Middle Cerebellar Peduncle Lesions and Their Relation to Affective and Cognitive Impairment in Multiple Sclerosis

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Abstract

Background: Cerebellum has long been known to modulate not only motor coordination but also affective and cognitive functions. This study aimed to assess the impact of middle cerebellar peduncle (MCP) lesions on affective and cognitive function in patients with multiple sclerosis (MS).

Methods: This was a cross-sectional study conducted on patients with relapsing-remitting MS (RRMS). All patients were subjected to 3-Tesla magnetic resonance imaging (3T MRI), brief international cognitive assessment for MS (BICAMS), and Depression, Anxiety, and Stress Score-21 (DASS-21) upon recruitment.

Results: Of the 30 patients recruited, 33.3% and 36.7% had right and left MCP lesions, respectively. Patients with right MCP lesions had significantly worse symbol digit modality test (SDMT) scores (P=0.036), worse California verbal learning test (CVLT) immediate recall scores (P=0.011), and worse CVLT delayed free recall scores (P=0.049), whereas patients with left MCP lesions had lower DASS-21 scores (P<0.005). On multivariate regression analysis, the presence of left MCP lesion was associated with an 8.9-point reduction in DASS-21 scores (CI: -16.985- -0.805, P=0.033), whereas right MCP lesions did not have an independent effect on BICAMS scores after adjustment for age and educational level.

Conclusion: Left MCP lesions were associated with significantly lower DASS-21 scores, whereas none of the MCP lesions had an independent impact on cognition.

Keyword: BICAMS; Cerebellum; Cognitive dysfunction; DASS-21; Depression; Middle cerebellar peduncle

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Introduction

Cerebellum is commonly involved in multiple sclerosis (MS), and middle cerebellar peduncle (MCP) lesions have long been reported to be common in MS.[1,2] Cerebellar peduncle lesions are highly suggestive for MS, and their presence favors the diagnosis of MS rather than other mimics.[3] Being rich in myelinated axons, MCPs are vulnerable to demyelination and are affected in more than two-thirds (approximately 68%) of patients with MS.[4,5] MCPs contain the heaviest load of cerebellar afferent connections,[4] and because the cerebellum has a high afferent to efferent ration, i.e. 40 to 1, MCPs are involved in mediating almost all cerebellar functions.[4]

The cerebellum does not only mediate motor coordination, but it is also involved in as memory processing, attention, language, motor learning, thinking, emotional responses, and many other cognitive and affective functions.[6-9] In MS, the impact of cerebellar damage on motor dysfunction, disability progression, and long-term prognosis has been heavily investigated.[1,5,10-13] However, scarce data are available about its impact on cognitive and affective functions in patients with MS.

As the MCPs carry most cerebellar afferents,[4] we aimed to study the impact of MCP lesions, in particular, on affective and cognitive functions in a cohort of patients with relapsing remitting MS (RRMS).

Methods

Participants and Procedures

This was a cross-sectional study conducted on adult patients diagnosed with RRMS according to the revived 2017 McDonald's criteria[14] attending the MS clinic for regular visits. Other phenotypes of MS were excluded from this study.

Data Collected

Data collected during patients' clinical interview included age, sex, marital status, educational level, body mass index (BMI), smoking, age at MS onset, MS disease duration in years, total number of relapses, average annualized relapse rate (ARR) since disease onset, expanded disability status scale (EDSS) score, and functional domains affected at time of recruitment (e.g., visual, brainstem, pyramidal, cerebellar, sensory, bowel/

bladder, cerebral, and/or ambulation). Fatigue was also assessed via a self-administered validated Arabic version of fatigue severity scale (FSS).[15]

All patients had brain and spinal magnetic resonance imaging (MRI) on a 3 tesla (3T) Philip's machine at the university hospital radiology department. The number of periventricular lesions, the presence of cortical/juxtacortical lesions, corpus callosum lesions, temporal lesions, MCP lesions, cerebellar lesions, T1 blackholes, and spinal lesions were recorded.

