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Original Article

Thalamic atrophy in active and inactive secondary progressive multiple sclerosis patients: A comparative study

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Abstract

Background: Thalamic atrophy may be an indicator of neurodegeneration in people with secondary progressive multiple sclerosis (pwSPMS). The atrophy usually begins asymmetrically, and the thalamic asymmetry index (TAI) can be used to estimate the severity of neurodegeneration. SPMS is commonly divided into two groups of active and inactive. No study has compared TAI between SPMS groups and examine its relationships with cognitive and motor measures in pwSPMS. This study aimed to compare the TAI between active and inactive pwSPMS and to examine its relationship with key clinical, cognitive, and motor variables.

Methods: In this cross-sectional study, 38 pwSPMS (15 active and 23 inactive) were enrolled from February to November 2024. MRI-based volumetric measurements were used to determine thalamic volumes and calculate the TAI. Cognitive and motor tests, including the SDMT, PASAT, and 9HPT were also administered alongside clinical examinations.

Results: Active SPMS patients had significantly lower NTV compared to inactive patients (Cohen's d = -1.58, $p < 0.001$). No significant difference in TAI was observed between groups. NTV correlated with cognitive scores in both active ($r = 0.74$, $P = 0.002$) and inactive ($r = 0.65$, $p < 0.001$) groups and with disability in the inactive group ($r = -0.5$, $P = 0.014$). Active SPMS patients showed worse cognitive and motor performance.

Conclusion: Thalamic atrophy is more severe in active SPMS and is associated with worse cognitive and motor outcomes. While thalamic asymmetry did not differentiate between subgroups, it may serve as a marker for functional status in SPMS.

Keywords: Multiple sclerosis, SPMS, Thalamic atrophy, Cognitive performance, MRI, Neurodegeneration.

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Multiple sclerosis (MS) is a progressive inflammatory and degenerative disorder of the central nervous system (CNS) that is characterized by demyelination and neuroaxonal loss (1). In MS, cortical and subcortical regions are affected, and demyelination frequently involves gray matter structures such as the thalamus, hippocampus, caudate, putamen, and globus pallidus (2, 3). The thalamus plays a key role in sensory integration, motor coordination, and higher cognitive functions (4). It also helps regulate attention, memory, emotion, and levels of consciousness (5). Given its unique connectivity and susceptibility to MS neuropathology, the thalamus is frequently affected from the earliest disease stages (6). Thalamic atrophy exceeds that typically observed with aging and is associated with reductions in information processing speed and other cognitive abilities (7, 8). Moreover, previous studies have shown that thalamic atrophy may develop asymmetrically, and left–right volume differences may serve as early markers of structural disruption in MS (9-11).

This asymmetry along with brain atrophy, have been observed in different types of MS (9, 11). A recent study has demonstrated a significant relationship between thalamic atrophy asymmetry and relapsing-remitting MS (RRMS) disease progression (9). Secondary progressive MS (SPMS) often emerges after a prolonged relapsing–remitting course and is defined by a steady accumulation of disability with or without the presence of relapses (12). Recent studies have classified SPMS into active and inactive categories, based on clinical relapses or MRI evidence of new enhancing or T2 lesions (13, 14). Active SPMS is associated with younger age, greater inflammatory activity, and faster disability progression, whereas inactive SPMS is characterized by gradual worsening without radiological or clinical activity (13, 14). Thalamic and brain atrophy are recognized as important predictors of neurodegeneration and subsequent cognitive decline in SPMS (15). Accordingly, this study aimed to compare thalamic atrophy and asymmetry between active and inactive SPMS and to examine how thalamic volumetric measures relate to cognitive and motor performance.

Methods

Participants: This cross-sectional study included 38 SPMS patients referred to Kashani MS Clinic and Hakim MS Clinic in Isfahan from February to November 2024. The diagnosis of SPMS was conducted by expert neurologists based on the McDonald 2016 criteria (16). To determine whether patients had active or inactive SPMS, MRIs from the last 5 years, the patient's disease history, and recent relapses have been reviewed. SPMS patients with MRI activity (new T2 lesions or T1 gadolinium-enhancing lesions) or recent relapse has been classified as active SPMS, whereas those with stable progression and no clinical or MRI activities were considered inactive SPMS (13, 17, 18).

