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Comparison of Brain Atrophy, Cognition and Optical Coherence Tomography Results Between Multiple Sclerosis Patients and Healthy Controls

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ABSTRACT

Introduction: Cognitive impairment is also an important cause of disability in MS in addition to motor, sensory, visual, and cerebellar affections. The aim of this study is to show the relation between the cognitive disability in MS with brain atrophy and retinal nerve fiber layer (RNFL).

Methods: Forty-three multiple sclerosis (MS) patients, and 15 healthy individuals as controls were included in the study. MS patients were divided into three groups as relapsing-remitting MS (RRMS), relapsing-remitting with optic neuritis (RRMS+ON), and secondary-progressive MS (SPMS). An experienced psychologist performed modified Wechsler Memory Scale Revised form (WMS-R), Lines Orientation test, Stroop Color Word Interference test (STROOP), Standard Raven Progressive Matrices (SRPM), Benton Facial Recognition Test, verbal fluency test, and Paced Auditory Serial Addition tests in all cases. Optic coherence tomographies (OCT) were done. Cranial subcortical volumes of all subjects were measured using 3-dimensonal T1A imagines obtained by the cranial subcortical 1.5 tesla MR device (fully automatic Freesurfer program). Brain parenchymal fractions were calculated by proportioning the obtained volume measurements to the total intracranial volume.

Results: Fifty-eight subjects (65.5% female, 34.5% male) were enrolled in the study. There were significant differences among the groups in terms of parenchymal thickness, volumes of third ventricle, and white matter. There was a significant correlation between the volumes of the deep gray matter, mesial temporal structures and lateral ventricular volumes, and the test results of the WMS-R. OCT scores of all MS patients, whether or not they experienced optic neuritis, had increased, being worse especially in the SPMS group. Correlation between RNFL and the brain parenchymal fractions of the patients were statistically significant.

Conclusion: Manual methods instead of automatic segmentation method are being more commonly used in the studies with brain atrophy and MS in our country. A significant correlation between OCT scores and brain atrophy is shown with our present study, and this is followed as a reflection of decrease in cognitive tests that provides valuable and reliable knowledge for the literature.

Key words: Multiple sclerosis, brain atrophy, cognition

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INTRODUCTION

MS is a chronic, inflammatory and demyelinating central nervous system disease which starts in early adulthood, progresses with recurrent neurological dysfunctions and its etiology has not been known yet (1–3). Besides the motor, sensory, visual and cerebellar responses, cognitive inefficiency is also one of the significant reasons of disability in MS. Cognitive dysfunctions are commonly observed in MS. Patients mostly complain about memory, attention and concentration disorders (4–6).

Cognitive disorder is observed in 40–60% of MS cases with different clinical types (7,8). This situation is a significant issue which effects daily activities, social life and productivity of the individuals independently from the physical disability caused by the disease (9). However, it is generally ruled out since the physical disability due to disease attracts the attention of the patient, patient's relatives and the physican more, and the classical scales used in standard evaluation (Expanded Disability Status Scale (EDSS), mental status test (MMST)) are insufficient in this area. Therefore, it is generally not adequately identified. Detailed neuropsychological evaluation performed in half of the subjects who do not have the mental disorder findings in routine neurological test reveals the presence of cognitive inefficiency. Cognitive dysfunctions are rarely observed in the early stages of MS especially as an initial symptom whereas it is more commonly observed in the later stages of the disease (10). Cognitive inefficiency becomes intense in memory, attention, learning, information processing speed, talking, and visual spatial ability. It has been found that the processing speed, visual learning, and memory are the cognitive functions being affected at most in MS (11).

Scientists believe that cognitive inefficiencies are associated with cortical disconnection related to demyelinating plaques formed in subcortical white matter. Plaques are most frequently located in frontal lob and

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lateral ventricular areas in which they influence the connections between subcortical tissues and cerebral cortex (12).

