plus one standard deviation of the value achieved in the control group) in 68% of patients with ET [17]. Asymmetry in ET also occurred in half of the patients involved in the study by Whaley *et al.* [18].

While trying to explain the observed, unexpectedly large asymmetry of ET in the patients from our study group, one may refer to the disease duration. Indeed, it is the duration of the disease that is believed to be the main factor in the development of symptom asymmetry. Of similar significance appears to be an earlier onset of the disorder.

The average history of the disorder in our patients with ET was relatively short (7.2 ± 7 years), and the mean age was rather low (48.2 ± 17.5 years) as compared with the patient populations studied by other authors. These factors, therefore, may have affected our results.

Until now, scientists have not succeeded in explaining the relation between hand dominance and tremor severity. Most authors think that hand dominance has an effect on the asymmetry of symptoms, but some of them would argue whether it is the dominant side or the non-dominant side which has a predisposition for intensified symptoms. It is estimated that about 90% of the population is right-handed. The basis of lateralization lies in the anatomical and functional organization of the cerebral hemispheres. Studies have shown the occurrence of asymmetry of some brain structures and neurotransmitters [19], such as asymmetry of the corticospinal tract, with a bigger pyramid on the left side (innervating the dominant body side) than on the right side [20]. A transcranial magnetic stimulation study demonstrated that the sensitivity threshold of cortical neurons is lower on the opposite side to the dominant hand, regardless of whether the person is right- or left-handed [21]. Repeated performance of trained, highly precise movements may lead to further reorganization of the motor cortex and asymmetry between the sides.

In 62% of patients with ET in our study group, we observed greater intensity in the non-dominant hand, including two left-handed persons. Similar results were obtained by Louis *et al.* and Hornabrook and Nagurney [6,7]. Other authors, however, recorded more cases of severe tremor on the dominant side [8,16].

While the occurrence of structural and functional asymmetry in the nervous system is a fact, we have no data on the susceptibility of one or the other side to possible disorders. The relation between the dominant hand and the severity of tremor in ET – proved by some authors – may be due to the fact that most patients begin seeking medical help when the tremor affects their dominant limb, thus limiting its functions. A considerable number of patients fail to notice a slight tremor in the non-dominant hand.

However, in our study, as well as in the studies conducted by the above quoted authors, a higher intensity of tremor was recorded in the non-dominant hand in most patients with ET. One can assume that inferior aptitude in the non-dominant limb resulting from ontogenesis can lead to more serious perturbations when performing precision movements. Higher amplitude tremor in the non-dominant hand of a patient with ET may reflect unsatisfactory precision and control of movements in this limb, and lack of mechanisms of separating undesirable mechanical and reflex disturbances [7].

Our observations and the findings of other authors seem to indicate that people with ET may have normal or almost normal values of tremor intensity [17,22,23].

In 10% of patients in our study group, the rates of intensity were similar to the rates in the control group, but this low-amplitude tremor occurred in the less affected limb only.

In the study of Farkas *et al*., the proportion of patients with low intensity was higher than in our group of patients with ET. In their study group, the tremor intensity in the more affected limb did not exceed 2 m/s^2 in 15% of patients with ET, which constituted the mean value + one standard deviation in the control group [17].

Mostly, the studies conducted so far did not investigate whether the asymmetry of tremor intensity is related to the frequency asymmetry.

In the study by Farkas *et al.* and in our study, the frequency in patients with ET was comparable in both hands, in spite of significant differences in tremor intensity. Quite a contrary observation was made by Calzetti *et al.*, who recorded about 1 Hz lower frequency in the hand with higher tremor intensity as compared with the lower intensity tremor [23]. Yet, Burkhard *et al.* discovered asymmetry of frequency in patients with ET but it was not dependent on the intensity asymmetry [24]. A similar variety of frequency between both hands in ET was described by O'Suilleabhain and Matsumoto, using the term 'frequency dissociation' in order to label the simultaneous occurrence of tremor of different frequencies in separate muscle groups [25]. The observed symmetry of frequency in patients with ET points to the occurrence of interhemispheric junctions of central oscillators in this type of tremor. These observations are consistent with the observations by Hellwig *et al.*, who proved that tremor recorded in electromyography was coherent with EEG activity recorded in the sensorimotor cortex of both sides [26].

