Neurology Asia 2021; 26(2) : 341 – 346

The relationship between cerebellar volume, clinical disability and cognitive changes in multiple sclerosis patients

[1]Onural OZTURK, [2]Seda OZTURK, [3]Sedat GUL, [2]Sena Destan BUNUL, [2]Husnu EFENDI, [4]Isa CAM

[1]Department of Radiology, Gediz Public Hospital; [2]Department of Neurology, Kocaeli University; [3]School of Medicine, Kocaeli University & [4]Department of Radiology, Kocaeli University, Kocaeli, Izmit, Turkey

Abstract

Background & Objective: Multiple Sclerosis (MS) is an inflammatory, demyelinating and degenerative disease of the central nervous system. To determine the extent of disability and loss of functions, we used the Expanded Disability Status Scale (EDSS), Timed 25 Foot Walk Test (T25-FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modalities test (SDMT) and the Montreal Cognitive Assessment Test (MOCA). In this study, we focused on the effects of cerebellar volume and the correlation between cerebellar atrophy and functional test results. *Methods:* We retrospectively recruited 58 MS patients and 30 healthy controls. Cranial magnetic resonance imaging (MRI) and functional tests were obtained from all subjects. Duration between clinical tests and MRI acquisition was no longer than two weeks. Volumetric MRI evaluation was performed with the volBrain automatic segmentation pipeline. Results were analyzed by t-test and Spearman correlation analysis to determine the relationship between variables and to compare the two groups. *Results:* Mean values for age (p=0.351) and distribution in gender (p=0.834) were similar for patients and controls. Mean disease duration in patients was 5.85±5.45 years. Mean values for cerebellar volume and normalized cerebellar volume were significantly reduced in patients compared to controls (p=0.036 and p=0.022, respectively). Cerebellar volumes were significantly correlated with the results of the SDMT, MOCA and timed T25-FW tests.
Conclusions: The results suggest functional disability as well as cognitive changes are associated with cerebellar volume in MS. Further studies may identify the extent of cerebellar volume changes as a predictor of disease progression.

Keywords: Multiple sclerosis, cerebellum, cognition

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory, demyelinating and degenerative disease of the central nervous system. It is the most common cause of disability in young adults.[1] The disease process usually starts between the ages 20-40 years and it is more common among people of European descent.[2] Initially, MS was thought to be a white matter disease that resulted in the loss of the myelin sheath of nerves. However, recent evidence suggests that it affects both white and gray matter.[3]

The clinical course of the disease is unpredictable with symptoms and prognosis varying greatly. Four disease subtypes have been defined in order to classify the clinical courses. These subtypes are relapsing remitting multiple sclerosis (RRMS), primary progressive multiple sclerosis (PPMS), secondary progressive multiple sclerosis (SPMS) and progressive relapsing multiple sclerosis (PRMS). The two most common forms are RRMS and PPMS, seen in 80% and 15% of patients, respectively.[1] The clinical presentation of RRMS is characterized by attacks, in which patients have neurologic deficits, followed by periods of remission. During periods of remission progression of disability is not seen.[4] PPMS presents with insidious, progressive myelopathy that leads to functional impairment and disability.[5]

MS affects all aspects of patient functionality. To measure the extent of disability, loss of function and disease progression, standardized

Address correspondence to: Onural OZTURK, Department of Radiology, Gediz Public Hospital, Turkey. Email: onuralozturk@gmail.com
Date of Submission: 6 January 2021; Date of Acceptance: 15 March 2021

tests are used. The expanded disability status scale (EDSS) is the most well-known and most comprehensive clinical evaluation method to show current clinical disability, as well as cognitive and psychological changes.[6] Other commonly used tests include the Timed 25-Foot Walk (T25-FW), the Nine-Hole Peg Test (9-HPT), the Symbol Digit Modalities Test (SDMT) and the Montreal Cognitive Assessment Test (MOCA).[7,8]

Recently, in conjunction with improving imaging techniques, which are now capable of accurately measuring brain structure volumes, the changes in brain volumes in MS and correlation of functionality and disease progression have attracted interest from MS researchers. Several studies have shown diffuse gray matter damage in MS patients involving cortical and subcortical structures.[9] In addition, atrophic changes in other infratentorial structures, such as the cerebellum and brainstem have been demonstrated, but are not yet well characterized.

