Impaired integrity of commissural and association fibers in essential tremor patients: Evidence from a diffusion tensor imaging study

Abstract

**Background/aim:** Evolving definition of essential tremor (ET) introduced us a new concept of neurodegenerative disease pointing to diffuse brain network involvement with a wide spectrum of associated motor and non-motor symptoms. Considering the fact that the white matter should also be affected by the nature of the disease, our study aimed to evaluate integrity of white matter and its clinical correlations in ET patients.

**Materials and methods:** 40 patients diagnosed with ET and 40 age-and gender-matched control subjects (ranged between 18-80 years old) were included in the study. Sociodemographic characteristics and clinical features of the patients were recorded. Tremor was assessed using “Fahn-Tolosa-Marin Tremor Rating Scale” (FTM-TRS). Diffusion Tensor Imaging (DTI) was performed to evaluate the integrity of white matter. The selected white matter regions used for DTI assessment were corpus callosum (CC) (i.e., largest commissural tract in human brain), superior longitudinal fasciculus (SLF), and inferior longitudinal fasciculus (ILF) (i.e., largest association fiber bundles).

**Results:** The mean age of ET patients and control subjects were $44.23 \pm 18.91$ and $37.45 \pm 10.95$ years ($p = 0.542$). The fractional anisotropy (FA) values of the CC body ($p = 0.003$) and ILF ($p = 0.016$) and the average diffusion coefficient (ADC) values of the CC body ($p = 0.001$) and genu ($p = 0.049$), SLF ($p < 0.001$), and ILF ($p < 0.001$) were differed between groups. After controlling for age and gender, there was no correlation between tremor severity and DTI parameters, but impaired integrity in genu of CC FA ($p = 0.035$, $r = 0.442$) and splenium of CC ADC ($p = 0.007$, $r = 0.543$) were related with longer duration of tremor.
Finally, positive family history was correlated with splenium of CC FA and ADC ($p = 0.008$, $r = 0.536$; $p = 0.027$, $r = -0.461$) and ILF ADC ($p = 0.011$, $r = -0.519$).

**Conclusions:** In our study, major white matter structures changes were found in ET patients. The result suggest that possible neurodegeneration also affects white matter structures in ET patients and duration of tremor and family history are related with impaired integrity of white matter.

**Keywords:** Essential tremor; white matter; neurodegeneration; diffusion tensor imaging; fractional anisotropy; average diffusion coefficient

1. Introduction

Essential tremor (ET) is one of the most common movement disorders globally [1,2]. The prevalence of ET is 4.0% for ages 40 and above [3]. It is a slowly progressive disorder characterized by postural and kinetic tremors predominantly in the forearms and hands, ultimately spreading to the head and other body regions [1,4]. ET is also associated with a number of motor and non-motor manifestations including cognitive deficits, neuropsychiatric symptoms [anxiety, depression, specific personality traits], sleep disorders and sensory deficits [5-16]. In recent years, according to systematic postmortem and neuroimaging studies, our knowledge of the symptomatology and neuropathology of this disease has grown substantially. Postmortem examinations in ET patients revealed reactive gliosis in cerebellum, depletion of locus coeruleus neurons and Lewy body pathology [17,18,19]. Early changes in cerebellar cortex include damage in both the axonal and dendritic purkinje cell compartments, eventually leading to purkinje cell death. As a result, reduced purkinje cell inhibitory output and impaired fiber connections between cerebellar
cortex and dentate nucleus were observed [20, 21]. Functional and structural neuroimaging studies identified the involvement of cerebellar pathways [16,22,23-29].

Neuroimaging studies also demonstrated structural changes in grey matter regions as frontal, temporal and occipital cortex [22,30-33], insula, precuneus [22,31], basal ganglia, red nucleus, substantia nigra and thalamus [34]. Neurodegenerative nature of the disease and a number of accompanying non-motor symptoms suggest that this neurodegeneration may also spread to white matter. Thus, several recent studies reported changes in white matter structures [34-37]. In addition of impaired integrity of cerebellar peduncles [36], in limited number of ET studies, the researchers reported disease related changes of corticospinal tract, internal capsule, superior longitudinal fasciculus (SLF) and corpus callosum (CC) [36-38].

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that is used to map the three-dimensional diffusion of water as a function of spatial location. Several DTI parameters are used to assess diffusion and indirectly, fiber tract microstructure. Fractional anisotropy (FA), measures the anisotropic diffusion of water molecules and average diffusion coefficient (ADC) describes the magnitude of the average molecular displacement by diffusion. DTI shows where neuronal/axonal loss occurs as a result of neurodegeneration [39].

