Electrophysiological investigation of tremor in movement disorders

PhD Theses

Dr. Zsuzsanna Farkas

Semmelweis University Postgraduate School
Szentágothai János Neuroscience Program

Supervisor: Dr. Anita Kamondi Ph.D.

Opponents: Dr. Attila Fonyó D. Sc.
Dr. Ferenc Nagy Ph.D.

Budapest
2008

INTRODUCTION

Tremor is a rhythmic, involuntary oscillatory movement of any body parts. It appears as the summarized activity of mechanical, reflex and central oscillators. Low intensity so called physiologic tremor is present in every healthy person. Dysfunction of the central and/or peripheral oscillators leads to pathologic tremor. The pathophysiology of the various tremors is unknown, therefore the classification of tremor syndromes is based on clinical sings: anamnesis, activating conditions, affected body parts, frequency range, presence or absence of additional neurological symptoms. The determination of the specific tremor syndrome provides the basis of further diagnostic and therapeutic steps.

Tremor is a common symptom of a variety of neurological disorders. Using well-defined diagnostic criteria the majority of tremor syndromes can be classified, however in the early phase of the diseases, when the unambiguous symptoms are missing, or when the tremor amplitude is too small to be recognized by physical examination, the differentiation might be challenging. It is also known, that a given disorder may present with different tremor types and vice versa. The most common movement disorders causing tremor are essential tremor (ET) and Parkinson' s disease (PD). Previous surveys indicated a high misdiagnosing rate in both ET (33%) and PD (15%). Although life expectancy of patients with tremor is similar to healthy subjects, significant disability can occur in both diseases.

Our aims were to introduce a new test system (CATSYS 2000) for objective assessment of tremor syndromes in Hungary, and to evaluate the role of this method in the differential diagnostic workup in the daily clinical routine. Based on our results we examined in more detail the amplitude-frequency relationship and symmetry of tremor parameters in ET and PD,

and the motor coordination in ET. We evaluated the features of drug induced tremor and motor disturbances, which may help to elucidate the pathomechanism of different human movement disorders.

METHODS

Tremor, motor coordination and postural stability were measured by a computer assisted test system (CATSYS 2000 version, Danish Product Development Ltd., Snekkersten, Denmark).

Tremor was recorded by a two-axis micro-accelerometer embedded in the tip of a tremor pen in pen holding and postural position at first for 8.2 s, later for 32.8 s. Normalized power spectrum was calculated from the time series by Fast Fourier Transformation. Four parameters of tremor were analyzed: tremor intensity (TI, defined as the root mean square of acceleration, m/s^2), center frequency (CF, which is the median of the area below the power, Hz), frequency dispersion (FD, frequency band, which contains 66 % of the power around the center frequency, Hz), and harmonic index (HI, which compares the tremor frequency pattern with the pattern of a single harmonic oscillation).

Postural stability was tested by a force plate, which records the movement of the force center of the body in the XY-plane in time. Subject was asked to stay on the force plate surface with opened eyes. Sway area was defined as the area of smallest polygon, which includes the total trajectory of the force center in the horizontal plane.

Motor coordination was tested by rhythmic tests. Subjects were asked to hit the drum with the index finger (tapping) and to do alternating hand pronation-supination movement with the drum in hand, as close to a constant metronome beat as possible. Deviation in time from the

metronome signal of the subject's beat was measured. Performance was characterized by the standard deviation of the time offsets. Motor coordination were examined by slow (1 Hz) as well as fast (2,5 Hz) stimulus frequency. Maximum frequency of finger tapping and hand pronation-supination by linear accelerating metronome beats was also calculated.

Reaction time was measured by a traditional stimulus-response test. Subjects were asked to click with the thumb on a switch for random sound signals.

Statistical analysis were performed by Statistica 6.0 software. Distribution of data was tested by Kolmogorov-Smirnov test. In case of normal distribution, parametric tests were used, in other cases data were logarithmically transformed or nonparametric tests were used. Level of significance was $p<0.05$.