Earlier studies showed a relationship between the frequency of essential tremor and the age of a patient [27-31]. In our research, a similar significant correlation was observed between these two variables in patients with ET. We have recorded lower frequency rates in older patients, while in younger patients the tremor was of higher frequency, comparable to physiological tremor.

Elble emphasizes the fact that frequency in ET is a function of age rather than duration of the disorder [30]. Similarly, in our observation there was no significant correlation between the duration of the disease and the frequency in ET, as well as in the control group. The duration of the disease might often be underestimated as many patients ignore mild symptoms at the beginning of the disease.

The relationship between the age of patients and the frequency of ET may reflect certain changes in the cerebellum associated with the ageing process. In patients with ET, metabolic hyperactivity of the cerebellum was observed, while studies conducted on animals demonstrated that damage to the cerebellum decreased tremor frequency (from 8-12 Hz to 6-7 Hz) caused by harmaline, which is regarded as an experimental model for ET.

Moreover, it was found that enhanced rhythmic activity in the olivocerebellar loop produced by harmaline leads to excitotoxic damage of Purkinje cells. It is suggested that similar mechanisms may also apply to ET [29,30].

We have also assessed the relationship between tremor intensity and its frequency. Both in the patients with ET and in healthy subjects we discovered an inverse relationship between tremor intensity and centre frequency and frequency of spectral peak; this applies to both the hand with lower and with higher tremor intensity.

Farkas *et al.* reported slightly different observations. They observed the above relationship in ET only in the hand with greater tremor intensity [17]. Yet, the findings of the control group were comparable in our study and the quoted study. Elble *et al*. also demonstrated an interdependence between these two variables in patients with ET, but it was assessed only for one limb in all patients [27,32].

Apart from the intensity and frequency, we studied two other characteristics which are interrelated and reflect the degree of tremor regularity. One of them is the standard deviation of the centre frequency, which measures dispersion and gives the degree of tremor discoordination. We recorded nearly 2.4 times lower values of standard deviation of the centre frequency in patients with ET as compared to the values in the control group. In patients with ET there was characteristic asymmetry of the standard deviation from centre frequency between the sides. Its value was significantly lower in the hand with greater tremor intensity as compared with the less affected hand. In the healthy subjects, no significant difference between the hands was observed.

Except for one publication of Farkas *et al*., we could not find any other papers analysing the symmetry of tremor coefficient between the more and less affected hand [17]. The asymmetry of the standard deviation of the centre frequency observed in our study is different from the findings of the above-mentioned authors, who recorded no asymmetry of this coefficient in patients with ET.

The last parameter studied in our research was the harmonic index, which is used for quantitative description of oscillation regularity [11,12]. This index was significantly higher in patients with ET than in the control group. However, the asymmetry between the limb with greater and smaller tremor intensity was of a significant value both in ET and in healthy subjects. The harmonic index was higher in the hand with higher tremor intensity.

Use of the quantitative evaluation of certain parameters allows for arbitrary collection of information on tremor. Clinical analysis did not suggest any significant difference in the severity of tremor between the sides, yet accelerometric testing showed that the asymmetry of intensity is a characteristic feature of ET. The remaining two coefficients reflecting the rhythmicity and regularity of tremor also differed considerably between the limbs. The tremor frequency, though, was similar in both limbs.

Conclusions

1. Accelerometric registration revealed that asymmetry of intensity and symmetry of frequency are characteristic features of ET.
2. The remaining two coefficients reflecting the rhythmicity and regularity of tremor also differed considerably between the hands.

Disclosure

Authors report no conflict of interest.

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