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Cerebellum and brain stem volume loss in relapsing remission multiple sclerosis by MRI volumetry: relation to neurological disability score and number of relapses

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Abstract

Background: MRI is the method of choice in the diagnosis of MS as well as in monitoring the disease activity. MRI volumetry is used to assess whole or regional brain volume loss which reflects neurodegenerative aspect of the disease and plays an important role in all stages of disease. The aim of this work is to study MRI volumetry in the evaluation of cerebellum and brain stem volume loss in RRMS patients and its correlation with neurological disability score and number of relapses.

Results: Volumes of whole brainstem, medulla, and pons showed a significant decrease in RRMS cases compared to controls ($p < 0.05$). Brainstem volume had a mean volume of 22.17 and 25.09 cm^3 in cases and controls, respectively. However, midbrain volume showed no significant difference between cases and controls ($p = 0.134$). Volume of left cerebellar cortex showed a significant decrease in RRMS cases compared to controls ($p < 0.001$). It had mean volumes of 81.64 and 92.14 ml in cases and controls, respectively, at left cerebellar hemisphere, while right cerebellar hemisphere cortex volumes were 80.37 and 91.97 ml in cases and controls, respectively. Cerebellar white matter showed no significant volume decrease in cases and controls.

Conclusion: Volumetric MR imaging is an important tool for quantifying the MS disease, assesses MS activity, progression, and tissue loss. The degree and the pattern of atrophy on MRI images correlate significantly with the neurological disability score and number of relapses.

Keywords: MRI volumetry in RRMS, Brain stem volume loss in MS, Cerebellar volume loss in MS

Background

Multiple sclerosis (MS) is a central nervous system (CNS) chronic demyelinating, inflammatory disease with axonal loss. The development of lesions throughout the CNS is its distinguishing criteria. MS characterized by progressive CNS atrophy and is thought to be a better correlated with permanent disability than T2 lesion load [1].

It was believed that MS associated with loss of white matter (WM) volume, but recent studies have confirmed greater grey matter (GM) volume loss. Moreover, patients who converted into clinically definite MS over a period of 3 years develop significant brain volume loss, thus confirming early brain atrophy can present in some patients [2, 3].

The positive correlation between progression of MS and brain atrophy is widely accepted. Magnetic resonance imaging (MRI) studies of MS patients clarify that brain atrophy related to demyelination and axonal loss. Demyelination is potentially reversible process whereas axonal loss is not [4, 5].

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While there have been many studies focused on brain and spinal cord volume loss, relatively little researches have focused on volume loss of the brain stem and cerebellum in MS. The brain stem is a common site for MS affection which can cause vertigo, eye movement disorders, urinary problems, tremors, facial pain, hemiplegia, paralysis, and hearing problems. Many of these manifestations may develop early in MS [6].

The cerebellum is functionally and anatomically a fascinating but complex structure. The cerebellum has the highest growth rate of all brain structures during the late fetal and early postnatal life, reaching its adult cell count only by the age of 2 years. It is segregated in parallel cortico-nuclear sub-circuits that are integrated in various sensory-motor and cognitive-behavioral networks. Therefore, MS-related tissue damage of the cerebellum affects a magnitude of brain functions and significantly contributes to the development of disability [7, 8].

Brain volume measurements are correlated with the clinical status of patients and are important predictive feature of their clinical evolution. Progressive loss of regional or whole brain volume can be detected in vivo by MR imaging, mainly with the use of quantitative measures acquired by automated techniques [9].

MR imaging has become the modality of choice in evaluation of MS and is used to help the diagnosis and track the natural course of the disease. The ability to detect and characterize the disease burden, including occult microscopic disease invisible when using conventional MR techniques, has largely improved with the advent of newer quantitative MR techniques including volumetric MR imaging, diffusion tensor imaging (DTI), magnetization transfer imaging (MTI), and proton MR (1H-MR) spectroscopy. Today, MR imaging is the most important paraclinical tool for MS, and MR imaging-derived measures have been established as standard outcome markers to monitor the treatment response in various MS clinical trials [10].

There are various software programs to calculate volumetric changes and assess extension of atrophic changes in the affected regions that happen during a certain disease. One of these programs is 3D Slicer software which is a free open-source software application for medical image computing used to assess volumetric changes that occur in the brain stem and cerebellum in MS [11].

The aim of this work is to study MRI volumetry in the evaluation of cerebellum and brain stem volume loss in RRMS patients and its correlation with neurological disability score and number of relapses.

Methods

Patients population

This prospective study included 60 subjects (30 case groups, 30 control groups). Thirty patients (case group/group I) diagnosed with RRMS by clinical examinations and conventional MRI according to modified McDonald's criteria referred to diagnostic radiology department from the neurology department throughout period extending from December 2017 to March 2020. Thirty healthy subjects (control group/group II) with age and sex distribution similar to case group were selected as control group, with no medical or neurological disorders. Patients with cardiac pacemaker, clipped aneurysm or cochlear implant, or who refuse examination were excluded from study.