RESULTS

1. Complex tremor analysis in the diagnosis of essential tremor and Parkinson's disease

In our first study, our aim was to introduce a computer assisted tremor-coordination test system (CATSYS 2000) and to analyze the power of discrimination between parkinsonian and essential tremor. Similar method for diagnostic questions has not been used in daily neurological clinical routine earlier.

Methods

18 healthy subjects, 39 patients with Parkinson's disease and 37 patients with essential tremor were examined by the full version of CATSYS with test parameters advised by the producer. Differences among groups, between right and left hand and between more and less trembling hand were statistically evaluated.

Results

Tremor intensity in ET group was significantly higher compared to controls. There was no significant difference between data of right and left hand in any groups. Data of the more and less trembling hand were significantly different in ET.

Center frequency and *frequency dispersion* were similar in patients and healthy subjects. Data of right and left hand did not differ significantly in any groups. We found significant difference between the more and less trembling hands of parkinsonian patients.

Harmonic index was significantly higher in ET compared to control group. Data of right vs left and more vs less trembling hands were similar in all groups.

In case of *motor coordination*, the hand pronation-supination for fast stimulus frequency and the slow finger tapping was significantly less precise in both patient groups compared to healthy subjects. We found significant difference in fast finger tapping between ET and controls. Maximum frequency of both movements was significant lower in PD compared to controls. Reaction time of PD patients was significant slower than controls.

Sway area used for measuring postural stability was higher in ET compared to healthy subjects.

Conclusions

Data of our healthy subjects were similar to results of the large normal population reported in the literature, which implies the reliability of our measurements. Our data suggest that electrophysiological parameters of tremor (TI, CF, FD, HI) overlap in different tremor syndromes, therefore per se they are not sufficient to differentiate between them. However, the following observations could be valuable in differential diagnosis: 1. tremor intensity is asymmetric and frequency related parameters (CF and FD) are symmetric in ET, while in parkinsonian tremor there is a significant side difference in all parameters. 2. the precision of fast alternating movements is damaged not only in PD, but in ET. Measuring postural stability with sway-plate did not help differentiating between ET and PD.

2. Symmetry of tremor parameters in parkinsonian and essential tremor

Asymmetry of tremor intensity in Parkinson's disease is a well known phenomena in clinical practice. Essential tremor has been considered a symmetric disorder, but recent studies proved, that asymmetry of tremor intensity is a basic feature of ET. Although it is known, that tremor amplitude is inversely related to tremor frequency no systematic investigation has been carried out to determine if there exists any asymmetry of frequency related tremor parameters in correlation with asymmetry of tremor intensity in PD and/or ET. In those studies where amplitude and frequency measurements were unilateral this question could not be addressed. In most clinical investigations, where registration was

bilateral data of the two sides were either combined, or were analyzed according to the right and left side. In the present study, we used bilateral accelerometry to test our hypothesis, that there is an asymmetry of frequency parameters related to the laterality of tremor severity in PT but not in ET. The results might help the differentiation of ET and PT and provide further data for the unresolved question of tremor genesis.

Methods

Measurements were carried out in 37 healthy subjects, 48 parkinsonian patients and 47 patients with essential tremor, who were not participants of our previous study. Test parameters were modified based our experience of previous measurements. Tremor intensity, center frequency and frequency dispersion were examined. Each tremor parameter was evaluated by three different ways: (a) combining the data of both hands in each group, (b) separating the parameters of the right and left hand and (c) separating the parameters of the more affected and less affected hand, according to tremor intensity. We also investigated the tremor parameters in a subgroup of patients where (1) tremor intensity of the more affected hand was not higher than the average + 1 SD of the control group (n_{PD}=22, n_{ET}=7), and (2) where tremor intensity difference between the two hands was higher than the average + 1 SD of the controls (n_{PD}=21, n_{ET}=32). The intensity-frequency relationship was evaluated by regression analysis.