There is a close relationship between periventricular lesion load and cognitive dysfunction. Several measurements such as total brain atrophy, cortical atrophy, and lesion volume can be done by using volume measurements obtained with magnetic resonance imaging (MRI) device and 3-dimensonal T1A images (fully automatical Freesurfer program). Studies have shown that patients with higher number of lesions have more cognitive dysfunctions compared to the patients with lower number of lesions (13,14).

A strong relationship was detected between the third ventricle width and cognitive state. Gray substance and white matter atrophy are related to the performance of some special cognitive abilities (15). Left frontal atrophy is associated with verbal memory tests whereas right frontal atrophy is associated with visual memory and working memory (16). Central atrophy measurements (e.g. lesion load) was found more effective in showing the cerebral cognitive change in MS compared to conventional methods. Furthermore, brain atrophy at the early stage of the disease may be a sign of potential cognitive inefficiency which will occur within the next 5 years (17).

RNFL measurement with OCT is a novel imaging method which provides cross-sectional images of the retina anatomy. OCT may be an assisting analytical method as an easily applicable imaging technique with high patient compliance in determination of neurodegeneration that is clinically not evident, in monitoring and following the treatment (18). Average RNFL is 110–120 µm in young adults. In healthy individuals 0.017% loss is expected under normal conditions, and a decrease of 10–20 µm is only monitored during 60 years of age. In RNFL measurements with OCT, retina thickness was found less in MS patients compared to the control group. The correlation between the decrease in RNFL measurements and cognitive inefficiency was shown (19).

METHODS

The prospective study was performed in the Neurology Department of Uludağ University's Medical Faculty (U. U. Ethical Committee for Clinical Studies; Approval date: 28 May 2009 Decision no: 2009-10/6) in Multiple Sclerosis Polyclinic between September 2008–2009. Forty-three MS patients who consulted in Neurology Department, MS polyclinic and/or were under monitoring, diagnosed with MS according to McDonald diagnosis criteria and who accepted the study and signed the informed consent form, and 15 controls with normal ocular examination who were under monitoring in Headache Polyclinic, had their cranial MRIs done, did not have detected pathology were enrolled in the study. MS patients enrolled in the study were divided in three groups, namely RRMS, RRMS+ON and SPMS. Thyroid dysfunction and vitamin B12 level were studied in the subjects enrolled in the study, as these factors may effect the cognitive performance. Presence of depression was excluded with Hamilton depression scale. The fact that there were no ocular, additional neurological or severe systemic diseases in the subjects which may effect the RNFL scores was taken into consideration.

Age, gender and educational levels of the patient and control groups were determined as the main demographical characteristics in the evaluation. Duration of MS disease, presence of ON, EDSS scores, RNFL scores, cognitive evaluation tests, subcortical brain volume measurements were taken into evaluation as variables related to the disease.

Neuropsychological Evaluation

In our study, 2-hour tests were applied to the subjects by a psychologist (Table 1) and the related brain areas were examined (Table 2). Subjects were evaluated with Hamilton depression scale and subjects under depression were not enrolled in the study.

Table 1. Neuropsychological tests and the functions it tests

Test	Function Tested
Verbal memory process test	Verbal memory
Wechsler Memory Scale (WMS) VI. sub test and delayed recalling	Visual memory
WMS IV subtest A story, B story	Verbal memory and continuing the attention (Logical memory)
WMS V subtest	Attention
WMSIII	Mental control
Fluency tests	Executive functions, preservation and memory evaluation
Line Direction Determination Test	Measurement of visual-spatial perception and orientation functions
PASAT	Processing speed and working memory
Benton Face Recognition test	Visual Spatial Processes
Raven Standard Progressive Matrix Test (RSPM)	Measurement of regular accurate thinking, management of reasoning
Stroop	Response inhibition and category change (data processing speed)