The inclusion criteria were as follows: participants had to be between 18 and 55 years old and have a confirmed diagnosis of SPMS. Participants were excluded if they had the diagnoses of Alzheimer's disease, Parkinson's disease, stroke, central nervous system infections, bipolar disorder, schizophrenia, schizoaffective disorder, psychosis, brain tumor, seizures, obsessive-compulsive disorder, primary post-traumatic disorder, alcohol or substance abuse, major depressive disorder, suicidal behavior, or traumatic brain injury. Additionally, participants could not have previous diagnoses of dysarthria, dysphagia, or vision disturbances and needed to have a visual acuity of 20/40 or better. They also needed at least nine years of literacy education and proficiency in reading Latin numbers. The exclusion criteria included unwillingness to continue participation or to undergo MRI, pregnancy, corticosteroid use within the last 3 months, left-handedness, and any contraindications to MRI.

Clinical and demographic data: During examinations and interviews, demographic data of the patients including age, sex, and year of diagnosis, were collected. Additionally, the Expanded Disability Status Scale (EDSS) was assessed as the primary clinical measure.

Cognitive assessments: Symbol Digit Modalities Test (SDMT) and Paced Auditory Serial Addition Test (PASAT) were applied to assess cognitive function. The SDMT is a common test of information processing speed (19). The duration of this test is 90 seconds. The standard administration method which has been validated in Persian was administered (20). The PASAT measures information processing speed and attention. We used the standard administration method in this study (21). The Persian version of this test has shown acceptable validity and reliability (20).

Motor performance: The 9-HPT is a test of upper extremity function in MS. We used the standard administration method in this study (22).

MRI acquisition and image processing: Imaging was conducted using a Siemens Avanto MRI scanner system with a 1.5 Tesla magnet from Siemens, Germany. High-resolution T1-weighted images (T1-MPRAGE) were obtained for volumetric analysis with the following sequence parameters:

- Repetition time (TR) = 2200 milliseconds
- Echo time (TE) = 2.73 milliseconds
- Inversion time (TI) = 900 milliseconds
- Flip angle = 8°
- Field of view (FOV) = 256×256 millimeter
- Slice thickness = 1 millimeter

After undergoing initial quality control checks, the raw MRI data were subjected to segmentation using the advanced Volbrain system (23). Volbrain, an online system for brain volumetry, automatically segmented the images, and thalamic and total intracranial volume segmentation masks were extracted. Two experienced individuals using the ITK-SNAP software (24) (http://www.itksnap.org) reviewed the thalamic segmentation masks in the axial direction and verified them in the coronal and sagittal directions. Corrections were made as needed and approved by a trained neuroradiologist. Thalamic volumes and total intracranial volume (TIV) were then calculated. Thalamic

volumes were normalized by dividing them by TIV to adjust for individual differences in cranial volume. The normalized left thalamus volume (NLTV), normalized right thalamus volume (NRTV), and normalized whole thalamic volume (NWTV) were calculated as follows (9): NLTV = left thalamic volume/TIV. NRTV = right thalamic volume/TIV. NWTV = (left thalamic volume + right thalamic volume)/TIV. The thalamic asymmetry index (TAI) was calculated using a specific formula, which takes into account the differences between the left and right thalamic volumes.

This index is a key component of our research methodology. TAI = 100 * (NLTV - NRTV) / (0.5 * (NLTV + NRTV)). A negative TAI value signifies a rightward shift of the thalamus, indicating greater volume on the right compared to the left. The absolute value of TAI, termed "abs TAI," was also calculated (25, 26).

Statistical analysis: Data analysis was performed using SPSS Statistics for Windows (IBM, Version 25). Categorical data were reported as frequencies (percentages), and continuous data were summarized as means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on their distribution. Data normality was evaluated using the Kolmogorov-Smirnov test, Q-Q plots, and kurtosis and skewness statistics.

Demographic and clinical characteristics, and thalamic indices, were compared between SPMS groups using independent-samples t-tests or Mann-Whitney U tests, depending on the data distribution. Categorical variables were compared using the chi-squared test. Linear regression analyses were conducted, and results are presented as beta (β) coefficients, confidence intervals (CI), and p-values. Pearson's correlation coefficient was calculated to examine relationships among variables. Statistical significance was set at $p < 0.05$ for all analyses.

