Investigation of pathomechanism of tremors caused by lesions of the central nervous system

Doctoral theses

Andrea Kovács MD

Semmelweis University
János Szentágothai Doctoral School of Neurosciences

Supervisor:
Anita Kamondi MD, DSc.

Official opponents:
Zsuzsanna Arányi MD, DSc.
János Martos MD, Ph.D.

Chair of comprehensive exam:
Dániel Bereczki MD, DSc.
members:
Szilvia Gulyás, MD, Ph.D.
István Valálik MD, Ph.D.

Budapest
2019

Introduction

Tremor is the most common hyperkinetic movement disorder. Its pathomechanism is unclear. All central nervous system structures which participate in motor control were linked to the pathomechanism of tremor. The cerebellum gained increased attention, as its pathological and functional alterations were demonstrated in essential tremor (which is the most common tremor syndrome).

The anterior lobe of the cerebellum (motor cerebellum), connected to the primary motor cortex, is responsible for motor coordination: it anticipates the consequences of action driven by the cortex and adjusts motor patterns to the goal of the movement. The posterior lobe of the cerebellum (cognitive cerebellum), connected to associative areas of the brain, contributes to cognitive and affective brain processes. Upper limb movements are represented in three somatotopic areas in the cerebellum: in lobule V of the anterior lobe, respectively in lobule VIII and lobule VI of the posterior lobe.

The cerebellum is involved in the pathomechanism of numerous neurodegenerative tremor syndromes: essential tremor (degenerative pathological and functional changes), Parkinson's disease (compensatory hyperactivity), multiple system atrophy, fragile X tremor-ataxia syndrome, spinocerebellar ataxias. Contrary, focal lesions of the cerebellum (ischemic lesions, tumours, contusions) might also cause tremor, designated as cerebellar tremor.

There are only scarce data on cerebellar tremor. Animal experiments showed that lesions of various cerebellar structures might evoke cerebellar tremor, or in spite of experimental lesions, the tremor might appear only after harmaline injection. Its frequency is around 3 Hz, which may decrease to 1,5 Hz if peripheral tremor components change. The first human observations were made by Gordon Holmes. According to Holmes, more tremor types might appear in focal cerebellar lesions: „static" – postural, „kinetic" – intentional, and a third type which affects the head and the trunk. Human neurophysiological studies found various tremor frequencies among these patients of both 5-7 Hz and 8-12 Hz. Information on cerebellar tremor in tremor consensus statements - frequency of cerebellar tremor is < 5 Hz - is probably based on animal experiments, however, they do not refer to any objectives measurements. Tremor consensus statement in 2018 equated cerebellar tremor with intentional tremor. According to previous studies, lesion of the dentato-rubro-thalamic tract plays a key role in its pathomechanism. However, the dentato-rubro-thalamic tract is an ideal deep brain stimulation target in other tremor syndromes, too. There is no data on temporal change of cerebellar tremor. It is demonstrated that other cerebellar symptoms like limb ataxia spontaneously cease in 2-4 weeks.

Besides focal lesions, toxic agents might also affect the cerebellum eg. alcohol, litium and thus, might cause tremor. Drug-induced tremors are mostly enhanced physiological tremors (eg. methylxantines). Some drugs

might cause Parkinsonian syndrome and thus pathological tremors (eg. valproic acid, antipsychotics). Tremorogenic side effect of antiepileptic drugs raises questions about pathomechanism of tremor. Both GABA-agonists and sodium-channel inhibitors would be expected to decrease (physiologic) tremor amplitude. However, both types might induce pathological tremor. Tremorogenic side effect of lamotrigine has not been systematically analysed yet. Previous studies showed that lamotrigine might cause other cerebellar signs like vertigo, ataxia, nystagmus. These raise the question if lamotrigine causes tremor through modulating the cerebellum.