Table 2. Neuropsychological tests and related brain areas

Test name	Related brain area	Cognitive property/process measured
Stroop test	Frontal lob	Focused attention, response inhibition, resistance against destroying effect, data processing speed
Wechsler memory scale	Temporal hippocampus, limbic system frontal lob	Attention, concentration, verbal memory, visual memory, immediate memory, delayed memory
Digit span learning	Temporal hippocampus, limbic system frontal lob	Learning, short-term memory
Raven	Right hemisphere, parietal lob, common brain areas	Visual spatial perception, category changeability, working memory, abstraction and scrutinizing, general ability

Morphometric Evaluation

Images in DICOM format obtained with high resolution MR imaging were transferred into a computer with Linux operating system FreeSurfer (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki) programme was used during morphometric analysis. Firstly, the sliding that arised during shooting due to patient movements was corrected in the images. Brightness variations in the images originated from the changes in B1 magnetic area were corrected. Afterwards, images were placed on the Talairach coordinate system. This transformation enabled pre-labelling operation by making the use of previously formed standard ready brain template possible, increased the success of segmentation, and decreased the errors originated from pathologies. Cranium was automatically erased, and the remaining part was used as brain mask during labelling and segmentation. Results of automatic labelling and segmentation

operations were evaluated in terms of success. Parts found unsuccessful were corrected by a neurologist by hand, and volume calculations were repeated. Volume values of more than 40 different brain regions obtained for each volunteer were divided to the own volume value of the individual, normalized, and the values were used in the statistical analysis in this state.

Statistical Methods

Kruskal-Wallis test or one-directional variance analysis were performed according to the distribution structure of the data when comparing more than 2 groups. In paired comparison of the groups, Kruskal-Wallis test was followed by Mann-Whitney U test, and one-directional variance test was followed by Benferroni multiple comparison test. Pearson chi-square and accurate chi-square test of Fisher, and the corrected chi-square test of Yates were used in the comparison of variables. Spearman correlation analysis was used in the examination of relationship between variables. Minimum and maximum values were given along with average value, standard deviation, and median as descriptive statistics ($p<0.05$ was accepted as statistically significant). SPSS 13.0 was used as the statistical programme.

RESULTS

38 (65.5%) females and 20 (34.5%) males (in total 58 subjects) were enrolled in this study, and followed for 1 year in a prospective way. There were no subjects leaving the study. Average age of the subjects was 35.4±7.8. No statistically significant difference was detected between groups in terms of age and gender. Patients were divided into three groups as primary education, secondary education, and higher education. It was observed that educational level increases as the progression of MS disease increases. A significant correlation was found between the progression of the disease, and educational level ($p<0.05$, $r=0.380$). Positive significant correlation was detected between EDSS scores, 3. ventricle, and lateral ventricle fractioned volume measurements ($p<0.05$, $r=0.382$). Statistically significant difference was detected between groups in terms of OCT scores ($p<0.001$).

When the eye with optic neuritis was compared to the eye without optic neuritis in patients with optic neuritis, significant difference was detected both in OCT scores, and right-left eye RNFL measurements (Table 3). No significant correlation was detected between RNFL and duration of the disease in MS patient group (RRMS, RRMS+ON, SPMS) ($p>0.05$), whereas a negative correlation was found between RNFL scores and EDSS ($p<0.05$, $r=-0.498$).

Table 3. Comparison of OCT scores and RNFL measurements of ON+patients

	TOTAL (n=23)	RRMS.ON+ (n=13)	SPMS (n=10)	p
OCT (median (min-max))	1.0 (0–3)	0.0 (0–2)	1.5 (0–3)	0.004
RNFL ON+ side	86.6±21.35	99.8±11.01	69.5±19.3	<0.0001
RNFL ON-side	88.13±16.2	96.7±10.66	76.9±15.5	0.002

SPMS: Secondary progressive multiple sclerosis, RRMS: Relapsing Remitting Multiple Sclerosis,
OCT: Optic coherence tomogprahy, RNFL: Retinal nerve fiber layer thickness