Approval of Research Ethics Committee (REC) and informed written consent were obtained from all participants in the study after full explanation of the benefits and risks of the procedure. Privacy and confidentiality of all patient data were guaranteed. All data provision were monitored and used for scientific purpose only.

All patients were subjected to the following

Full neurological examination

Magnetic resonance imaging (MRI) Magnetic resonance imaging was done for all patients using a 1.5 Tesla MRI system (GE sigma explorer).

a) MRI protocol

Sagittal 3D T1-weighted spoiled gradient (SPGR) utilizing the following parameters in Table 1.

Table 1 Parameters of volumetric MRI protocol

Imaging parameters	3D T1W SPGR
Plane	Sagittal
Mode	3D
Pulse sequence	SPGR
Prep. time	500 ms
TE	Minimum full
TR	7.2 ms
FOV	256 × 256 mm
Phase FOV	1.0
Frequency	16 kHz
Slice thickness	1.2 mm
Number of slices	160
Slice spacing	0
Flip angle	10°
Matrix	192 × 192
Freq DIR	S/I
NEX	1.0
Shim	Auto
Phased array uniformity enhancement (PURE)	On
Surface coil intensity correction (SCIC)	Off

b) Image analysis

Volumetric analysis has been done by 3D Slicer software package version 4.6 using semi-automated technique to calculate the volumes of cerebellar gray matter, cerebellar white matter, midbrain, pons, medulla oblongata, and whole brain stem. 3D Slicer software is an open source medical image computing platform for biomedical research and freely downloadable. Semi-automatic slice-by-slice segmentations of every data set have been performed. As hardware platform, we used a computer with Intel Core i7-750 CPU, 4 × 2.66 GHz, 8 GB RAM, with Windows 10 Professional × 64.

c) Image interpretation

Interpretation of MR images and volumetric analysis were done by two experienced radiologists with at least 5 years of experience in neuroradiology.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. Comparison of MR volumetric findings with normal values was done using one sample *t* test. Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

Results

Case group (group I) included 30 patents with RRMS (18 female & 12 male), their ages ranged from 24 to 38 years with a mean age of 30.93 ± 3.67 years. Control group (group II) included 30 healthy subjects (19 female and 11 male), their ages ranged from 25 to 38 years with a mean age of 31.13 ± 3.62 years. Most of the subjects included in the study were females (60% in the cases group and 63.3% in the control group). Different body measurements were nearly the same in both groups including height (mean height 178.16 ± 7.12 in case group\168.47 ± 8.26 in control group) and body weight (mean body weight 85.98 ± 10.96 in case group\84.96 ± 14.46 in control group), the above findings were listed in Table 2.

Pyramidal dysfunction was detected in 25 cases, sensory dysfunction (19 cases), cerebral dysfunction (11 cases), cerebellar dysfunction (18 cases), bowel and bladder dysfunction (16 cases), visual problems (22 cases), and mental problems (2 cases). More than one complains detected in the same patient. The disease duration ranged between 1 and 13 years with a mean disease duration was 6.78 ± 3.17 years. The EDSS score ranged from 0.5 to 5 with a mean of 2. The number of relapses was ranges between 1 and 7 with a mean of 3. These findings were listed in Table 3.

Table 2 Age and sex distribution in the studied subjects (*n* = 60)

Age and sex distribution in the studied control group (*n* = 30)						
Age in years	**Sex**				**Total**	
	Male		**Female**			
	No.	**%**	**No.**	**%**	**No.**	**%**
25–> 30	4	13.33	6	20	10	33.33
30–> 35	4	13.33	10	33.33	14	46.66
35–≥ 40	3	10	3	10	6	20
Age and sex distribution in the studied case group (*n* = 30)						
Age in years	**Sex**				**Total**	
	Male		**Female**			
	No.	**%**	**No.**	**%**	**No.**	**%**
25–> 30	3	10	2	6.66	5	16.66
30–> 35	6	20	12	40	18	60
35–≥ 40	3	10	4	13.33	7	23.33

Magnetic resonance volumetry was done for all subjects (case and control groups) to assess volume of medulla oblongata, pons, midbrain, whole brain stem, left cerebellar white matter, left cerebellar grey matter, right cerebellar white matter, and right cerebellar grey matter.

