Egyptian Journal of Radiology and Nuclear Medicine

RESEARCH

Open Access

MR volumetry in detection of brain atrophic changes in MS patients and its implication on disease prognosis: retrospective study

Nermeen Mahmoud El Garhy, Marwan M. El Toukhy and Mona Mohammed Fatouh*

Abstract

Background: Multiple sclerosis is a chronic demyelinating disease of the central nervous system. It may lead to disability and cognitive impairment. Our study aimed at evaluation of the role of MR volumetry technique in detection of brain atrophic changes in patients with multiple sclerosis and its impact on disease prognosis.

Results: This study was carried out on thirty healthy control with mean age 26.23 years and thirty patients with remitting relapsing multiple sclerosis, with a mean age of 28.18 years. Patients with multiple sclerosis were distributed across six subgroups based on the *z*-score cut-off of − 1.96 for regional and whole brain atrophy. We found that 2 patients (6.6%) showed no thalamic or brain atrophy, 28 patients (93.3%) showed whole brain atrophy only and 10 patients (33.3%) showed both, thalamic and BP atrophy. No patients showed only thalamic atrohy, 4 patients showed whole brain atrophy with other structure atrophy rather than thalamus (13.3%), 10 patients with whole brain and more than one structure atrophy (33.3%). Relation between subgroups and degree of increase in the Expanded Disability Status Scale (EDSS) as well as presence of cognitive decline were assessed. No significant relation were found between RRMS patients subgroups with whole brain atrophy, subgroup with isolated thalamic atrophy or subgroup with multiple structure atrophy and increase of EDSS or cognitive decline.

Conclusion: We found that MRI volumetry is a very useful technique in the assessment of the atrophic changes that occur as a consequence of multiple sclerosis affecting the whole brain, deep grey matter as well as corpus callosum. Although our study did not prove significant relation between presence of brain atrophic changes and disability or cognitive impairment, presence of atrophy warrants careful clinical evaluation of those patients to detect any possible further progression of disability or cognitive decline.

Keywords: Multiple sclerosis, Magnetic resonance imaging, Magnetic resonance volumetry, Atrophy-prognosis

Background

Multiple sclerosis (MS) is a physical and neurological cognitive disability progressive neurological disorder [1], 2.5 million people worldwide might suffer from it. In the US, there are approx. 400,000 people currently diagnosed with MS. The disease usually begin in early adulthood and its prognoses are variable [2].

In addition to the lesion load as a marker for disease activity detected by conventional MR imaging, atrophic changes of brain measured by MR volumetry technique was considered in recent years as an important biomarker of destruction of the tissues and neurological degeneration in (MS) [3–7].

One of the studies showed that brain atrophy pointed to increase of disability and cognitive decline [3]. This was supported by the increase of the Expanded Disability Status Scale (EDSS) (which is a scale used to measure degree

*Correspondence: monafatouh@yahoo.com
Radiology Department, Faculty of Medicine, Cairo University, Cairo, Egypt

of physical disability) that was documented to be associated with whole brain atrophy, in several studies [8–10].

In addition to whole brain and thalamic atrophy, the volume of subcortical structures were found to be reduced in MS, like putamen [11, 12], and caudate nucleus [12], as well as the corpus callosum [13, 14].

The thalamus was found to be especially susceptible to atrophy at early stages of MS [12, 15, 16], and early thalamic atrophy has even been discussed as a marker to predict the transition from clinically isolated syndrome (CIS) to clinically definite MS [17].

Thalamic atrophy was associated with progression of disability in MS patients as reported in previous studies [16]. Although some other studies found only a weak [12] or negative relation between reduction of thalamic volume and increase of the EDSS [18], measurement of both whole brain and thalamic atrophy could allow detection of progression of any clinical manifestations in individual MS patients.

Alexander et al. [19] documented that the thalamus and basal ganglia have important role in information processing system (IPS), as they reported parallel cortico-basal ganglia-thalamo-cortical loops connecting basal ganglia and thalamus with frontal cortex, which demonstrated the role of these structures in cognition. Beside this, basal ganglia and thalamus are identified to be in a unique position to modulate information processing efficiency, and may have an important role for rapid and efficient processing during the execution of complex attention and executive function tasks [20]. Therefore, it seems reasonable that atrophy of these DGM (deep grey matter) structures, as shown here, significantly contributes to slowed or inefficient processing of information in MS [21].

The main goal of this study was to detect the usefulness of MR volumetry in detection of MS patients with whole brain, thalamic or deep grey matter structural atrophy in a single time point by assessing MS patients from our neurological outpatient clinic. As most of the previous studies assessed presence of brain, thalamic and deep grey matter volume changes between two examination time points.

Detection of atrophic changes at single time point required comparison of whole brain parenchyma (BP), thalamic, caudate, putamen and corpus callosum volumes of MS patients against corresponding volumes of a cohort of healthy control subjects.

Methods

This retrospective study was carried out on thirty healthy control volunteers (16 females and 14 males). Their ages ranged from 20 to 35 years with mean age of 26.23 years and thirty symptomatic patients (19 females and 11 males). Their ages ranged from 20 to 40 years, with a mean age of 28.18 years.

The current study had been approved by the institutional Research and Ethical committee.

Informed consent was taken from the patients and has been approved by the ethical committee.

All patients and healthy volunteers were referred to the diagnostic radiology department from outpatient clinics of neurology.

Patients with definite relapsing–remitting (RRMS) were included upon first visit at an outpatient facility specialized to MS.

Exclusion criteria were MRI acquisition with deviating sequence parameters or strong MRI artifacts and a primary progressive disease course.

Subjects that did not complain from any clinical symptoms as ensured by an experienced neurologist and without evidence of pathological findings on the MRI scan of the brain as confirmed by the neuro radiologist were included as healthy control subjects.

Clinical assessment of group of MS patients

By referring to the neurology clinician, the disability and cognitive impairment of our patients were assessed. They used EDSS [22] for assessment of degree of disability and cognitive impairment assessed subjectively as symbol digit modalities are difficult to be interpreted by the patients.

The EDSS measures disability in eight functional systems, and the results can range from 0(normal neurological exam) to 10 (death due to MS).

Disease duration was estimated as time since first symptoms were documented.

MRI acquisition

Brain MRI was performed for patients and control group on a 1.5TGE Signa (General Electric, Milwaukee, WI, USA) closed-configuration whole body scanner using a standard quadrature head coil. Each MRI examination included Sagittal 3D T1 weighted spoiled gradient (SPGR) utilizing the following parameters: A repetition time (TR) of 7.2 ms, an echo time (TE) of 120 ms, a slice thickness of 1.2 mm, FOV = 256 × 256 mm, preparation time 500 ms, FOV 256 × 256 mm. Phase FOV1.0, slice thickness 1.2 mm, number of slices 160, slice spacing 0, matrix 192 × 192, flip angle 10 degrees, frequency 16 kHz, frequency direction S/I, NEX 1.0, shim auto, Phased Array Uniformity Enhancement (PURE) on, Surface Coil Intensity Correction (SCIC) off.

MRI-based brain volumetry

Cortical reconstruction and volumetric segmentation was done with the free surfer image analysis suite. The

technical details of these procedures are described in previous publications [24].

Free surfer morphometric procedures have been demonstrated to show good test–retest reliability across scanner manufacturers and across field strengths [24].

A seg Atlas information

The a seg atlas was formed from 40 subjects acquired using the same mp-rage sequence (by people at Wash U ages ago in collaboration with Randy Buckner). The subjects that make up the atlas are distributed in 4 groups of 10 subjects each: (1) young, (2) middle aged, (3) healthy older adults, (4) older adults with AD.

Longitudinal processing

To extract reliable volume and thickness estimates, images where automatically processed with the longitudinal stream [24] in Free Surfer.

Adjustment of brain volumes

Corrected volumes of the whole brain, thalamus, caudate, putamen, and corpus callosum were measured by dividing the structure volume on the intra cranial volume.

MRI image analysis

Cut-off value and grouping of MS patients

95% of the brain volume values were noted to be within the area of the mean ± 1.96 standard deviation, (assuming a normal distribution in the cohort of healthy control subjects). 5% Only of the brain volume numbers are expected to be greater or fewer. Because of this, we assumed that *z*-scores below − 1.96 represent a significant brain volume loss with an error probability of 2.5% at most.

The *z*-score cut-off of − 1.96 was applied to individual MS patients, and based on their BP and thalamus volumes, they were divided into the following subgroups:

- Group 0: no thalamic or BP atrophy (i.e., both within the normal range; *z*-scores greater than − 1.96)
- Group 1: whole brain atrophy (*z* score below − 1.96)
- Group 2: thalamic and BP atrophy (both *z*-scores below − 1.96)
- Group 3: thalamic (*z*-score below − 1.96) but no BP atrophy (*z*-score greater than − 1.96)
- Group 4: whole brain atrophy with other structure atrophy (rather than thalamus)
- Group 5: multiple structures atrophy

Statistics

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data were summarized using mean, standard deviation, median, minimum and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test in normally distributed quantitative variables, while non-parametric Mann–Whitney test was used for non-normally distributed quantitative variables [25]. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5 [26]. Correlations between quantitative variables were done using Pearson correlation coefficient [27]. *P* values less than 0.05 were considered as statistically significant.

Results

This study was carried out on thirty patients (11 males and 19 females) diagnosed with remising and relapsing MS referred to us from neurology outpatient clinic, their age ranged from Their ages ranged from 20 to 40 years, with a mean age of 28.18 years. In addition thirty healthy control volunteers were included in our study, (16 females and 14 males). Their ages ranged from 20 to 35 years with mean age of 26.23 years (Tables 1 and 2; Figs. 1, 2). The duration of illness was estimated as time since first symptoms were documented, mean duration was 6.1 years ± 2 SD (Table 3).

