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Utility of Magnetic Resonance Spectroscopy and Diffusion Tensor Imaging of the Brain in Patients with Hashimoto's Thyroiditis with Normal Appearing Conventional Brain MRI

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Abstract

Background: **Hashimoto's thyroiditis (HT) is a known autoimmune disease of the thyroid gland and is usually associated with cognitive disorders.** ***Aim:*** **To investigate the utility of brain magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) in the detection of any metabolic or microstructural changes in HT patients who have normal conventional brain MRI, in correlation to thyroid peroxidase antibodies (TPOAb) levels and disease duration. This case-control study involved 40 patients with HT and 20 healthy controls. All the patients were euthyroid at the examination time and underwent hormonal assessment (TSH, T3, T4), TPOAb titer, brain MRS, and DTI. Correlations between MRS ratios, DTI values, TPOAb titer, and disease duration were performed.** ***Results:*** **Lower NAA/Cr and higher mI/Cr ratios in posterior cingulate gyrus (PCG) and parietal white matter (PWM) were observed in patients than in healthy controls (p= 0.001). A lower value of fractional anisotropy (FA), radial diffusivity (RD), and higher mean diffusivity (MD), and axial diffusivity (AD) were observed in patients versus control groups. Moderate positive correlation between disease duration and mI/Cr in PCG and PWM areas, and RD in the corpus callosum (p= 0.021, 0.013, 0.025, respectively), a moderate negative correlation between TPOAB and NAA/Cr in PCG, FA in the posterior limb of the internal capsule (PLIC) (r=– 0.536, p= 0.001, r= –0.436, p= 0.028 respectively).** ***Conclusion:*** **Brain MRS and DTI showed metabolic and microstructural changes in neurocognitive-related regions in patients with HT, which will help in understanding the concomitant neurocognitive deficits and disease management.**

Keywords: DTI, fractional anisotropy, Hashimoto's thyroiditis, MRS.

Introduction

Hashimoto's thyroiditis (HT) is a known autoimmune disease of the thyroid gland[1,2]. The prevalence of HT is about 10-12% among all populations, with middle-aged women being the more frequently affected group[1,2]. It is usually associated with affective and cognitive disorders, which are commonly overlooked, with a progressive course, and can affect the patient's quality of life[2,3]. Few studies are concerned about the presence of cognitive disorders in patients who have HT and who are euthyroid, in whom there are memory, focusing, and attention difficulties[4-8]. In clinical practice; cognitive event-related potentials (ERP) represent

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the way to assess both cognitive and intellectual functions in an objective way[9-13], this clinical assessment needs the active contribution of the examined patient and represents an indicator of functional activity and integrity at the cortical and subcortical neural networks levels of the brain[11-17]. The conventional brain MRI displays normal brain features in the majority of patients, the remaining patients were manifested by many patterns that are non-specific as the presence of vasogenic edema, features suggesting demyelinating, ischemic-like processes, or even brain atrophic changes[3,6-8]. The newly addressed functional MR techniques enable the assessment of metabolic and microstructural alterations and allow deeper evaluation of the brain at both pathophysiological and cellular levels. Magnetic resonance spectroscopy (MRS) enabled the detection of any metabolic abnormalities or changes, even when the brain appeared structurally normal on conventional MRI[10]. A newly developed promising technique; diffusion tensor imaging (DTI) can detect and evaluate the brain structural changes or abnormalities in many various diseases, and expressed through objective measurable values known as fractional anisotropy (FA), and axial diffusivity (AD), mean diffusivity (MD), radial diffusivity (RD)[11-17]. These previously mentioned advanced MR techniques can provide potentially unique data and new insight and give clearer data about the pathophysiology of HT-induced CNS changes. This study aims to investigate the role and utility of magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI) of the brain in the detection of any metabolic or microstructural alterations in patients with HT who have normal conventional brain MRI, in correlation to thyroid peroxidase antibodies (TPOAb) levels and disease duration.

Subjects/Materials and Methods

This study was approved by the local institutional ethics committee, and all study participants signed a written informed consent.