The aim of this study was (i) to show possible white matter involvement in ET neuropathology using region of interest (ROI) DTI method and (ii) to evaluate the correlations of this possible white matter alterations.

2. Materials and methods

2.1. Participants
In this observational case control study, we recruited 84 (ranged between 18- 80 years old) consecutive patients with initial diagnosis with ET between March 2018 to July 2018. The study was conducted according to the Helsinki Declaration ethical principles and was approved by the Bezmialem Foundation University Hospital Ethics Committee. Written informed consent was obtained from the participants after the details of the procedures were fully explained. All participants were carefully examined by a movement disorder specialist. The diagnosis of ET confirmed by using Movement Disorder Society criteria [40]. Our exclusion criteria were: metabolic causes of tremor (vitamin B12 or folate deficiency, anemia, hypo or hyperthyroidism), causes of possible brain damage (e.g. history of significant head trauma, brain surgery or stroke history), mental disorders or dementia, clinical dementia rating (CDR) [41] scale score > 0.5 (all patients aged 65 years and older were administered CDR), use of medication known to cause tremors. Patients with prosthetics, metal inserts (metal knee caps and pacemakers) that are not compatible with MRI, together with claustrophobic patients were excluded from the study. As a result of these exclusion criteria, the final sample of our patient group, which we started with 84 patients was 40 patients. Pursuant thereto, forty age and gender matched control subjects were included in to study group amongst patients’ non blood relatives and hospital workers.

2.2. Clinical Evaluation

Sociodemographic characteristics, family history (first and second degree), disease duration and tremor localizations of the patients were recorded. The patients were grouped into two according to their tremor localizations. Group 1 consisted of patients with tremor only on upper extremities and Group 2 consisted of patients with cranial tremor accompanying to upper extremities. Fahn-Tolosa-Marin Tremor Rating Scale (FTM-TRS) was used to evaluate tremor severity [42]. This scale is a method for measuring resting, postural and
action tremor. There are 5 scores (0–4) for each category that represent severity. Increasing scores mean increasing severity of the disease.

2.3. MRI Protocol

All patients were examined using a 1.5T MRI system (Siemens, Avanto, Erlangen, Germany) with a maximum gradient strength of 43 mT/m and an 18-channel head coil. First, routine brain imaging protocol included T1-weighted (T1W) spin echo (TR/TE, 460/14 ms), T1W with fat suppression (TR/TE, 715/7.5 ms) without contrast, T2-weighted (T2W) turbo spin echo (TR/TE, 2500/80 ms), FLAIR (TR/TE, 8000/90 ms) sequences. Then the 3D T1W volumetric sequences (TR/TE/TI, 12.5/5/450 ms) without contrast were applied using a magnetization-prepared rapid acquisition of gradient echo sequence (MPRAGE) with an isotropic voxel resolution of 1 mm. Parallel imaging by using generalized auto calibrating partially parallel acquisition (GRAPPA) with an integrated parallel acquisition technique (iPAT) factor of 2 was applied. The DTI protocol included a single-shot, spin-echo, echo-planar sequence with TR/TE, 2700/89 ms; matrix, 128 × 128; field of view, 230 mm and slice thickness 5 mm and 64 diffusion-encoding directions were used at b = 0 s/mm² and b = 1000 s/mm². Parallel imaging by using GRAPPA with an iPAT factor of 3 was applied. A semi-automated system was used for ROI based DTI analysis. The ADC and FA maps were reconstructed on a Leonardo console (software version 2.0; Siemens) utilizing the DTI data. 3D T1 and T2-weighted images were used as anatomic references at the placement of the ROIs. These images were then matched with the corresponding regions in ADC and FA maps at the same anatomic level. The ROIs were drawn manually on axial color encoded FA maps in all subjects with simultaneous assessment of an experienced radiologist (H.O.) who identified the adaptation of the sizes and placement of the ROIs by dissecting white matter tracts: Interactive DTI teaching atlas [43]. Localization regions were CC (genu, body,
spleenium) (i.e. the largest commissural tract), SFL and inferior longitudinal fasciculus (ILF) (i.e. the largest bundle of association fibers). To standardize the measurements, all ROIs were obtained from the left side.