Objectives

1. To examine characteristics of tremor caused by focal cerebellar lesions:
   a. prevalence of cerebellar tremor
   b. neurophysiological characteristics of cerebellar tremor
   c. correlation between tremor occurence/parameters and localisation of cerebellar lesions
   d. the recovery of cerebellar tremor
2. To examine characteristics of tremor caused by lamotrigine:
   a. prevalence and neurophysiological characteristics of lamotrigine-induced tremor
   b. fine motor performance (repetitive hand and finger movements) in lamotrigine-treated patients

Methods

Cerebellar tremor

We examined 90 patients with focal lesions affecting the cerebellum and/or its pathways who were treated between 2014 and 2017 in the National Institute of Clinical Neurosciences, Budapest, Hungary, and 30 age-matched right-handed healthy controls. Tremor parameters were measured using a computerized test system (*CATSYS 2000, Danish Product Development Ltd., Snekkersten, Denmark*). Tremor was recorded for 20 s in six different positions: (1) at rest (RT): the forearm and the hand were fully supported on a table; (2) in postural position with eyes open (PTeo): the arm and hand were held against gravity in an outstretched, horizontal, prone position with eyes open; (3) in postural position with closed eyes (PT): the arm and hand were held against gravity in an outstretched, horizontal, prone position with eyes closed; (4) in postural position with weight load (PTwl): the arm and hand were held against gravity in an outstretched, horizontal, prone position with eyes closed and with a load of 200 g which was secured at the level of the metacarpophalangeal joints of the hand; (5) in a kinetic precision task (kinetic tremor; KT): on a 14.10-in. screen the patient with his index finger followed the tip of an arrow moving with a uniform rectilinear motion with a speed of 0.015 m/s; (6) in a static precision task (intention tremor; IT): the patient with his index finger pointed to the tip of an arrow, stable on the screen. Tremor was registered using a biaxial micro-accelerometer (weight 10.50 g,

sensitivity > 0.30 m/s2), fixed between the second and the third metacarpal bone, 2 cm proximal to the metacarpophalangeal joint. Accelerometry signals of the two axes were digitized at 128 Hz. Data between 0.9 and 25 Hz were analyzed. Tremor parameters were derived from fast-Fourier power spectra. The following parameters described in previous studies were automatically calculated by the built-in software of CATSYS tremor recording system: (1) *Tremor intensity (TI, m/s2),* which is related to tremor amplitude, was calculated as the root-mean square of acceleration. (2) *Frequency dispersion (FD, Hz)* which reflects the regularity of tremor was defined as the half width of the frequency band centered on the peak frequency containing 68% of the total power. The frequency dispersion of physiologic tremor is broad (3–4 Hz), while it is reduced (0.5–1 Hz) in pathological tremors like parkinsonian or essential tremor. (3) *Center frequency (CF, Hz)* is the frequency below which lies 50% of the power in the spectrum. We introduced for the first time a new measure, the (4) *proportional power of 0.90–3.00 Hz frequency range (PP 0.90–3.00 Hz, %),* which quantifies the contribution of the low-frequency range to the total power in percentage. The proportional power of 0.90–3.00 Hz range is expected to increase in pathological low frequency tremors. Pathological values in adult patients were defined as low or high outliers from the control group. Pathological values in children were defined as lower or higher values than the mean ± 2SD. Tremor was considered pathological if the center frequency was lower

than 5.20 Hz in postural and 4.81 Hz in intentional position. All patients underwent skull MRI examination. In case of 34 patients, high-resolution 3D T1-weighted structural image series were acquired on a 3T Magnetom Verio MRI scanner (*Siemens, Erlangen, Germany*) using a magnetization prepared rapid gradient echo (MPRAGE) sequence. We used the SPM12-toolbox (*Wellcome Trust Centre for Neuroimaging, University College, UK*) and custom MATLAB (*The Mathworks*) codes for pre-processing. The images were reoriented with the horizontal line defined by the anterior and posterior commissures (ACPC orientation) and the sagittal planes parallel to the midline. Every lesion was defined manually with MRIcron and saved as region of interest (ROI) files. Lesions were identified on the T1-weighted images, with respect to the T2-weighted sequence. The margins of the lesion were determined according to the signal intensity change visible on the T1 weighted images, regardless of the fact if it was produced by the lesion itself or the sorrounding edema. The spatially unbiased infratemporal template (SUIT) of the cerebellum toolbox 3.2 was used for normalization, cerebellar lobule segmentation, and cerebellar lesion detection. SUIT was designed for cerebellar lobule segmentation and cerebellar lesion detection. It can show if the brainstem is affected, but it is not able to distinguish the brainstem nuclei. Therefore, the affected brainstem regions were determined based on traditional structural MRI technique. We used voxel-based morphometry to define the size of each ROI. Statistical

analysis was performed using the Statistica software package *(Statsoft Inc., 8.0 version, Tulsa, OK, USA)*.

