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Cognitive impairment in paediatric onset multiple sclerosis and its relation to thalamic volume and cortical thickness of temporal lobe by magnetic resonance imaging

Nahed S. Ahmed[1], Mona A. AbdAllah[1*], Ayman M. Nassef[1], Alaa Eldeen A. Mohamed[2] and Maha A. Nada[1]

Abstract

Background: Pediatric onset multiple sclerosis (POMS), defined as an age at onset younger than 18 years, which occurs in 5% of patients with MS. cognitive dysfunction is one of the prominent disabling sequelae of Multiple sclerosis. Brain volumetric studies by magnetic resonance images revealed the decline of whole and regional brain volumes along the disease course. This work aimed to investigate the relationship between cognitive impairment in pediatric MS patients with thalamic atrophy and cortical thickness of temporal lobe. This study included 50 patients who were diagnosed as POMS and 50 healthy control participants matched for age and sex. Both groups were compared for volumetric measurements of thalamic volumes and temporal lobes cortical thickness using a computerized program called FreeSurfer.MS group was evaluated for cognitive dysfunction using Arabic version of fifth edition of Standford–Benit test. A correlation between volumetric results and neuropsychological evaluation of MS group was done.

Results: Our study showed that the MS group has the lowest value regarding their thalamic volumes and their cortical thickness of temporal lobes in relation to the healthy control group, while there was a significant relation between cognitive impairment and decrease in thalamic volume and specific areas in cortical thickness, such as superior temporal thickness, middle temporal thickness, inferior temporal thickness, fusiform thickness and para hippocampal thickness of temporal lobe in pediatric onset MS patients.

Conclusions: POMS affects specific brain areas such as thalamus and cortical thickness of temporal lobes regarding their volume and thickness which influence the neuropsychological evaluation detected by Standford–Benit test.

Keywords: POMS, Cognitive impairment, Thalamic volumes, Cortical thickness

Background

Multiple Sclerosis (MS) is a chronic disease affecting central nervous system (CNS) which characterized by different stages of structural brain and spinal cord damage. The prevalence of MS in Egypt has been shown to be 13.7/100,000 [1] and 25/100,000 in two studies, respectively [2, 3]. The demographics and clinical and paraclinical data of Egyptian MS patients are comparable with other registries in the Middle East and North Africa region and in Europe with a slight lower mean age at onset and lower incidence of family history [4]. Pediatric onset multiple sclerosis (POMS), defined as an age at onset younger than 18 years, which occurs in 5% of patients with MS. POMS is distinguished from adult-onset MS (AOMS) by several clinical and radiological features, which may suggest age-dependent pathophysiological differences. One of the most important thing in POMS is that chronic inflammation occurs in the

*Correspondence: monaabdelsalam43@gmail.com

[1] Neurology Department, Faculty of Medicine, Ain Shams University, 11591, 38Abbasia, Cairo, Egypt
Full list of author information is available at the end of the article

developing central nervous and immune systems, which explain the differences seen in POMS as compared with AOMS [5]. Many evidences have indicated the importance of neurodegenerative processes affecting the grey matter (GM), as MS has traditionally been considered a demyelinating inflammatory disease with exclusive impairment of the white matter (WM),it is known that MS is characterized by a great clinical and neuro-radiological heterogeneity, MS can present with a lot of symptoms, including motor and sensory dysfunctions, ataxia, fatigue, sphincter and neuro-psychiatric manifestations, some of which only partially explained by focal damage and lesion burden [6]. An increasing great attention has been focused on the neuro-radiological correlates of cognitive dysfunctions in MS, to understand the influence of focal inflammation, neurodegeneration and their concomitant effects on the presence and severity of cognitive impairment, as well as its evolution [7], Some software packages have been developed for measuring brain tissue volume using Magnetic resonance imaging (MRI) with semi-automatic segmentation, such as FreeSurferc (The General Hospital Corporation, Boston MA, USA), FIRST (FMRIB's Integrated Registration and Segmentation Tool), FSL (FMRIB's Software Library), and SPM (Statistical Parametric Mapping) [8]. It is known that brain atrophy and lesion load may predict the long-term disability in MS. an association of cognitive dysfunctions with brain volume in particular of the cortical GM, lesion load and lesion site was reported, which are useful biomarkers to predict the patients' cognitive functions. However, uncertainty exists about the influence of the subcortical GM (scGM) structures that regulate cognition and affective functioning, and that previous studies have indicated to drive the disability worsening in MS [9]. A worse cognitive performance can be predicted in some conditions, such as younger age at onset, longer disease duration, higher disability levels and higher number of relapses in the year preceding cognitive assessment [10].