Patients

This current study is a case-control study that included 40 Hashimoto thyroiditis (HT) patients (29 females and 11 males), and another 20 healthy control subjects (13 females, and 7 males), over a period from June 2021 to June 2023. Patient's inclusion criteria are; a) Patients $\geq$ 18 years old with Hashimoto's thyroiditis diagnosed on a clinical basis, laboratory (high serum level of thyroid peroxidase autoantibodies; TPOAb), and classic thyroid sonographic features of HT[1], b) All patients showed normal thyroid hormones levels (euthyroid) and on regular treatment at the scheduled brain MRI examination time. While the control group included healthy volunteers with matched parameters concerning the age and gender of the study group. The exclusion criteria for both patient and control groups included: a) patients with chronic diseases (renal, cardiac, or diabetes mellitus), psychiatric disorders, and previous traumatic, vascular, neoplastic, or immunological CNS disorders. b) Contraindications to MRI and claustrophobia. All patients had Rt. Handed predominance at the time of the MRS and DTI examination. All participants underwent history taking, ultrasound examination of the thyroid gland, Laboratory tests, and brain MRI examination including conventional, MRS, and DTI.

History taking

Demographic information, complaints of decreased concentration, attention span time, memory, or sleep abnormalities.

Laboratory investigation
Thyroid hormonal profile (free T3, free T4, TSH, and TPOAb).

MRI examination of the brain
MRI scanner; Philips Medical Systems, Achieva 1.5 T A-series; was used for brain MRI scan performance. Interpretation of brain MRI studies was done by two radiologists who were blinded to patients' data either clinical, or laboratory, and of 15 years of experience in neurological MRI. Brain MRI imaging studies included conventional, MRS, and DTI studies of the brain, as in the following protocols:

1- Conventional MRI sequences
Examination protocol included axial T1W1, axial T2W1, axial FLAIR, sagittal T1W1, and coronal T1W1 according to the standard protocol.

2-Magnetic resonance spectroscopy (MRS)
A single-voxel spectroscopy method (PRESS sequence) was performed (TE; 30 ms, TR; 1400 ms, no. of acquisitions; 128, excitations number; 8). The voxel size was 2x2x2 cm and was placed in 2 regions; left-sided parietal white matter (PWM), and the cortex of the posterior cingulate gyrus (PCG). The spectrums were automatically generated to fit (4) known peaks (N-acetyl aspartate (NAA); 2.02 ppm, total creatine (Cr); 3.03 ppm, choline-containing compounds (Cho); 3.23 ppm, and myoinositol (mI); 3.56 ppm).

3- Diffusion tensor imaging (DTI)
The protocol involved a fat-suppressed single shot spinecho, echoplanar sequence with (TR/TE; 2,800/80 ms, matrix; 128 × 128, the field of view (FOV); 235 mm, and 5 mm slice thickness). Acquisition of 30 diffusion encoding directions at (b = 0, 1,000 s/mm^2) was done.

d) Post-processing of MRS and DTI images
Post-processing Consol (software version 2.0; Philips), and FSL post-processing programs were used for MRS and DTI raw-data post-processing, respectively. 1) Post-processing of MRS images enabled automatic calculation and assessment of metabolite different ratios (NAA/ Cr, Cho/Cr, and mI/Cr). 2) Post-processing workflow of DTI images involved the reconstruction of color-coded fractional anisotropy (FA), and mean diffusivity (MD) maps. Placing the regions of interest (ROIs) of (8 to 10 mm^2 size) was done with the aid of anatomic references to color-coded FA map, T1, and FLAIR images. FA, MD, axial diffusivity (AD), and radial diffusivity (RD) values were obtained automatically. According to known previous literature which site the most frequently affected locations in patients with encephalopathy due to HT [1, 4-8]; fifteen neuroanatomical areas were examined in both patient and control groups, as the following; anterior and posterior limbs of the internal capsule (PLIC), Cingulum gyrus, corpus callosum (genu and splenium), basal ganglia, thalamus, corona radiata, superior and inferior longitudinal fasciculus, cerebellar white matter, white matter of frontal and parietal lobes (Figure 1).