Results

Tremor intensity was significantly higher in ET compared to control and PD groups, while we did not find significant difference between data of the healthy and parkinsoninan subjects. Data of right and left hand were similar in the groups. When grouping data according to the more and less trembling

side, tremor intensity was similar on the two sides in controls, however it was significantly higher on the most affected compared to the less affected side in parkinsonian and ET patients. It is important to note, that on the less affected side in the PT group tremor intensity was not significantly higher than in controls. We also investigated the side difference of tremor severity by selecting those PT and ET patients whose tremor intensity on the more affected hand was in the range of healthy subject's. In these ET subgroups tremor severity of the more and less affected hand was similar, however there was an unexpected significant asymmetry in PT. Selecting ET and PT patients with high tremor intensity difference, due to the selection criteria there was significant difference between the more affected hand compared to the less affected hand in the ET and PD subgroup.

In case of center frequency and frequency dispersion, averaged data of hands were significantly lower in both patients group compared to controls, and also the values of PD and ET groups differed significantly. Data of right and left hands were similar in all groups. When grouping data according to less and more trembling side, there was a significant difference in PD patients, but not in ET and control subjects. In subgroup of patients with normal tremor intensity, CF and FD of the two hands were similar in ET, but we found significant difference in PD. In patients with high tremor intensity difference CF and FD of the more and less trembling hand were similar in ET, while in PD group CF and FD were significantly lower in the more compared to the less trembling side.

A strong inverse linear correlation was revealed between log tremor displacement and log center frequency in control subjects and in PT both on the more and less affected side. In ET, linear correlation was found only on the more trembling side, intensity and frequency were not related on the less affected hand.

Conclusions

According to our data, tremor intensity is asymmetric in both ET and PD. Symmetric decrease of CF and FD is characteristic for ET, while asymmetric decrease reveals PD, irrespectively of the difference in tremor intensity between the two hands. We found similar changes of tremor parameters in the subgroup of patients with normal tremor intensity, which suggest, that pathologic tremor generators are already active at the early stage of the disease, even when the tremor is visually hardly detectable. We conclude that decreased CF and FD reveals pathologic tremor even in case of normal tremor intensity. Asymmetric PD frequency on the two hands may suggest that regardless of the fine structure of the oscillatory network, there are separate, relatively independent hemispheric tremor generators in Parkinson's disease. In ET we found symmetrically low tremor frequency on both sides, even when intensity was considerably asymmetric, which might be explained by interconnected hemispheric generators. Our data show that bilateral measurement of tremor parameters can be used to distinguish the two most common tremor types if data of the two hands is grouped according to more and less trembling side and not to right and left side.

3. Examination of motor coordination in essential tremor

The pathomechanism of essential tremor is not known. Clinical observations, electrophysiological and functional imaging studies suggest that the cerebellum might be involved in the generation of ET. It has been hypothesized that the cerebellum is involved in the control of event-based timing of repetitive movements. We hypothesized that if cerebellar

structures involved in the pathomechanism of ET are also part of the event-based timing system, than the regulation of rhythmic, repetitive motor acts should be affected. To test this hypothesis we measured the variability and the maximum frequency of alternating hand and finger movements triggered by auditory stimulus in ET patients.

Methods

41 healthy subjects and 34 patients with essential tremor were examined. We measured tremor intensity, center frequency with CATSYS. Motor coordination was tested by rhythmicity of hand pronation-supination and finger tapping by slow and fast stimulus frequency. Maximum frequency of these movements was also measured.

Results

Since there was no statistically significant difference between the right/left and the higher/lower intensity sides in any of the subtests, data of the more trembling side were statistically evaluated.

The regularity of pronation/supination at 1 Hz was the same in the control and ET group. At 2.5 Hz, ET patients performed the task with significantly higher variability than controls. Rhythm of alternating hand movements in controls was significantly more precise at the fast than at the slow rate. Although in ET rhythmicity of movements at 2.5 Hz was less regular than at 1 Hz, the difference was not significant. The MF of pronation/supination in controls was significantly higher compared to ET.