In verbal memory tests, statistically significant difference was detected among four groups in terms of immediate memory, learning point, reaching the criteria, highest learning, learning error point, self-recalling, identifying, total recalling, and long-term memory error point. The most significant difference was between control group and SPMS group (Table 4). In visual memory tests, statistically significant difference was detected between groups in terms of immediate memory, self-recalling, and total recalling ($p<0.05$). In logical memory tests, significant difference was detected in total immediate and delayed points among four groups ($p<0.05$). In the attention tests, statistically significant difference was detected in counting up and total points whereas no significant difference was found in counting down points among four groups ($p<0.05$, $p>0.05$). In fluency tests, statistically significant difference was detected in total scores among four groups ($p<0.05$).

In Stroop test, no statistically significant difference was detected in comparison of the extraction of score for telling the color of word from the score for colorful reading among four groups ($p>0.05$). In Benton face recognition test, statistically significant difference was detected between the control group and SPMS group whereas no significant difference was found between RRMS and RRMS+ON group ($p>0.05$). No statistical significance was detected in line direction results among four groups

Table 4. Evaluation of verbal memory process tests between control group and SPMS group

Group	SBST Immediate memory	SBST Learning point	SBST Reaching the criteria	SBST Highest learning	SBST Learning error point	SBST Identifying	SBST Total recalling
Control	7.26±1.86	121.33±16.28	5.4±3.06	14.6±0.91	1.06±1.70	13.53±1.80	1.33±1.39
SPMS	4.85±1.35	72.35±31.57	0.64±2.40	10.0±3.50	1.64±1.64	7.0±5.51	4.92±3.07
p	0.001	<0.0001	0.001	<0.0001	0.001	0.001	0.001

SBST: Verbal memory process test SPMS: Secondary progressive multiple sclerosis

Table 5. Evaluation of neuropsychological tests between control group and SPMS group

Group	VMT	LMT Immediate	LMT Delayed	Attention	Benton	Raven	Fluency
Control	12.93±1.70	33.66±5.03	32.93±5.43	10.0±2.03	46.86±3.22	40.0±13.40	9.46±1.55
SPMS	6.07±4.81	23.71±9.91	19.5±10.17	7.73±2.78	41.30±6.58	25.75±12.28	6.42±2.65
p	<0.0001	0.004	<0.0001	0.016	0.026	0.017	0.005

VMT: Visual Memory Test LMT: Logical Memory Test SPMS: Secondary progressive multiple sclerosis

(p>0.05). No statistically significant difference was detected in PASAT test among groups (p>0.05). In Raven test, there was a statistical significance among four groups in terms of true responses whereas no significant difference was detected in terms of response time. The most significant test scores were detected between control group and SPMS group (Table 5).

In subcortical brain volume measurements of patients performed with automatic segmentation method, statistically significant difference was detected among four groups in terms of cerebrospinal fluid (CSF), left nucleus accumbance, left lateral ventricle, left thalamus, left nucleus caudatus, left putamen, left pallidum volumes, and right lateral ventricle, right thalamus, right putamen, right pallidum, right hippocampus, right nucleus accumbance, 3. ventricle, and white matter hypo-intensed volumes (p<0.05) whereas no significant difference was detected in terms of right amigdala, right nucleus caudatus, left amigdala and left hippocampus volumes (p>0.05).

In the comparison among groups, no significant difference was detected between control and RRMS group in terms of CSF volume whereas statistically significant difference was detected between control group and RRMS+ON and SPMS, RRMS and SPMS groups (p>0.05, p<0.05).

In the comparison among groups, significant difference was detected between control group and RRMS, RRMS+ON, SPMS groups, and RRMS and SPMS groups (p<0.5), whereas no statistically significant difference was detected between RRMS and RRMS+ON, RRMS+ON and SPMS groups (p>0.05).