Statistical analysis

For analysis, IBM Corporation, Armonk, New York's SPSS, windows version 22.0 was utilized. Numbers and percentages are used to represent categorical data, while mean ± SD and Fisher's exact test are used to analyze numerical data. Normally distributed continuous variables are compared using one-way ANOVA or unpaired Student's t-test, with Bonferroni post hoc correction applied when necessary for between-group comparison. To compare DTI data, the Mann-Whitney U test was employed. The statistical significance level is defined as $P < 0.05$. TPOAb

levels and the length of illness were evaluated for their impact on MRS, and DTI metrics using Spearman correlation.

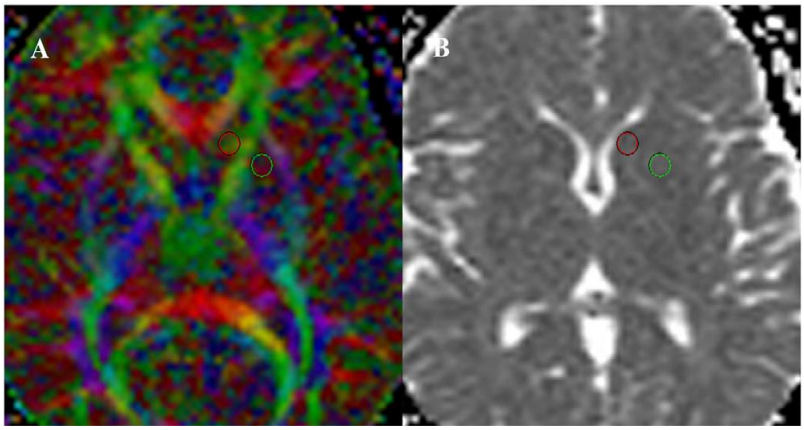

Figure 1. Region of interest (ROI) placement in a 37-year-old female patient with Hashimoto's thyroiditis, as the following: (A) for color-coded fractional anisotropy map, (B) mean diffusivity map measurements at the left caudate nucleus (red circle) and left putamen (green circle).

Results

This study involved 40 patients with HT (29 females and 11 males, with ages ranging from 19–57 years, and a mean age of 40.1 years), and 20 control participants (13 females, and 7 males, with an age mean of 41.3 years, and age ranged from 18-57 years). All patients were at the euthyroid status with normal serum fT3, fT4, and TSH levels. There are no statistical differences between patients and controls concerning demographic features such as gender, age, body mass index (BMI), and thyroid hormone levels. Meanwhile, as described in (Table 1), TPOAb levels were of higher values in patients with HT (471±342 IU/ml, P < 0.001). Patients with HT were of (3 to 16 years) disease duration, with the average duration of the disease being 30 months.

Table 1. Characteristics of the study groups

Variable	Control group (n=20)	HT group (n=40)	P value
Gender, females/males	13/7	29/11	0.612
Age, years	41.36±19.65	40.12±18.79	0.081
TBOAb (IU/ml)	7.2±1.65	471±342	<0.001
fT3 (pg/ml)	2.83±0.41	2.84±0.42	0.415
fT4 (ng/dl)	1.12±0.13	1.17±0.16	0.452
TSH (UIU/ml)	1.71±1.12	1.81±1.61	0.395

HT= Hashimoto's thyroiditis, TBOAB= thyroid peroxidase antibodies, fT3= free T3 hormone, fT4= free T4 hormone, TSH= thyroid stimulating hormone.
**P value < 0.05 considered significant*

Correlation between magnetic resonance spectroscopy (MRS) measurements and thyroid hormone levels: The study revealed statistically significant differences between patients and controls concerning MRS measurements; as follows, lower

