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Evaluation of the Thalamic Region with Proton Magnetic Resonance Spectroscopy in Patients with Essential Tremor

Esansiyel Tremorlu Hastalarda Talamus Bölgesinin Proton Manyetik Rezonans Spektroskopi ile Değerlendirilmesi

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Summary

Objective: Although essential tremor (ET) is the most common movement disorder, its pathogenesis is poorly understood. It is suggested that the ventral intermediate (VIM) nucleus of the thalamus is important in the pathophysiology disease.

Materials and Methods: The present study aimed to evaluate N-acetylaspartate (NAA), choline (cho), and creatinine (Cr) values via proton magnetic resonance spectroscopy (H-1 MRS) of the VIM of the thalamus in 16 control patients and 42 patients with ET.

Results: The mean NAA/Cr and NAA/Cho values of the thalamus VIM nucleus region in patients with ET was statistically significantly lower than the control group (p=0.001, p=0.005, respectively). In patients with ET, no significant relation was found between NAA/Cr, NAA/Cho values, and age, family history, disease duration, tremor severity, dominant extremity localization of tremor, and history of drug use (p>0.05).

Conclusion: Low NAA values in the thalamus region of patients with ET indicate neuron loss and cell death. Neuron loss in the thalamus region has been suggested to play a part in the pathophysiology of the disease, and may indicate that ET is a neurodegenerative disease.

Keywords: Essential tremor, magnetic resonance spectroscopy, thalamus

Öz

Amaç: Esansiyel tremor (ET) en sık görülen hareket bozukluğu olmasına rağmen patogenezi hala bilinmemektedir. Talamusun ventral intermediate (VİM) nükleusunun patofizyolojide rol oynadığı öne sürülmektedir.

Gereç ve Yöntem: Bu çalışmada 42 ET tanısı almış hasta ve 16 kontrol olgusunun proton manyetik rezonans spektroskopi (H-1 MRS) tetkiki kullanarak talamus bölgesinin N-asetilaspartat (NAA), kolin ve kreatinin değerlerinin incelenmesi amaçlandı.

Bulgular: ET hastalarında talamus VİM nükleus bölgesi ortalama NAA/Kreatinin ve NAA/Kolin değerleri kontrol grubuna göre istatistiksel olarak anlamlı derecede düşük olarak tespit edildi (sırasıyla p=0,001, p=0,005). ET hastalarının yaş, aile öyküsü, hastalık süresi, tremor şiddeti, tremor dominant ekstremite lokalizasyonu ve ilaç kullanım öyküsü ile NAA/Kreatinin, NAA/Kolin değerleri arasında anlamlı bir ilişki bulunmadı (p>0,05).

Sonuç: ET hastalarının talamus bölgesindeki düşük NAA değerleri, bu bölgedeki nöron kaybı ve hücre yıkımını işaret etmektedir. Hastalığın patofizyolojisinde rol oynadığı öne sürülen talamus bölgesindeki nöron kaybı, ET'nin nörodejeneratif bir hastalık olduğunun göstergesi olabilir.

Anahtar Kelimeler: Esansiyel tremor, manyetik rezonans spektroskopi, talamus

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Introduction

Essential tremor (ET) is a common movement disorder in adults and is characterized by postural tremor of the upper limbs and head. Although it has long been considered a mono-symptomatic disorder, recent identification of motor features such as cerebellar symptoms, non-motor features such as cognitive impairment, different personality types, and behavioral symptoms have expanded its clinical framework. These findings have led ET to be investigated as a more complex and heterogeneous disease (1,2).

Despite the high prevalence of the disease, its pathogenesis is still unknown. Although postmortem studies pointed towards cerebellar changes, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have revealed abnormalities in the cerebellum, thalamus, and triangle of Guillain-Mollaret, which is settled in the brain stem and inferior olive nucleus (3,4,5,6).

The two key points of ET disease are; a) development of auxiliary radiologic or biochemical methods that can provide early diagnosis and help in monitoring the course of the disease, and b) clear demonstration of etiologic factors. Proton magnetic resonance spectroscopy (H-1 MRS), which addresses one of these key points, is a non-invasive imaging method and provides chemical information about tissue metabolites such as N-acetylaspartate (NAA), choline (Cho), and creatinine (Cr). Decreased NAA levels is considered as an indicator for neuronal loss, thus neurodegeneration (7,8,9,10).

The aim of this study was to investigate the biochemical findings and metabolites of the thalamic region in patients with ET using H-1 MRS.