The role of the cerebellum in cognition has been recognized since late 1990's. Cerebellar dysfunction may cause impairments in executive functions. Prosperini *et al*. demonstrated a correlation between cerebellar lesion severity and balance impairment in MS patients.[10] In addition to lesions, atrophy plays and important role in clinical outcomes. A progressive volume loss in the cerebellum in MS patients is well known and is associated with the progressing disability. However, recently it has become possible, through advances in imaging technology, to accurately assess cerebellar volumes and this is now attracting attention in MS research. Very few cross-sectional studies have reported the loss of cerebellar volume in MS patients compared to healthy controls.[11] These studies reported different results in terms of white matter and gray matter losses and these volumetric changes were not correlated with the objective tests commonly used in assessment of MS patient. In this study, we aimed to investigate the correlation between cerebellar volume changes, cognitive changes, and the level of disability in the patients.

METHODS

Ethical approval for this retrospective study was granted by the Research Ethics Committee of our institution. Informed consent was obtained from the subjects in both the patient and control groups.

Patient recruitment

The patient group consisted of retrospectively recruited patients diagnosed with MS by the 2017 McDonald criteria and were aged between 18-60 years. The recruitment period was from October 2019 to June 2020 and the patients, with an existing diagnosis of MS, attended radiology department for an MRI assessment and were invited to participate in the study. Exclusion criteria were: suffering another chronic central nervous system disease other than MS; having a central nervous system neoplasm; having an inadequate MR imaging series; or being pregnant. During the recruitment period, 61 MS patients underwent 3T-MRI. Of these 61, three were excluded due to motion artifacts during MRI. Thus, 58 patients were included to the patient group.

In the patient group, three were illiterate and unable to perform the MOCA and SDMT tests while one other patient had total loss of motor power in all limbs and therefore only the EDSS test was performed in these four. In the remaining 54 patients, all tests were performed. Controls were recruited from patients undergoing cranial MRI for different reasons and had no intracranial abnormality. Thirty of these subjects were randomly selected in the recruitment period and agreed to participate in the study as controls.

Clinical tests and clinical evaluation:

SDMT, MOCA, T25-FW, 9-HPT were applied to all capable patients and the healthy controls by either an MS specialist nurse or neurology specialists. The EDSS was applied to all patients by experienced neurology specialists (with at least "C" grade EDSS certificate). The time between clinical tests and MRI acquisition was no longer than two weeks in any subject.

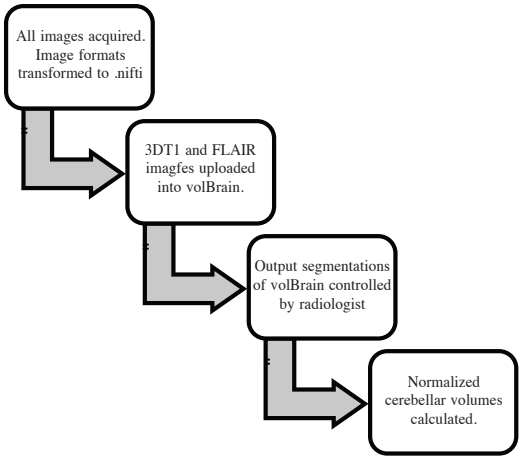
MRI acquisition and quantitative volume measurement

All patients and controls underwent cranial MR imaging using 3.0 T scanner (Achieva Intera: Philips Medical Systems, Eindhoven, The Netherlands) with 8 channel head coil. The MRI protocol for volumetric assessment included; axial 3DT1 Turbo field eco sequence: TR=11 msec, TE=5 msec, Slice thickness=1 mm, Slice gap=0 mm, Fluid Attenuated Inversion Recovery (FLAIR): TR=11000 msec, TE=140 msec, Slice thickness=5 mm, Slice gap=0.5 mm, matrix size=512x512.