The volume of medulla oblongata in the case group (3.09–3.71 cm^3) with a mean volume of 3.41 ± 0.25 cm^3. In control group (4.25–5.12 cm^3) with a mean volume of 4.71 ± 0.45 cm^3 with statistically significant difference between the two groups (p = 0.041). The volume of pons in case group (11.42–14.03 cm^3) with a mean volume of 12.08 ± 1.35 cm^3. In the control group (12.66–16.51 cm^3) with a mean volume of 14.16 ± 1.64 cm^3 with statistically significant difference between the two groups (p = 0.039). The volume of midbrain in the case group (4.74–5.97 cm^3) with a mean volume of 5.37 ± 0.45 cm^3. In the control group (5.24–6.33 cm^3) with a mean volume of 5.97 ± 0.59 cm^3 with no statistically significant difference between the two groups (p = 0.134). The

Table 3 Clinical presentations in the studied cases (*n* = 30)

Variable	Frequency	Percentage (%)
Pyramidal dysfunction	25	83.3
Sensory dysfunction	19	63.3
Cerebral dysfunction	11	36.7
Cerebellar dysfunction	18	60
Bowel and bladder dysfunction	16	53.3
Visual problems	22	73.3
Mental problems	2	6.7

whole brain stem volume in the case group (19.11–25.4 cm^3) with a mean volume of 22.17 ± 2.37 cm^3, in the control group (22.46–28.1 cm^3) with a mean volume of 25.09 ± 2.58 cm^3 with statistically significant difference between the two groups (p = 0.025). Volumetric analysis measurements of brain stem were listed in Table 4.

The best cut-off value of the whole brain stem volume to detect volume loss between cases and controls was < 23.25 cm^3. The area under the curve (AUC) at this point was 0.855 with 84% sensitivity, 86% specificity, 64% PPV, and 74% NPV as shown in Fig. 1.

The volume of left cerebellar white matter in the case group (18.86–24.1 cm^3) with a mean volume of 21.75 ± 2.87 cm^3 and in the control group (19.06–25.21 cm^3) with a mean volume of 22.04 ± 3.27 cm^3, no statistically significant difference between the two groups (p = 0.264). The volume of left cerebellar cortex (grey matter) in the cases group (76.33–86.52 cm^3) with a mean volume of 81.64 ± 4.8 cm^3 and in the control group (84.39–102.17 cm^3) with a mean volume of 92.14 ± 9.83 cm^3 with high statistically significant difference between the two groups (p < 0.001). Volumetric analysis measurements of left cerebellar hemisphere were listed in Table 5.

The right cerebellar white matter volume in the cases group (18.65–24.08 cm^3) with a mean volume of 21.41 ± 2.67 cm^3 and in the control group (18.55–25.54 cm^3) with a mean volume of 22.32 ± 3.18 cm^3 with no statistically significant difference between the two groups (p = 0.174). The volume of right cerebellar cortex (grey matter) in the cases group (75.92–85.11 cm^3) with a mean volume of 80.37 ± 4.68 cm^3 and in the control group (84.36–101.87 cm^3) with a mean volume of 91.97 ± 8.38 cm^3 with high statistically significant difference between the two groups (p < 0.001). Volumetric analysis measurements of right cerebellar hemisphere were listed in Table 5.

The best cut-off value of a mean cerebellar grey matter volume between cases and controls to detect volume loss was < 83.46 Scm^3. The area under the curve (AUC) at this point was 0.937 with 97.8% sensitivity, 95.7% specificity, 96.4% PPV, and 94.3% NPV. The best cut-off value of a mean cerebellar white matter volume to detect volume loss between control and case group was < 21.74 cm^3. The area under the curve (AUC) at this point was 0.774 with 62% sensitivity, 96% specificity, 88% PPV, and 95% NPV as described in Figs. 2 and 3.

Thirteen cases with EDSS score of (0.5–≤ 1) showed the following brain stem and cerebellar volume measurements; medulla (3.5–3.71 cm^3), pons (13–14.03 cm^3), midbrain (5.5–5.97 cm^3), whole brain stem (23.7–25.4 cm^3), left cerebellar white matter (23–24.1 cm^3), left cerebellar grey matter (83.55–86.52 cm^3), right cerebellar white matter (22.5–24.08 cm^3), and right cerebellar grey matter (82.7–85.11 cm^3). Eleven cases with EDSS score of (< 1–≤ 3) showed the following brain stem and cerebellar volume measurements: medulla (3.15–3.49 cm^3), pons (11.9–13.04 cm^3), midbrain (5.03–5.51 cm^3), whole brain stem (20.46–23.91 cm^3), left cerebellar white matter (19.7–23.38 cm^3), left cerebellar grey matter (78.15–84.02 cm^3), right cerebellar white matter (21.62–23.09 cm^3), and right cerebellar grey matter (77.5–82.73 cm^3). Six cases with EDSS score of (< 3–≤ 5) showed the following brain stem and cerebellar volume measurements: medulla (3.09–3.22 cm^3), pons (11.42–12.07 cm^3), midbrain (4.7–5 cm^3), whole brain stem (19.11–21.34 cm^3), left cerebellar white matter (18.86–20.03 cm^3), left cerebellar grey matter (76.3–79

Table 4 Volumetric MRI analysis measurements of brain stem in studied subjects (n = 60)