Materials and Methods

Forty-two patients with ET whose disease was diagnosed in accordance with the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) criteria, and 16 age- and sex-matched healthy volunteers were included in the study. Approval was obtained from Göztepe Training and Research Hospital Ethics Committee.

Patients with a history of cerebrovascular event, head trauma, intracerebral mass, metabolic disorders (hypo-hyperthyroidism, hypoglycemia), Wilson's disease, and patients who used medicines that could cause tremor were excluded from the study.

Routine physical and neurologic examinations were performed in the patient and control groups. All participants underwent a complete blood count, sedimentation rate, and routine biochemistry laboratory examinations (glucose, urea, Cr, liver function tests, serum electrolytes, and thyroid function tests). A detailed medical and family history were questioned of the patient group. The tremors of the patients with ET were examined. Tremors were evaluated in three groups, right dominant, left dominant, and bilaterally equal according to the dominant extremity of the tremor. Tremor severity levels were detected based on WHIGET diagnostic criteria. Postural tremor was evaluated while holding the arms stretched forward, and kinetic tremor was evaluated during 5 different tasks (pouring water, drinking water with glass, using a spoon to drink water, finger-to-nose maneuver, and drawing spirals). Postural and kinetic tremors were rated 0 to +3 according to this scale and tremor level was evaluated in three separate groups as low amplitude (0-1), moderate amplitude (2), and large amplitude (≥3).

All participants underwent cranial MRI and H-1 MRS examinations of the ventral intermediate (VIM) nucleus of the bilateral thalamic regions. H-1 MRS imaging results were evaluated by an expert radiologist who was unaware of the clinical information of the patients.

NAA, Cho, and Cr levels of both patient and control group were determined according to the bilateral thalamic H-1 MRS results. NAA/Cho and NAA/Cr ratios of the patient and control groups were compared. The relationship between NAA/Cho and NAA/Cr levels of patients and age, duration of disease, family history, tremor severity, localization of tremor dominancy, and treatment features were investigated. In addition, the relationship between tremor severity of patients with ET and age, family history, and duration of disease were investigated.

Proton Magnetic Resonance Spectroscopy

Proton MRS imaging was performed using a General Electric Signa HiSpeed 1.5 Tesla MRI scanner" in the Imaging Center of our hospital. Point resolved spectroscopy sequence (PRESS) was used with these parameters: Echo time (TE)=144 ms, 64 acquisition, 2x2x2 "Voxel size" and repetition time=1500 ms. Single-voxel spectroscopy was performed using axial or coronal T2 sequences. Proton Brain Exam-Single Voxel (PROBE/SV) software developed by General Electric Medical System was used in this study. Sequences were obtained using automatic 'shimming' (2-6 Hz) and 99% water suppression. The spectra obtained after automated post-processing by the aforementioned software was inspected again in terms of quality and was quantified automatically.

Proton Magnetic Resonance Spectroscopy Parameters

NAA, Cho and Cr values obtained from bilateral VIM nucleus regions of the thalamus using H-1 MRS via TE 144 sequence were used. Cr values were used as control values because they are constant in various diseases. Thus, new parameters were obtained by proportioning these values (NAA/Cho and NAA/Cr). These ratios were used for the intergroup comparison.

The evaluated regions and examples of the H-1 MRS examinations of the patients and control subjects are shown below (Figure 1, 2, 3).

Statistical Methods

Statistical Package for Social Sciences (SPSS) for Windows 15.0 was used for statistical analysis of data. In addition to descriptive statistical methods (mean, standard deviation), Student's t-test was used for parametric data, the Mann-Whitney U test was used for non-parametric data in case of quantitative data comparison, and the Chi-square test was used for qualitative data comparison. Correlations were evaluated using Pearson's correlation coefficient and logistic regression analysis. Results were evaluated in 95% confidence interval and significance level $p<0.05$.

Results

A total of 58 participants, 42 patients and 16 controls, were included in the study. The mean age of the patients with ET

and control group was 65.36±10.11 and 61.13±13.73 years, respectively. There were 30 (71%) men and 12 women in the patient group, and 9 (56%) men and 7 women in the control group. No statistical significant difference was detected between the two groups in terms of age and sex (p=0.27).

The patient group was evaluated in terms of demographic and clinical characteristics. The mean disease duration was found to be 9.76±10.5 years. Of the 42 patients, 30 (71%) had a family history of tremor. Postural and kinetic tremor in both upper limbs was present in all patients and kinetic tremor was more prominent. Twenty-two (52.4%) patients had bilateral equal tremors, 7 patients had right upper extremity and 13 patients had left upper extremity dominant tremor severity. Eleven (26%) patients had low, 22 (52%) had moderate, and 9 (22%) had large amplitude tremor severity. Sixteen (38.1%) patients had a history of drug (Primidone and Propranolol) use due to tremor. No statistically significant relation was found between tremor severity and age, duration of disease, and family history (p=0.26).