DISCUSSION AND CONCLUSION

MS has been historically known as a disease resembling a subcortical dementia syndrome, and affecting cerebral white matter in cognitive deficits. Recently, structural monitoring studies have emphasized the atrophy affecting the cortex as much as the deep gray matter. There are several different segmentation methods where manual or automatic techniques are used for brain volume evaluation. In their study, Flippi et al. manually segmented the cerebral hemisphere of 15 MS patients (RR or SP) by using whole brain technique, and compared the results with 15 healthy controls at the end of which they reported that MS patients have smaller whole brain volumes. (MS patients, 1488 ml; healthy control, 1572 ml) (20). More recently, several image analysis tools have been developed including but not limited to automatic and semi-automatic algorithms based on raw or normalized brain volume evaluations (21). All studies show that the volume is smaller in MS patients compared to control subjects at the same age regardless of the technique used in the evaluation of brain parenchymal volume (BPV) (22,23). Ge et al. studied the variety between groups, and found a difference between patients and control groups. However, this difference has been only seen in brain parenchymal fraction (BPF) (24). Being identified as the ratio of BPV to total intracranial volume, BPF has been used by several experts in the measurement of whole brain atrophy. Because BPF also accounts for the head size varieties in between individuals. These experts reported a BPF loss of 2.7–4.8% when they compared MS patients with controls. Chard et al. indicated that BPF decreased 3.3% when they compared 27 healthy subjects with 26 young MS patients (25). We also calculated the volumes we obtained by proportioning them to the total intracranial volumes, and by doing so we eliminated the errors which may be caused by the head size variability among individuals.

We found statistically significant difference in terms of left nucleus accumbens, left lateral ventricle, left thalamus, left caudal nucleus, left putamen, left pallidum volumes and right lateral ventricle, right thalamus, right putamen, right pallidum, right hippocampus, right nucleus accumbens, 3. ventricle and white matter hypo-intensed volumes. In their study performed with 71 MS, 17 clinically isolated syndrome and 38 health subjects, Ramasamy et al. used Freesurfer programme and detected decreased volumes in brain subcortical areas similar to that of in our study (26). Similarly, they detected decreased parenchymal volumes measured when the clinical view of MS disease worsened together with increased lateral ventricle volumes.

In our study, there was a significant difference between control group and SPMS group in terms of right hippocampus volumes. In their study including 3T MR with high resolution, Sicotte et al. compared RRMS and SPMS groups, and detected clear hippocampal atrophy in SPMS group (27). In their study, Ramasamy et al. did not detect any significant difference between control group and MS patient group in terms of hippocampal volume, and this result was explained with the different segmentation method they used. Yet there may be differences between the results of manual, automatic, and semi-automatic segmentation methods with different programmes (28).

The accuracy rate of the Freesurfer (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki) method which we used in our study for automatic segmentation is higher than that of the manual technique. The reliability of Freesurfer method was shown in literature, histological studies performed in old and pathological brains, and comparisons done with other analysis methods (29).

Although it is known that cognitive dysfunction is evident at the later stages of the disease, the studies performed so far emphasized it may arise in subjects at early stage where the first clinical findings arise, and even in the patients firstly diagnosed (30).

This situation is associated with tissue alterations arising during the early stage. It has been shown that decreased neocortical volume is directly associated with cognitive disorder (31). In our study, it was shown that especially verbal abilities, attention, and memory effects are present between control group and RRMS group. Achiron et al. studied cognitive changes in 67 subjects consulting for the first time who were diagnosed with MS, and detected influence in 53.7% of the subjects, and showed that the mostly seen changes were in verbal abilities and attention, subsequent data processing and memory influence (32).

In our study, we detected more evident defects between control group and SPMS group in terms of mainly immediate memory in verbal memory tests, learning point, reaching the criteria, highest learning, learning error point, self-recalling, identifying, total recalling, and long-term memory error points. Similarly, significant differences were detected between groups in visual, logical memory, attention, Raven, Benton, and Fluency tests. The most evident test performance decrease was detected between the control and SPMS groups.