Finger tapping at both speeds was significantly more regular in controls than in ET. We found significantly less precise finger tapping at the fast than at the slow rate in ET. In controls, rhythmicity at 2.5 Hz was more

regular than at 1 Hz, but the difference was not significant. The MF of finger tapping in controls was significantly higher than in ET.
There was no statistical correlation between TI and rhythmic performance in any of the 6 subtests in either groups. Similarly, tremor CF did not correlate with rhythmicity or MF in either groups. Regularity of rapid hand or finger movement did not show any correlation with MF.

Conclusions

Our findings demonstrate that ET patients are not able to precisely synchronize repetitive movements to extrinsic timing cues and this deficit is present both at slow and fast movement rate. Based on literature in healthy subjects there might be two different working modes of internal rhythm generators. For repetitive movements up to 2 Hz each motor act is regulated separately, while above 2 Hz, a program-like control of rhythm becomes operative, and transition from one to the other is necessary when changing movement rate. Our healthy subjects had smaller variability of rhythm at fast compared to slow rate, suggesting a shift from separate to program-like movement control. In ET, time keeping was not only worse at slow rate compared to controls, but a further deterioration of precision at higher movement frequency of hand and finger movements could also be demonstrated. This was not due to inability to perform fast movements, since MF of both finger and hand movements were much higher than 2.5 Hz, furthermore there was no correlation between MF and variability of repetitive movements. Therefore we concluded that in ET not only the event-based time keeping, but also the transition between the „slow" and „fast" working mode of rhythm production is impaired causing a deterioration of accuracy of more rapid repetitive movements.

Our results showed that there was no systematic association between TI or PF and rhythmic performance, suggesting the impairment of the central timing mechanisms rather than the interference of tremulous and rhythmic movements. Our data suggest that the cerebellar time keeping mechanisms are damaged in ET, but they are probably not part of the tremor generator circuitry. These findings support the emerging view that ET is not a monosymptomatic diseases but a complex disorder affecting different functional systems of the brain.

4. Quantitative assessment of subclinical tremor and dysrhythmia induced by valproic acid

Due to the lack of satisfactory animal models, analysis of drug induced motor disturbances in humans, may help to elucidate the mechanism of different movement disorders. In the present study, we quantitatively assessed the parameters of tremor and regularity of rhythmic hand and finger movements of epileptic patients, who were on chronic VPA monotherapy, and had no complaints or symptoms regarding tremor or motor performance. Our aim was to detect changes suggestive of pathological tremor and/or dysrhythmia, in order to disclose the involvement of cerebellar and/or basal ganglia pathways in the development of VPA induced movement disorders.

Methods

We examined 14 healthy controls, and 15 epilepsy patients receiving VPA monotherapy. Tremor was measured in rest and postural position, motor coordination was assessed by rhythmic tests.

Results

Tremor parameters of VPA patients were similar to that of controls. Analysis of individual normalized power values at each 1 Hz wide frequency bands showed significantly higher power in the 2-3, 3-4, 5-6 and 6-7 Hz bands in VPA patients than in controls. Power values in the 8-15 Hz frequency bands were similar in the two groups.

The mean standard deviation of the time offset between the signal and the subject's beat was significantly higher for both pronation/supination movements and finger tapping in VPA patients compared to controls. The maximum frequency of pronation/supination movements and finger tapping of VPA patients was significantly lower than that of controls. The averaged reaction time of the two groups was similar.

Conclusions

The main finding of the present study was, that both tremor generation and regularity of cued rhythmic movements were affected in VPA treated patients, despite that they were clinically asymptomatic regarding tremor and motor performance.