2.3. Statistical analysis:

All statistical analyses were performed using a commercially available SPSS release 20.0 software package (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). The results were presented as mean ± standard deviation. Chi square test was used to compare groups. Kolmogorov Smirnov test was used to assess normality. According to distribution of the data, independent T-test or Mann Whitney U test was used to compare groups. Partial correlation was used to evaluate all correlations between duration of tremor, FTM-TRS scores, family history and DTI metrics controlling for age and gender. P < 0.05 was accepted as statistically significant.

3. Results

The mean age of ET patients (n = 40) was 44.23 ± 18.91 years (ranged between 18-71 years); 70% of the patients were female (n = 28) and 30% were male (n = 12). The mean score of FTM-TRS scale was 21.03 ± 9.12 for all patients. The mean duration of tremor was 10.60 ± 8.86 years. Positive family history was found 70% of the patients (n = 28). Patients with tremor strictly localized to hands were 82.5% (n = 33), and patients with tremor in other body regions accompanying the hands were 17.5% (n = 7) (Table 1).

The study group was divided into two as those with ET (n = 40) and control group (n = 40). There were no significant differences between the groups when compared by age (44.23 ± 18.91 vs. 37.45 ± 10.95 years, p = 0.542) and gender (female: 70% vs. 50%, p = 0.110) (Table 1).
Comparison of major white matter tracts between groups showed significant changes in ET group in CC body FA and ADC (p = 0.003, p = 0.001), CC genu ADC (p = 0.049), SLF ADC (p < 0.001) and ILF FA and ADC (p = 0.016, p < 0.001) (Table 2).

The evaluation of partial correlation controlling for age and gender between family history and DTI data resulted in a significant correlation between the splenium of CC FA and ADC (p = 0.008, r = 0.536; p = 0.027, r = -0.461), and ILF ADC (p = 0.011, r = -0.519). No significant association was found between FTM-TRS scale and DTI data (p > 0.05). Tremor duration and the genu of CC FA value (p = 0.035, r = 0.442) and the splenium of CC ADC value (p = 0.007, r = 0.543) showed a significant association. There was no significant relationship between tremor localization and DTI parameters (Table 3).

3.1. Tables
<table>
<thead>
<tr>
<th></th>
<th>ET Patients (N = 40)</th>
<th>Healthy Controls (N = 40)</th>
<th>P* value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.23 ± 18.91</td>
<td>37.45 ± 10.95</td>
<td>0.54</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>%70 (n = 28)</td>
<td>%50 (n = 20)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>%30 (n = 12)</td>
<td>%50 (n = 20)</td>
<td>0.11</td>
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<tr>
<td>Clinical characteristics of ET patients</td>
<td></td>
<td></td>
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<tr>
<td>Duration of Tremor (years)</td>
<td></td>
<td>10.60 ± 8.86</td>
<td></td>
</tr>
<tr>
<td>Mean score of FTM-TRS**</td>
<td></td>
<td>21.03 ± 9.12</td>
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<tr>
<td>Family history</td>
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<tr>
<td>Positive:</td>
<td>70 % (n = 28)</td>
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<tr>
<td>Negative:</td>
<td>30 % (n = 12)</td>
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<tr>
<td>Tremor localization</td>
<td></td>
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<tr>
<td></td>
<td>82.5 % (n = 33)</td>
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<tr>
<td>Upper extremities:</td>
<td>17.5% (n = 7)</td>
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<td>Other body regions:</td>
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* Chi Square Test, ET: Essential tremor, FTM-TRS: Fahn Tolosa Marin Tremor Rating Scale
Table 2. Comparison of DTI metrics between groups (FA and ADC values are presented in units of \(10^{-6} \text{ mm}^2/\text{s}\).)