	Group I (case group) n = 30	Group II (control group) n = 30	p value
Medulla oblongata (cm^3)			
Mean ± SD	3.41 ± 0.25	4.71 ± 0.45	0.041*
Range	(3.09–3.71)	(4.25–5.12)	
Pons (cm^3)			
Mean ± SD	12.08 ± 1.35	14.16 ± 1.64	0.039*
Range	(11.42–14.03)	(12.66–16.51)	
Midbrain (cm^3)			
Mean ± SD	5.37 ± 0.45	5.97 ± 0.59	0.134
Range	(4.74–5.97)	(5.24–6.33)	
Whole brain stem (cm^3)			
Mean ± SD	22.17 ± 2.37	25.09 ± 2.58	0.025*
Range	(19.11–25.4)	(22.46–28.10)	

Data are expressed as mean ± SD, p probability
*Statistically significant (p < 0.05)

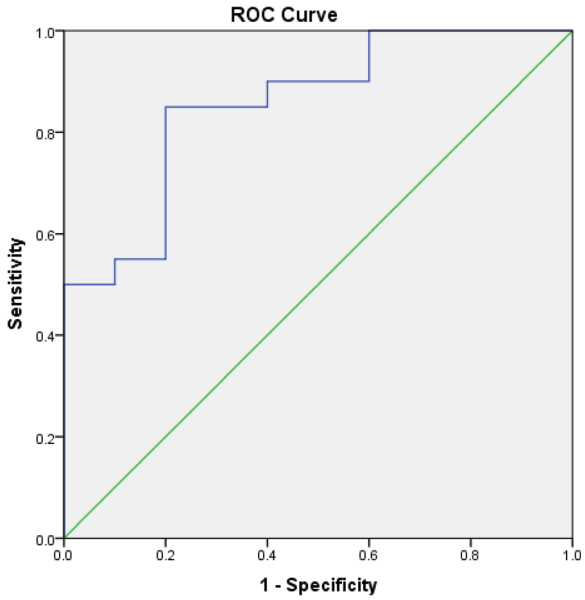

Fig. 1 ROC curve of prediction of whole brain stem volume loss in RRMS cases

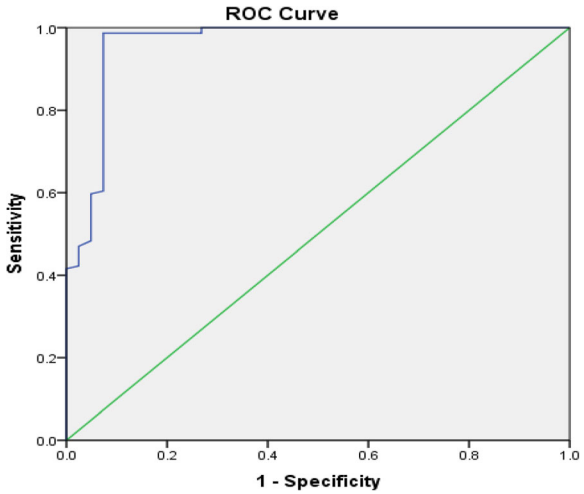

Fig. 2 ROC curve of prediction of cerebellar grey matter volume loss in RRMS cases

cm^3), right cerebellar white matter (18.65–21.63 cm^3), and right cerebellar grey matter (75.92–77.48 cm^3).

There was statistically significant moderate negative correlation between neurological disability and volumes of midbrain, pons, medulla oblongata, and the whole brain stem. Also, there was statistically significant strong negative correlation between neurological disability and volumes of cerebellar gray and white matter as shown in Table 6, Figs. 4, 5, and 6.

Nine cases with number of relapses (1 and 2) showed the following brain stem and cerebellar volume measurements: medulla (3.2–3.71 cm^3), pons (13.4–14.03 cm^3), midbrain (5.7–5.97 cm^3), whole brain stem (24.7–25.4 cm^3), left cerebellar white matter (23.4–24.1 cm^3), left cerebellar grey matter (82.78–86.52 cm^3), right cerebellar white matter (23.5–24.08 cm^3), and right cerebellar grey matter (83.7–85.11 cm^3). Fourteen cases with number of relapses of 3 and 4 showed the following brain stem and cerebellar volume measurements: medulla (3.13–3.39 cm^3), pons (11.4–13.34 cm^3), midbrain (5.73–5.59 cm^3), whole brain stem (21.46–23.91 cm^3), left cerebellar white matter (19.7–23.68 cm^3), left cerebellar grey matter (77.67–83.82 cm^3), right cerebellar

Table 5 Volumetric MRI analysis measurements of cerebellum in studied subjects (n = 60)

	Group I (30 cases)	Group II (30 case)	p value
Left-cerebellum-white-matter (cm^3)			
Mean ± SD	21.75 ± 2.87	22.04 ± 3.27	0.264
Range	(18.86–24.1)	(19.06–25.21)	
Left-cerebellum-cortex (grey matter) (cm^3)			
Mean ± SD	81.64 ± 4.8	92.14 ± 9.83	< 0.001*
Range	(76.33–86.52)	(84.39–102.17)	
Right-cerebellum-white-matter (cm^3)			
Mean ± SD	21.41 ± 2.67	22.32 ± 3.18	0.174
Range	(18.65- 24.08)	(18.55–25.54)	
Right-cerebellum-cortex (grey matter) (cm^3)			
Mean ± SD	80.37 ± 4.68	91.97 ± 8.38	< 0.001*
Range	(75.92–85.11)	(84.36–101.87)	