In accordance with the inclusion criteria, the intensity of tremor recorded in our VPA group, was within the range of physiological tremor. Although the center frequency was also normal, the detailed power spectra analysis showed significant increase of tremor power in the 2-4 Hz and in the 5-7 Hz frequency ranges. It is known, that tremors with a frequency of less than 5 Hz most often occur in lesions involving cerebellar pathways, while tremor with 5-7 Hz frequency is typical of Parkinson's syndrome. Therefore, we propose, that VPA induces tremor via at least two functional systems, i.e. the cerebellar and the basal ganglia circuitries.

We also found, that although our VPA patients did not have any clinical manifestation of dysrhythmia, their cued rhythmic finger and hand movements were significantly more irregular compared to controls. It was reported, that patients with acquired cerebellar lesions exhibited increased temporal variability on the finger tapping and intermittent circle-drawing test. Deficit in performing various timing tasks in Parkinson's disease has also been described, suggesting the role of the basal ganglia system in the precise motor representation of temporal information. We suggest, that the dysrhythmia caused by chronic VPA treatment, might result from the combined dysfunction of those cerebellar and basal ganglia pathways that are part of the event based timing system.

Summary

Tremor is a rhythmic, involuntary, oscillatory movement of any body parts. The most frequent tremor syndromes are essential (ET) and Parkinsonian (PT) tremor. The differentiation of these disorders in the initial stage may be difficult. Pathogenesis of ET and PT is unknown.

We introduced a new test system (CATSYS 2000) in Hungary to objectively assess tremor parameters, rhythmicity and maximum frequency of fast alternating hand and finger movements, reaction time and postural instability. Our data measured in healthy subjects were similar to those reported in the literature. Results of ET and PT groups suggest that decreased frequency and narrow frequency dispersion prove pathological tremor even in case of normal tremor intensity. Our method might be used to differentiate pathological tremors from physiological tremor in the early stage of the disorder.

We examined the relationship between tremor intensity and frequency in ET and PT and the side-to-side asymmetry of these parameters. We concluded that symmetric decrease of frequency parameters regardless of asymmetry of intensity is characteristic of ET, while asymmetric intensity and frequency data are the main features of PT. These results emphasize the significance of bilateral tremor measurement, because side difference of parameters might help to distinguish the two most common tremor types. We proved statistically that symptoms related to side difference might be detected only by grouping bilateral data according to more/less affected side, while right/left or dominant/non-dominant division might obscure these differences.

We demonstrated that ET patients are not able to synchronize repetitive movements to extrinsic timing cues and the transition between the slow and fast working mode of rhythm production is also impaired. Our results suggest that it might be caused by the impairment of the central timing mechanisms rather than by the interference of tremulous and rhythmic movements.

We also demonstrated that valproic acid induces low frequency tremor and leads to irregularity of rhythmic movements in epileptic patients with no complaints of tremor or dysrhythmia. This effect is probably due to the involvement of both the cerebellar and basal ganglia GABAergic systems.

PUBLICATIONS

1. Farkas Z, Csillik A, Palvolgyi L, Takacs A, Szirmai I, Kamondi A. Complex tremor analysis in the diagnosis of essential tremor and Parkinson's disease. Clin Neurosci/Ideggy Szle 2006 (59):45-54.

2. Farkas Z, Csillik A, Szirmai I, Kamondi A. Asymmetry of tremor intensity and frequency in Parkinson's disease and essential tremor. Park Rel Dis 2006 (12):49-55.

3. Farkas Z, Szirmai I, Kamondi A. Impaired rhythm generation in essential tremor. Mov Disord. 2006 (21):1196-9.

Abstracts:

1. Farkas Z, Csillik A, Pálvölgyi L, Takáts A, Szirmai I, Kamondi A. Complex tremor analysis in the diagnosis of essential tremor and Parkinson’s disease. Mov Disord 2004 (19) S9: 445.

2. Farkas Z., Gulyas S, Molnar R, Balogh A, Szirmai I, Kamondi A. Effect of antiepileptic drugs on tremor and motor coordination. Eur J Neurol 2006 (13) S2:P1168.