Results

Demographic and clinical characteristics: Table 1 summarizes the demographic and clinical characteristics of 38 study participants, divided into active (n=15) and inactive (n = 23) SPMS groups. Active SPMS patients had a mean age of 37 (SD = 2.78), which was significantly lower than that of those with inactive SPMS, who had a mean age of 40.96 (SD=7.41) (P= 0.027). The proportion of female patients was significantly different between the active SPMS group (93.3%) and the inactive SPMS group (60.9%) (P=0.056). Mean disease duration did not differ significantly between groups (active SPMS: 14.6 years, SD=5.9; inactive SPMS: 13.3 years, SD=5.3) (p-value of 0.502).

Clinical measures: The median EDSS was significantly higher in the active SPMS group [5 (range: 3.5 to 6.5)] compared to the inactive SPMS group [3.5 (range: 2 to 4)] ($p < 0.001$). Median 9HPT was significantly longer in active SPMS [44 seconds (range: 31 to 116.5)] compared to inactive SPMS [31.5 seconds (range: 22 to 43.5)] ($p< 0.001$) (table 1). Mean SDMT score was significantly lower in active SPMS (30.47, SD= 8.53) compared to inactive SPMS (42.13, SD = 6.91) ($p < 0.001$). Similarly, PASAT was lower in active SPMS (mean = 18, SD = 8.31) compared to inactive SPMS patients (mean = 31.61, SD= 8.22) ($p< 0.001$) (table 1).

Neuroimaging indices: Normalized left thalamic volume (NLTV) and normalized right thalamic volume (NRTV) were significantly reduced in active SPMS compared to inactive SPMS (0.0025 (0.0005) vs. 0.0033 (0.0005), $p< 0.001$, and 0.0024 (0.0005) vs. 0.0033 (0.0006), $p < 0.001$, respectively). Normalized thalamic volume (NTV) was also lower in active SPMS than in inactive SPMS patients (0.0049 (0.001) vs. 0.0066 (0.0011), p-value < 0.001, respectively) (table 1).

Table 1. Demographic and clinical characteristics of study participants (n = 38).

	Active SPMS (n = 15)	Inactive SPMS (n = 23)	Test Statistic	P-value
Age; mean (SD)	37 (2.78)	40.96 (7.41)	Coden's d = -0.65	0.027
Female	14 (93.3%)	14 (60.9%)	$Chi^2 = 4.93$	0.056
Disease Duration; mean (SD)	14.6 (5.9)	13.3 (5.3)	Coden's d = 0.22	0.502
EDSS; median [range]	5 [3.5 to 6.5]	3.5 [2 to 4]	MWU = 10.5 Z = -4.89	< 0.001
9HPT; median [range]	44 [31 to 116.5]	31.5 [22 to 43.5]	MWU = 44.5 Z = -3.83	< 0.001

	Active SPMS (n = 15)	Inactive SPMS (n = 23)	Test Statistic	P-value
SDMT; mean (SD)	30.47 (8.53)	42.13 (6.91)	Coden's d = -1.54	< 0.001
PASAT; mean (SD)	18 (8.31)	31.61 (8.22)	Coden's d = -1.65	< 0.001
NLTV	0.0025 (0.0005)	0.0033 (0.0005)	Coden's d = -1.505	< 0.001
NRTV	0.0024 (0.0005)	0.0033 (0.0006)	Coden's d = -1.577	< 0.001
NTV	0.0049 (0.001)	0.0066 (0.0011)	Coden's d = -1.584	< 0.001
TAI; Median [range]	2.04 [-26.15 to 19.03]	-1.15 [-12.84 to 37.86]	MWU = 132 Z = -1.21	0.226
Abs-TAI; Median [range]	5.23 [1.51 to 26.15]	3.1 [0.2 to 37.86]	MWU = 131 Z = -1.24	0.215

Abs-TAI: Absolute thalamic asymmetry index, EDSS: Expanded Disability Status Scale, 9HPT: Nine-Hole Peg Test, NLTV: Normalized left thalamic volume, NRTV: Normalized right thalamic volume, NTV: Normalized thalamic volume, PASAT: Paced Auditory Serial Addition Test, TAI: Thalamic asymmetry index, SDMT: Symbol Digit Modalities Test.