Data are expressed as mean ± SD, p probability
*Statistically significant (p < 0.05)

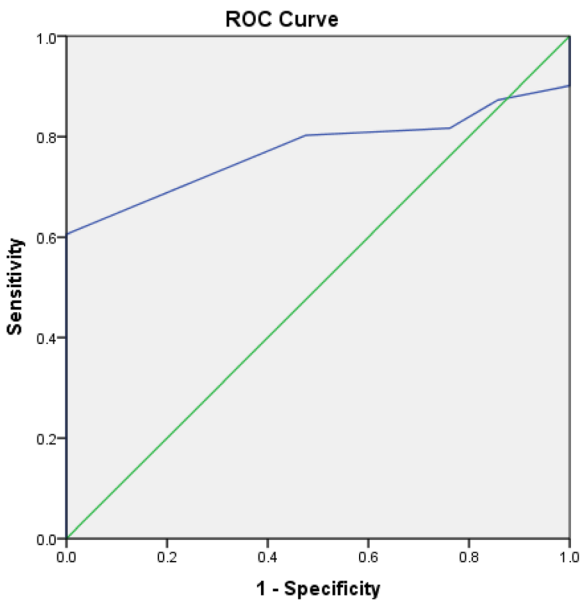

Fig. 3 ROC curve of prediction of cerebellar white matter volume loss in RRMS cases

Table 6 Correlation between EDSS score and different brain stem, cerebellum volumetric MRI measurements

EDSS		
Variable	***R***	***p***
Medulla (cm^3)	− 0.376	0.031*
Pons (cm^3)	− 0.408	0.005*
Midbrain (cm^3)	− 0.194	0.187
Whole brain stem (cm^3)	− 0.459	< 0.001*
Left-cerebellum-white-matter (cm^3)	− 0.215	0.089
Left-cerebellum-cortex(grey matter) (cm^3)	− 0.712	< 0.001*
Right-cerebellum-white-matter (cm^3)	− 0.254	0.067
Right-cerebellum-cortex (grey matter) (cm^3)	− 0.644	< 0.001*

r Spearman's correlation
*Statistically significant ($p < 0.05$)

white matter (21.37–23 cm^3), and right cerebellar grey matter (76.5–83.73 cm^3). Seven cases with number of relapses of 5 to 7 showed the following brain stem and cerebellar volume measurements: medulla (3.09–3.12 cm^3), pons (11.42–12.26 cm^3), midbrain (4.7–4.93 cm^3), whole brain stem (19.11–21.1 cm^3), left cerebellar white matter (18.86–19.73 cm^3), left cerebellar grey matter (76.3–78.9 cm^3), right cerebellar white matter (18.65–21.83 cm^3), and right cerebellar grey matter (75.92–77.79 cm^3).

There was negative correlation between number of relapses and volumes of medulla, pons, midbrain, and whole brain stem. All these correlations were statistically significant except the midbrain. Also, there was statistically significant strong negative correlation between number of relapses and volume of cerebellar gray and white matter as shown in Table 7, Figs. 4, 5, and 6.

Discussion

Multiple sclerosis (MS) is an idiopathic demyelinating chronic disabling CNS illness common in young adults. MRI is a highly sensitive modality to detect lesions [12].

Using EDSS score alone as an outcome measure had several limitations, it is based on neurological examination, which is inherently subjective. Also, the clinical state of the patient does not reflect the true activity of MS in the CNS. Hence, an objective method is preferred by most practitioners [13].

Brain atrophy and lesion load on MRI are important biomarkers and associated with long-term disabilities [14]. Brain volume loss in MS patients occurs at a faster rate than in the healthy population: 0.5–1.0% vs. 0.1–0.3% per year. The exact mechanism of brain atrophy in MS is not clear, it may related to myelin and axonal loss [15].

Loss of medulla oblongata volume is associated with spinal cord damage and disability in a cohort of MS patients with a mean disease duration of 7.1 years, supporting that medulla atrophy is an important pathology in MS [16].