NAA/Cr ratio in HT patients than in the control group (P=0.001), meanwhile, a higher mI/Cr ratio was observed in HT patients than in controls (P= 0.001). A significant positive moderate correlation is noted between the mI/Cr ratio in the PCG area and serum TPOAb level (r= 0.491, P= 0.014), as displayed in (Figure 2). While the NAA/Cr ratio in the PCG area displayed a moderate negative correlation with the serum TPOAb level (r= – 0.536, P= 0.001). However, the metabolic ratios in parietal white matter elicited no significant correlations to the TPOAB level (P= 0.59). The study evoked a moderate positive correlation between disease duration and the mI/Cr ratio measurement in both the PCG and PWM areas (r= 0.477, P= 0.021; r= 0.519, P= 0.013, respectively), as described in (Figure 3). While a moderate negative correlation between the disease duration and the NAA/Cr ratio measurement was observed in both PCG and PWM regions (r= -0.468, P= 0.002; r= – 0.492, P= 0.003; r= – 0.418, P= 0.01) respectively.

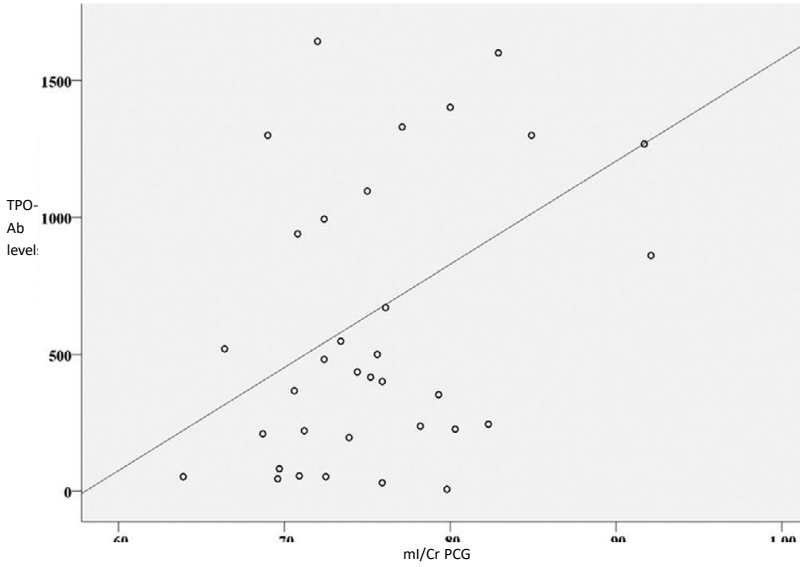

Figure 2. Scatter plots showed a moderate positive correlation is noted between the mI/Cr ratio in the posterior cingulate gyrus area (mI/Cr PCG) and TPOAb level (r = 0.491, p = 0.014).

Diffusion tensor imaging (DTI) measurements and thyroid hormones correlation:

The study evoked obvious differences among patients and controls regarding detected fractional anisotropy (FA) values, which were lower in patients than in controls in the cingulum, globus pallidus (GP); P value (= 0.001), and cerebellar white matter (CWM); P value (< 0.001). While the mean diffusivity (MD) values of CWM recorded higher values in the patient rather than in the controls (P= 0.003). The Radial diffusivity (RD) values at the cingulum and CWM were higher in HT patients versus controls (P< 0.001, and 0 .01 respectively). Also, the axial diffusivity (AD) values at the putamen, cingulum, GP, and posterior limb of the internal capsule (PLIC) areas were observed to be of lower values in patients versus the controls (P= 0.033, 0.023, 0.027, 0.031) respectively. As described in (Tables 2, and 3), all DTI measurement values data in different neuroanatomical regions were represented. This study demonstrated a moderate negative correlation between serum TPOAb levels and PLIC fractional anisotropy (r= –0.436, P= 0.028); (Figure 4). A moderate positive correlation be-

tween serum TPOAb levels and corona radiata mean diffusivity (r= 0.523, P= 0.021). While a moderate positive correlation was recorded between the mean duration of disease and splenium of the corpus callosum radial diffusivity (r= 0.547, P= 0.025). As regards the intra-observer bias; there was excellent intra-observer consistency for the analysis and measurements (0.982).