Ruggieri et al. enrolled 50 RRMS patients and 50 healthy controls in their study where they researched cognitive loss in MS patients, and they detected significant difference in WMS, Benton, and Raven tests as we did in our study (33).

In the attention tests, statistically significant difference was detected in counting up and total points whereas no significant difference was found in counting down points among four groups. Although the success of MS patients in these tests vary, a slight influence was detected in the study performed by Rao et al. (34). It is considered that the variety of the results is caused by the homogeneity of the samples.

In our study no significant difference was detected among four groups in PASAT test results used in the determination of information processing

speed which is frequently present in studies, whereas lower scores were obtained compared to healthy subjects in the study performed by Forn et al. in 30 patients and 30 healthy controls by using PASAT test (35).

MS patients showed significant defects also in Stroop test measuring information processing speed and attention, which requires focusing on more than one stimulant. In another study, Locatelli et al. detected clear defects in Stroop and PASAT tests performed on 39 RRMS patients (36). However, in our study, Stroop test, no statistically significant difference was detected in comparison of the extraction of score for telling the color of word from the score for colorful reading among four groups. It was considered that this situation was caused by educational level which increases as the MS disease progression increased. There was a positively significant correlation between the disease progression, and educational level.

In our study, we found a significant difference between the affected eye and non-affected eye in terms of RNFL scores in the group with optic neuritis. We detected a significant difference of OCT scores in all patients diagnosed with MS compared to control patient group. RNFL scores of all patients diagnosed with MS were worse than that of healthy controls regardless of optic neuritis experience. In their study, Siger et al. enrolled 51 MS (20 ON+MS, 31 ON-MS) and 12 controls, and detected a clear decrease of RNFL scores in MS patient group in MS ON+ patients. Furthermore, no significant difference was detected between control group and ON-MS patient group like our study (37). Even the non-labelled eyes of the patients had abnormal values compared to healthy subjects. This finding shows that brain atrophy in MS is a reflection of atrophy causing thinning in RNFL independently from optic neuritis story of the patient.

In another study, Castello et al. showed that there was a RNFL loss of 10–40µm in 75% of MS patients during 3–6 months during the monitoring of MS patients with acute optic neuritis (38). OCT may be used as a non-invasive approach in monitoring the progress of the disease because of the neural elements carried by retinal structure.

Containing axone, glia, and no myelin, retina is an ideal structure which allows the examination of neurodegeneration, neuroprotection, and neurorestoration in the central nervous system. The fact that OCT enables the reconstruction of retinal anatomy with high resolution in a fast and reproducable way is an ideal situation to establish the disease process of MS in the right way.

In conclusion, a cognitive inefficiency was detected which develops in correlation with the brain atrophy since the early stage in MS patients, and is especially present in attention and memory processes. In our study, the importance of neurocognitive influence was remarked, and it was emphasized that cognitive inefficiency may be detected in MS patients when evaluated with detailed neuropsychological tests although there is no dysmnesia complaint.

Furthermore, the use of OCT which has been accepted in the monitoring of glaucoma and macular degeneration, in MS patients was emphasized, and a significant correlation was detected between RNFL and brain atrophy. In this respect, OCT will be helpful in understanding the tissue damage mechanisms. It can be also used in future for determining novel treatment strategies focused on the neuroprotection of novel central axonal and neuronal structures. Developments in OCT give rise to the thought that it may have a gradually increasing role in studying of axonal and neuronal degeneration processes in all neurological diseases, primarily MS. In conclusion, retinal imaging methods like OCT may be used for the follow up of disease progression in MS.

Ethics Committee Approval: Ethics committee approval for this study was taken from the Ethics Committee of Uludağ University Medical Faculty Hospital (28/05/2009-10/6).

Informed Consent: Written informed constent was obtained from the participants.

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