The purpose of the present study is to detect the effect of POMS on brain volume loss especially thalamic volume and cortical thickness of temporal lobes and to investigate its relation to cognitive dysfunction in POMS patients.

Methods

Our participants are chosen as simple random samples, the study included 50 patients who were diagnosed pediatric onset MS and 50 healthy control participants matched for age and sex. Adult patients and parents signed a written consent form before performing any procedures. Our study included patients with an established diagnosis of MS who had their first demyelinating event before age of 18, all of them have been followed up after the first attack of CNS demyelination and were diagnosed as MS based on demonstration of clinical and MRI evidence of new disease event according to 2017 revised MCDonald's criteria and IPMSSG 2013 criteria for pediatric onset MS. We exclude participants who had their first demyelinating event before age of 18ys but did not fulfill diagnostic criteria of MS, also children and adolescents who had incidental finding of brain MRI lesions suggestive for MS but did not fulfill diagnostic criteria of MS, Children who met diagnostic criteria of ADEM, Participants for whom the clinical, MRI or laboratory findings suggestive for alternative diagnosis and children who have cognitive impairment due to other causes rather than MS also patients were excluded if they were illiterate, or had a history of any neuropsychiatric disorder other than MS, a history of drug abuse or cognitive enhancing medication, or having systemic diseases or metabolic disorders that may impair cognition, any visual, or hearing problem that could interfere with performance of the neuropsychological test.MS cases were subjected to: full neurological history about the disease including: detailed history about the first demyelinating attack (type of the attack, duration of the attack, treatment received during the attack and any residual from the attack),evaluation of the first MRI brain and cervical spinal cord with contrast.

Neuropsychological evaluation

We assessed the cognitive function of the MS group only, in the psychiatry clinic in Maadi military hospital by trained psychologists using the fifth edition of Standford–Benit test which is a neuropsychological test used for assessment of cognitive ability and intelligence that used in young children to diagnose developmental or intellectual deficiencies. This test measures five factors and consists of both verbal and nonverbal subtests. The five factors being tested are knowledge, quantitative reasoning, visual–spatial processing, working memory, and fluid reasoning. The psychologist gives fixed instructions to all participants through reading it from the book of instructions using a clear voice and explaining it using the same words to all participants. There is a training period given by the psychologist to the participant before each subtest, all participants were tested in the same clinic which was a quiet room away from noise.

Imaging processing

For both cases and controls, volumetric measurements were done for thalami volumes and temporal lobes cortical thickness in 3D MR imagesT1 weighted images from 3T MRI (general electric, Discovery MR750 3.0T, USA), using a computerized program called FreeSurfer contains a set of programs with a common focus of analyzing MRI

scans of brain tissue. FreeSurfer includes tools for the reconstruction of topologically correct and geometrically accurate models of both the gray/white and pial surfaces, for measuring cortical thickness, surface area and folding, and for computing, example Figs. 1 and 2. Both case and control groups were compared for relative thalamic volumes and cortical thickness in temporal lobes. A correlation was done in MS group between results of neuropsychological evaluation and volumetric studies which included relative thalamic volumes and cortical thickness of temporal lobes.