The image formats transformed from *DICOM (Digital images and communication in medicine)*

*to .nifti extension via MRIcron (*www.nitrc.org) open source software. Upon transformation, 3DT1 turbo field eco image series was uploaded into volBrain (https://www.volbrain.upv.es/) automatic image analysis pipeline.[12] This open source program performs preprocessing operations, such as de-noising and inhomogeneity corrections. After these, further steps were: Intracranial Cavity Extraction, tissue classification, hemisphere segmentation and subcortical structure segmentation.[13] Processed images were checked by an experienced radiologist with more than six years interpreting Cranial MRI imaging. In order to normalize the effect of varying intracranial cavity size, cerebellar volume was divided by the intracranial cavity volume and converted into percentage values, which can be expressed by following equation:

$$\text{Normalized Cerebellar volume (\%)} = \frac{\text{Cerebellar white + gray matter volume (cc)}}{\text{Inracranial cavity (cc)}}$$



Statistical analysis

Statistical analysis was performed using SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA). Normality of distribution was investigated via Kolmogorov-Smirnov and Shapiro-Wilk tests. The mean values of the numerical variables between two groups was evaluated with T-test for normally distributed variables and with Mann-Whitney U test for non-parametric variables. The relationship between categorical variables was analyzed with Chi-Square test. Spearman correlation analyses were performed to investigate the relationship between variables. For two tailed hypothesis a $p<0.05$ was assumed to indicate statistical significance.

RESULTS

The patient group consisted of 58 subjects (44 females, 75.9%), and control group consisted of 30 subjects (24 females, 80%). The mean±SD age of the patients was 37.17±10.25 years and that of control group was 35.37±7.53 years. Mean values for age (p=0.351) and distribution in gender (p=0.834) were similar for patients and controls. Mean disease duration in patient group was 5.85±5.45 years.

Mean±SD value of cerebellar volume for patients was 118.19±19.89 cm^3 and normalized cerebellar volume was 9.23±0.87%. The same values for controls were 126.90±14.33 cm^3 and 9.63±0.50%, respectively. Comparison of patients and controls showed a significant difference for both cerebellar volume (p=0.036) and normalized cerebellar volume (p=0.022).

In the patient group correlation between cerebellar volumes and normalized cerebellar volume and the results of the clinical tests and evaluations was investigated with Spearman correlation analysis (see Table 1). Cerebellar volume and normalized cerebellar volume showed significant correlation with SDMT, MOCA, T25-FW and EDSS. On the other hand, EDSS showed significant correlation with higher coefficients with almost all tests performed.

Although this study aimed to investigate cerebellar volume and the effect on measures of clinical change, for completeness all the following parameters were investigated by correlation analysis: total brain volume, total gray matter volume and total white matter volume. Total white matter volume showed significant negative correlation with SDMT total time (ϱ -0.278, p=0.042) and disease duration (ϱ -0.401, p=0.002) and positive correlation with MOCA (ϱ 0.380, p=0.004). Total gray matter volume showed significant negative correlation with T25-FW (ϱ -0.327, p=0.013) and disease duration (ϱ -0.274, p=0.037). Total brain volume correlated significantly and negatively with SDMT total time (ϱ -0.308, p=0.023), disease duration (ϱ -0.361, p=0.005) and T25-FW (ϱ -0.346, p=0.008), and positively with MOCA (ϱ 0.302, p=0.025). No other significant correlations were found with other clinical or evaluation results and total white matter, total gray matter and total brain volumes.