The whole brain volume as well as the volume of the subcortical structures including the thalamus, caudate, putamen and corpus callosum were measured in patients and control subjects. The mean and cut off value of whole brain and each of subcortical structures volumes of the control group were calculated according to which the patients were assessed

Table 1 Number and percent of males and females in both cases and control groups

	Cases		Controls		*P* value
	Count	%	Count	%	
Sex					
Male	11	36.7	14	46.7	0.432
Female	19	63.3	16	53.3	

Table 2 Age mean and standard deviation in both cases and control groups

	Cases		Controls		*P* value
	Mean	SD	Mean	SD	
Age	28.18	4.81	26.23	5.03	0.130

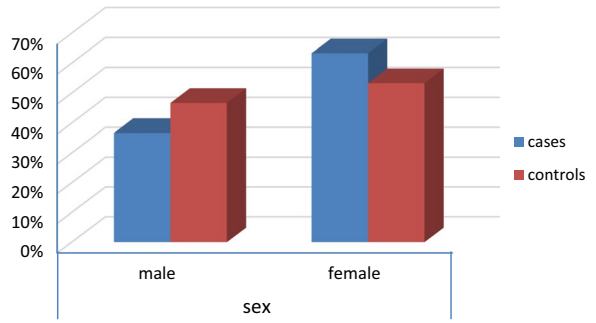


Fig. 1 Number and percent of males and females in patients and control groups

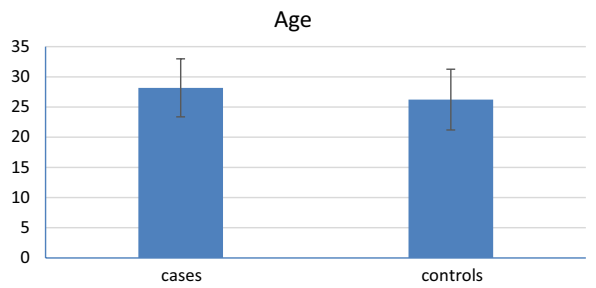


Fig. 2 Age in patients and control groups

Table 3 Duration of illness in group of patients

	Cases	
	Mean	**SD**
Duration	6.17	2.07

for whole brain and subcortical structures atrophy and results are displayed in (Tables 4 and 5). Results for each patients as well as the number and percent of patients with and without whole brain, thalamic, caudate, putamen, corpus callosum and multiple structure atrophy are displayed in Tables 6 and 7 and Figs. 3, 4, 5, 6, 7 and 8.

Grouping of the MS patients according to different structures and BP atrophy

The distribution of MS patients across the six subgroups based on the *z*-score cut-off of − 1.96 for regional and whole BP atrophy is shown in (Table 8) Group 0: 2 MS patients (6.6%) showed no thalamic or BP atrophy, Group 1: 28 MS patients (93.3%) showed whole BP atrophy only (Figs. 9, 10, 11 and 12), Group 2: 10 MS patients (33.3%) showed both, thalamic and BP atrophy (Fig. 13). Group 3:0 patients showed only thalamic atrophy, Group 4: 4 patient showed whole brain atrophy with other structure atrophy rather than thalamus (13.3%) (Fig. 14), Group 5: 10 patients with whole brain and more than one structure atrophy (33.3%) (Fig. 15).

Relation between sub grouping of MS patients and clinical data (EDSS score and cognitive impairment)

EDSS in RRMS patients ranged from 1 to 5 with mean value 3.1 (Table 9).

We assessed the relation between the groups of patients with whole brain atrophy, isolated thalamus atrophy and multiple structures atrophy and the degree of increase in The EDSS score: we found no significant relations between the group of patients with whole brain atrophy, isolated thalamic atrophy or multiple structures atrophy and increase in EDSS with *P* values 0.66, 0.68 and 0.18, respectively (Table 10).

Table 4 Comparison of mean volume of thalamus, whole brain, caudate and putamen and corpus callosum in between cases and control groups

	Cases		Controls		*P* value
	Mean	**Standard Deviation**	**Mean**	**Standard Deviation**	
Thalamus (volume relative to intracranial volume)	0.0038	0.0006	0.0052	0.0007	< 0.001
Caudate (volume relative to intracranial volume)	0.0020	0.0003	0.0024	0.0003	< 0.001
Putamen (volume relative to intracranial volume)	0.0030	0.0003	0.0034	0.0004	< 0.001
Corpus callosum	0.0018	0.0003	0.0023	0.0004	< 0.001
Whole brain (volume relative to intracranial volume)	0.5725	0.0583	0.7470	0.0634	< 0.001

Table 5 Cutoff value for diagnosis of atrophy of thalamus, whole brain, caudate, putamen and corpus callosum

	Controls		Cutoff value for atrophy diagnosis
	Mean	SD	
Thalamus (volume relative to intracranial volume)	0.0052	0.0007	0.0038
Caudate (volume relative to intracranial volume)	0.0024	0.0003	0.0018
Putamen (volume relative to intracranial volume)	0.0034	0.0004	0.0026
Corpus callosum	0.0023	0.0004	0.0015
Whole brain (volume relative to intracranial volume)	0.7470	0.0634	0.6202

Table 6 Number and percent of patients with and without thalamic, whole brain, caudate, putamen, corpus callosum and multiple structures atrophy

	Cases	
	Count	%
Thalamus		
Yes	17	56.7
No	13	43.3
Caudate atrophy		
Yes	7	23.3
No	23	76.7
Putamen atrophy		
Yes	2	6.7
No	28	93.3
Corpus callosum atrophy		
Yes	7	23.3
No	23	76.7
Whole brain atrophy		
Yes	28	93.3
No	2	6.7
Multiple structures atrophy		
Yes	10	33.3
No	20	66.7

Cognitive impairment detected in 19 MS patients 63%. The relation between presence of cognitive impairment and presence of whole brain atrophy, isolated thalamic atrophy as well as multiple structure atrophy were assessed no significant association were found with *P* value 1, 1, 0.1, respectively (Table 11; Figs. 16, 17 and 18).

Effect of disease duration

It was not accessible statistically to assess the effect of disease duration and presence of whole brain atrophy as 28 patients were positive and only 2 were negative.

As regard the presence of significant relation between the presence of thalamic atrophy and longer the disease duration we found that no significant relation (*P* value 0.885) (Table 12).

We studied the relation between the disease duration and the degree of loss of whole brain volume in patients with atrophy of the whole brain (28 patients) and we found that there was no significant relation (*P* value 0.069) (Table 13; Fig. 19).

In addition there was no significant relation between the duration of the disease and reduction of thalamic volume in patients with atrophic changes of the thalamus (17 patients) (*P* value 0.361) (Table 14; Fig. 20)

The duration of MS disease did not significantly affect the presence of multiple structure atrophy (*P* value 0.106) (Table 15).

Discussion

Multiple sclerosis is an autoimmune chronic disease that causes neurological problems and progressive disability. Brain atrophy related to MS is a result of both underlying pathology (neuro inflammation) and neuro-axonal loss. In MS patients, brain volume loss occurs in a faster rate than in the healthy population: 0.5–1.0% vs. 0.1–0.3% per year [28]. Early in the disease course atrophy may be found even before detection of clinical symptoms and lead to long-term neurological disability [29].

Magnetic resonance imaging (MRI) is an important tool not only in diagnosis of MS disease, but also in the monitoring of disease activity and prediction of effects of treatment [30].

The primary objective of this study was to evaluate the brain atrophic changes in MS patients using MR-based quantitative volume measurements.

MRI-based brain volumetry at a single time point was applied to MS patients in our study, to evaluate its possible role in identifying MS patients at risk of disease progression. Patients were divided into six groups as following: Those with no thalamic or BP atrophy i.e., both within the normal range; *z*-scores greater than − 1.96(group 0), whole brain atrophy (*z* score below − 1.96(Group 1): thalamic and BP atrophy both *z*-scores below − 1.96(Group 2): thalamic

Table 7 Display results of each patient

ID	Thalamus atrophy	Caudate atrophy	Putamen atrophy	Corpus callosum atrophy	Whole brain atrophy	Multiple structure atrophy	Duration of illness years	EDSS	Cognitive decline
1	No	No	No	No	Yes	No	7	4	+
2	No	Yes	No	Yes	Yes	Yes	6	4	+
3	No	No	No	Yes	Yes	No	5	3	+
4	Yes	No	No	No	Yes	No	8	4	+
5	No	No	No	No	Yes	No	9	4	+
6	Yes	Yes	Yes	Yes	Yes	Yes	3	1	–
7	No	No	No	No	Yes	No	7	3	+
8	Yes	No	No	No	Yes	No	9	4	+
9	Yes	Yes	No	No	Yes	Yes	8	4	+
10	Yes	No	No	No	Yes	No	4	2	–
11	No	No	No	No	No	No	6	3	–
12	No	Yes	No	Yes	Yes	Yes	5	3	–
13	Yes	No	No	No	Yes	No	5	3	+
14	No	No	No	No	Yes	No	4	2	–
15	Yes	No	No	No	Yes	No	9	5	+
16	Yes	No	No	No	Yes	No	7	4	+
17	Yes	Yes	No	No	Yes	Yes	8	4	+
18	Yes	No	No	Yes	Yes	Yes	6	3	+
19	No	No	No	No	Yes	No	2	1	–
20	No	No	No	No	No	No	7	3	+
21	Yes	Yes	No	No	Yes	Yes	3	2	–
22	No	No	No	No	Yes	No	9	4	+
23	Yes	No	No	No	Yes	No	8	4	+
24	Yes	No	No	No	Yes	No	4	3	+
25	Yes	No	No	No	Yes	No	6	3	–
26	Yes	No	No	Yes	Yes	Yes	3	2	–
27	No	No	No	No	Yes	No	9	4	+
28	Yes	No	No	No	Yes	No	7	4	+
29	No	Yes	Yes	No	Yes	Yes	5	2	–
30	Yes	No	No	Yes	Yes	Yes	6	3	–