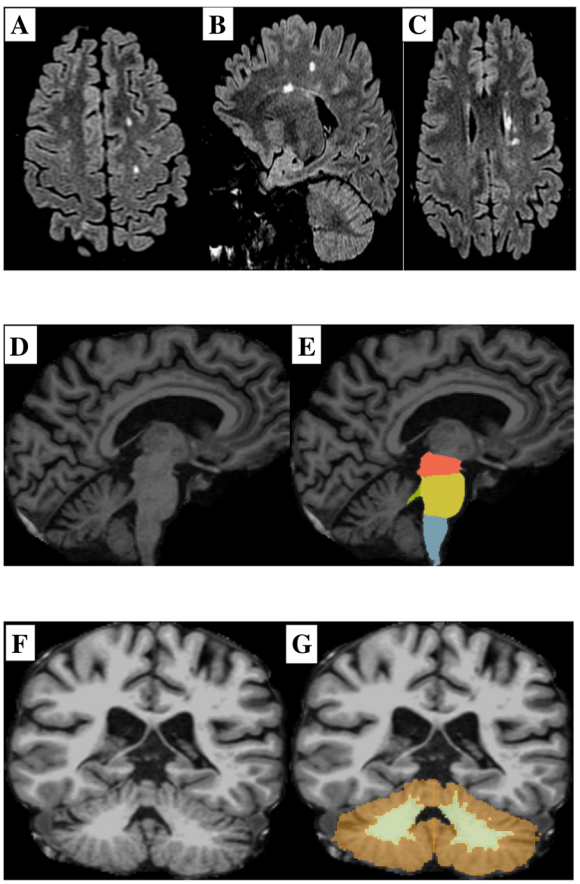

Fig. 4 A 29-year-old male patient with RRMS, EDSS score of 2, and a relapse rate of 2, complaining of sensory and pyramidal dysfunction. Axial and sagittal Flair sequences (**a**–**c**) showed multiple plaques of high SI seen at both parietal lobes; in periventricular white matter, pericallosal areas and centeum semiovale. The periventricular plaques are perpendicular to the ventricle giving Dawson's finger appearance. 3D T1WI in sagittal view (**d**, **e**) for brain stem segmentation and in coronal view (**f**, **g**) for cerebellar white and grey matter segmentation; (**d**, **f**) raw unprocessed T1W image, (**e**, **g**) 3D T1 image after processing with 3D Slicer with colored segmented brain stem and cerebellum. The brain stem and cerebellar segmentation results showed the following data: midbrain 5.82 (N 5.24–6.33 cm^3), pons 12.83 (N 12.66–16.51 cm^3), medulla 3.87 (N 4.25–5.12 cm^3), whole brain stem 22.52 (N 22.46–28.10 cm^3), left cerebellar white matter 23.47 (N 19.06–25.21 cm^3), left cerebellar grey matter 83.94 (N 84.39–102.17 cm^3), right cerebellar white matter 22.82 (N 18.55–25.54 cm^3), and right cerebellar grey matter 83.16 (N 84.36–101.87 cm^3). Patient with EDSS score of 2 and a relapse rate of 2 had a moderate decrease in the volumes of the medulla and cerebellar grey matter bilaterally

MS is the most common cause of non-traumatic disability in young adults typically begins at the ages of 20–40 years. Also, women are affected approximately twice as often as men [17]. We reported in current study predominant female affection (60% in the cases group and 63.3% in the control group) with a mean age of 30.93 years in cases group and 31.13 ± 3.62 years in control group.

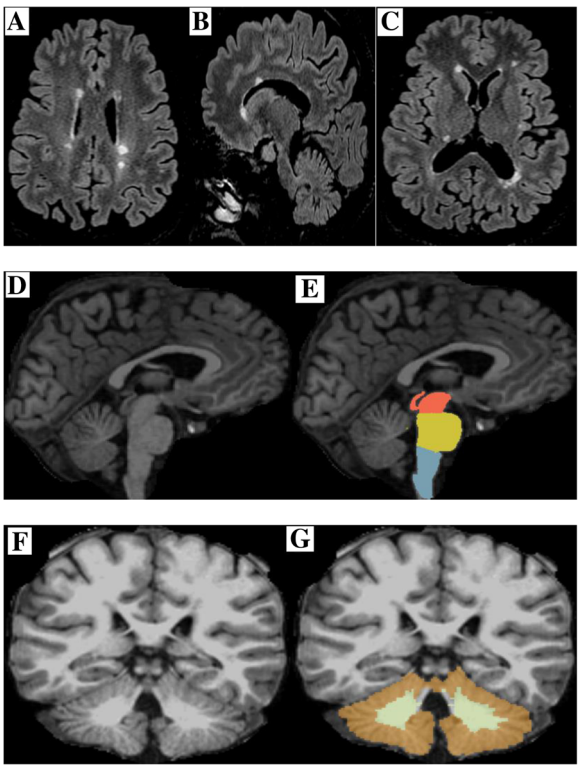

Fig. 5 A 25-year-old female patient aged 25 years old with RRMS, EDSS score of 0.5, and a relapse rate of 1, complaining of pyramidal dysfunction. Axial and sagittal Flair sequences (**a**–**c**) showed multiple plaques of high SI seen at both parietal lobes; in periventricular white matter, pericallosal areas right deep white matter (basal ganglia). 3D T1W images in sagittal view (**d**, **e**) for brain stem segmentation and in coronal view (**f**, **g**) for cerebellar grey and white matter segmentation; (**d**, **f**) raw unprocessed T1W image, (**e**, **g**) 3D T1image after processing with 3D Slicer with colored segmented brain stem and cerebellum structures. The brain stem and cerebellum segmentation results showed the following data: midbrain 5.9 (N 5.24–6.33 cm^3), pons 13.85 (N 12.66–16.51 cm^3), medulla 3.63 (N 4.25–5.12 cm^3), whole brain stem was 23.38 (N 22.46–28.10 cm^3), left cerebellar white matter 24 (N 19.06–25.21 cm^3), left cerebellar grey matter 84.59 (N 84.39–102.17 cm^3), right cerebellar white matter 23.7 (N 18.55–25.54 cm^3), and right cerebellar grey matter 84.5 (N 84.36–101.87 cm^3). Patient with EDSS score of 0.5 and a relapse rate of 1 had a mild decrease in the volume of the medulla oblongata only