DISCUSSION

MS is the second most common reason for disability in young adults. The role of conventional MRI and advanced MRI techniques has expanded

Table 1: Correlation coefficients and "p" values of EDSS and normalized cerebellar volume with other variables in patient group

	EDSS	Normalized Cerebellar volume
EDSS	-	p: 0.010 Correlation Coefficient: -0.275
Normalized Cerebellar Volume	p: 0.010 Correlation Coefficient: -0.275	-
Age	p:<0.001 Correlation coeficcient: 0.512	p: 0.236 Correlation Coefficient: -0.125
Nine hole peg test dominant hand	p:0.008 Correlation coeficcient: 0.348	p: 0.746 Correlation Coefficient: -0.35
Nine hole peg test non dominant hand	p: 0.008 Correlation Coefficient: 0.348	p: 0.239 Correlation Coefficient: -0.127
DSMT total time	p: 0.008 Correlation coefficient: 0.356	p: 0.003 Correlation Coefficient: -0.317
DSMT total correct answers	p: 0.003 Correlation coefficient: -0.401	p: 0.069 Correlation Coefficient: 0.199
DSMT correct answers in 90 sec	p: 0.006 Correlation Coefficient: -0.367	p: 0.015 Correlation Coefficient: 0.265
Montreal cognitive assesment test	p: 0.054 Correlation coeficcient: -0.261	p: 0.047 Correlation Coefficient: 0.216
Time 25 feet walk test	p:0.020 Correlation coeficcient: 0.307	p: 0.028 Correlation Coefficient: -0.234
Disease Duration	p: 0.025 Correlation coeeficient: 0.294	p: 0.895 Correlation coefficient: -0.018

over time. This includes the ability to perform volumetric studies which have attracted much attention in MS research recently. Reasons for the interest in volumetric studies have included the search for new predictors of the disease process, as well as to investigate space-based progression of MS. Furthermore, novel studies using high field power MR devices such as 7T or higher have revealed MS lesions in cortical gray matter which are not evident when using 3T or lower field power MRI devices in MS patients, suggesting that the disease process and inflammation also damages grey matter and related structures.[14] The cerebellum and its infrastructure have not been well investigated in MS and it was an aim of this study to expand and add to the scarce evidence of the changes in the cerebellum in MS patients.

Our results showed consistency with previous studies. Weier *et al*. reported significantly reduced total cerebellar volume in patients with RRMS compared to healthy controls. In this study, mean disease duration was 8 years (range: 1-17 years).[15] Anderson *et al*. showed that cerebellar cortex atrophy was seen in MS patients and the extent of atrophy may be used as a marker for cerebellar dysfunction.[9] These authors also reported greater cerebellar atrophy in an SPMS group compared to an RRMS group, although both groups had very similar disease duration. This finding prompted the authors to suggest cerebellar atrophy as a marker of disease progression. A further finding in this study was that gray matter atrophy was much more significant in SPMS patients and may be clinically more relevant to disability compared to white matter atrophy.[9] In our correlation analysis, cerebellar volume and normalized cerebellar volume was found to be significantly correlated with measures of patient function including EDSS, SDMT, MOCA and T25-FW.

In a later study, Weier *et al*. identified a correlation between decreased total cerebellar volume and the degree of cerebellar disability.[16] Patients with cerebellar signs performed significantly worse in the SDMT and Paced Auditory Serial Addition Test, which may suggest a relationship between cerebellar dysfunction and cognitive dysfunction.

In our study, no correlation was found between cerebellar volumes and the 9-HPT. In some previous studies similar findings have been