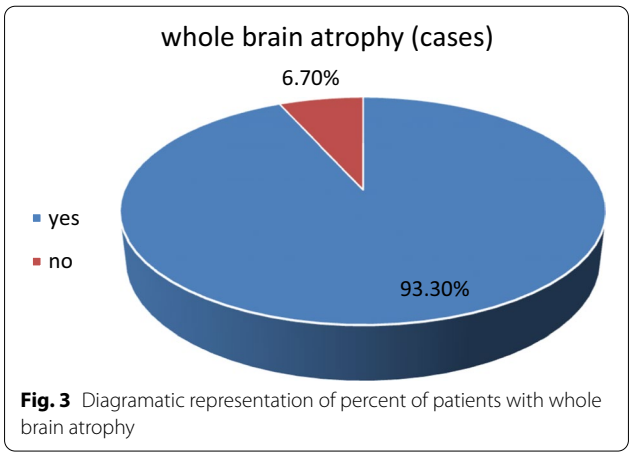


Fig. 3 Diagramatic representation of percent of patients with whole brain atrophy

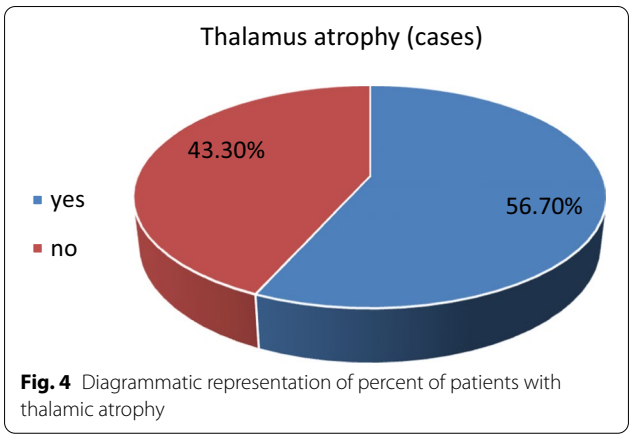


Fig. 4 Diagrammatic representation of percent of patients with thalamic atrophy

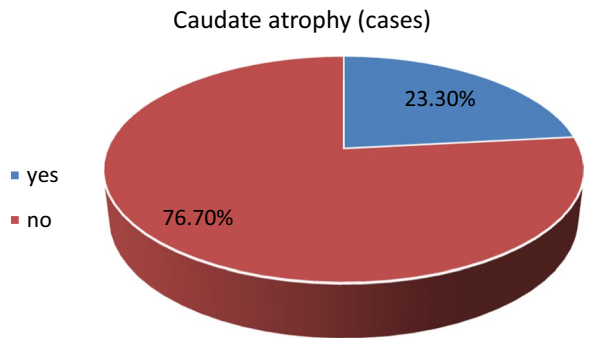


Fig. 5 Diagrammatic representation of percent of patients with caudate atrophy

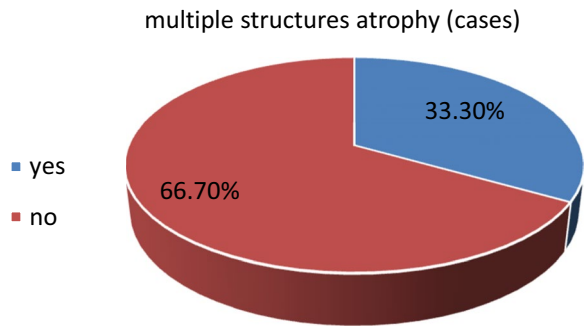


Fig. 8 Diagrammatic representation of percent of patients with multiple structures atrophy

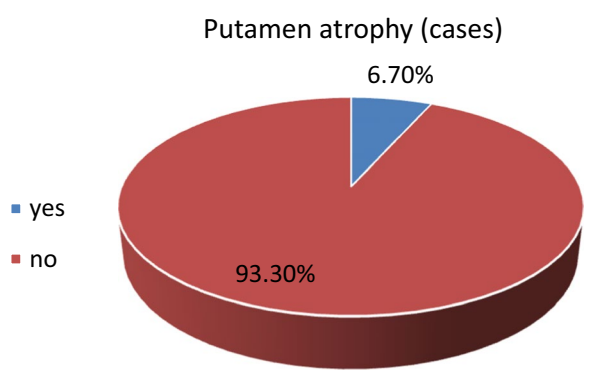


Fig. 6 Diagrammatic representation of percent of patients with putamen atrophy

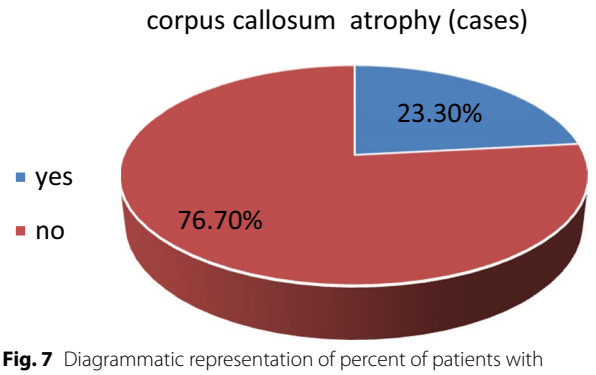


Fig. 7 Diagrammatic representation of percent of patients with corpus callosum atrophy

Table 8 Grouping of MS patients

Group 0	**No brain or structure atrophy**	**2**	**6.6%**
Group 1	Whole brain atrophy	28	93.3%
Group 2	Whole brain with thalamic atrophy	17	56.7%
Group 3	Thalamic atrophy only	0	0%
Group 4	Whole brain and other structure rather than thalamus	4	13.3%
Group 5	Whole brain and more than one structure atrophy	10	33.3%

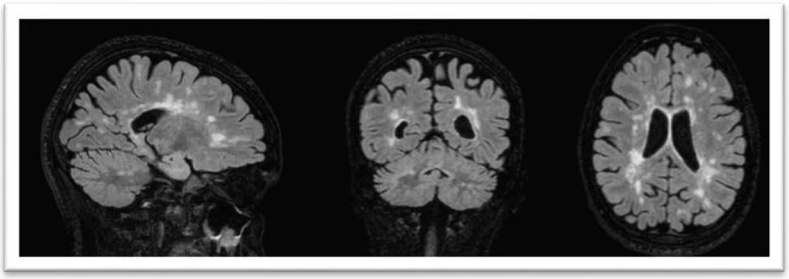
(*z*-score below − 1.96) but no BP atrophy *z*-score greater than − 1.96(Group 3) whole brain atrophy with other structure atrophy (rather than thalamus) (group 4), multiple structure atrophy (Group 5).

We demonstrated twenty eight out of thirty MS patients showed BP atrophy according to the predefined *z*-score cut-off of − 1.96. Only two of MS patients showed no brain atrophy despite of long duration of illness 6 and 7 years. This indicated that whole brain atrophy is the most frequent pattern of atrophy and this was most probably due to the long duration of illness that led to global brain atrophy.

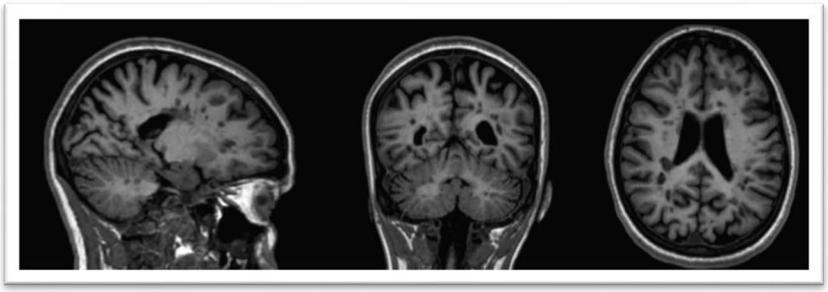
We showed that seventeen patients (56.7%) had whole brain atrophy associated with isolated thalamic atrophy as compared to 2 patients with whole brain atrophy and isolated corpus callosum atrophy 1 patient with whole brain atrophy with corpus callosum and caudate, one patient brain atrophy with caudate and putamen atrophy without thalamic

(See figure on next page.)

Fig. 9 19 year old female diagnosed with MS 7 years ago with EDSS (4) and cognitive impairment. (**A**) 3D FLAIR images: showing multiple foci and patchy areas of high signal intensity implicating the peri ventricular and juxta cortical white matter being perpendicular on the ventricular ystem and giving the characteristic dowsn finger appearance. (**B**) 3DT1WI showing multiple foci and patchy areas of low signal intensity implicating the peri ventricular and juxta cortical white matter being perpendicular on the ventricular system and giving the characteristic Dowsn finger appearance. (**C**) MR volumetry images

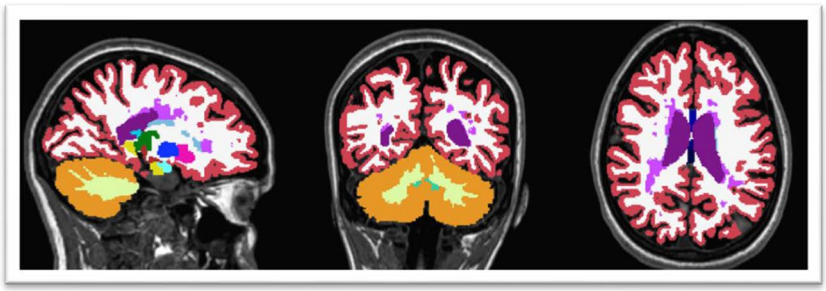


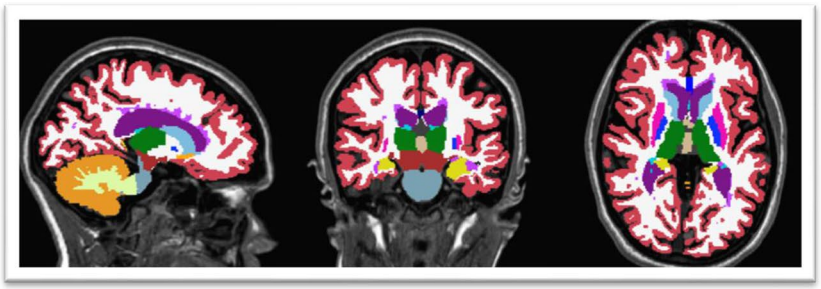
(A)