Table 2. Measurements of DTI parameters (FA and MD) in different neuroanatomical areas of both study groups

Anatomical area	Fractional anisotropy (FA)		P value	Mean diffusivity (MD) (x 10−3 mm^2/second)		P value
	Control (n=20)	HT (n=40)		Control (n=20)	HT (n=40)	
CWM	0.386±0.07	0.186±0.07	<0.001*	0.699±0.02	0.896±0.07	0.003*
Cingulum	0.698±0.02	0.475±0.01	0.001*	0.773±0.04	0.787±0.06	0.679
ALIC	0.571±0.02	0.575±0.01	0.841	0.776±0.03	0.764±0.04	0.872
PLIC	0.713±0.03	0.722±0.04	0.316	0.712±0.07	0.709±0.7	0.108
putamen	0.165±0.06	0.173±0.05	0.243	0.758±0.08	0.732±0.06	0.072
GP	0.284±0.06	0.201±0.03	0.001*	0.757±0.06	0.752±0.08	0.711
GCC	0.799±0.07	0.819±0.06	0.081	0.812±0.04	0.799±0.07	0.147
SCC	0.826±0.06	0.834±0.05	0.249	0.776±0.02	0.754±0.03	0.101
FWM	0.408±0.02	0.431±0.01	0.296	0.799+0.04	0.771±0.05	0.061
PWM	0.412±0.04	0.471±0.03	0.042	0.791±0.03	0.775±0.04	0.091
Thalamus	0.302±0.04	0.295±0.04	0.331	0.759±0.02	0.783±0.08	0.085
Corona radiata	0.496±0.03	0.424±0.01	0.196	0.759±0.02	0.768±0.03	0.279
ILF	0.597±0.05	0.511±0.05	0.223	0.817±0.08	0.851±0.07	0.327
SLF	0.533±0.01	0.504±0.02	0.683	0.761±0.01	0.764±0.01	0.902
Caudate nucleus	0.194±0.02	0.182±0.01	0.329	0.778±0.03	0.749±0.05	0.274

All the data represent mean ± standard deviation.
*n, number of subjects; CWM, cerebellar white matter; ALIC, anterior limbs of the internal capsule; PLIC, posterior limbs of internal capsule; GP, globus pallidus; GCC, genu of corpus callosum; SCC, splenium of corpus callosum; FWM, frontal white matter; PWM, parietal white matter; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus. *shows statistically significant results after multiple comparison corrections, P value < 0.05 considered significant.*

Discussion

Patients with Hashimoto's thyroiditis (HT) may exhibit nonspecific clinical features secondary to hypothyroidism and may rarely cause Hashimoto's encephalopathy (HE) [18]. No remarkable findings were found in conventional brain MRI in most cases or only non-specific findings as non-specific T2 hyperintense foci in subcortical, periventricular region, or deep white matter[18,19]. Our findings are consistent with a decreasing trend of NAA/Cr ratio in patients with HT and showed results comparable to those previously published studies[10,20,21]. All previous studies found a lower NAA/Cr ratio of the HT compared to healthy controls. In Bladowska et al. study[10], examined the metabolic changes detected in patients with HT patients with normal brain conventional MRI studies. They found lower NAA/Cr ratio in both posterior cingulate gyrus (PCG) and parietal white matter (PWM) regions with a positive correlation to free T3 hormone level. While a study by Su T. et al.[20] also

recorded decreased levels of NAA and mI. They studied the magnetic resonance spectroscopy (MRS) findings in a 52-year-old female patient with HT who developed features of Hashimoto's encephalopathy.

Table 3. Measurements of DTI parameters (AD and RD) in different neuroanatomical areas of both study groups.