Assessment of Cognition

Cognition was evaluated via an Arabic validated version of the Brief International Cognitive Assessment for MS (BICAMS) tests that included Symbol Digit Modality Test (SDMT), Brief Visuospatial Memory Test (BVMT), and California verbal learning tests version 2 (CVLT-II)[16]. The BICAMS is the most common cognitive battery used for evaluation of cognitive functions in MS. The Arabic version was validated in two studies: An Egyptian study that validated that test on 90 patients with MS and 85 healthy controls[16] and a Lebanese study that validated the test on 43 patients with MS and 180 healthy controls[17]. In the Egyptian dialect, patients with MS had significantly lower BICAMS tests scores than healthy control ($P < 0.001$) with a test-retest reliability r values of 0.85, 0.68, and 0.61 for the SDMT, BVMT, and CVLT total scores, respectively.[16] In the Lebanese dialect, the BICAMS test was able to discriminate between MS and healthy controls with a test-retest reliability of 0.43 and 0.92 in patients with MS and 0.67 and 0.73in healthy controls.

Assessment of Affective Symptoms

Affective symptoms were assessed via a self-administrated validated Arabic version of Depression, Anxiety, And Stress Scale-21 (DASS-21).[18] The DASS-21 scale is an easy to administer, valid, and reliable tool for the diagnosis of depression, anxiety, and stress. The reliability of the test has excellent Cronbach's values of 0.81, 0.89, and 0.78 for diagnosis of depression, anxiety, and stress, respectively.[19] The internal consistency and convergent and discriminant validity of the DASS-21 were reported to be excellent.[20]

Statistics and Data Analysis

All data were fed to a computer and analyzed using IBM Statistical Package for the Social Sciences (SPSS) software version 22.0. Numbers and percentages were used to express qualitative variables. The Kolmogorov-Smirnov and Shapiro-Wilk tests was used for verification of the normality of distribution of variables. Mean and standard deviation were used to express normally distributed quantitative variables, whereas median and interquartile range (IQR) were used to express abnormally distributed

quantitative variables. Student t test and Mann Whitney tests were used to compare between normally distributed and abnormally distributed quantitative variables among two groups, respectively. Chi-square test was used to compare between qualitative variables. Linear regression analysis was used to identify the most independent variable affecting DASS-21 and BICAMS scores. Univariate analysis was initially conducted on demographic, clinical, and radiological factors that might have impacted the cognitive and affective functions. Then, multivariate analysis was performed on the factors that showed significant association in univariate analysis. The level of significance was set at 5%.

Ethical considerations

Ethical approval was obtained from the Ethics Committee of Alexandria University Faculty of Medicine which operates according to the International Conference of Harmonization Good Clinical Practice (ICH GCP) and applicable local and institutional regulations and guidelines.[21] The Ethics Committee has a federal wide assurance (FWA)[22] since 2010.

Informed consent

An informed consent was obtained from all patients to obtain their anonymous data for research purposes.

Results

Of the 30 patients recruited, 76.7% were women. The mean ± SD age of the patients was 34.5 ± 7.46 years. The disease duration ranged from 5-10 years with a median of 6.8 years (IQR: 6.0-7.0). Cerebellar peduncle lesions were seen in 17 (56.7%) patients. Eleven patients (36.7%) had left MCP lesions, and 10 patients (33.3%) had right MCP lesions. Five (16.7%) patients had bilateral MCP lesions.

Comparing Clinical, Affective, and Cognitive Profiles in Patients With and Without MCP Lesions

Table 1 details the differences between patients with and without right and left MCP lesions. Of note, patients with right MCP lesions had significantly worse SDMT scores ($P = 0.036$), worse CVLT immediate recall scores ($P = 0.049$), worse short-term free recall scores ($P = 0.011$), and worse delayed free recall scores ($P = 0.049$) than patients without right MCP lesions. Patients with left MCP lesions, on the other hand, had worse depression, anxiety and stress scores ($P < 0.005$) than patients without left MCP lesions.