(B)

(C)MR Volumetry





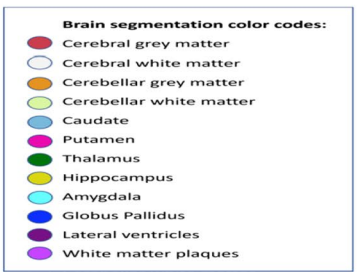
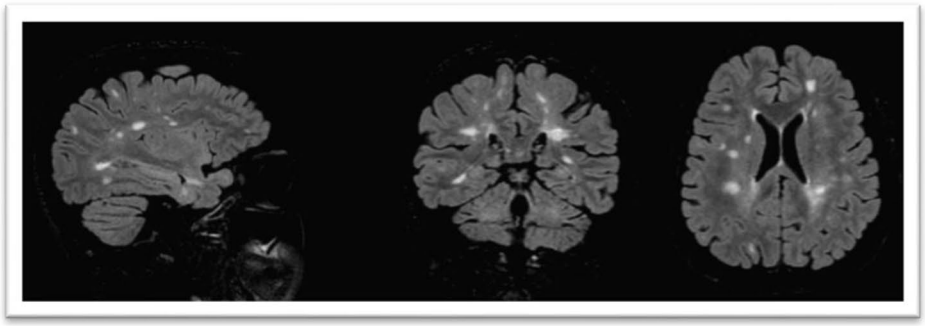
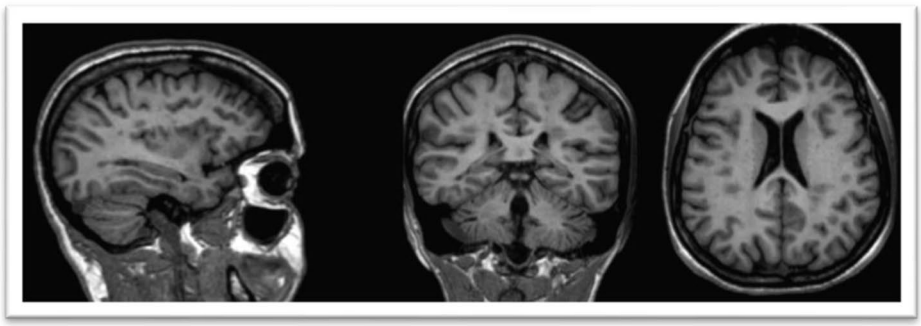


Fig. 9 (See legend on previous page.)



(A)



(B)

(C)MR Volumetry

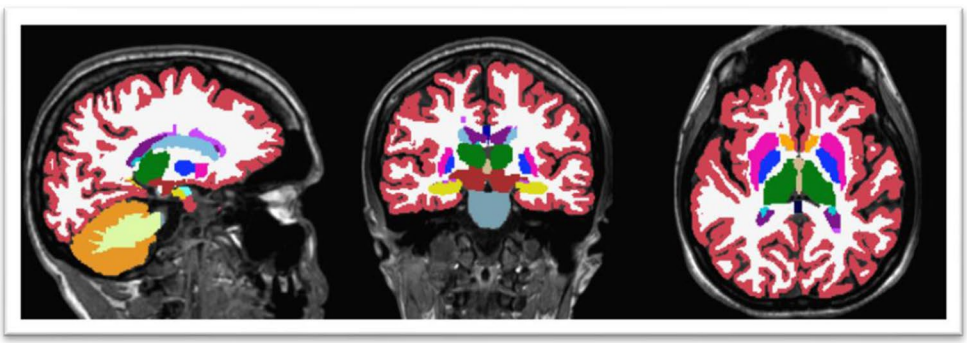
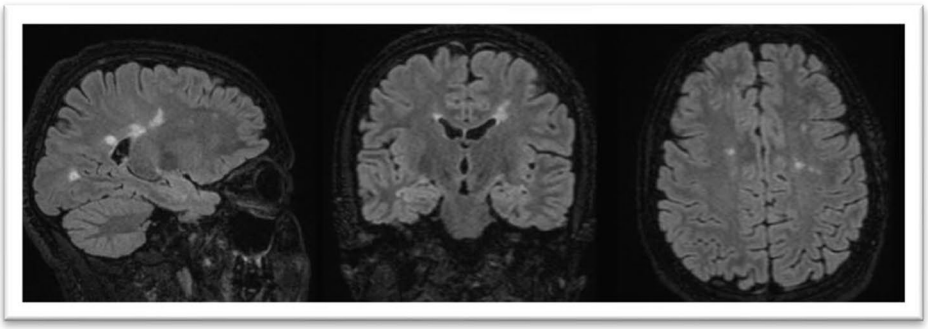
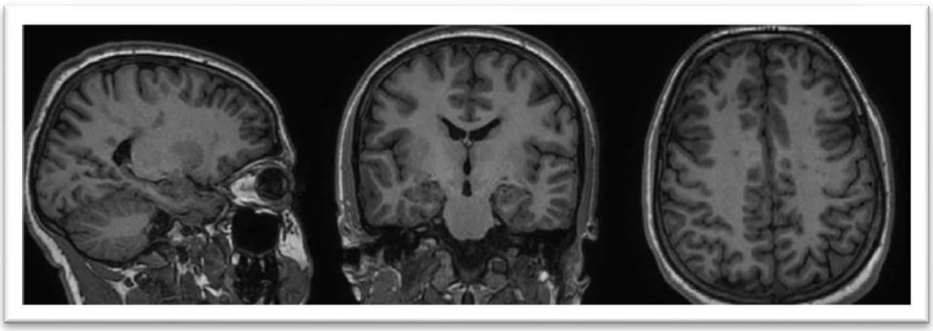


Fig. 10 22 year old female diagnosed with MS 6 years ago with EDSS (4) with features of cognitive impairment. (**A**) 3D FLAIR images showing multiple foci and patchy areas of high signal intensity implicating the peri ventricular and juxta cortical white matter (**B**) 3D T1 images showing multiple foci and patchy areas of slightly low signal intensity implicating the peri ventricular and juxta cortical white matter. (**C**) MR Volumetry



(A)



(B)

(C)MR Volumetry

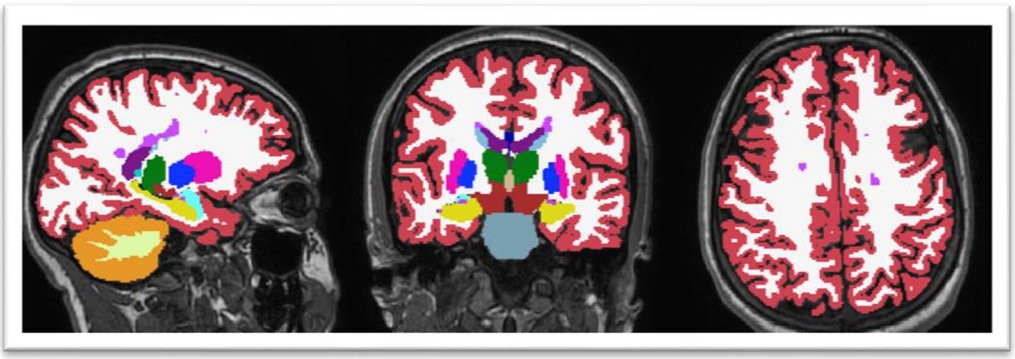
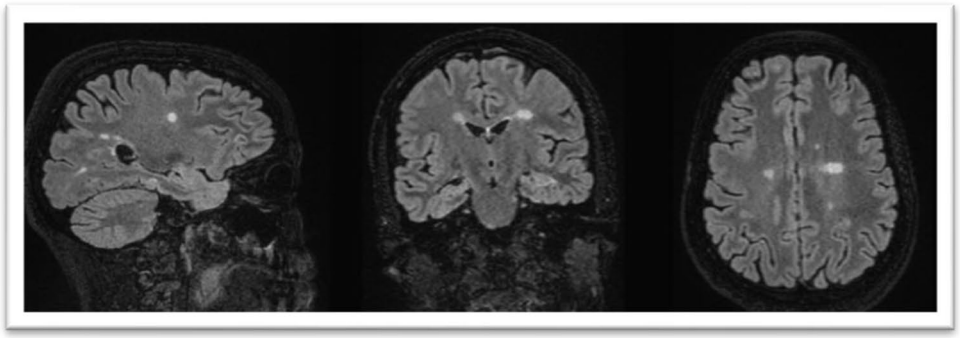
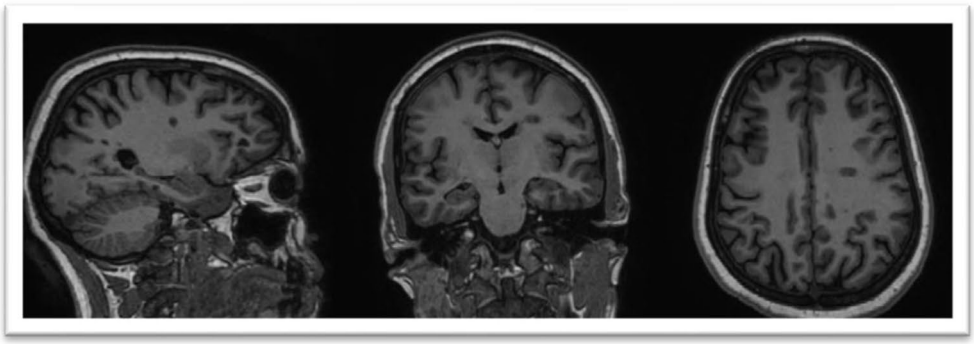


Fig. 11 27 year old male diagnosed with MS 5 years ago with EDSS (3) with features of cognitive impairment: (**A**) 3D FLAIR images showing multiple foci and patchy areas of high signal intensity implicating the peri ventricular and juxta cortical white matter. (**B**) 3D T1 images showing multiple foci and patchy areas of slightly low signal intensity implicating the peri ventricular and juxta cortical white matter. (**C**) MRI Volumetry