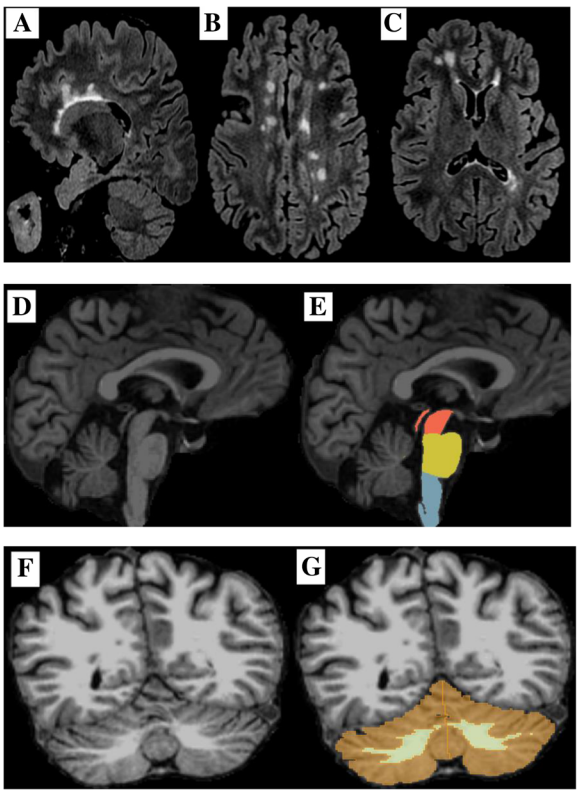

Fig. 6 A 35-year-old female patient with RRMS, EDSS score of 4, and a relapse rate of 6, complaining of visual problems, cerebellar dysfunction, bowel, and bladder dysfunction. Axial and sagittal Flair sequences (**a**–**c**) showed multiple plaques of high SI at both parietal lobes; in periventricular white matter, pericallosal and callosomarginal areas, juxtacortical junction, and centeum semiovale. The periventricular plaques are perpendicular to the ventricle giving Dawson's finger appearance. 3D T1W images in sagittal view (**d**, **e**) for brain stem segmentation and in coronal view (**f**, **g**) for cerebellar grey and white matter segmentation; (**d**, **f**) raw unprocessed T1W image, (**e**, **g**) 3D T1image after processing with 3D Slicer with colored segmented brain stem and cerebellum structures. The brain stem and cerebellum segmentation results showed the following data: midbrain 5.02 (N 5.24–6.33 cm^3), pons 11.7 (N 12.66–16.51 cm^3), medulla 3.1 (N 4.25–5.12 cm^3), whole brain stem 19.82 (N 22.46–28.10 cm^3), left cerebellar white matter 19.42 (N 19.06–25.21 cm^3), left cerebellar grey matter 76.57 (N 84.39–102.17 cm^3), right cerebellar white matter 20.61 (N 18.55–25.54 cm^3), and right cerebellar grey matter 76.07 (N 84.36–101.87 cm^3). Patient with EDSS score of 4 and a relapse rate of 6 had a minimal decrease in the volume of the midbrain, severe decrease in the volumes of the pons, medulla, whole brain stem, and cerebellar grey matter bilaterally

In the current study, volumes of the whole brainstem, medulla, and pons showed a significant decrease in MS cases compared to control cases ($p < 0.05$). Brainstem volume had a mean volume of 22.17 and 25.09 cm^3 in cases and control cases, respectively. However, midbrain volume was not significantly different between cases and controls ($p = 0.134$).

Daams et al. [18] reported a 5.2% normalized brain volume reduction in MS patients compared to healthy controls. Normalized brainstem volume was significantly decreased in MS cases (27.71 ml) compared to control cases (29.6 ml). In contrast to the present study, Lee et al. [14] reported as regards medulla oblongata volume, there was no significant difference between cases and controls (4.33 in MS vs. 4.35 cm^3 in controls—$p > 0.05$). There was a significant decrease in the size of pons and midbrain volumes in MS cases compared to controls ($p < 0.05$). The normalized volumes of whole brainstem were significantly reduced in MS subjects compared to controls. Midbrain had mean sizes of 5.5–6 cm^3,

Table 7 Correlation between number of relapses and different brain stem, cerebellum volumetric MRI measurements

Number of relapses		
Variable	***R***	***p***
Medulla (cm^3)	− 0.402	0.009*
Pons (cm^3)	− 0.475	0.001*
Midbrain (cm^3)	− 0.213	0.132
Whole brain stem (cm^3)	− 0.657	< 0.001*
Left-cerebellum-white-matter (cm^3)	− 0.187	0.324
Left-cerebellum- grey matter (cm^3)	− 0.661	< 0.001*
Right-cerebellum-white-matter (cm^3)	− 0.303	0.102
Right-cerebellum-grey matter (cm^3)	− 0.655	< 0.001*

r Spearman's correlation
*Statistically significant ($p < 0.05$)

whereas pons had mean sizes of 13.22–14.05 cm^3 in MS cases and controls, respectively.