Regression Analysis of Factors Affecting DASS-21 Scores

Factors that might affect DASS-21 scores were included in a univariate analysis as shown in Table 2. Marital status, pyramidal domain affection, bowel/bladder domain affection, FSS score, and the presence of left MCP lesions were the factors that had a significant impact on

Table 1. Comparison Between Patients With and Without Right and Left Middle Cerebellar Peduncle Lesions

	Right MCP Lesion				Left MCP Lesion			
	Yes (n=10)	No (n=20)	Sig. Test	*P* Value	Yes (n=11)	No (n=19)	Sig. Test	*P* Value
Age (mean±SD)	35.2±5.71	34.2±8.31	t=-0.341	0.736	34.0±6.43	34.8±8.15	t=0.239	0.842
Gender (n, %)								
Male	5 (50)	2 (10)	χ^2=5.963	0.026*	4 (36.4)	3 (15.8)	χ^2=1.648	0.200
Female	5 (50)	18 (90)			7 (63.6)	16 (84.2)		
Educational level (n, %)			χ^2=11.438				χ^2=4.450	0.487
Primary school	3 (30)	2 (10)		0.043*	2 (18.2)	3 (15.8)		
Prep/secondary school	4 (40)	5 (25)			5 (45.5)	4 (21.1)		
Faculty/postgraduate	3 (30)	10 (50)			4 (36.4)	12 (6.32)		
Marital status (n, %)								
Single	1 (10)	3 (15)	χ^2=4.800	0.308	2 (18.2)	2 (10.5)	χ^2=4.163	0.384
Married	8 (80)	16 (80)			9 (81.8)	15 (78.9)		
Separated/divorced	1 (10)	1 (5)			0 (0)	2 (10.5)		
Age at MS onset (mean±SD)	28.2±5.18	27.5±8.14	t=-0.247	0.807	27.1±6.22	28.1±7.85	t=0.366	0.717
MS disease duration (median (IQR)	6.5 (5.57-8.25)	7.0 (6.00-7.00)	U=92.00	0.746	6.0 (5.0-9.0)	7.0 (6.0-7.0)	U=103.0	0.966
Total number of relapses (median (IQR))	7.0 (3.00-9.00)	5.0 (4.00-6.00)	U=83.50	0.475	5.0 (4.0-9.0)	5.0 (4.0-7.0)	U=95.5	0.582
Average ARR (median (IQR))	0.9 (5.75-8.25)	0.7 (0.57-0.96)	U=87.00	0.588	0.7 (0.5-0.7)	0.8 (0.6-1.0)	U=99.5	0.832
EDSS (median (IQR))	3.8 (2.87-5.50)	3.5 (2.13-4.00)	U=84.00	0.502	3.5 (2.0-5.5)	3.5 (2.5-4.0)	U=100.5	0.866
Domains affected								
Visual	6 (60)	15 (75)	χ^2=0.714	0.331	6 (54.5)	15 (78.9)	χ^2=1.975	0.161
Brainstem	4 (40)	8 (40)	χ^2=0.000	0.656	6 (54.5)	6 (31.6)	χ^2=1.531	0.197
Pyramidal	8 (80)	18 (90)	χ^2=0.577	0.407	8 (72.7)	18 (94.7)	χ^2=2.921	0.126
Cerebellar	9 (90)	17 (85)	χ^2=0.144	0.593	8 (72.7)	18 (94.7)	χ^2=2.291	0.126
Sensory	10 (100)	20 (100)	-	-	11 (100)	19 (100)	-	-