(A)



(B)

(C) MR Volumetry

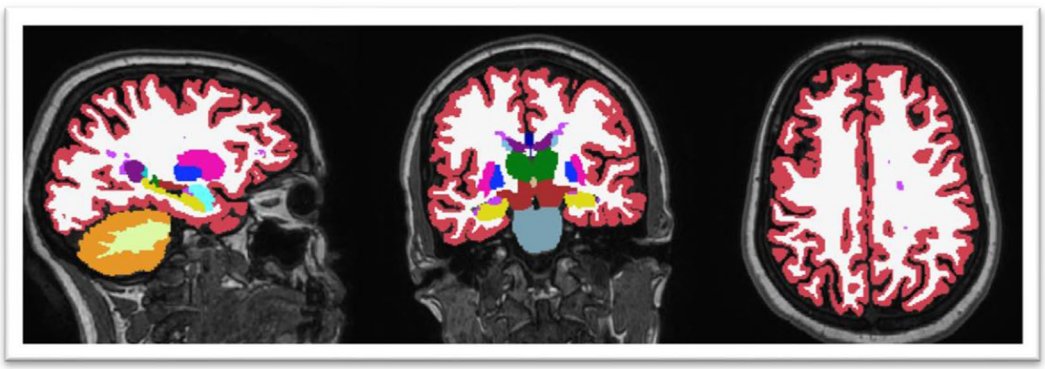
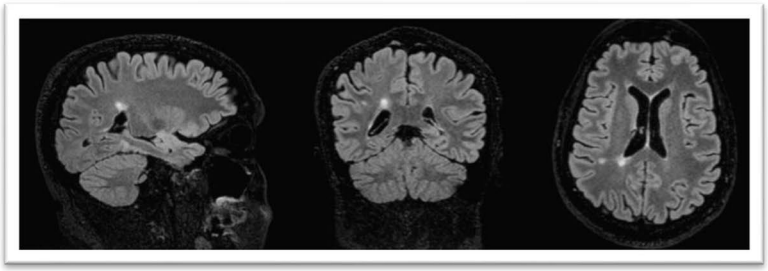
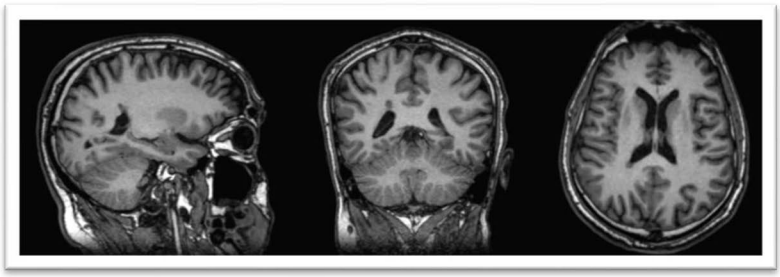


Fig. 12 29 year old male diagnosed with MS 8years ago with EDSS (4) with features of cognitive impairment. (**A**) 3D FLAIR images showing multiple foci and patchy areas of high signal intensity implicating the peri ventricular and juxta cortical white matter. (**B**) 3D T1 images showing multiple foci and patchy areas of slightly low signal intensity implicating the peri ventricular and juxta cortical white matter. (**C**) MR Volumetry

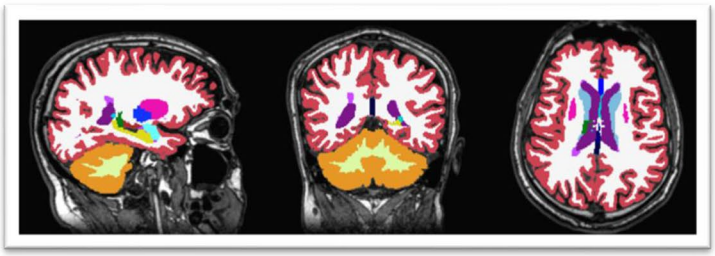


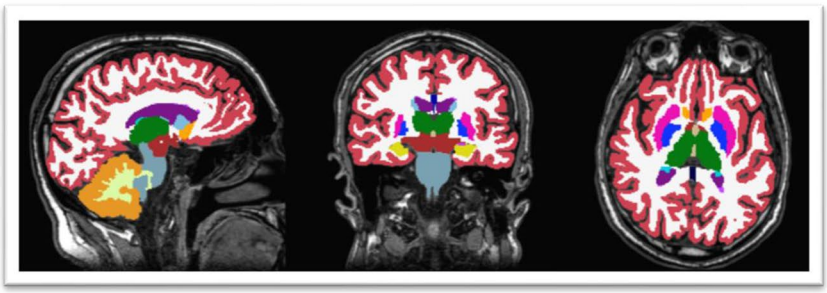
(A)



(B)

(C)MR Volumetry:





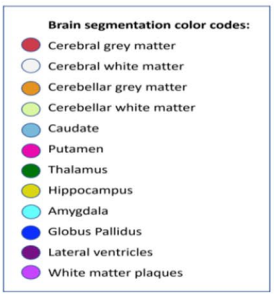
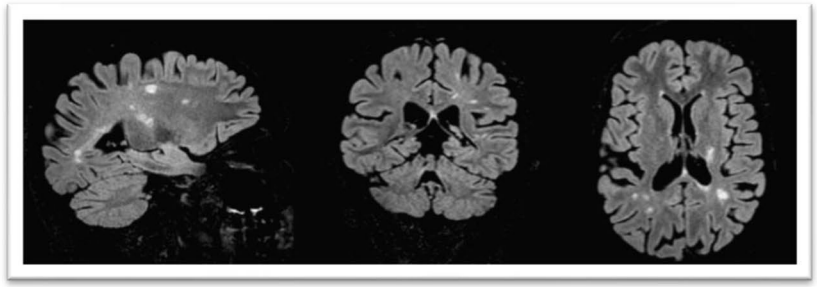
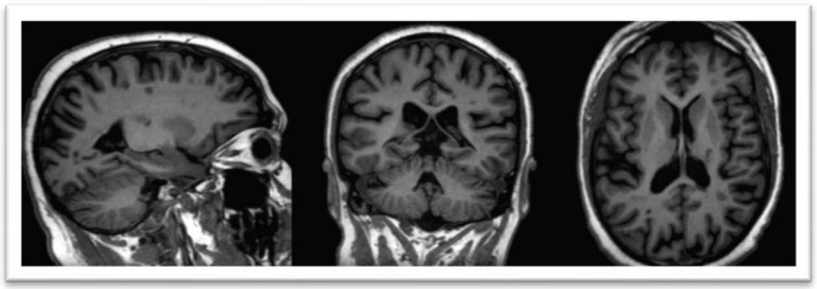


Fig. 13 32 year old male diagnosed with MS 9 years ago with EDSS (4) with cognitive impairment. (**A**) 3D FLAIR images showing multiple foci and patchy areas of high signal intensity implicating the peri ventricular and juxta cortical white matter. (**B**) 3D T1 images showing multiple foci and patchy areas of slightly low signal intensity implicating the peri ventricular and juxta cortical white matter. (**C**) MR Volumetry



(A)



(B)

(C)MRI Volumetry

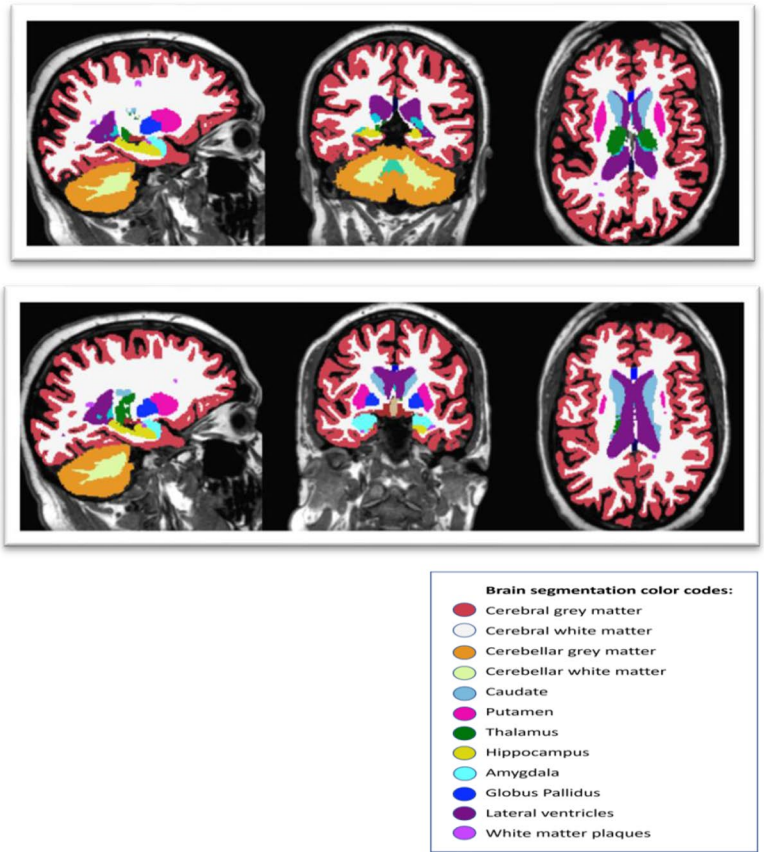


Fig. 14 24 year old female diagnosed with MS 3years ago with EDSS (1) and no cognitive impairment. (**A**) 3D FLAIR images showing multiple foci and patchy areas of high signal intensity implicating the peri ventricular and juxta cortical white matter. (**B**) 3D T1 images showing multiple foci and patchy areas of slightly low signal intensity implicating the peri ventricular and juxta cortical white matter. (**C**) MR Volumetry

atrophy. This indicates that the thalamus is the most frequent structure to be affected with whole brain atrophy (56.7%).