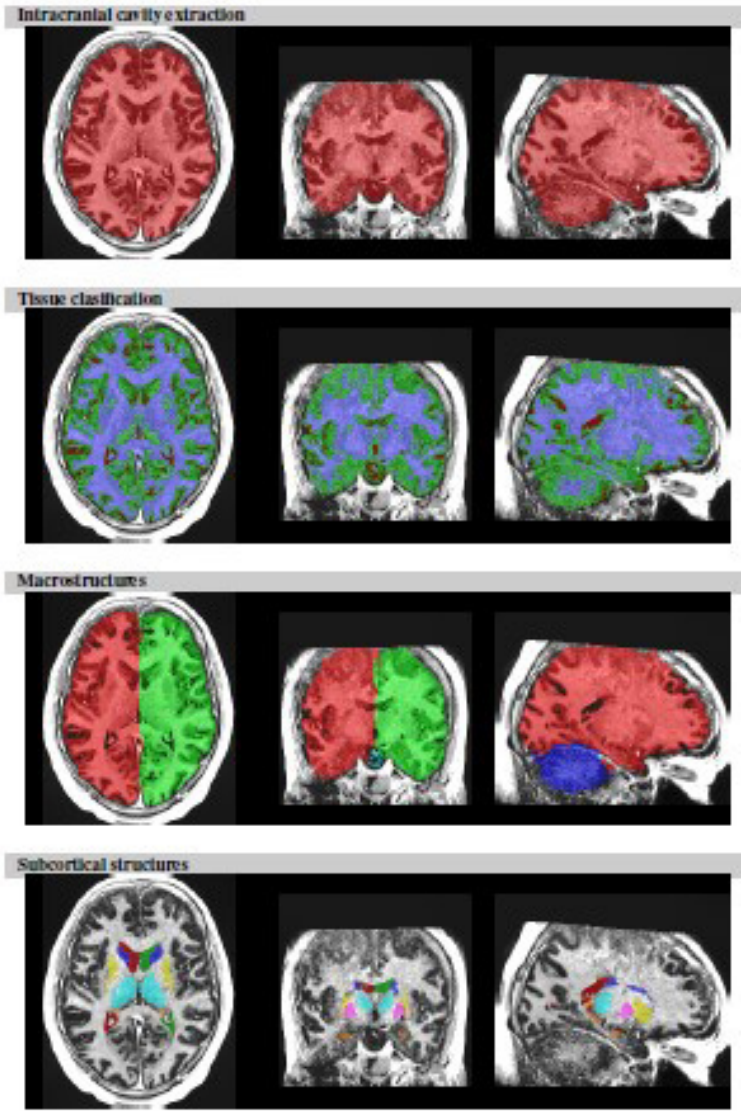


Figure 1: Post-processing and segmentation samples of volBrain automatic segmentation pipeline.

reported and no correlation was found between 9-HPT and cerebellar gray matter volume.[17] Cocozza *et al*.[18] reported in their study that 9-HPT performance was influenced by cerebellar metrics, mainly cerebellar lesion load, rather than atrophy. This may explain the lack of correlation with cerebellar volumes. However, Cocozza *et al* also failed to identify any correlation between cerebellar atrophy, EDSS results and functional status.

Cerebellar volume was more closely correlated with SDMT values than total brain volume, total white matter volume and total gray matter volume. However, total white matter and total brain volumes showed better correlation with MOCA results. Given this, we believe that cerebellar volume is not superior as a marker of likely cognitive assessment compared to total white matter and total brain volumes.

Disease duration showed no correlation with cerebellar volume despite patients having significantly smaller mean cerebellar volume than controls. This suggests that cerebellar atrophy is a component of disease but as it is not correlated with duration, may vary from patient to patient, or perhaps from subtype to subtype of MS. Cerebellar atrophy did correlate with the results of both the EDSS assessment and clinical findings. Total white matter, total gray matter and total brain volumes were negatively correlated with disease duration. Therefore, although extensive volume loss is expected over the long-term course of MS

specific cerebellar atrophy may not always play a part in this process.

The major limitations of this study were that cerebellum volume was not quantified with a lobule-based approach. In addition, patients were not followed up after volumetric assessment so that it was not possible to establish any relationship between study findings and prognosis of disease progression. Further shortcomings include a lack of data on the location of acute attacks, number of attacks, baseline EDSS values, and educational status of subjects, and thus may be confounders. Future studies in this field should take account of educational status. In addition, future studies should investigate the relationship between acute attack number and location and substructural volumetric measures and clinical test results.