In the present study, volume of left cerebellar hemisphere cortex showed a significant decrease in MS cases compared to controls ($p < 0.001$). It had mean volumes of 81.64 and 92.14 cm^3 in cases and controls, respectively, while right cerebellar hemisphere cortex volumes were 80.37 and 91.97 cm^3 in cases and controls, respectively. On the contrary, cerebellar white matter showed no significant volume decrease in cases and controls.

These results agreed with Anderson et al. [19], and they reported that volume of cerebellar white matter not statistically different between MS cases and controls (20.8 cm^3 in RRMS, 18.9 cm^3 in PPMS, and 20.4 cm^3 in controls). However, PPMS had lower cerebellar grey matter volumes (93.3 cm^3) compared to RRMS (97.2 cm^3), and healthy controls (97.5 cm^3).

In contrast to current study, Ge Y et al. [20] reported a significant loss of cerebellar white matter rather than gray matter in the early stage of MS which might indicate a different mechanism of atrophy in MS versus other neurodegenerative diseases. Lee et al. [14] reported that there was no significant difference in normalized cerebellar volume between MS cases and controls (0.119 vs. 0.117 in MS and controls, respectively—$p > 0.05$). Unfortunately, they did not assess both white and grey matter volumes separately.

As regarding brain stem volume, we reported MRI sensitivity and specificity of 84 and 86%, respectively, with an accuracy of 82% by using a cut-off value of 23.25 cm^3. Also using a cut-off value of 83.46 cm^3 for cerebellar grey matter, MRI had sensitivity and specificity of 87.8 and 95.7%, respectively, with an accuracy of 95.2%.

Daams et al. [18] reported a significant negative correlation between EDSS score and normalized brainstem volume ($r = -0.293$—$p < 0.001$). Also, between EDSS score and normalized cerebellar volume ($r = -0.242$—$p < 0.01$). Lee et al. [14] reported normalized brainstem volume showed a moderate to strong positive correlation with normalized supratentorial brain volume ($p = 0.027$). In the present study, EDSS score and number of relapses showed a significant negative correlation with medulla, pons, whole brain stem volumes, in addition to both right and left cerebellar cortical volumes ($p < 0.05$) and could be used a predictor for disease severity in such cases.

Our study had several limitations; small sample size, study design, and imaging protocol did not include mean upper cervical cord area measurement, which has been reported to be an important predictor of motor dysfunction and disability in MS subjects. Moreover, the effect of treatment on brainstem and cerebellar volumes should have been assessed. Therefore, more studies handling the previous parameters should be conducted in the near future.

Conclusion

Volumetric MR imaging is an important tool for quantifying the MS disease, assess MS activity, progression, and tissue loss. The degree and the pattern of atrophy on MRI images correlate significantly with the neurological disability score and number of relapses.

Abbreviations

1H-MR: Proton MR; 3D: Three dimensions; AUC: Area under the curve; CNS: Central nervous system; DTI: Diffusion tensor imaging; EDSS: Expanded disability status scale; GM: Grey matter; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; MTI: Magnetization transfer imaging; NPC: Negative predictive value; PPV: Positive predictive value; PURE: Phased array uniformity enhancement; REC: Approval of research ethics committee; RRMS: Relapsing remission relapse; SCIC: Surface coil intensity correction; SPGR: Sagittal 3D T1-weighted spoiled gradient; WM: White matter

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Authors' contributions

MD suggested the research idea, ensured the original figures and data in the work, minimized the obstacles to the team of work, correlated the study concept and design and had the major role in analysis, ME collected data in all stages of manuscript, performed data analysis. ND supervised the study with significant contribution to design the methodology, manuscript revision, and preparation. MK correlated the clinical data of patient and matched it with the findings, drafted and revised the work. All authors read and approved the final manuscript for submission.

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Availability of data and materials

The authors confirm that all data supporting the finding of the study are available within the article, and the raw data and data supporting the findings were generated and available at the corresponding author on request.

Ethics approval and consent to participate

Informed written consents taken from the patients and healthy volunteers, the study was approved by ethical committee of Tanta University Hospital, Faculty of Medicine. Committee's reference number: 31619/06/17.

Consent for publication
All participants included in the research gave written consent to publish the data included in the study.

Competing interests
The authors declare that they have no competing of interests.

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