Study done by Alaleh et al. [23] agreed with us that corpus callosum, putamen and the caudate nucleus show a lower susceptibility for atrophic processes compared with the thalamus. The frequency of corpus callosum, caudate and putamen atrophy in our study was much lower than of the thalamus in 17 patients (56.7%) as compared to corpus callosum atrophy in 7 patients (23.3%), caudate atrophy in 7 patients (23.3%) and 2 patients with putamen atrophy (6.7%).

In our study, we showed that no patients with thalamic, caudate, putamen or corpus callosum atrophy without whole brain atrophy this may suggest that the whole brain volume affected more than isolated structure atrophy, or this may be due to long disease duration (mean duration of the cases was 6.1 years ± 2 SD) that affected the whole brain volume.

Our study showed ten patients (33.3%) with multiple structure atrophy.

Our findings differed from those documented in previous study done by Alaleh et al. [23], their study demonstrated thalamic atrophy without whole brain atrophy furthermore, almost no patients show whole brain atrophy, without thalamus atrophy. This disagreed with us as we noticed that 28 of 30 MS patients (93.3%) showed whole brain atrophy and the remaining 2 patients (6.7%) without whole brain atrophy did not show any other structure atrophy. No thalamic or other structures atrophy occurred without whole brain atrophy. In our research we did not detect a subgroup of MS patients with isolated thalamic atrophy in contrary to their study.

Our study results were matching with those detected by Sonia et al. [21] who reported a significant reduction of basal ganglia and thalamic volumes in MS patients relative to normal controls. DGM atrophy was most prominent for thalamus as compared to caudate and putamen.

The study done by Bergsland et al. [31] showed similar results to us, as they found that the early RRMS group showed significant decreases in multiple SDGM (thalamus, caudate and globus pallidus). They differed from us as they compared deep grey matter atrophy between patients with RRMS and patient with CIS. In our study, we compared atrophy of different grey matter structures and of corpus callosum in patients with RRMS to detect the most frequently affected structure that can be an early indicator of brain atrophy and disease progression.

A previous study done by Massimiliano et al. [32] detected presence of thalamic atrophy in remitting relapsing MS as in our study and found that the regional analysis of deep and cortical grey matter atrophy suggests an association between the neurodegenerative process taking place in the striatum—thalamus—frontal cortex pathway and the development of fatigue in relapsing—remitting multiple sclerosis.

In our study, we found no significant association between the presence of whole brain atrophy, isolated thalamic atrophy or multiple structure atrophy and increase of EDSS, this may be due to narrow range of variation of EDSS between MS patients and small sample size.

In our study, we showed no significant relation detected between the presence of cognitive impairment and, presence of whole brain, thalamic and multiple structure atrophy.

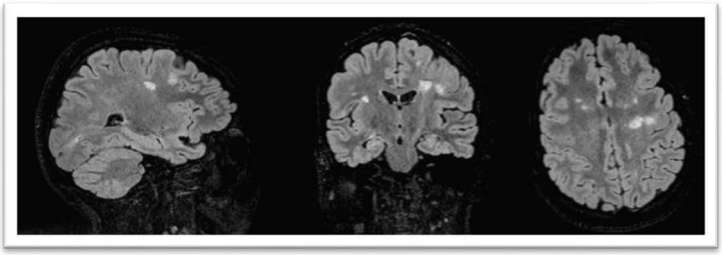
We were agreeing with Alaleh et al. [23], in that they did not found significant relation between increase in EDSS and presence of isolated thalamic atrophy but they successed to prove that there was significant relation between higher EDSS and subgroup of whole brain and associated thalamic atrophy.

We disagreed with Datta et al. [23], who found a weak association between EDSS and thalamic volume.

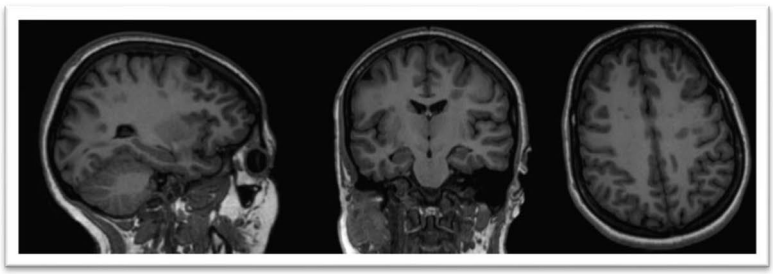
We found that no significant relation between the disease duration and degree of thalamic atrophy as well as between the disease duration and presence of multiple structures atrophy. The relation between the duration of illness and degree of loss of whole brain volume was insignificant and this might be due to the small sample size as its P value was 0.069 approaching significance, increase the sample size might increase significance. There was no significant relation between the presence of thalamic atrophy and disease duration. We could not assess the relation between the longer the disease duration and presence of whole brain atrophy as the number of patients without atrophy was too small to study this relation.

(See figure on next page.)

Fig. 15 33 year old female diagnosed with MS 9years ago with EDSS (4) and showed features of cognitive impairment. (**A**) 3D FLAIR images showing multiple foci and patchy areas of high signal intensity implicating the peri ventricular and juxta cortical white matter. (**B**) 3D T1 images showing multiple foci and patchy areas of slightly low signal intensity implicating the peri ventricular and juxta cortical white matter. (**C**) MR volumetry

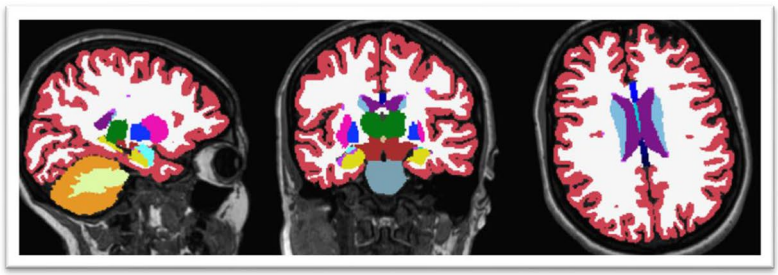


(A)



(B)

(C)MR Volumetry



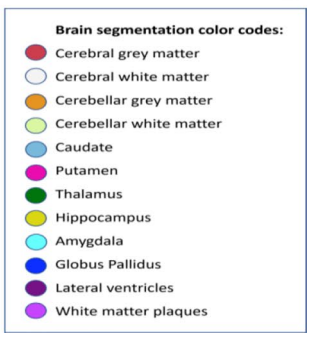


Fig. 15 (See legend on previous page.)

Table 9 EDSS in MS patients

	Mean	SD	Median	Minimum	Maximum
EDSS	3.17	0.99	3.00	1.00	5.00

Table 10 Relation between EDSS and whole brain, thalamic, multiple structure atrophy

	EDSS					*P* value
	Mean	SD	Median	Minimum	Maximum	
Whole brain atrophy						
Yes	3.18	1.02	3.00	1.00	5.00	0.662
No	3.00	0.00	3.00	3.00	3.00	
Thalamus atrophy						
Yes	3.24	1.03	3.00	1.00	5.00	0.680
No	3.08	0.95	3.00	1.00	4.00	
Multiple structures atrophy						
Yes	2.80	1.03	3.00	1.00	4.00	0.183
No	3.35	0.93	3.50	1.00	5.00	

Table 11 Relation between cognitive impairment and whole brain, thalamic and multiple structure atrophy

	Cognitive decline				*P* value
	+		−		
	Count	Column *N* %	Count	Column *N* %	
Whole brain atrophy					
Yes	18	94.7%	10	90.9%	1
No	1	5.3%	1	9.1%	
Thalamus atrophy					
Yes	11	57.9%	6	54.5%	1
No	8	42.1%	5	45.5%	
Multiple structures atrophy					
Yes	4	21.1%	6	54.5%	0.108
No	15	78.9%	5	45.5%	

Our results regarding the effect of duration of illness were different from those found by Alaleh et al. [23], as they studied only the effect of duration on the presence of thalamic and whole brain atrophy and they found