Anatomical area	Axial diffusivity (AD) (x 10−3 mm²/second)		P value	Radial diffusivity (RD) (x 10−3 mm²/second)		P value
	Control (n=20)	HT (n=40)		Control (n=20)	HT (n=40)	
CWM	0.955±0.04	0.937±0.03	0.593	0.529±0.08	0.622±0.10	0.01*
Cingulum	1.475±0.15	1.212±0.17	0.023*	0.401±0.07	0.586±0.14	<0.001*
ALIC	1.349±0.11	1.347±0.11	0.788	0.484±0.04	0.482±0.05	0.916
PLIC	1.478±0.13	1.186±0.18	0.031*	0.351±0.04	0.359±0.04	0.611
putamen	0.925+0.05	0.811+0.03	0.033*	0.688±0.04	0.683±0.03	0.314
GP	0.989±0.06	0.824±0.04	0.027*	0.672±0.05	0.668±0.05	0.496
GCC	1.875±0.11	1.866±0.12	0.863	0.363±0.06	0.311±0.04	0.064
SCC	1.815±0.14	1.746±0.15	0.215	0.263±0.02	0.264±0.02	0.893
FWM	1.162±0.13	1.157±0.12	0.661	0.617±0.04	0.598±0.03	0.087
PWM	1.154±0.17	1.143±0.14	0.473	0.603±0.04	0.554±0.03	0.066
Thalamus	1.068±0.12	1.074±0.12	0.403	0.659±0.02	0.676±0.02	0.092
Corona radiata	1.132±0.16	1.157±0.15	0.884	0.512±0.08	0.541±0.10	0.521
ILF	1.343±0.16	1.410±0.14	0.877	0.541±0.03	0.575±0.01	0.192
SLF	1.238+0.12	1.241+0.12	0.551	0.509±0.07	0.504±|0.06	0.839
Caudate nucleus	0.912±0.08	0.891±0.09	0.149	0.701±0.03	0.698±0.03	0.585

All the data represent mean ± standard deviation.
*n, number of subjects; CWM, cerebellar white matter; ALIC, anterior limbs of the internal capsule; PLIC, posterior limbs of internal capsule; GP, globus pallidus; GCC, genu of corpus callosum; SCC, splenium of corpus callosum; FWM, frontal white matter; PWM, parietal white matter; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus. *shows statistically significant results after multiple comparison corrections, P value < 0.05 considered significant*

Meanwhile, the current study results also agreed with the following results: Marta W. et al[21], also found low NAA/Cr and high mI/Cr ratios in the PCG and PWM areas. Also, correlations were evoked between these ratios and disease duration, as in our study. Both NAA and mI are considered biomarkers for neuronal integrity and glial cell inflammation, respectively. With increased disease duration there is a greater decrease in NAA/CR ratio in HT patients which indicates a decrease in neuronal activity, also a much higher mI/Cr ratio which correlated to more glial cell inflammation and gliosis. These changes are responsible for more neuronal affection and dysfunction[21,22]. The observed metabolic changes either in our study or other studies by adding MRS to conventional brain MRI denote early cerebral metabolic alterations or changes. These changes were observed in PCG, a known area that is highly involved in cognitive function and has an important role in episodic memory, and spatial attention. So, MRS may be a sensitive imaging biomarker to early cognitive dysfunction in patients with HT [22], which allows early management, delays disease progression, and improves patients' life quality[15,16]. Thyroid hormones have an important effect on brain myelination[11,15,16]. Cerebral diffusion tensor imaging is an important developing imaging biomarker of the

brain that has been used to study various neurological and psychiatric disorders[19]. Several studies have been conducted to investigate microstructural changes in the nervous system by DTI. Low fractional anisotropy (FA) and axial diffusivity (AD) values were reportedly established. High mean diffusivity (MD) and radial diffusivity (RD) values were also observed in cases of hyperthyroidism, autoimmune dis., diabetes, neurodegenerative diseases, and demyelinating diseases[9,10, 22-25]. Contrary to previous studies[26-30]; in this study, all participating patients were euthyroid and had normal thyroid hormone levels to examine and highlight the autoimmune effects and rule out the effects of thyroid hormone abnormalities in HT patients.

