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The relationship between white matter abnormalities and cognitive functions in new-onset juvenile myoclonic epilepsy

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ABSTRACT

Diffusion tensor imaging (DTI) has revealed evidence of subcortical white matter abnormalities in the frontal area in juvenile myoclonic epilepsy (JME). Decreased fractional anisotropy (FA) and increased mean diffusivity (MD) in the corticothalamic pathway have been detected in adult patients with JME. It has been demonstrated that, in adult patients with JME, frontal dysfunction is related to subcortical white matter damage and decreased volume in frontal cortical gray matter and the thalamus. Many studies have focused on adult patients.

Twenty-four patients and 28 controls were evaluated. The group with JME had significantly worse results for the word fluency, trail-B, and Stroop tests that assessed executive functions. A significant decrease in FA values in the dorsolateral prefrontal cortex (DLPFC), the supplementary motor area (SMA), the right thalamus, the posterior cingulate, the corpus callosum anterior, the corona radiata, and the middle frontal white matter (MFWM) and an increase in ADC values in patients with JME were detected. The correlation between FA values in DLPFC and the letter fluency test results was positive, and the correlation with the Stroop and trail-B test results was negative. We found a negative correlation between SMA, anterior thalamus, and MFWM FA values and the trail-B test results and a positive correlation between the SMA, anterior thalamus, and MFWM FA values and the letter fluency test results.

We detected white matter and gray matter abnormalities in patients with new-onset JME using DTI. In addition, we determined the relationship between cognitive deficit and microstructural abnormalities by evaluating the correlation between the neuropsychological test battery results and DTI parameters. We evaluated newly diagnosed patients with JME in our study. That leads us to believe that microstructural abnormalities exist from the very beginning of the disease and that they result from the genetic basis of the disease.

1. Introduction

Juvenile myoclonic epilepsy (JME) is the most widely observed form of idiopathic generalized epilepsy [1] and comprises 4–11% of all epilepsy cases. The underlying pathogenesis of JME is not clear; however, the generalized 3- to 4-Hz spike–slow wave complex seen on electroencephalograms (EEGs) consists of thalamocortical interaction [2]. Autopsy studies have shown that cortical and subcortical dystrophic neurons and microscopic structural anomalies occur in JME [3,4]. Structural neuroimaging studies have revealed a decrease in thalamic volume in JME and other idiopathic generalized epilepsies [5]. In recent years, various studies have focused on diffusion tensor imaging (DTI) and magnetic resonance imaging (MRI) sequences. Anisotropy of water can be evaluated using fractional anisotropy (FA) and the apparent diffusion coefficient (ADC), which are DTI parameters [6,7]. Diffusion tensor imaging has the potential to reveal the epileptogenic lesions that are invisible in conventional MRI and that indicate microstructural anomalies in white matter.

Diffusion tensor imaging has revealed evidence of subcortical white matter abnormalities in the frontal area in JME [8–10]. The corticothalamic pathway in the white matter in this area connects the frontal cortex supplementary motor area (SMA) and the anterior thalamus [11]. Decreased FA and increased mean diffusivity (MD) in the corticothalamic pathway have been detected in adult patients with JME [12,13]. Decreased FA in the prefrontal white matter, the anterior cingulated cortex, and the posterior internal capsule has been shown in pediatric patients with idiopathic generalized epilepsies [14]. Evaluations of the thalamofrontal cycle by measuring white and gray matter volume have revealed decreased volume in the right thalamus and frontal lobe of patients with newly diagnosed pediatric JME [15]. To our knowledge, there has been no study using DTI to evaluate

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white matter damage and microstructural changes in the frontal cortex and thalamus in pediatric patients with new-onset JME. Therefore, there is a need to explore this issue.

Numerous studies have discussed cognitive deficit and frontal dysfunction in JME [16–19]. It has been demonstrated that, in adult patients with JME, frontal dysfunction is related to subcortical white matter damage and decreased volume in frontal cortical gray matter and the thalamus [20–23]. Many studies have focused on adult patients. A study evaluating the correlation between cognitive deficit and frontal white matter damage in patients with newly diagnosed pediatric JME found that reduced volume in the right thalamus and frontal lobe is correlated with reduced executive functions [15]. To our knowledge, no study has employed neuropsychological tests in examining patients with newly diagnosed JME to evaluate the frontal white matter, the frontal cortex, and the thalamus using DTI region of interest (ROI) measurements or to evaluate the radiologic and cognitive correlations.

The aim in this research was therefore to detect white and gray matter abnormalities in patients with new-onset JME using DTI and to detect the presence of cognitive deficit that might be a clinical reflection of this abnormality. To do this, we compared the patients to healthy controls using a battery of detailed neuropsychological tests. Furthermore, by observing the correlation between neuropsychological tests scores and DTI parameters, we aimed to reveal the relationship between cognitive deficit and microstructural abnormalities.