Linear regression results of thalamic volume indices and SPMS clinical subtypes: The linear regression analyses presented in table 2 examine the relationship between thalamic volume indices and clinical subtypes of progressive MS (active SPMS vs. inactive SPMS). The models are adjusted for age, sex, EDSS, and disease duration. The β coefficient for the association between TAI and SPMS subtypes was 4.736 (95% CI: -3.826 to 13.297, P = 0.269), indicating no significant relationship between TAI and active and inactive SPMS. This relationship, after being adjusted for EDSS (β = 9.041, 95% CI [-3.548, 21.630], P= 0.153) and for disease duration (β = 5.608, 95% CI: -2.963 to 14.178, P = 0.192), remained insignificant (table 2). There was no significant association between abs-TAI and SPMS subtypes (β = 4.09, 95% CI: -2.094 to 10.274, P= 0.188), even after adjusting for EDSS (β = 1.916, 95% CI: -7.241 to 11.073, P= 0.673) or disease duration (β = 4.230, 95% CI: -2.122 to 10.581, P = 0.185) (table 2).

NTV exhibited a significant inverse relationship with SPMS subtypes (β = -0.002, 95% CI: -0.003 to -0.001, p< 0.001). This association remained significant after adjusting for disease duration (β = -0.002, 95% CI: -0.002 to -0.001, p< 0.001), not EDSS (β = 0, 95% CI: -0.002 to 0.001, P= 0.481) (table 2).

Correlation between thalamic volume indices, disease duration, EDSS, and SDMT: Table 3 details correlations between thalamic volume indices, disease duration, EDSS, and SDMT in SPMS patients. There was no significant correlation between TAI, disease duration, EDSS, and SDMT in both active and inactive SPMS patients (p-value > 0.05 for all). EDSS exhibited significant correlations with abs-TAI (r = 0.453, P = 0.034) and NTV (r = -0.504, P= 0.014) among inactive SPMS patients. The NTV had significant correlations with NTV in both active (r = 0.738, P = 0.002) and inactive SPMS patients (r = 0.656, p< 0.001).

Table 2. Linear regression analyses of thalamic volume indices and progressive MS clinical subtypes.

Thalamic Volume Indices		Groups (Active SPMS vs. Inactive SPMS) 95% CI for β			
		β	LCI	UCI	P-value
TAI[a]		4.736	-3.826	13.297	0.269
	EDSS*	9.041	-3.548	21.630	0.153
	Disease duration**	5.608	-2.963	14.178	0.192
Abs-TAI		4.090	-2.094	10.274	0.188
	EDSS*	1.916	-7.241	11.073	0.673
	Disease duration**	4.230	-2.122	10.581	0.185
NTV		-0.002	-0.003	-0.001	<0.001

EDSS*	0.000	-0.002	0.001	0.481
Disease duration**	-0.002	-0.002	-0.001	<0.001

[a] crude model. * Model adjusted for expanded disability status scale. ** Model adjusted for disease duration. In addition, all models were adjusted for age and sex. Abs-TAI: absolute thalamic asymmetry index, EDSS: Expanded Disability Status Scale, TAI: thalamic asymmetry index, NTV: normalized thalamic volume.

Table 3. Pearson correlation between active SPMS (n = 15) and inactive SPMS (n = 23).

	Disease Duration				EDSS				SDMT			
	Active SPMS		Inactive SPMS		Active SPMS		Inactive SPMS		Active SPMS		Inactive SPMS	
	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value
TAI	-0.219	0.432	-0.107	0.636	-0.232	0.406	-0.374	0.086	0.113	0.689	0.216	0.335
Abs-TAI	-0.45	0.874	0.037	0.869	-0.157	0.577	0.453	0.034	0.040	0.888	-0.374	0.086
NTV	-0.46	0.081	-0.393	0.064	-0.410	0.129	-0.504	0.014	0.738	0.002	0.656	<0.001

Abs-TAI: absolute thalamic asymmetry index, EDSS: Expanded Disability Status Scale, TAI: thalamic asymmetry index, NTV: normalized thalamic volume, SDMT: Symbol Digit Modalities Test.