Statistical method

Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean ± standard deviation and ranges when their distribution was parametric (normal), while non-normally distributed variables (non-parametric data) were presented as median with inter-quartile range. In addition, qualitative variables were presented as number and percentages. Data were explored for normality using Kolmogorov–Smirnov and Shapiro–Wilk Test. *The following tests were done: Independent-samples t test* of significance was used when comparing between two means. The Comparison between groups with qualitative data was done using *Chi-square test* and *Fisher's exact test* instead of Chi-square test only when the expected count in any cell less than 5. *Pearson's correlation coefficient (r)* test was used to assess the degree of association between two sets of variables. Value of "r" ranges from −1 to 1 0 = no linear correlation 1 = perfect positive correlation; 1 = perfect negative correlation. *Positive* = Increase in the independent variable leads to increase in the dependent variable and *Negative* = Increase in the independent variable leads to decrease in the dependent. Scatter plot: a graph in which the values of two variables are plotted along two axes, the pattern of the resulting points revealing correlation present. The confidence interval was set to 95% and the margin of error accepted was set to 5%. Therefore, the p value was considered significant as the following: Probability (p-value) p-value < 0.05 was considered significant. p-value < 0.001 was considered

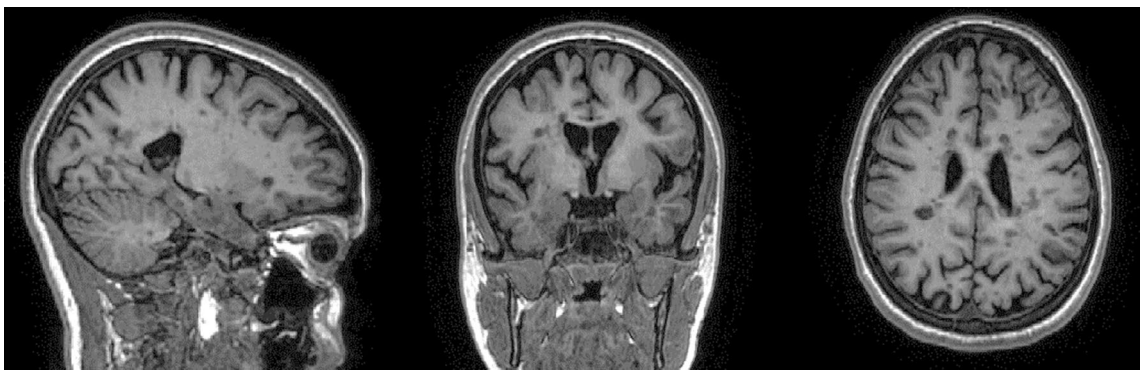

Fig. 1 Axial, coronal and sagittal cuts of 3DT1 images

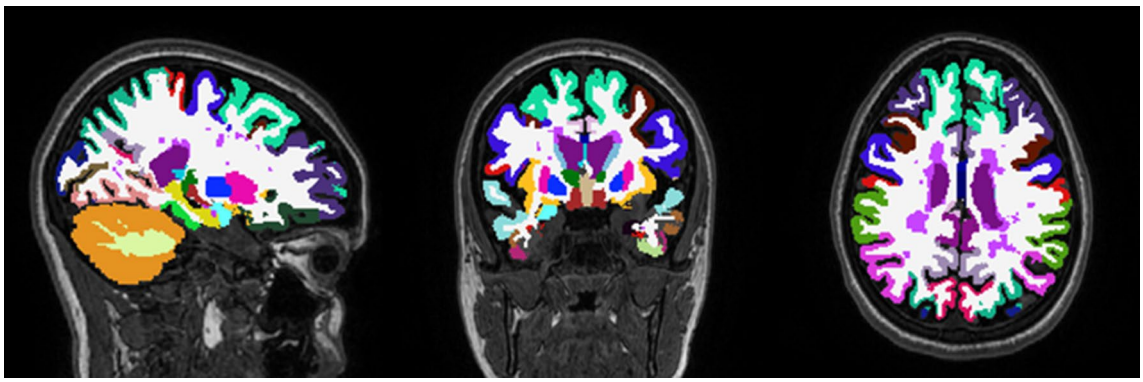

Fig. 2 Cortical and deep gray matter segmentation using free surfer software

p-value < 0.001 was considered as highly significant. p-value > 0.05 was considered insignificant.

Results

Demographic and clinical factors: The study included 50 patients diagnosed as paediatric onset MS, 42 females and 8 males, the youngest was 16 years, while the oldest was 35 years. Fifty healthy controls, ages and sex matched, for measurement of thalamic volume and cortical thickness of temporal lobe their MRI brain, with the same inclusion and exclusion criteria in both group. The two groups were comparable in age and there is no statistically significant difference between the groups with p value ($p = 0.202$), Samples characteristics are demonstrated.