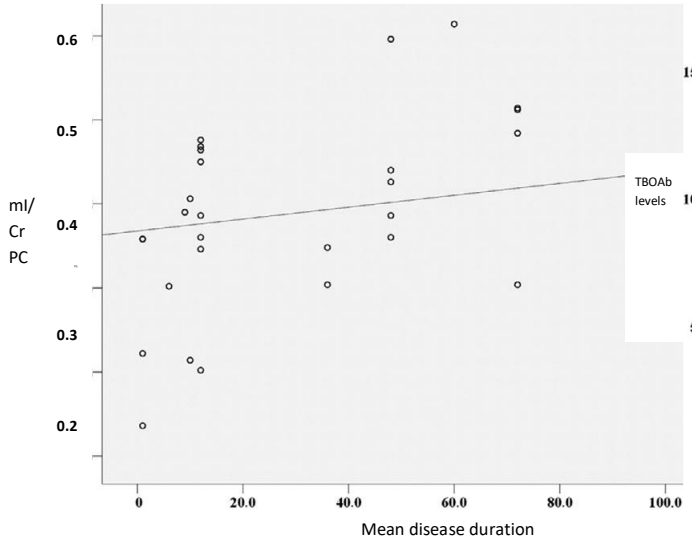

Figure 3. Scatter plots showed a moderate positive correlation between the mI/Cr ratio measurement in the posterior cingulate gyrus area (mI/Cr PCG), and the mean disease duration (r = 0.477, p = 0.021).

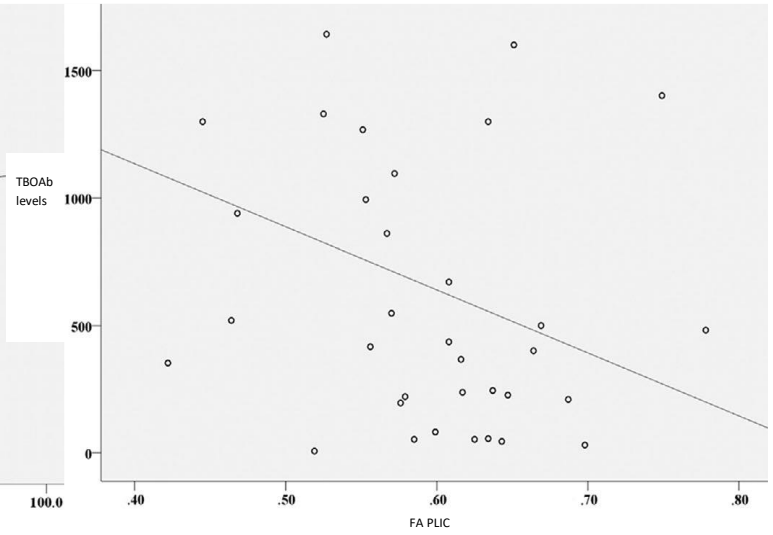

Figure 4. Scatter plots showed a moderate negative correlation between the fractional anisotropy (FA) values at the posterior limb of internal capsule (FA PLIC) and TPOAb levels (r = –0.436, P = 0.028).

This current study's observations are matched and consistent with those of Mehmet A. G. et al.[17] that FA values in globus pallidus (GP) and cerebellar white matter (CWM) patients were lower in HT patients compared to controls. The mean diffusivity (MD) and radial diffusivity (RD) in CWM were higher in patients compared to controls, meanwhile, lower axial diffusivity (AD) was recorded in basal ganglia in studied patients. These findings may indicate axonal injury, neuronal degeneration, and white matter fiber disorganization in HT patients. In agreement with Blodwaska et al[10] results, the current study revealed a correlation between DTI values, serum TPOAB levels, and duration of the disease. These findings may be related to the loss of integrity and/or demyelination of the white-matter tracts. In contrast to previously published studies[31,32], that found no association or relationship between elevated TPOAB levels and neurological symptoms was induced. Although the current study is one of the few studies concerned with the investigation of the utility of brain MRS and DTI in patients with HT, a few limitations of the study's small sample size, this study did not examine the correlation of brain MRS, DTI results to the cognitive dysfunction severity. So, more future prospective studies including larger sample sizes with detailed psychomotor and cognitive func-

tion assessment, and correlation to MRS and DTI values are needed to provide stronger results and improve the external validity of the obtained results.

Conclusions

In conclusion, Brain MRS and DTI in patients with HT revealed metabolic and microstructural changes in neurocognitive-related regions, and these findings will lay out new insights for understanding the concomitant neurocognitive deficits and disease management.

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