Lamotrigine-induced tremor

We have examined 30 epilepsy patients taking lamotrigine (LTG) monotherapy and 30 age- and sex-matched healthy controls. Epilepsy patients on lamotrigine monotherapy were randomly selected from the Epilepsy Outpatient Unit of the National Institute of Clinical Neurosciences, Budapest, between March and October 2018. We used a biaxial accelerometry to registrate tremor and repetitive hand and finger movements (*CATSYS, Danish Product Development Ltd., Snekkersten, Denmark*). Tremor was recorded for 20 s in four different positions: (1) at rest (rest tremor; RT); (2) in postural position with open eyes; (3) in postural position with closed eyes (postural tremor; PT); (4) in a static precision task (intention tremor; IT). The following tremor parameters were used: (1) *tremor intensity* (m/s^2), (2) *frequency dispersion (Hz)*, (3) *center frequency (Hz)*. Regularity and maximum frequency of repetitive finger- and alternating hand movements were examined using a touch sensitive drum as previously described. For finger tapping measurements, subjects hit the drum with the index finger while the wrist was supported. Alternating hand movements were investigated with the drum on the table. Subjects were instructed to perform pronation/supination movements for 10 s, keeping precise pace with the 2.50 Hz acoustic signal generated by the computer. The time offset (ms) between the signal and the subject's beat was measured. Moreover,

subjects were instructed to perform finger tapping or hand pronation/supination paced by gradually accelerating (from 1.60 to 7.50 Hz) acoustic signal. To compensate for random errors, the subject was allowed to miss one hit if the next two were recorded. The last legal hit determined the maximum frequency. This principle distinguishes well between controlled and chaotic movements. Simple motor reaction time (ms) was measured in a traditional stimulus-response test using a handle switch. The computer gave random auditory signals to which the subject had to press the handle switch with the thumb. Reaction times shorter than 0.10 s or longer than 0.50 s were excluded. Pathological tremor induced by lamotrigine was identified based on decrease of frequency dispersion because (1) tremor frequency is not able to differentiate various tremor syndromes; (2) tremor intensity is increased in enhanced physiological tremor as well; (3) previous studies showed that decreased frequency dispersion is a sensitive marker of pathological tremor. We considered the tremor pathological if frequency dispersion was a low outlier from the control group. Statistical analysis were carried out with Statistica software package (*Statsoft Inc., 8. verzió, Tulsa, OK, USA*).

Results

Cerebellar tremor

We examined 90 patients, and 68 patients were included into the study. Most of the patients were right-handed, middle-aged adults (91.18%), who suffered in cerebellar stroke (28 patients, 41.17%) or tumour (29 patients, 42.64%). Six patients (8.82%) were diagnosed with chronic vascular lesion, two patiens with abscess, two other patients with cavernoma, one patient with tumefactive multiple sclerosis. Cerebellar signs were seen in 48 patients (70.58%). Clinical examination revealed no rest tremor in any of the patients; intentional and/or postural tremor was detected in 13 patients (19.11%). Quantitative tremor analysis showed pathological tremor in 47.06% of patients. We identified three tremor patterns: A.) *low frequency tremor LFT (N=25, 36.76%)*: center frequency was lower than normal in at least two recording positions ($\leq$ 5.20 Hz in PT and $\leq$ 4.80 Hz in IT); frequency dispersion was lower than normal; relative power of the 0.90-3.00 Hz frequency range was significantly increased; tremor intensity was elevated in only seven patients out of 25. B.) *physiologic tremor (N=36, 52.94%)*; C.) *high intensity-normal frequency tremor HINFT* (*N=7, 10.29%)*: tremor intensity was higher than normal only unilaterally, ipsilaterally to the cerebellar lesion ($\geq$ 0.30 m/s^2 in PT and $\geq$ 0.33 m/s^2 in IT); center frequency was normal. Statistical analysis showed that tremor parameters were significantly different among the three tremor groups