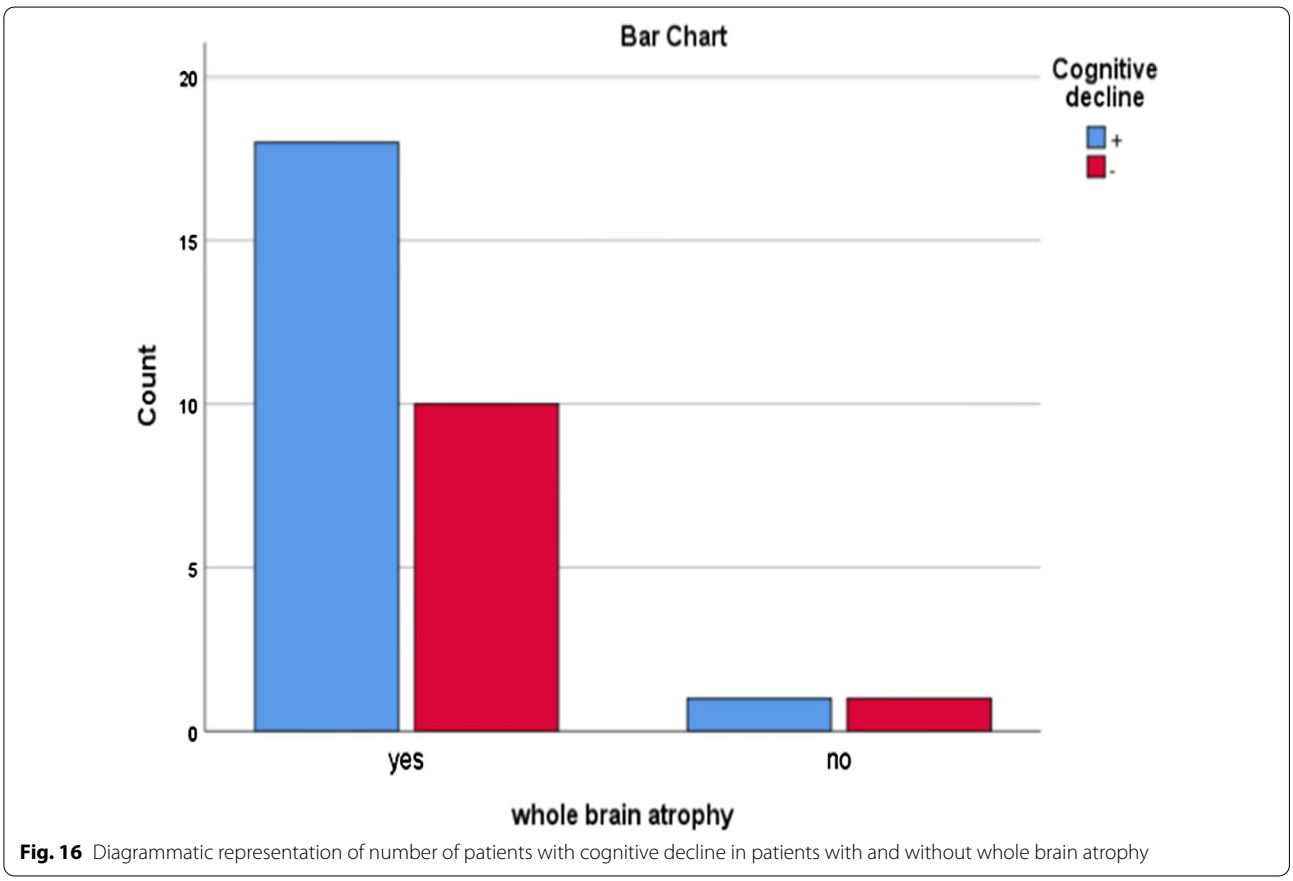


Fig. 16 Diagrammatic representation of number of patients with cognitive decline in patients with and without whole brain atrophy

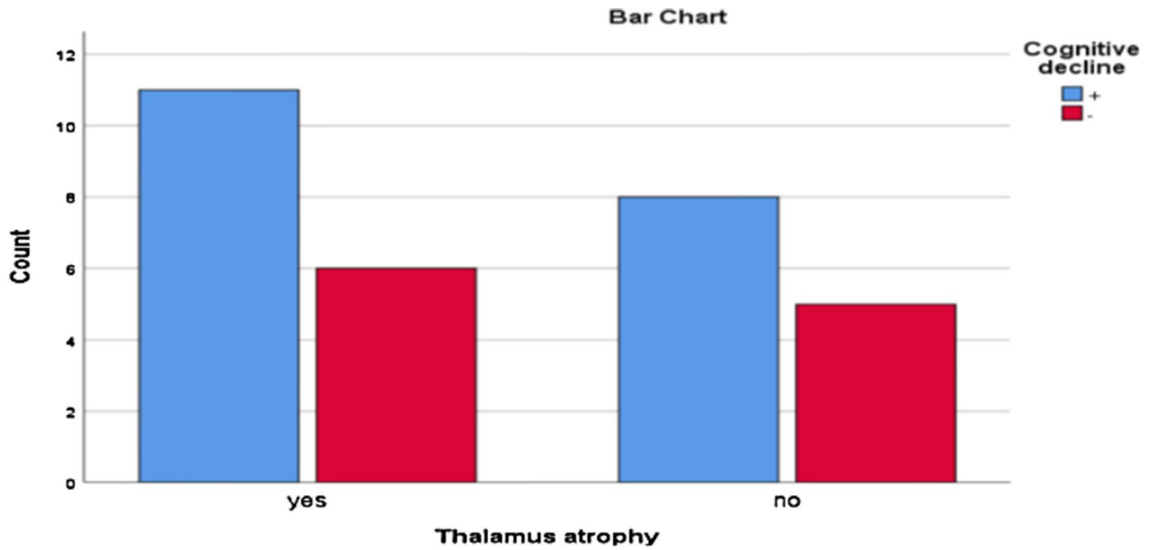


Fig. 17 Diagrammatic representation of number of patients with cognitive decline in patients with and without thalamic atrophy

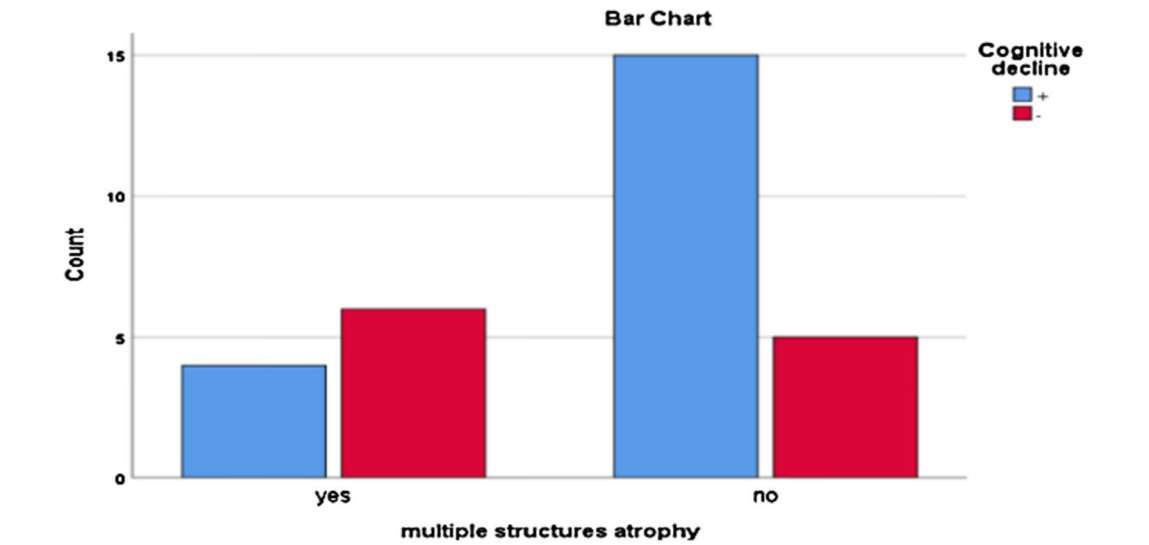


Fig. 18 Diagrammatic representation of number of patients with cognitive decline in patients with and without multiple structures atrophy

significant relation between the longer disease duration and presence of atrophy (P value = 0.036).

The limitations of our study were the small number of patients group the more number of cases the more the accuracy and impact of the study. The patients included in our study were diagnosed with remising and relapsing MS no patients with primary or secondary progressive MS. Relative long duration of illness (mean disease duration of the cases was 6.1 years ± 2 SD) short disease duration allows detection of early atrophic changes.

Other studies with larger number of cases and more variable types of MS subtype are highly recommended. In spite of small size of our sample and lack of variability of MS subtypes, we recommend to use MR volumetry technique in all patients diagnosed with MS for early detection of brain atrophic changes (which indicates progressive course of the disease and need of more aggressive therapy), as well as in the follow up of therapy to ensure the efficacy of the used medication.

Table 12 Relation between the duration and presence of thalamic atrophy

	Thalamus atrophy				*P* value
	Yes		No		
	Mean	SD	Mean	SD	
Duration	6.12	2.12	6.23	2.09	0.885

Table 13 Relation between duration of illness and degree of volume loss of the whole brain in patients with whole brain atrophy

Whole brain (volume relative to intracranial volume)	
Duration	
R	**0.348**
P value	0.069
N	28

Table 14 Relation between duration of illness and degree of volume loss of thalamus in patients with thalamic atrophy

Thalamus (volume relative to intracranial volume)	
Duration	
R	**0.236**
P value	0.361
N	17

Conclusion

Single time point MRI-based brain volumetry with predefined cut-offs for *z*-scores allows reliable and standardized differentiation between MS patients in variable stages of atrophy which markedly affect the clinical status and management of the patients.

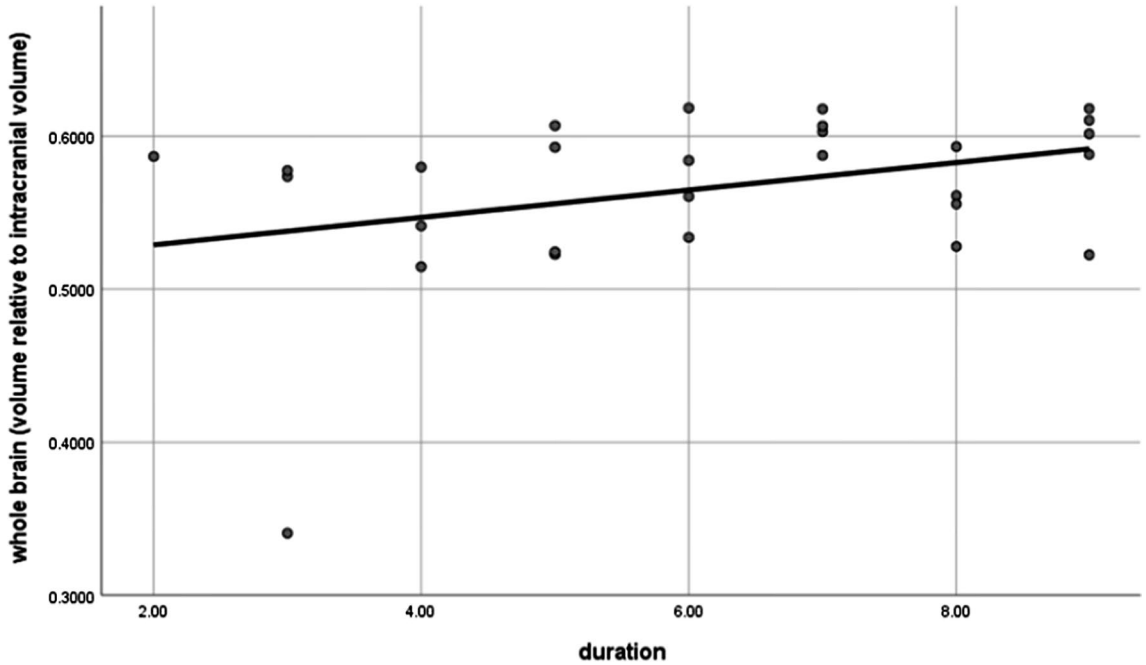


Fig. 19 Relation between loss of whole brain volume and duration of illness in patients with whole brain atrophy