Compared with the control group, the mean NAA/Cr and NAA/Cho values of the right and left thalamic VIM region of the patient group was found to be statistically significantly lower (p=0.001, p=0.005, respectively). The mean NAA/Cr and NAA/Cho values of the patient and control group are shown in Table 1.

The relationship between NAA/Cr and NAA/Cho values, demographics, and clinical characteristics such as age, duration of disease, family history, tremor severity, localization of tremor dominancy, and patients' drug use history were investigated and no statistically significant relationship was found (p>0.05) (Table 2).

Table 1. Mean N-acetylaspartate/Creatinine and N-acetylaspartate/Choline values of patient and control group

	NAA/Cr (Mean±SD)	NAA/Cho (Mean±SD)
Patient (ET)	2.01±0.46	1.47±0.3
Control	2.5±0.4	1.98±0.61
p*	0.001	0.005
Total	2.14±0.49	1.61±0.47

NAA: N-acetylaspartate, Cr: Creatinine, Cho: Choline, SD: Standard deviation, ET: Essential tremor, *p<0.05 is significance level

Discussion

ET is a common movement disorder in adults and is characterized by postural tremor of the upper limbs and head. The pathogenesis of the disease is still unknown. Although postmortem studies point towards cerebellar changes, PET and fMRI studies have revealed abnormalities in the cerebellum, thalamus, and triangle of Guillain-Mollaret, which is settled in the brain stem and inferior olive nucleus. Researchers argue that the postural tremor of ET arises from spontaneous firing of inferior olivary nucleus (ION), which connects the cerebellum and its output pathways to the cerebral cortex and then to the spinal cord through VIM of the thalamus (11,12,13,14,15,16,17). Studies have shown that ET amplitude could be significantly reduced with thalamic lesions or thalamic stimulation, and the thalamus has been suggested to play a major role in the formation or transmission of ET (18,19).

There are few proton MRS studies on the cerebellum and thalamus regions, which are thought to be mainly affected in the pathophysiology of ET (20). Louise et al. (7) compared the cerebellar cortex, white matter, vermis, thalamus and basal ganglia of 16 ET patients and 11 healthy subjects using H-1 MRS examination and they found that the mean cerebellar cortex total creatine (tCR) NAA/tCR values of patients with ET were significantly lower than the control group. No statistically significant difference could be detected in the cerebellar white matter, vermis, thalamus, and basal ganglia regions. Although authors indicated that the small number of cases had a limiting effect on the study, they suggested that they found the decrease in the NAA/tCR ratio in the cerebellar cortex meaningful in terms of neuronal loss and development of neurodegeneration in ET. Another study by the same researchers that included more patients was conducted through the evaluation of the two regions separately, as left and right, instead of mean values. Similar to the previous study, the results of the study supported reduced NAA values in the cerebellar cortex region and neuronal loss (8). In a recent study by Louis et al. (11) on 12 patients with ET, decreased NAA levels in the cerebellum were shown to be associated with increased blood level of hormones. Pagan et al. (9) determined similarly decreased NAA/Cr and NAA/Cho ratios in the cerebellum of patients with ET compared with the controls. Although the authors found no significant difference between the patient and control group in the thalamus region, the right thalamus NAA/Cr ratio was detected to be higher than the left thalamus; however, the authors did not compare these ratios statistically.

Table 2. The relationship between N-acetylaspartate/Creatinine and N-acetylaspartate/Choline values and demographic and clinical characteristics of patient group

		Age	Duration of disease	Family history	Tremor severity	Localization of tremor	Drug use history
Mean NAA/Cr	r	-0.090	0.174	0.584*	0.292	0.175	0.754*
	p*	0.571	0.271	0.466	0.061	0.267	0.689
Mean NAA/Cho	r	-0.236	0.069	0.404*	0.060	0.121	0.410*
	p	0.132	0.666	0.427	0.704	0.445	0.429

NAA: N-acetylaspartate, Cr: Creatinine, Cho: Choline, *p<0.05 is significance level