Discussion

In this cross-sectional study, thalamic volumes and their asymmetry were compared between patients with active and inactive SPMS. Furthermore, we investigated the relationships between thalamic volumes, asymmetry, clinical features, and cognitive function in these patients. Our findings showed that NTV, NRTV, and NLTV were significantly reduced in active SPMS compared with inactive SPMS. In contrast, TAI and absolute TAI did not differ meaningfully between the two groups. Additionally, NTV correlated with cognitive function in both active and inactive SPMS patients, whereas, it was associated with disability solely in the inactive SPMS patients.

Although relapses may occur less frequently in SPMS patients, regular MRI evaluation is essential for assessment of disease activity (27, 28). According to the MAGNIMS consensus guidelines, the use of MRI can improve the accuracy of identifying active SPMS (29, 30). However, MRI assessments are often performed less frequently in patients with older age and longer disease duration (30). Notably, limited research has investigated the differences in MRI measurements and their associations with various factors between active and inactive SPMS patients.

In MS, subcortical gray matter, particularly the thalamus, is among the earliest and highly affected regions (31). Thalamic atrophy can appear even in early disease stages and often precedes brain volume loss (32). SPMS patients show an accelerated pattern of gray matter degeneration compared with RRMS patients (33, 34). Prior research has indicated that thalamic atrophy is associated with the progressive subtype of MS, with the thalamus being the first region to exhibit atrophy in primary progressive MS, whereas in patients with clinically isolated syndrome and RRMS, atrophy of the posterior cingulate cortex and paracuneus occurs earlier than that of the thalamus (35).

The TAI was reported as positive in RRMS patients and negative in SPMS patients (9). Negative TAI values indicate a relative reduction in the left thalamus compared to the right, commonly referred to as a rightward shift (9). Prior research indicated that thalamic atrophy in patients with different phenotypes of MS is often bilateral (36). However, other research highlights a lateralized degenerative process that predominantly affects the left thalamus (37).

In a recent study, thalamic volume differed between patients with active and inactive SPMS. However, overall thalamic atrophy appeared the same, which indicates that asymmetry may not be a distinguishing characteristic.

Thalamic atrophy reflects underlying demyelination and neurodegeneration that lead to the development of clinical disabilities and cognitive impairments in people with MS (PwMS) (33, 38, 39). The associations between thalamic atrophy, disability, and cognitive performance have been established previously (40, 41). In PwMS with mild disability or cognitive impairment, thalamic atrophy is usually unilateral and extends to the opposite side with disease progression (42). Alterations of the thalamic nuclei are associated with neurological deficits in PwMS (10). The inverse correlations between volumes of the left pulvinar nuclei and the right pulvinar medial nucleus and disability

suggested that these regions may play a role in the neurodegenerative processes of MS (10). Therefore, using thalamic atrophy as an indicator of disability progression may help improve the identification of patients who are suspected of transitioning to SPMS (43).

This study had some limitations that need to be acknowledged. Several eligible SPMS patients were unable to complete the MRI scans due to their disability. This led to reduction of the sample size and limited the generalizability of the findings. Additionally, the cross-sectional design of this study prevents us from establishing causal relationships between changes in thalamic volume and disease progression in SPMS patients. Although we adjusted for some of the key factors such as age, sex, EDSS score, and disease duration in our models, other potentially important confounders, such disease modifying therapies were not consistently available for all participants and were therefore not included in our models. These factors can influence cognitive performance and neuroimaging measures, and could therefore have affected the associations we found. Future research is warranted to control these variables and establish a more reliable understanding of thalamic changes in SPMS.

In conclusion, thalamic atrophy was more prominent during the active phase of SPMS than the inactive phase. However, no links were found between thalamic asymmetry indices and SPMS subtypes. Furthermore, thalamic volume was associated with cognitive performance and disability in SPMS patients. These findings suggest that thalamic asymmetry may not be a dependable marker for distinguishing active from inactive SPMS. Future research with larger sample sizes and longitudinal designs is necessary to better understand the role of the thalamus among SPMS patients.

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