Bowel/bladder	8 (80)	12 (60)	χ^2=1.200	0.251	6 (54.5)	14 (73.7)	χ^2=1.148	0.250
Cerebral	8 (80)	14 (70)	χ^2=0.341	0.452	8 (72.7)	14 (73.7)	χ^2=0.003	0.637
Ambulation	9 (90)	15 (75)	χ^2=0.938	0.326	8 (72.7)	16 (84.2)	χ^2=0.574	0.380
FSS score (mean±SD)	41.19±19.04	46.4±14.29	t=0.873	0.390	36.7±18.61	49.1±12.47	t=2.193	0.037*
3T MRI findings								
Periventricular lesions (median (IQR))	10.0 (9.25-21.25)	9.5 (9.50-16.50)	U=80.0	0.397	10.0 (7-17)	10.0 (7-20)	U=103.0	0.966
Cortical/juxtacortical (n, %)	5 (50)	9 (45)	χ^2=0.067	0.550	6 (54.5)	8 (42.1)	χ^2=0.433	0.390
Corpus callosum (n, %)	9 (90)	16 (80)	χ^2=0.480	0.449	10 (90.9)	15 (78.9)	χ^2=0.718	0.381
Temporal (n, %)	7 (70)	13 (65)	χ^2=0.075	0.560	6 (54.5)	14 (73.7)	χ^2=1.148	0.250
Cerebellar hemisphere (n, %)	5 (50)	6 (30)	χ^2=1.148	0.250	4 (36.4)	7 (36.8)	χ^2=0.001	0.646
T1 blackholes (n, %)	8 (80)	11 (55)	χ^2=1.794	0.175	8 (72.7)	11 (57.9)	χ^2=0.660	0.341
Spinal (n, %)	5 (50)	5 (25)	χ^2=1.875	0.169	5 (45.5)	5 (26.3)	χ^2=1.148	0.250
DASS-21 scores (mean±SD)	31.7±17.30	33.8±13.79	t=0.361	0.721	23.91±16.86	38.42±10.63	t=2.903	0.007*
Depression scores	20.2±14.22	23.0±10.33	t=0.617	0.542	14.9±13.28	26.2±9.71	t=2.877	0.008*
Anxiety scores	17.8±13.74	18.3±10.33	t=0.112	0.912	12.7±12.34	21.3±9.71	t=2.101	0.045*
Stress scores	25.4±9.05	26.3±10.58	t=0.230	0.820	20.2±10.75	29.4±7.92	2.685	0.012*
BICAMS scores								
SDMT (mean±SD)	25.3±13.67	37.3±14.29	t=2.198	0.036*	29.5±15.86	35.5±14.44	t=1.071	0.293
BVMT (mean±SD)	18.4±8.96	19.9±7.51	t=468	0.644	18.5±8.07	19.9±7.96	t=0.475	0.638
CVLT-II (median (IQR))								
Immediate recall	54.0 (35.5-60.0)	61.0 (55.25-63.0)	U=55.50	0.049*	56.0 (46-63)	60.0 (52-63)	U=94.5	0.672
Short-term free recall	9.5 (7.25-13.50)	14.0 (11.00-14.75)	U=59.5	0.074	13.0 (8-14)	14.0 (10-15)	U=74.5	0.200
Short-term cued recall	13.0 (9.75-14.00)	15.0 (13.25-16.00)	U=43.00	0.011*	13.0 (10-15)	14.0 (13-16)	U=73.5	0.185
Delayed free recall	2.0 (8.00-12.00)	15.0 (14.00-16.00)	U=55.50	0.049*	15.0 (9-16)	12.0 (12-16)	U=78.5	0.268
Delayed cued recall	14.5 (13.0-16.00)	16.0 (15.25-16.0))	U=62.50	0.100	15.0 (13-16)	16.0 (15-17)	U=62.0	0.070