<table>
<thead>
<tr>
<th></th>
<th>ET Patients ((N = 40))</th>
<th>Healthy Controls ((N = 40))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Superior longitudinal fasciculus</strong></td>
<td>FA (530.87 \pm 68.04)</td>
<td>554.97 (\pm 77.12)</td>
<td>0.126*</td>
</tr>
<tr>
<td></td>
<td>ADC (725.67 \pm 43.58)</td>
<td>771.85 (\pm 44.26)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td><strong>Inferior longitudinal fasciculus</strong></td>
<td>FA (543.77 \pm 96.64)</td>
<td>496.80 (\pm 72.44)</td>
<td>0.016**</td>
</tr>
<tr>
<td></td>
<td>ADC (843.70 \pm 83.95)</td>
<td>752.85 (\pm 60.58)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td><strong>Corpus Callosum Splenium</strong></td>
<td>FA (795.92 \pm 83.96)</td>
<td>788.17 (\pm 50.84)</td>
<td>0.223*</td>
</tr>
<tr>
<td></td>
<td>ADC (817.82 \pm 78.76)</td>
<td>811.90 (\pm 59.91)</td>
<td>0.908*</td>
</tr>
<tr>
<td><strong>Corpus Callosum Body</strong></td>
<td>FA (625.67 \pm 84.62)</td>
<td>681.12 (\pm 80.96)</td>
<td>0.003*</td>
</tr>
<tr>
<td></td>
<td>ADC (1098.10 \pm 294.82)</td>
<td>944.40 (\pm 204.25)</td>
<td>0.001*</td>
</tr>
<tr>
<td><strong>Corpus Callosum Genu</strong></td>
<td>FA (781.72 \pm 64.20)</td>
<td>802.35 (\pm 55.38)</td>
<td>0.128**</td>
</tr>
<tr>
<td></td>
<td>ADC (851.07 \pm 103.33)</td>
<td>812.70 (\pm 78.76)</td>
<td>0.049*</td>
</tr>
</tbody>
</table>

*Independent Sample T Test, **Mann Whitney U Test, Bonferroni Corrected \(p\) value is 0.01. FA: Fractional Anisotropy, ADC: Average diffusion coefficient
Table 3. The evaluation of partial correlation controlling for age and gender between clinical data in ET patients and DTImetrics

<table>
<thead>
<tr>
<th></th>
<th>Family History*</th>
<th>FTM-TRS*</th>
<th>Tremor duration*</th>
<th>Tremor Localization*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>r value</td>
<td>p value</td>
<td>r value</td>
<td>p value</td>
</tr>
<tr>
<td>Superior</td>
<td>FA</td>
<td>0.394</td>
<td>0.063</td>
<td>-0.299</td>
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<tr>
<td>longitudinal</td>
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<tr>
<td>fasciculus</td>
<td>ADC</td>
<td>0.063</td>
<td>0.082</td>
<td>0.710</td>
</tr>
<tr>
<td>Inferior</td>
<td>FA</td>
<td>0.235</td>
<td>0.0280</td>
<td>0.062</td>
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<tr>
<td>longitudinal</td>
<td></td>
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<tr>
<td>fasciculus</td>
<td>ADC</td>
<td>0.011</td>
<td>0.259</td>
<td>0.233</td>
</tr>
<tr>
<td>Corpus</td>
<td>FA</td>
<td>0.536</td>
<td>0.008</td>
<td>-0.404</td>
</tr>
<tr>
<td>Callosum Genu</td>
<td></td>
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<tr>
<td></td>
<td>ADC</td>
<td>0.027</td>
<td>0.130</td>
<td>0.221</td>
</tr>
<tr>
<td>Corpus</td>
<td>FA</td>
<td>0.162</td>
<td>0.459</td>
<td>0.048</td>
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<tr>
<td>Callosum Body</td>
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<tr>
<td></td>
<td>ADC</td>
<td>0.069</td>
<td>0.753</td>
<td>*0.270</td>
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<tr>
<td></td>
<td>FA</td>
<td>0.109</td>
<td>0.621</td>
<td>-0.299</td>
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<tr>
<td>Corpus</td>
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<tr>
<td>Callosum</td>
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<tr>
<td>Splenium</td>
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<tr>
<td>ADC</td>
<td>-0.044</td>
<td>0.842</td>
<td>-0.111</td>
<td>0.615</td>
</tr>
</tbody>
</table>

* Partial correlation analysis controlling for age, gender, FTM TRS: Fahn Taloso Marin Tremor Rating Scale,
4. Discussion

It is essential to identify the affected brain regions in ET in order to understand this disease more comprehensively. Our study was planned considering that the integrity of major white matter bundles (CC, SFL and inferior longitudinal fasciculus) might be impaired and this finding, could reflect the neuropathology of the disease. As a result of this study, micro-structural tissue breakdown was found in all three major white matter regions. Microstructural changes of splenium of CC and ILF were positively correlated with family history. In addition, micro-structural changes in the genu of CC and the splenium of CC were related with longer duration of tremor.