$p<0.001$. Tremor intensity reached level of significance only in intentional position $p=0.04$. The above mentioned tremor patterns were associated with various lesion locations or age groups: the LFT was associated with acute cerebellar stroke and tumour (both metastases and primary malignant tumours). Physiologic tremor was associated with chronic vascular lesions and meningeomas. The HINFT was common among children and rare in adults. 3D T1 MRI images were available in 34 patients, therefore detailed analysis of cerebellar lesions could be carried out in these 34 patients. No significant correlation was found between the size of the lesion and tremor parameters. Low frequency tremor was caused by lesions of various location: lesions affecting the midline, the anterior lobe and the posterior lobe. The mesencephalon was affected in both patients with high intensity-normal frequency tremor. Overlapping lesions might have caused various tremor types. There was no significant difference between patients with unilateral and bilateral lesions. Similarly, lesions affecting the deep cerebellar nuclei did not produce pathological tremor more frequently and were not associated with higher TI or lower FD, CF than lesions with intact deep nuclei. Prevalence of pathological tremor was around 45-65% in case of any cerebellar lobule or deep nucleus. The prevalence of pathological tremor increased if the brainstem was affected, too (81.81%). Lesions affecting lobules I-IV ($p=0.002$ in PT and $p<0.001$ in IT) and lobule V ($p=0.02$ in PT, $p=0.003$ in IT) resulted significantly higher tremor intensity than those sparing lobules I-IV and V, in all recording positions. Lesions

affecting lobule VI were associated with higher tremor intensity only in IT (p=0.03). Lesions affecting the brainstem (30% of all lesions) were associated with the same tremor patterns as lesions affecting the cerebellum only. In patients with lesion affecting the brainstem, tremor intensity was significantly higher in PT (p=0.01); center frequency (p=0.03) and frequency dispersion (p=0.03) was significantly lower in IT; relative power of 0.90-3.00 Hz frequency range was significantly higher in IT (p=0.04), than in lesions affecting the cerebellum only. Follow-up tremor measurements were carried out in ten patients with acute cerebellar stroke. Follow-up measurements showed a gradual increase of frequency dispersion and center frequency with time. The speed of recovery varied among patients (min. 1, max. 8 weeks) but tremor spontaneously recovered in 3.65 ± 2.66 weeks after symptom onset in all followed-up patients.

Lamotrigine-induced tremor

Ten patients receiving lamotrigine monotherapy complained about upper limb tremor or head tremor (35.71%) and one patient noticed upper limb myoclonus (3.57%). The upper limb tremor limited patients' daily activities (eating, playing an instrument) in only three patients (10.71%) and only one patient (3.57%) wanted to stop lamotrigine therapy due to the upper limb tremor, which emerged three months after starting the treatment. Clinical examination did not reveal rest tremor in any patient; three patients presented both postural and intentional tremor (10.71%), whereas one patient (3.57%)

presented postural tremor only. Objective tremor assessment revealed pathological action tremor in seven patients (25.00%). Pathological rest tremor was not detected. Three patients (10.71%) developed pathological intentional tremor only. Pathological postural and intentional tremor was found in four patients (14.28%). The pathological tremor detected in those seven patients (25.00%) was a bilateral upper limb action tremor with normal center frequency in both postural (8.42 ± 0.80 Hz) and intentional (8.07 ± 1.17 Hz) position. The average frequency dispersion was low but it still remained in normal range in postural position (3.13 ± 1.45 Hz), whereas it was lower than normal in intentional position (1.76 ± 0.39 Hz). Average tremor intensity was slightly elevated in postural tremor but it did not reach pathological values (0.27 ± 0.05 m/s^2). In intentional tremor, tremor intensity was higher than normal (0.37 ± 0.05 m/s^2). We registered physiologic tremor in 75% of lamotrigine-treated patients (21 patients). Repetitive finger and hand movements as well as reaction time were normal in all patients. Subjects were grouped into three groups: 1) LTG-treated patients with pathological tremor; b) LTG-treated patients with physiologic tremor; c) control subjects. Center frequency did not differ but tremor intensity ($p=0.003$ in PT and $p<0.001$ in IT) and frequency dispersion ($p<0.001$ in PT and in IT) were significantly different among these groups. We did not find significant difference in serum LTG level, duration of LTG treatment and age between LTG-treated patients with pathological tremor and those with physiologic tremor.