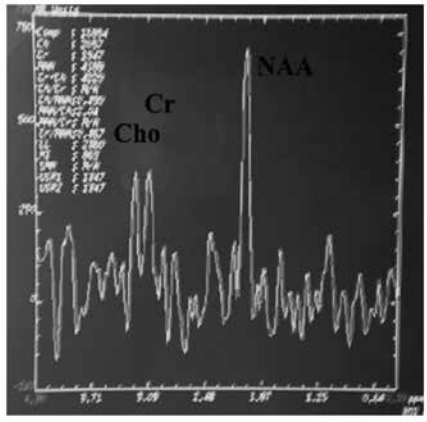

Figure 1. H-1 magnetic resonance spectroscopy examination example of a control subject
NAA: N-acetylaspartate, Cr: Creatinine, Cho: Choline

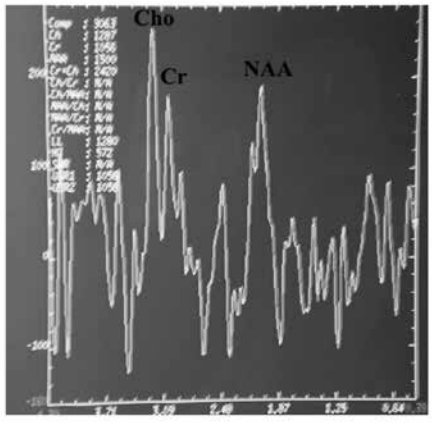

Figure 2. H-1 magnetic resonance spectroscopy examination example of an essential tremor patient
NAA: N-acetylaspartate, Cr: Creatinine, Cho: Choline

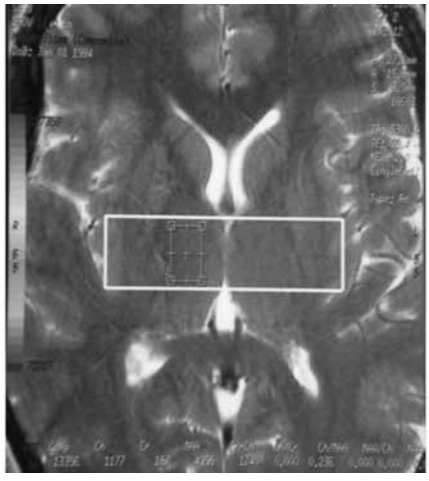

Figure 3. Imaging of ventral intermediate nucleus regions of the thalamus

Kendi et al. (10) conducted an MRS study on the thalamic regions of patients with ET and found statistically significantly lower NAA/Cr ratios in the left thalamus compared with the right thalamus, but found no significant differences when compared with the control group. The authors considered that the presence of right upper limb tremor dominancy in all patients restricted the study, but they also expressed that the decrease in NAA levels in the contralateral thalamus could indicate involvement of the thalamus in the pathophysiology of ET. In our study, the mean thalamic NAA/Cr and NAA/Cho values of patients with ET were found to be statistically significantly lower than the control group (p=0.001, p=0.005, respectively).

In both studies by Louise et al., (7,8) an inverse relationship was determined between the dominant limb tremor severity level and age with ipsilateral cerebellar cortical NAA/tCR values. In our study, similar to the studies of Pagan, Kendi (9,10) and colleagues, no relationship was found between age and tremor severity. In addition, similar to other studies, no relationship was found between NAA/Cr and NAA/Cho values and duration of disease, tremor severity, localization of tremor dominancy, family history, and drug use history for tremor.

Limiting factors in our study were absence of volume measurements because of technical shortcomings, cross-sectional evaluation of the patients, and absence of follow-up MRS evaluations.

Along with all this information, our study has the largest series of H-1 MRS examinations of the thalamus region in patients with ET. The thalamus is suspected to play a role in the pathophysiology of ET and the decreased NAA levels in patients with ET compared with the control group favor neuronal loss in the thalamus. This provides additional evidence to that found in PET and fMRI studies, which support the hypothesis that the thalamus plays a role in the pathophysiology of tremor.

Authorship Contributions

Ethics Committee Approval: The study were approved by the Göztepe Research and Training Hospital of Local Ethics Committee, Informed Consent: Consent form was filled out by all participants, Concept: Adile Özkan, Fatma Candan, Design: Adile Özkan, Fatma Candan, Nihal Işık, Data Collection or Processing: Adile Özkan, Semra Arı, Özgur Öztop Çakmak, Analysis or Interpretation: Adile Özkan, Fatma Candan, İlknur Aydın Cantürk, Tunahan Ayaz, Literature Search: Adile Özkan, Writing: Adile Özkan, Peer-review: Externally peer-reviewed, Conflict of Interest: No conflict of interest was declared by the authors. Financial Disclosure: The authors declared that this study has received no financial support.

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