We measured temporal lobe cortex thickness (left side) in both groups (Fig. 3): There were significant difference between two groups according to superior temporal thickness with p value ($p < 0.001$). The lowest value was found in MS group (2.14 ± 0.19) compared to Control group (2.81 ± 0.15). In addition, there was a significant difference between two groups according to middle temporal thickness with p-value ($p < 0.001$). The lowest value was found in MS group (2.17 ± 0.18) compared to Control group (2.83 ± 0.14). Furthermore, there was a significant difference between two groups according to inferior temporal thickness with p-value ($p < 0.001$). The lowest value was found in MS group (2.60 ± 0.18) compared to Control group (2.74 ± 0.16). As well as, there was significant difference between two groups according to fusiform thickness with p-value ($p = 0.002$). The lowest value was found in MS group (2.61 ± 0.14) compared to Control group (2.70 ± 0.13). As notices that there was a significant statistically difference between two groups according to parahippocampal thickness with p-value ($p < 0.001$). The lowest value was found in MS group (2.09 ± 0.31) compared to Control group (2.78 ± 0.29). Meanwhile, there was a significant statistically difference between two groups according to average of temporal lobe cortex thickness at left side with p-value ($p < 0.001$). The lowest value was found in MS group (2.46 ± 0.16) compared to Control group (2.85 ± 0.14).There is no significant statistically difference between groups according to entorhinal thickness with p-value ($p > 0.05$ NS). We also measured Temporal lobe cortex thickness (Right Side) (Fig. 4): There were a significant statistically difference between two groups according to superior temporal thickness with p-value ($p = 0.004$). The lowest value was found in MS group (2.73 ± 0.14) compared to Control group (2.81 ± 0.15). In addition, there was a statistically significant difference between two groups according to middle temporal thickness with p-value ($p < 0.001$). The lowest value was found in MS group (2.12 ± 0.23) compared to Control group (2.81 ± 0.16). Furthermore, there was a statistically significant difference between two groups according to inferior temporal thickness with p-value ($p < 0.001$). The lowest value was found in MS group (2.67 ± 0.13) compared to Control group (2.77 ± 0.12). As well as, there was a statistically significant difference between two groups according to fusiform thickness with p-value ($p = 0.007$). The lowest value was found in MS group (2.61 ± 0.17) compared to Control group (2.71 ± 0.16). As notices that there was a statistically significant difference between two groups according to parahippocampal thickness with p-value ($p < 0.001$). The lowest value was found in MS group (1.99 ± 0.26) compared to Control group (2.69 ± 0.19). Meanwhile, there was a statistically significant difference between two groups

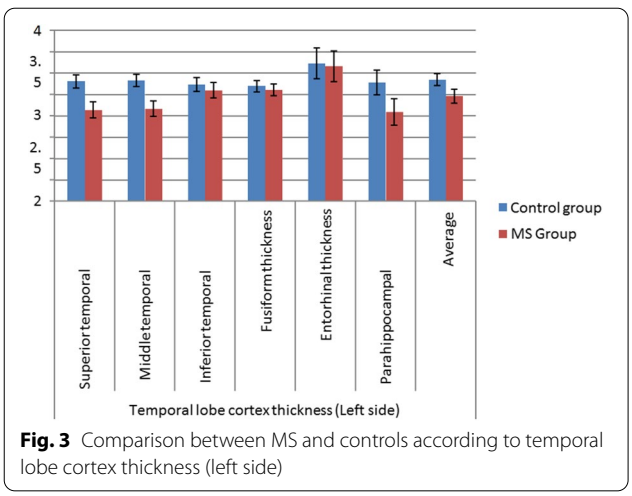

Fig. 3 Comparison between MS and controls according to temporal lobe cortex thickness (left side)