In conclusion, this study has shown that cerebellum volume may be related with clinical disability as well as cognitive changes in MS. MS patients show mild to moderate cerebellar volume loss compared to healthy controls. Substructural changes, including changes in white and gray matter volumes, were correlated with performance test results in our cohort of MS patients. Further studies will illuminate the role of cerebellar volume as disease process predictor.

ACKNOWLEDGEMENTS

The authors are grateful to Mr Jeremy Jones of the Academic Writing Department of Kocaeli University, Izmit, Turkey, for his assistance in editing the English used and for his help and advice concerning the contents of this article.

DISCLOSURE

Financial support: None

Conflict of interest: None

REFERENCES

1. Tornes L, Conway B, Sheremata W. Multiple Sclerosis and the *Cerebellum Neurol Clin* 2014;32:957-77.
2. Hellwig K. Pregnancy in multiple sclerosis. *Eur Neurol* 2014;72 Suppl 1:39-42.
3. Calabrese M, Mattisi I, Rinaldi F, *et al*. Magnetic resonance evidence of cerebellar cortical pathology in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2010;81(4):401-5.
4. Kamińska J, Koper OM, Piechal K, Kemona H. Multiple sclerosis - etiology and diagnostic potential. *Postepy Hig Med Dosw* 2017;71:551-63.
5. Miller DH, Leary SM Primary-progressive multiple sclerosis. *Lancet Neurol* 2007;6:903-12.
6. Kurtzke JF. On the origin of EDSS. *Mult Scler Relat Disord* 2015;4:95-103.
7. Demir S. Multiple sclerosis functional composite. *Noro Psikiyatr Ars* 2018;55:S66–S68.
8. Kalb R, Beier R, Benedict RH, *et al*. Recommendations for cognitive screening and management in multiple sclerosis care. *Mult Scler* 2018;24:1665-80.
9. Anderson VM, Fisniku LK, Thompson AJ, Miller DH. MRI measures show significant cerebellar gray matter volume loss in multiple sclerosis and are associated with cerebellar dysfunction. *Mult Scler* 2009;(7):811-7.
10. Prosperini L, Kouleridou A, Petsas N, *et al*. The relationship between infratentorial lesions, balance deficit and accidental falls in multiple sclerosis. *J Neurol Sci* 2011;304:55-60.
11. Cocozza S, Pontillo G, Russo C, *et al*. Cerebellum and cognition in progressive MS patients: functional changes beyond atrophy? *J Neurol* 2018;265(10):2260-6.
12. Manjón JV, Coupé P. volBrain: An Online MRI brain volumetry system. *Front Neuroinform* 2016;10:30.
13. Zidan M, Boba J, Bjelan M, *et al*. Thalamic volume loss as an early sign of amnestic mild cognitive impairment. *J Clin Neurosci* 2019;68:168-73.
14. Kollia K, Maderwald S, Putzki N, *et al*. First clinical study on ultra-high-field MR imaging in patients with multiple sclerosis: comparison of 1.5T and 7T. AJNR *Am J Neuroradiol* 2009;30:699-702.
15. Weier K, Beck A, Magon S, *et al*. Evaluation of a new approach for semi-automatic segmentation of the cerebellum in patients with multiple sclerosis. *J Neurol* 2012;259(12):2673-80.
16. Weier K, Penner IK, Magon S, *et al*. Cerebellar Abnormalities Contribute to Disability Including Cognitive Impairment in Multiple Sclerosis. *PloS One* 2014;22;9(1):e86916.
17. Anderson VM, Wheeler-Kingshott CAM, Abdel-Aziz K, *et al*. A comprehensive assessment of cerebellar damage in multiple sclerosis using diffusion tractography and volumetric analysis. *Mult Scler J* 2011;17:1079-87.
18. Cocozza S, Petracca M, Mormina E, *et al*. Cerebellar lobule atrophy and disability in progressive MS. J *Neurol Neurosurg Psychiatry* 2017;47:1065-72.