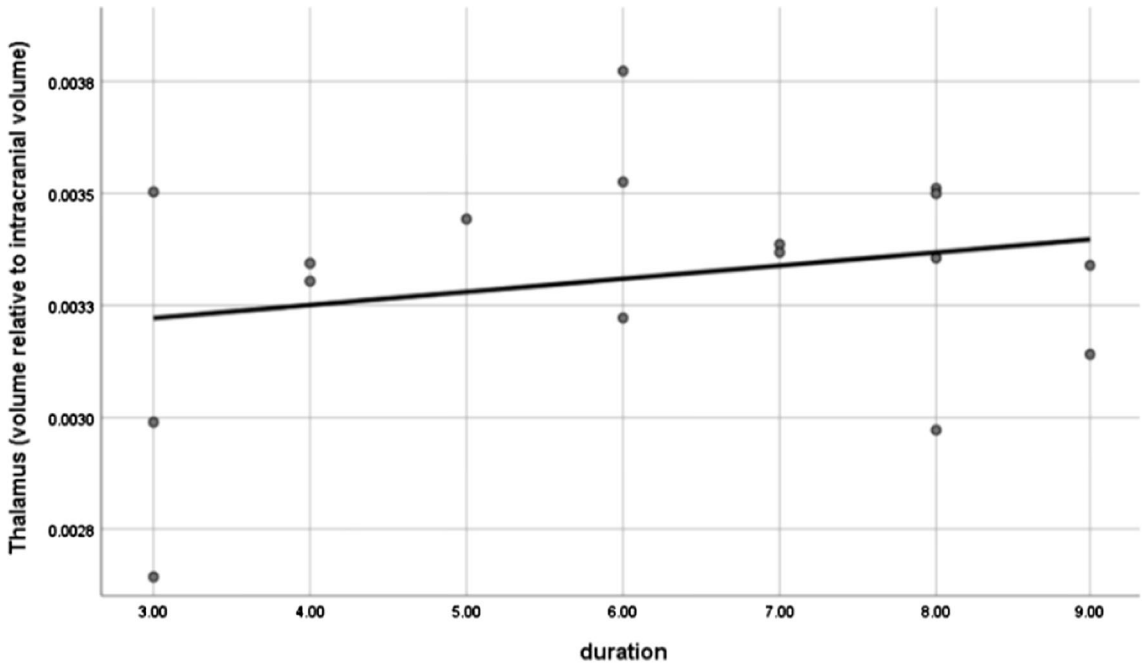


Fig. 20 Relation between loss of thalamic volume and duration of illness in patients with thalamic atrophy

Table 15 Relation between the duration of illness and presence of multiple structure atrophy

	Multiple structures atrophy				*P* value
	Yes		No		
	Mean	SD	Mean	SD	
Duration	5.30	1.89	6.60	2.06	0.106

Abbreviations

MS: Multiple sclerosis; BV: Brain volume; CNS: Central Nervous System; CIS: Clinically isolated syndrome; IPS: Information processing system; DGM: Deep grey matter; GM: Grey matter; WM: White matter; RRMS: Relapsing-remitting; SPMS: Secondary Progressive Multiple Sclerosis; SDMT: Symbol Digit Modalities Test; EDSS: Expanded Disability Status Scale; BP: Brain parenchyma; TIV: Total Intracranial Volume; OASIS: Access Series of Imaging Studies; MR: Magnetic resonance; MRI: Magnetic resonance imaging; 3D: 3 Dimension; Fig: Figure; GE: General electric; T: Tesla; TFE: Turbo Field Echo; FSPGR: Fast Spoiled Gradient Echo; VISTA: Volume Isotropic Turbo spin echo Acquisition; EDSS: Expanded Disability Status Scale.

Acknowledgements

We would like to express our gratitude to Dr. Ayman El Basmy, Assistant professor of radiology Cairo university, The completion of this work couldn't have been possible without his support. All efforts are appreciated from all the patients, staff members of neurology department, operators and colleagues.

Authors' contributions

NE put the design of the study. NE and MF analyzed and interpreted the patient data regarding the conventional MRI brain and MR volumetry results in MS patients. ME revised all the data interpreted by other authors. All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The current study had been approved by Cairo University Kasr Alainy Faculty of Medicine Research and Ethical committee. The committee's reference number is not applicable. Informed consent had been obtained from the patients.

Consent for publication

Not applicable because of the retrospective type of study.

Competing interests

The authors declare that they have no competing interests.

Received: 22 September 2021 Accepted: 14 February 2022
Published online: 31 March 2022

References

1. Lassmann H (1998) Neuropathology in multiple sclerosis: new concepts. Mult Scler 4(3):93–98
2. Bermel RA, Bakshi R (2006) The measurement and clinical relevance of brain atrophy in multiple sclerosis. Lancet Neurol 5(2):158–170
3. De Stefano N, Airas L, Grigoriadis N et al (2014) Clinical relevance of brain volume measures in multiple sclerosis. CNS Drugs 28:147–156
4. Wattjes MP, Rovira A, Miller D et al (2015) Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis–establishing disease prognosis and monitoring patients. Nat Rev Neurol 11:597–606

5. Azevedo CJ, Pelletier D (2016) Whole-brain atrophy: ready for implementation into clinical decision-making in multiple sclerosis? Curr Opin Neurol 29:237–242
6. Wang C, Beadnall HN, Hatton SN et al (2016) Automated brain volumetrics in multiple sclerosis: a step closer to clinical application. J Neurol Neurosurg Psychiatry 87:754–757
7. De Stefano N, Silva DG, Barnett MH (2017) Effect of fingolimod on brain volume loss in patients with multiple sclerosis. CNS Drugs 31:289–305
8. Fisher E, Rudick RA, Simon JH et al (2002) Eight year follow-up study of brain atrophy in patients with MS. Neurology 59:1412–1420
9. Fisniku LK, Chard DT, Jackson JS et al (2008) Gray matter atrophy is related to long-term disability in multiple sclerosis. Ann Neurol 64:247–254
10. Popescu V, Agosta F, Hulst HE et al (2013) Brain atrophy and lesion load predict long term disability in multiple sclerosis. J Neurol Neurosurg Psychiatry 84:1082–1091
11. Calabrese M, Rinaldi F, Mattisi I et al (2011) The predictive value of gray matter atrophy in clinically isolated syndromes. Neurology 77:257–263
12. Datta S, Staewen TD, Cofield SS et al (2015) Regional gray matter atrophy in relapsing remitting multiple sclerosis: baseline analysis of multi-center data. Mult Scler Relat Disord 4:124–136
13. Vaneckova M, Kalincik T, Krasensky J et al (2012) Corpus callosum atrophy—a simple predictor of multiple sclerosis progression: a longitudinal 9-year study. Eur Neurol 68:23–27
14. Yaldizli O, Penner IK, Frontzek K et al (2014) The relationship between total and regional corpus callosum atrophy, cognitive impairment and fatigue in multiple sclerosis patients. Mult Scler 20:356–364
15. Audoin B, Davies GR, Finisku L et al (2006) Localization of grey matter atrophy in early RRMS. Longitudinal Study J Neurol 253:1495–1501
16. Bergsland N, Horakova D, Dwyer MG et al (2012) Subcortical and cortical gray matter atrophy in a large sample of patients with clinically isolated syndrome and early relapsing-remitting multiple sclerosis. AJNR 33:1573–1578
17. Zivadinov R, Havrdová E, Bergsland N et al (2013) Thalamic atrophy is associated with development of clinically definite multiple sclerosis. Radiology 268:831–841
18. Jacobsen C, Hagemeier J, Myhr KM et al (2014). Brain atrophy and disability progression in multiple sclerosis patients: a 10-yearfollow-upstudy. J
19. Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9:357–381
20. Leyden J, Kleinig T (2018) The role of the basal ganglia in data processing. Med Hypotheses 71(1):61–64
21. Sonia B, Robert Z, Marietta H et al (2011) Basal ganglia, thalamus and neocortical atrophy predicting slowed cognitive processing in multiple sclerosis. ÓSpringer-Verlag 1 July
22. Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis. an expanded disability status scale (EDSS). Neurology 33:1444–1452
23. Alaleh R, Ann-Christin O, Roland O et al (2018) MRI-based brain volumetry at a single time point complements clinical evaluation of patients with multiple sclerosis in an outpatient settingront. Neurol V 9:545
24. Reuter M, Schmansky NJ, Rosas HD et al (2012) Within–subject template estimation for unbiased loungitudinal image analysis. Neuroimage 61(4):1402–1418
25. Chan YH (2003) Biostatistics 102: quantitative data—parametric & non-parametric tests. Singap Med J 44(8):391–396
26. Chan YH (2003) Biostatistics 103: qualitative data—tests of independence. Singap Med J 44(10):498–503
27. Chan YH (2003) Biostatistics 104: correlational analysis. Singap Med J 44(12):614–619
28. Eshaghi A, Prados F, Brownlee WJ et al (2018) Deep gray matter volume loss drives disability worsening in multiple sclerosis. Ann Neurol 83:210–222
29. Megna R, Alfano B, Lanzillo R et al (2019) Brain tissue volumes and relaxation rates in multiple sclerosis: implications for cognitive impairment. J Neurol 266:361–436
30. Miller DH, Grossman RI, Reingold SC et al (1998) The role of magnetic resonance techniques in understanding and managing multiple sclerosis. Brain 121(Pt 1):3–24
31. Bergsland N, Horakova D, Metros G, Dwyer O et al (2012) Subcortical and cortical gray matter atrophy in a large sample of patients with clinically isolated syndrome and early relapsing-remitting multiple sclerosis. AJNR Am J Neuroradiol 33:1573–78
32. Massimiliano C, Francesca R, Irene M et al (2010) Basal ganglia and frontal/parietal cortical atrophy is associated with fatigue in relapsing—remitting multiple sclerosis. Pub Med 16(10):1220–1228

Publisher's Note