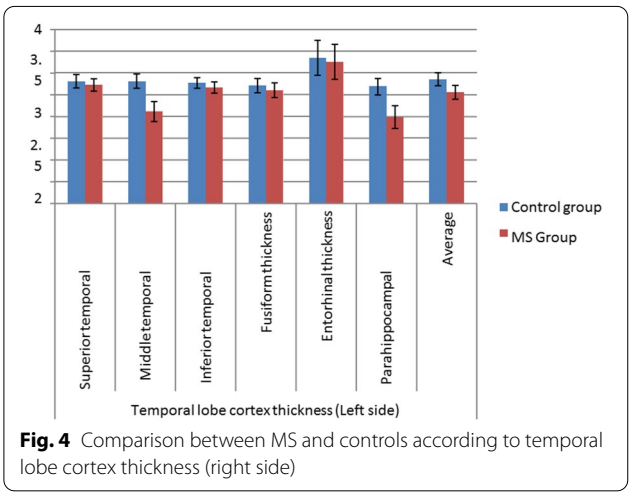

Fig. 4 Comparison between MS and controls according to temporal lobe cortex thickness (right side)

Table 1 Comparison between control groups and MS group according to relative thalamic volume

Relative thalamic volume	Control group ($n=50$)	MS Group ($n=50$)	Test value	p-value
Left			11.632	< 0.001**
Mean ± SD	0.0053 ± 0.0006	0.0039 ± 0.0006		
Range	0.0040–0.0067	0.0024–0.0049		
Right			16.284	< 0.001**
Mean ± SD	0.0052 ± 0.0007	0.0032 ± 0.0006		
Range	0.0038–0.0072	0.0017–0.0042		

Using: *t*-Independent Sample

*p-value > 0.05 NS; *p-value < 0.05 S; **p-value < 0.001 HS*

according to average of temporal lobe cortex thickness at right side with p-value ($p<0.001$). The lowest value was found in MS group (2.56 ± 0.16) compared to Control group (2.86 ± 0.15).There is no statistically significant difference between groups according to entorhinal thickness with p-value ($p>0.05$ NS).

When we compare the relative volume of the thalami in both groups showed a statistically significant difference between two groups according to left and right relative thalamic volumes with p value ($p<0.001$). The lowest value was found in MS group compared to Control group, as shown in Table 1.

As shown in Tables 2 and 3, we assessed cognitive functions of MS group using Standford–Benit Test-5.

We did a Correlation between temporal lobe cortex thickness (right and left) and Standford–Benit Test-5 (Non-Verbal, Verbal, Non-Verbal IQ, verbal IQ and full scale IQ we found that: in non-Verbal sub tests there was a statistically significant correlation between average of temporal lobe cortex thickness (left) with verbal-fluid reasoning ($p=0.041$) and a statistically significant correlation between average of temporal lobe cortex thickness (left) with Quantitative reasoning($p=0.003$) and Visual spatial processing in verbal sub tests ($p=0.011$). In addition, there were a statistically significant correlation between parahippocampal thicknesses (right) with verbal-fluid reasoning in nonverbal sub tests ($p=0.007$). In verbal sub tests: there were a statistically significant correlation between Inferior temporal thickness with knowledge ($p=0.011$); in addition, there was statistically significant correlation between entorhinal thickness with knowledge ($p=0.017$).Finally a significant correlation

Table 2 Standford–Benit Test-5 distribution among MS group ($n=50$)

Standford–Benit Test-5	Borderline (< 6 score)		Low average (6–7 score)		Average (8–12 score)		High average (≥ 13 score)		Range	Mean ± SD
	n	%	*n*	%	*n*	%	*n*	%		
Non Verbal										
Fluid reasoning	3	6.0	12	24.0	35	70.0	0	0	4–12	8.54 ± 2.01
Knowledge	13	26.0	26	52.0	11	22.0	0	0	2–10	6.62 ± 1.79
Quantitative reasoning	19	38.0	14	28.0	17	34.0	0	0	1–10	6.22 ± 2.61
Visual spatial processing	12	24.0	15	30.0	23	46.0	0	0	3–11	7.00 ± 2.15
Working memory	17	34.0	14	28.0	19	38.0	0	0	1–12	6.42 ± 2.71
Verbal										
Fluid reasoning	7	14.0	11	22.0	13	26.0	19	38.0	1–16	10.08 ± 4.11
Knowledge	31	62.0	7	14.0	10	20.0	2	4.0	1–13	4.50 ± 3.48
Quantitative reasoning	5	10.0	2	4.0	32	64.0	11	22.0	2–15	10.30 ± 2.95
Visual spatial processing	7	14.0	11	22.0	30	60.0	2	4.0	2–13	8.22 ± 2.93
Working memory	24	48.0	12	24.0	10	20.0	4	8.0	2–19	6.56 ± 3.65