As we mentioned, there are several studies with small sample size on this subject. In a study comparing DTI results of 10 ET patients and 8 control groups, a significant decrease in FA value was detected in the right half of the pons, bilateral cerebellum, left retrolbulbar area, and orbitofrontal, lateral frontal, parietal and temporal deep white matter [27]. In another study which assessed white matter abnormalities in ET for 14 ET patients and 20 control groups participants, both ROI based model and tract-based model DTI methods were used. Using ROI analysis, increased MD bilaterally in the inferior cerebellar peduncles and reduced FA in the right-sided inferior cerebellar peduncles, as well as increased FA in left parietal white matter of ET patients were detected. As a result, micro-structural alterations in the cerebellum and cerebellar white matter were identified [36].

In Saini et al.’s study, clinical and MRI data from 20 patients with ET and 17 controls were collected prospectively. The DTI data were analyzed using tract based spatial statistics (TBSS). Further ROI analysis was carried out in the genu of CC, internal capsule, corticospinal tract, and cerebellar peduncles. Patients with ET in comparison to controls
showed significant increase of mean diffusivity (MD) in right internal capsule and left
corticospinal tract. Axial diffusivity (AD) increase was seen in right inferior cerebellar
peduncle and corticospinal tract. ROI analysis also revealed a decrease in FA values in left
superior cerebellar peduncle and right corticospinal tract. As can be seen, cerebellum and
associated pathways, has been shown to be affected in most of the studies altogether with
large white matter bundles such as the CC [37].

Nestrail et al., investigated the correlation between tremor severity and neuroimaging in ET
patients. Tract-based and voxel-based approaches were utilized to compare DTI data from
12 ET patients and 10 age-and gender-matched healthy individuals. ET patients
demonstrated significant correlations between bilateral corticospinal tracts, superior
longitudinal fascicles, and the CC but also in non-motor regions including the inferior fronto-
occipital and longitudinal fascicles, cingulum bundles, anterior thalamic radiations, and
uncinate fascicles. The results show significant correlations between objective tremor
measures (combined TremScore, tremor frequency) and diffusivity metrics primarily in the
white matter regions. In contrast, a relationship between white matter changes and FTM-
TRS was not detected in the present study [38]. These conflicting results on relationship
between tremor severity and DTI parameters could be a result of larger sample size used in
our study. In addition to FTM-TRS, Nestrail et al., also used accelerometry to evaluate
tremor severity. Accelerometry tremor parameters showed robust correlation with changes
in white matter of the primary and associative motor areas, which were not detectable with
FTM-TRS. The lower inter-rater reliability and the subjective nature of the FTM-TRS could
also explain the different results detected in our study.

Recently, a neuroimaging study investigating the further deterioration of white matter
compared to grey matter deterioration of brain structures conducted with 19 ET patients and
White matter abnormalities were detected in corticospinal tract, anterior thalamic radiation, SFL and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and superior and middle cerebellar peduncles in ET patients compared to control group. The white matter abnormalities (CC, corticospinal tracts, SLF and cerebellar peduncles) significantly correlated with tremor severity [44]. This study demonstrated that while the grey matter damage in ET was limited to the thalamus, white matter damage was widespread, involving the majority of white matter bundles. In our study, similarly, significant DTI differences were observed between ET patients and CS in major white matter bundles. Again, in contrast with this study we did not find a relationship between these DTI parameters and tremor severity except the duration of tremor.

When interpreting our DTI results, one should consider that many things can affect FA (and the other diffusion metrics such as ADC, MD, radial diffusivity [RD], AD). And while FA values typically decrease in disease and in the presence of neurodegeneration, neuroinflammation sometimes can have the opposite effect on FA similarly in other values. For example, acute shear injury can produce axonal retraction balls thought to increase FA or, in acute stroke, FA is increased through a relatively greater decrease in the isotropic diffusion component. The other statements about RD and AD, one should consider still largely supposition; the exact pathophysiological representation of these changes still being an active area of research [45-49].

This study must be interpreted within several limitations: 1. Only ROI based model was used as the DTI method, tract-based model was not used. 2. Specific white matter structures were evaluated in our study; however, whole-brain analysis of the data was not performed.

5. Conclusion
Our results showed impaired integrity of major white matter bundles in brains of ET patients, which supports the hypothesis of possible widespread neurodegeneration in ET involving white matter structures. Previous limited number of DTI studies in ET confirmed an involvement of the brain white matter structures. Similar findings were also observed in our study. But, correlation of white matter microstructural changes with motor and non-motor signs in ET remains unclear. Evaluation of the relationship between both motor and non-motor symptoms and white matter structures in future studies will provide information to better understanding.

References


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