3T: 3 tesla, ARR: annualized relapse rate, BICAMS: brief international cognitive assessment of multiple sclerosis, BVMT : brief visuospatial memory test, CVLT-II: California verbal learning test version 2, DASS-21: Depression anxiety stress scasle-21, EDSS: expanded disability status scale, FSS: fatigue severity scale, IQR: Interquartile range, MCP: middle cerebellar peduncle, MRI: magnetic resonance imaging, MS: multiple sclerosis, n: number, SD: standard deviation, t: Students t test, U: Mann Whitney test.
*Statistically significant at *P*≤0.05.

DASS-21 scores. On multivariate analysis, the presence of left MCP lesions and pyramidal domain involvement continued to have a significant independent impact on DASS-21 score i.e., the presence of left MCP lesions was associated with an 8.9-point reduction in DASS-21 scores (*P*=0.030, Figure 1). Involvement of pyramidal domain was associated with a 16.7-pont increase in DASS-21 scores (*P*=0.008).

Table 2. Regression Analysis of Factors Affecting DASS-21 Scores

	Univariate Regression			Multivariate Regression[a]		
	B	95% CI	*P* value	B	95% CI	*P* value
Age	0.031	-0.736 – 0.799	0.934			
Gender	8.329	-4.580 – 21.239	0.197			
Marital status	5.743	0.280- 11.207	0.040*	3.024	-1.558- 7.605	0.185
Smoking	-5.310	-11.332- 0.712	0.082			
BMI	0.778	-0.269- 1.822	0.140			
Educational level	0.773	-3.025- 4.571	0.680			
Disease duration	0.981	-2.890- 4.852	0.608			
Age at MS onset	-0.007	-0.802- 0.787	0.985			
EDSS scores	2.404	-1.522- 6.330	0.220			
Visual symptoms	11.254	-0.228- 22.736	0.054			
Brainstem symptoms	-2.806	-14.242- 8.631	0.095			
Pyramidal symptoms	21.827	8.555- 35.099	0.002*	16.674	4.845- 28.502	0.008*
Cerebellar symptoms	6.462	-9.904- 22.827	0.809			
Cerebral symptoms	0.648	-12.076- 13.372	0.918			
Bowel/bladder symptoms	11.650	1.239- 22.061	0.030*	1.289	-7.968- 10.546	0.776
Ambulation symptoms	11.792	-1.517- 25.100	0.080			
FSS score	0.468	0.178- 0.758	0.003*	0.164	-0.097- 0.426	0.206
Periventricular lesion no	-0.534	-1.333- 0.265	0.182			
Cortical/juxtacortical lesions	0.750	-10.527- 12.027	0.893			
Temporal lesions	4.200	-7.627- 16.027	0.473			
Cerebellar hemisphere lesions	-5.900	-17.353- 5.554	0.300			
Right MCP lesions	-2.100	-14.011- 9.811	0.721			
Left MCP lesions	-15.694	-24.982- -6.405	0.002*	-8.895	-16.985- -0.805	0.033*
T1 blackholes	-4.148	-15.716 – 7.419	0.469			

B: Unstandardized Coefficients, BMI: body mass index, CI: Confidence interval, EDSS: expanded disability status scale, FSS: fatigue severity scale, MCP: middle cerebellar peduncle, MS: multiple sclerosis,
[a] All variables with *P*<0.05 was included in the multivariate analysis, *Statistically significant at *P*≤0.05.
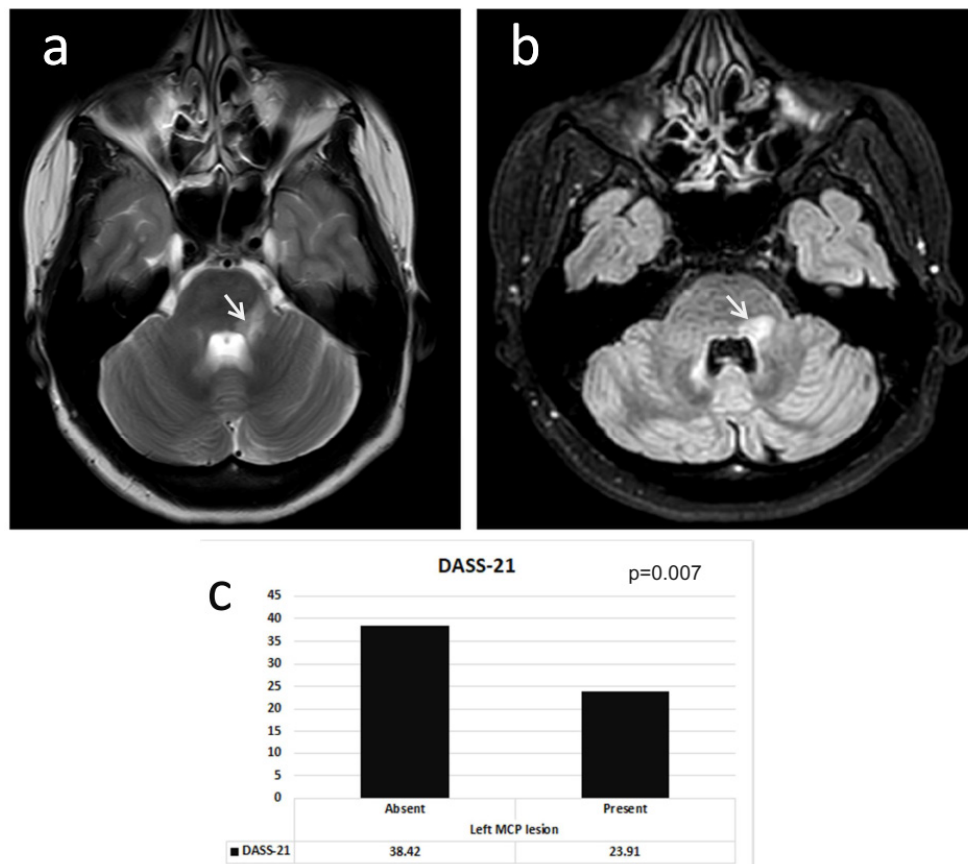

Figure 1. The Relation Between Middle Cerebellar Peduncle Lesions and DASS-21 Scores. Images A and B represent T2 and FLAIR hyperintense lesion in the left middle cerebellar peduncle. Image C represents the DASS-21 scores among patients with and without left middle cerebellar peduncle lesions.