Table 3 Full scale IQ, non-verbal IQ and verbal IQ distribution among MS group ($n=50$)

	Average		Low average		Borderline impaired		Mildly impaired		Range	Mean ± SD
	n	%	*n*	%	*n*	%	*n*	%		
Full scale IQ	20	40.0%	19	38.0%	6	12.0%	5	10.0%	60–104	86.16 ± 10.36
Nonverbal IQ	13	26.0%	16	32.0%	18	36.0%	3	6.0%	68–101	83.38 ± 9.51
Verbal IQ	27	54.0%	3	6.0%	14	28.0%	6	12.0%	63–104	87.10 ± 11.26

was observed between average of temporal lobe cortex thickness (left) with full scale IQ ($p=0.003$), non-verbal IQ ($p=0.027$) and verbal IQ ($p=0.018$); and a statistically significant correlation between average of temporal lobe cortex thickness (right) with full scale IQ ($p=0.036$), non-verbal IQ ($p=0.041$)and verbal IQ ($p=0.043$).

We compared between relative thalamic volumes (right and left) and Standford–Benit Test-5 We found that, there were a statistically significant correlation between relative left and right thalamic volumes with non-verbal: visual spatial processing ($p=0.032$), ($p=0.039$), while there were statistically significant correlation between relative left and right thalamic volumes with verbal: quantitative reasoning ($p=0.019$), ($p=0.002$).

Discussion

Multiple sclerosis (MS) is one of the leading causes of disability in young adults. The onset of MS during developmental age makes pediatric patients particularly susceptible to cognitive impairment, resulting from both disease-related damage and failure of age-expected brain growth. The median age at first attack in most POMS cohorts is between 11 and 13 years [11]. Cognitive impairment is defined as having one-third or more test scores in the impaired range [12]. The neurodegenerative and inflammatory impact of MS meets the brain during a critical time period and may disturb myelination process and other maturation processes of the brain [13]. Radiological evaluation is focusing on the presence of typical WM lesions of MS, involving their morphology and location. Another important component of MS pathology is neurodegeneration which cause brain atrophy—has been identified as an important prognostic factor for disease progression in the research field [14]. In our study, we compared MS and controls, regarding the cortical thickness of all parts of temporal lobes including "superior, middle and inferior temporal thickness, fusioform, enthorinal and para hippocampal thickness" in both hemispheres. We found a difference in the thickness of temporal lobe cortex, the lowest value was related to the MS group. In the same context a study done in 2020, comparing GM volume between MS group and healthy control group, the results showed GM volumes were significantly decreased by approximately 5% in both sexes in MS group [15]. In addition, Sugijono et al. showed that significant reductions in GM volume, especially in the frontotemporal cortex, and this GM volume reduction progressively occurred in patients with progressing lesions in their WM [16]. We also study the relative thalamic volumes in both hemispheres comparing it with the controls and we found that there was significant difference between the two groups, the lowest value was found in MS group. According to Minagar et al., the thalamus is the most vulnerable structure to be atrophied in all MS subtypes. Nuclei of the thalamus are GM structures which influence cognition, sensory and motor functions due to their major role in activation of the cortex and relaying sensory information to the higher centers of the cortex. A wide range of neuropsychological manifestations, including cognitive impairments and motor deficits found in MS patients are due to involvement of these structures, which might become a biomarker of disease progression [17]. Another study reported that, in comparison to healthy controls the reduction in thalamic volumes in MS patients was about 17%, with a significant correlation between the width of the third ventricle and thalamus atrophy ($r=-0.59$; $p<0.05$), also atrophy in GM Subcortical structures occurred in almost all MS patients, also the rate of atrophy of subcortical GM in MS patients was faster than that of other brain areas [18].We studied the cognitive functions of the MS group using the fifth version of Standford–Benit test, we found in nonverbal subtests that knowledge and quantitative reasoning are the most affected cognitive domains, while in verbal subtests, knowledge and working memory are the most affected cognitive domains, also non-verbal IQ was more affected than verbal and full IQs. In MS group, we did a correlation between temporal lobe cortex thicknesses and relative thalamic volumes with Standford–Benit Test-5. We found that there were a significant correlations between impairment that was found in specific cognitive domains like fluid reasoning, quantitative reasoning and visual spatial processing with decrease in volumes of temporal lobe cortical thicknesses and relative thalamic volumes. In 2014 a study was done used structural and functional MRI to understand the mechanisms responsible for cognitive impairment in POMS, in Comparing to the controls, MS patients showed reduced resting-state functional connectivity of the precuneus, a multivariable model identified diffusivity abnormalities of the cingulum and corpus callosum and the precuneus as the covariates more strongly associated with cognitive impairment (C-index = 0.99) [19]. Till et al. dictated that thalamic volume accounted for significant incremental variance in predicting global IQ, processing speed, and expressive vocabulary and was the most robust MRI predictor of cognitive impairment relative to other MRI metrics [20].