2. Methods

2.1. Subjects

The ethics committee of Adıyaman University approved this prospective study. All participants gave written informed consent prior to study inclusion. Twenty-four pediatric patients (in the 12–17 age range) who were evaluated at the neurology clinic at the Adıyaman University Training and Research Hospital were prospectively monitored for at least one month. These patients had experienced epilepsy for up to five months and had been diagnosed with JME. The patients were classified using the International League against Epilepsy (ILAE) classification system [24]. Inclusion criteria for JME were as follows:

1) myoclonic seizures, especially early in the morning; generalized tonic–clonic seizures with or without myoclonic onset; and absence seizures;
2) to observe typical 3-Hz generalized spike–wave discharge along with the normal background activity in at least one EEG; and
3) pathology not determined using conventional MRI.

Group participants with JME were receiving valproate (VPA) monotherapy, levetiracetam (LEV) monotherapy, and VPA + LEV polytherapy. Seizures were under control, and no seizure history was recorded in the last months. Patients with comorbid neurologic, psychological, and systemic disease were not included in the study. No drug use was present, except for antiepileptic drugs. Demographic characteristics, age at seizure onset, duration of epilepsy, seizure type, seizure number, birth history, presence of previous febrile convulsions, and family story were recorded.

As a control group, 28 healthy children who matched the patient group in terms of age, gender, and education level were included. Each child underwent a detailed neurological checkup, and any child with neurologic, psychological, or systemic disease and a family history of epilepsy was excluded.

2.2. Neuropsychological evaluation

All neuropsychological tests were performed in a blinded fashion by an experienced psychologist who did not know the clinical diagnosis. In order to exclude patients with significant cognitive dysfunction, the Wechsler Intelligence Scale for Children—Revised (WISCR-R) was applied to all patient and control group members, and those who scored under 80 were not included in the study. Information, similarities, arithmetic, digit span subtests of verbal IQ and block design, object assembly, coding, and picture completion subtest of performance IQ were administered by a psychologist in two sessions with a break of 10 min on the same day.

The neuropsychological test battery was used to evaluate different cognitive areas and consisted of the following: the California Verbal Learning Test—Children's version (CVLT-C) for verbal memory and the Wechsler Memory Scale—III (WMS-III), a visual memory subtest for nonverbal memory; the trail-making test part A for attention and working memory; and the trail-making test part B, the Stroop color and word test (word, color, word–color), and the letter fluency test (words starting with the letters "F", "A" and "S") for executive functions.

2.3. MRI–DTI

Diffusion tensor imaging (DTI) was obtained in all participants, both the control group and the patient group. It was first established that the patients did not have seizures in the previous 24 h because studies have shown that seizures after status epilepticus can affect diffusion measurements. Magnetic resonance imaging (MRI) was conducted with the same 1.5-T superconductive MRI device (Philips Achieva, Holland). For anatomic reference, a T1-weighed, three-dimensional gradient echo sequence that included 160 sections was acquired from the participants in each group (matrix = 256 × 256 pixels; TR = 7.2 ms, TE = 33 ms; NSA = 1; FOV = 256 mm; slice thickness = 1 mm; gap = 0 mm; flip angle = 8°). The DTI pulse sequence used was an echo-planar imaging (EPI) sequence. In order to fill diffusion tensor, 32 different dimensions were collected from diffusion-weighted images with 1000 s/mm^2 b value and from nondiffusion-weighted images with b = o s/mm^2 a value. Sixty axial images were obtained in 2-mm section thicknesses. The image parameters were as follows: matrix = 128 × 128; field of view = 256 mm with a measured voxel size of 2.69 × 2.69 × 2.7 mm and a reconstructed voxel size of 2.00 × 2.00 × 2.7 mm; TE = 90 ms, TR = 10,150.5 ms; SENSE factor = 2; EPI factor = 67; b = 1000 s/mm^2; NSA = 3; slice thickness = 2.3 mm; and gap = 0 mm. All images were sent to a workstation to be processed. Using a workstation, ADC and FA evaluations were conducted twice, with a 15-day interval between each evaluation. These evaluations were performed by a radiologist who had 12 years of experience with MRI and who had no information about any of the participants in line with the previous literature. The ROI evaluations were of the dorsolateral prefrontal cortex (DLPFC), the SMA, the right thalamus, the posterior cingulate (PC), the corpus callosum anterior (CCA), the corona radiata (CR), the middle frontal white matter (MFWM), the uncinate fasciculus (UF), and the anterior frontal cortex (AFC).

2.4. Statistical analyses

The Statistical Package for Social Sciences (SPSS, version 18, SPSS Inc., Chicago, Illinois, USA) program was used for statistical analyses. Continuous variables with normal distribution were shown as mean ± standard deviation. Categorical variables were shown as numbers. An independent sample t-test was used to compare the demographic data of the JME and control groups. All the neuropsychological test results of the group participants with JME and control group participants were compared using independent sample t-tests. Independent sample t-tests were also used in the FA and ADC analysis to compare the DLPFC, SMA, right thalamus, PC, CCA, CR, MFWM, UF, FA in the AFC, and ADC values of the group members with JME with those of the control group members.

A Pearson test was used for correlation analysis. Considering the functional relationship, negative and positive correlations between