None of patients had toxic serum LTG level. There was no significant correlation between tremor parameters and serum LTG-level, duration of LTG-treatment or age. Our logistic regression model (built up with the above mentioned factors) showed that serum LTG-level had the the most important impact on tremor occurence: the odds ratio for 1 μmol/L increase in serum LTG-level was 1.32. This model predicted correctly 60% of patients with pathological tremor and 100% of patients with physiologic tremor.

Conclusions

Cerebellar tremor

1.) Focal cerebellar lesions might cause pathological tremor in 50% of patients.
2.) Patients might develop postural and intentional tremor. None of them develop rest tremor.
3.) Cerebellar tremor has low frequency (lower than 3 Hz) and usually low amplitude; therefore, bedside clinical examination reveals it only in about 20% of the cases. Cerebellar tremor intensity is significantly higher in intentional compared to postural position: the observation of this phenomenon might help the diagnosis of cerebellar tremor in clinical settings.
4.) To reliably detect cerebellar tremor, quantitative registration, including the measurement of frequency components below 3 Hz, is essential.

5.) Increased proportional power (higher than 25%) in the low-frequency range (0.9–3 Hz) together with narrow frequency dispersion (less than 2–3 Hz) strongly suggest cerebellar tremor.

6.) There is no statistically significant correlation between the size of the lesion and tremor occurence.

7.) There is no statistically significant correlation between the cerebellar lesion localization and the occurrence or type of pathological tremor. Lesions in the same cerebellar site might result in different tremor types.

8.) The involvement of the brainstem is associated with higher prevalence of pathological tremor than lesions affecting the cerebellum only. This suggests that both the cerebellum and the brainstem are parts of a complex tremor generator network, and they cooperate in the regulation of tremor frequency and intensity.

9.) Tremor induced by acute focal cerebellar lesion recovers spontaneously in 8 weeks. The improvement of center frequency and frequency dispersion might be assessed by quantitative tremor recordings.

Lamotrigine-induced tremor

10.) Objective measurements detected pathological intention tremor in 25% of epilepsy patients treated with lamotrigine monotherapy. We recommend early and regular assessment for timely detection of LTG-related tremor.

11.) Lamotrigine-induced tremor is a pathological intentional tremor. Tremor frequency was similar to that of physiologic tremor (around 8 Hz) but frequency

dispersion was about half of the normal values (around 1.75 Hz).

12.) The tremorogenic effect of lamotrigine showed significant interindividual variability, unexplained by lamotrigine serum level, age, and duration of drug administration.

13.) Alternating hand movements and finger tapping were not affected. Our data suggest that lamotrigine probably does not affect dopaminergic pathways and does not cause Parkinsonian signs.

14.) Our results raise the possibility of cerebellar involvement in the pathomechanism of lamotrigine-induced tremor.

Personal reference list

Publications related to the doctoral dissertation

1.) A. Kovács, M. Kiss, N. Pintér, I. Szirmai, A. Kamondi. *Characteristics of tremor induced by lesions in the cerebellum*, The Cerebellum, 2019; 18: 705-720.

2.) A. Kovács, Zs. Farkas, A. Kelemen, V. Juhos, A., Szűcs, A. Kamondi. *Lamotrigine induces tremor among epilepsy patients probably via cerebellar pathways.* The Tohoku Journal of Experimental Medicine 2019; 248(4):273-284.

3). Ch. Lawrenson, M. Bares, A. Kamondi, A. Kovács, B. M. Lumb, R. Apps, P.Philip, M. Manto. *The mystery of the cerebellum: clues from experimental and clinical observations,* Cerebellum and Ataxias, 2018; 5:8.

Independent publications

1.) Szűcs A., Horváth A., Fabó D., Szabó G., Kovács A., Halász P.: *Psychiatric disorders in epilepsy* (*Pszichiátriai zavarok epilepsziában: klinikai jelenségek),* Neuropsychopharmacol Hung 2017; 19(3): 147-158.

2.) Kovács A., Kocsis K., Vass I., Szabó M., Fazakas Z.: *Add-on therapy in patients with type 2 diabetes mellitus* (*Kiegészítő kezelés alkalmazása 2-es típusú cukorbetegek körében)*, Orvostudományi Értesítő, 2012, 85(2): 86-90.