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White matter lesions predict cognitive dysfunction in patients with essential tremor

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ABSTRACT

Objective: Previous researches are not sufficient to explain why cognitive deficits occur in patients with essential tremor (ET). The aim of this study is to evaluate the relationships among vascular risk factors, MRI measures of white matter lesions (WMLs), and the rate of decline in the global cognitive functioning of elderly patients with ET. **Method:** We used the Mini-Mental State Examination (MMSE) to assess cognitive decline in patients with ET. The MMSE results of 106 patients were compared with those of 67 age- and sex-matched controls. All participants underwent cranial MRI examinations to exclude other possible causes of cerebellar or extrapyramidal disorders. WMLs were identified via T2-weighted MR scans and then evaluated. We examined correlations of MMSE scores with vascular risk factors, cranial MRI findings, and factors of age, educational level, and sex. **Results:** Lower MMSE scores were related to WMLs and age in the patient group ($p < 0.05$), and WMLs independently predicted mental status in this group (*Beta* value = −0.233, $p = 0.016$). We found no correlation between MMSE scores and commonly seen vascular risk factors. **Conclusion:** Cognitive assessments should be part of clinical dialogs with elderly patients with ET, and prospective neuro-imaging studies and detailed neuropsychological tests should be performed when cognitive impairment related to ET is suspected.

1. Introduction

Essential tremor (ET) is among the most prevalent movement disorders, with an estimated prevalence of 4.6% among people aged 65 years and older.[1] ET is a benign movement disorder that is progressive, monosymptomatic, and frequently familial; it is infrequently associated with incapacitating tremor and very rarely associated with other neurological symptoms, such as gait ataxia.[2,3] Cognitive functioning is related primarily to cortical and subcortical structures, and recent research has found that cognitive problems may be seen in patients with ET.[4–6] Patients with ET demonstrate several deficits in various executive functions, including attention, language, and verbal memory (immediate and delayed). ET is more common in elderly individuals, and it has been established that age is a prominent risk factor for late-life cognitive declines related to attention, memory, and global cognition.[7] On the other hand, it has also been established that comorbid conditions such as hypertension, diabetes mellitus, white matter lesions (WMLs) related to small vessel disease, and low and high serum TSH levels are associated with an increased risk of cognitive decline in elderly individuals.[8–10] Although cognitive deficits may be observed in patients with ET, the effects of comorbid conditions mentioned above on cognitive dysfunction have not been well established. In the present study, we examined correlations of Mini-Mental State

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Examination (MMSE) scores with WMLs, vascular risk factors, and other variables such as age, educational level, and sex.

2. Materials and methods

2.1. Study population

The current study was conducted in the outpatient neurology clinics of Medeniyet University Teaching Hospital. The records of all ET patients diagnosed between May 2011 and May 2013 were evaluated retrospectively and prospectively. All the patients met the criteria for ET (11). The main inclusion criteria were the presence of cognitive function evaluation using the validated Mini Mental State Examination (MMSE) in the registration card for the patients included in retrospective analysis. No patients have symptoms of Parkinson disease (PD) or another neurologic disease that could account for the presence of tremor. The patients neither took antidopaminergic drugs, valproic acid, lithium, nor other drugs that cause tremor. Individuals with dementia, depression or other psychiatric disorders, head injury, serious illnesses such as severe anemia or active or ongoing cardiovascular or cerebrovascular disease were excluded. Sociodemographic and clinical assessment included age, gender, presence of diabetes and hypertension, alcohol use, smoking status, presence of coronary artery, cerebrovascular and peripheral artery diseases and current medications. After evaluation of the records of 245 ET patients, 106 subjects were enrolled in the study. All subjects underwent the following assessments: medical history, physical examination and office blood pressure (BP) measurements. Fasting blood samples were measured for serum hemoglobin, glucose, blood urea nitrogen, creatinine, sodium, thyroid-stimulating hormone, low-density lipoprotein cholesterol, AST and ALT. The vascular risk factors were recorded for all the participants. Hypertension was considered to be present if at the time of diagnosis the subjects had a systolic BP >140 mmHg or a diastolic BP >90 mmHg, and if treatment for high BP was administered previously. Previous coronary artery disease and a related history of ischemia were considered to be present if the subjects had previously been treated for these. Hypercholesterolemia was considered to be present in subjects with serum cholesterol >200 mg/dL. Hyperglycemia was considered to be present in subjects with a serum level of >110 mg/dL, or if treatment for diabetes had previously been started. Smoking was considered to be present in subjects with cigarette smoking ≥20 pack years. Alcohol was considered to be present in subjects with alcohol consumption ≥24 g/day. MMSE results were compared with MMSE of age and sex matched 67 controls without tremor. None of the controls had a history of head injury, neurologic disease, psychiatric disease, or drug addiction. The controls and patients had comparable levels of education and socioeconomic status. All participants had cranial MRI. Then the relationships between MMSE results and vascular risk factors were analyzed for the significances. Informed consent was obtained from all participating patients and controls. Permission for the study was obtained by the local ethics committee.

2.2. Procedure

The neurologic examination was performed first by a junior neurologist and then by a neurologist experienced in movement disorders. The neurologic examination included a general physical examination and the motor portion of the Unified Parkinson's Disease Rating Scale. ET was marked by initially low-amplitude tremors of mid to high frequency.[11] For patients with ET, global disability ratings (on a scale of 0–4) as 0: no disability, 1: %1–25 disabled, 2: %26–50 disabled, 3: %51–75 disabled, and 4: %76–100 disabled were provided by the patient and the examiner. Tremor electromyography (EMG) was studied on ET patients when the clinical picture is complicated or when clinical signs are subtle. Then the MMSE examining orientation, immediate and short-term memory, attention and executive function, language and praxis was performed. The MMSE scores of patients change between 0 and 30.[12]

2.3. MRI exam

All participants had cranial MRI exam to exclude other possible causes of cerebellar or extra pyramidal disorders. MRI exam was also used in order to exclude other diseases with brain damage and cognitive problems i.e. hemorrhages, large or multiple infarctions, strategic infarctions, tumors, vasculitis, demyelization or hydrocephalus. All subjects underwent MR imaging using a standard protocol. Magnetic resonance imaging was performed on 1.5-T imagers and included a 3-dimensional, T1-weighted, gradient-echo sequence (coronal views, 1.5-mm section thickness, and 1-mm in-plane resolution) and a fast fluid attenuated inversion recovery sequence (axial views, 5-mm contiguous sections, and 1-mm in-plane resolution). Then, WMLs identified on T2-weighted MR scans were evaluated.[13] The degree of white matter changes is rated on a 4-point scale. Ratings were done on MRI images on computer screen with either proton density and T2-weighted images or T2 and FLAIR images. White matter changes on MRI were defined as ill-defined hyperintensities >5 mm on both T2 and proton density/FLAIR images. Lacunes were defined as well-defined areas of >2 mm with signal characteristics (on MRI) the same as cerebrospinal fluid. All visual ratings were carried out by Koçer and Okay who was blinded to clinical information. Although WMLs could be found in different locations such as the subcortical, central, and periventricular white matter, the results were recorded as present or absent in the present study (Table 1).

2.4. Statistical analysis

Statistical analysis was performed by using SPSS 11.0 statistical software (SPSS Inc, Chicago, IL). The Kolmogorov–Smirnov test which is based on the empirical distribution function and used to decide if a sample comes from a population with a specific distribution was used to determine whether the continuous variables were normally distributed or not. Parametric tests were applied with normal distribution, whereas nonparametric tests were used without normal distribution. Normally distributed variables were given as mean standard deviation, while those variables featured by