A longitudinal prospective, study of MS patients identifies of GM MRI markers and associated clinical symptoms and impact to unemployment. Subcortical deep grey matter (SDGM) atrophy showed a strong association with unemployment, whereas cortical atrophy showed a weaker, yet significant relationship with employment status. Thalamus, pallidus, putamen and hippocampus are the more area out of the SDGM

structures that have the lowest volumes, and are found to be associated with unemployment [21]. This is in line with a cross sectional study of 50 RRMS patients showing significantly more thalamic atrophy in unemployed patients [22]. Lorefice et al. documented that, thalamus has the smallest volume among the reported scGM structures, observed in cognitive impaired patients, and this result agree with previous studies that documented the relation between thalamic atrophy and cognitive decline in RRMS patients, indicating its important predictor tool for memory and executive deficits [23]. In 2016 a study done showed alterations in right and left thalamic shape were found to correlate with change in performance on the symbol digit modality test (p value = 0.011) [24].

Our study has some limitations. First, lack of data about our patients' base line cognitive function before or at time of their diagnosis by MS. Second, we did not assess the disease modifying therapy effect on both cognitive function and on brain volume loss. Finally, we did not involve the number of relapses nor the *Expanded* Disability Status Scale in our study.

Conclusions

Our study showed that the MS group has the lowest value regarding their thalamic volumes and their cortical thickness of temporal lobes in relation to the healthy control group, while there was a significant relation between cognitive impairment and decrease in thalamic volume and specific areas in cortical thickness like superior temporal thickness, middle temporal thickness, inferior temporal thickness, fusiform thickness and para hippocampal thickness of temporal lobe in pediatric onset MS patients.

Abbreviations

MS: Multiple sclerosis; CNS: Central nervous system; POMS: Pediatric onset multiple sclerosis; AOMS: Adult onset multiple sclerosis; WM: White matter; GM: Grey matter; SDGM: Subcortical deep grey matter; scGM: Sub cortical grey matter; MRI: Magnetic resonance imaging.

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Author contributions

All authors have participated in designing of the study, acquisition of data, data interpretation and revising. All authors read and approved the final manuscript.

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Availability of data and materials

All raw data will be available on the editor request.

Declarations

Ethical approval and consent to participate

The study protocol was approved by the local Research Ethics Committee (REC) and quality assurance unit, faculty of medicine, Ain Shams in January 2019. Participation was voluntary and all contributors or their first-degree relatives received detailed information about the aims of this research work and an informed consent was obtained prior to the commencement of the study.

Consent for publication

A written informed consent for the publication was obtained from all the participants (or their first degree relatives).

Competing interests

The authors declare that they have no competing interests. The authors have no conflict of interest to disclose.

Author details

[1]Neurology Department, Faculty of Medicine, Ain Shams University, 11591, 38Abbasia, Cairo, Egypt. [2]Radiology Department, Military Medical Academy, 7 Ehsan Abd Al Kodoos, Mansheya El-Bakry, Heliopolis, Cairo, Egypt.

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