Regression Analysis of Factors Affecting BICAMS Scores

Univariate and multivariate regression analysis were performed to identify the independent effect of different factors that might affect SDMT (Table 3), CVLT immediate recall scores (Table 4), CVLT short-term cued scores (Table 5), and CVLT delayed free recall scores (Table 6).

As detailed in the tables, although right MCP lesions had a significant impact on the three scores univariate regression analysis (P< 0.05), multivariate regression negated any independent effect of these lesions on BICAMS score. The main independent factors affecting BICAMS scores were age and educational level (P< 0.05).

Table 3. Regression Analysis of Factors Affecting SDMT Scores

	Univariate Regression			Multivariate Regression[a]		
	B	95% CI	P value	B	95% CI	P value
Age	-1.207	-1.830- -0.582	<0.001*	-0.602	-1.070- -0.170	0.009*
Gender	10.267	-2.632- 23.166	0.0114			
Smoking	-3.358	-9.680- 2.965	0.286			
BMI	-0.647	-1.722- 0.427	0.228			
Educational level	7.833	5.437-10.229	<0.001*	4.745	2.166- 7.324	0.001*
Disease duration	-3.188	-6.936- 0.560	0.092			
Periventricular lesion no	-1.257	-1.938- -0.576	0.001*	-0.264	-0.792- 0.264	0.311
Cortical/juxtacortical lesions	-6.991	-18.109- 4.127	0.208			
Temporal lesions	-9.150	-20.731- 2.431	0.117			
Cerebellar hemisphere lesions	-11.096	-22.136- -0.055	0.049*	0.054	-7.353- 7.462	7.462
Right MCP lesions	-12.000	-23.184- -0.816	0.036*	-2.758	-9.964- 4.133	0.146
Left MCP lesions	-6.072	-17.683- 5.539	0.293			
T1 blackholes	-16.033	-26.124-5.943	0.003*	-7.741	-15.592- 0.110	0.053

B: Unstandardized Coefficients, BMI: body mass index, CI: Confidence interval, MCP: middle cerebellar peduncle, MS: multiple sclerosis,
[a] All variables with P<0.05 was included in the multivariate analysis, * Statistically significant at P≤0.05.

Table 4. Regression Analysis of Factors Affecting CVLT-II Immediate Recall Scores

	Univariate Regression			Multivariate Regression[a]		
	B	95% CI	P value	B	95% CI	P value
Age	-0.585	-1.176- 0.006	0.052			
Gender	6.739	-3.919- 17.398	0.206			
Smoking	-2.500	-7.658- 2.658	0.329			
BMI	-0.440	-1.321- 0.441	0.315			
Educational level	4.913	2.413- 7.414	<0.001*	2.913	0.036- 5.790	0.047*
Disease duration	-0.159	-3.366- 3.048	0.920			
Periventricular lesion no	-0.930	-1.507- -0.352	0.003*	-0.402	-1.015- 0.211	0.189
Cortical/juxtacortical lesions	-4.464	-13.605- 4.677	0.326			
Temporal lesions	-4.400	-14.097- 5.297	0.361			
Cerebellar hemisphere lesions	-5.574	-14.960- 3.812	0.234			
Right MCP lesions	-9.700	-18.801- -0.599	0.038*	-3.345	-11.667- 4.581	0.378
Left MCP lesions	-2.416	-12.002- 7.169	0.610			
T1 blackholes	-12.512	-20.836- -4.187	0.005*	-6.263	-14.379- 1.872	0.125

B: Unstandardized Coefficients, BMI: body mass index, CI: Confidence interval, MCP: middle cerebellar peduncle, MS: multiple sclerosis.
[a] All variables with P<0.05 was included in the multivariate analysis, * Statistically significant at P≤0.05.

Table 5. Regression Analysis of Factors Affecting CVLT-II Short-term Cued Recall Scores

	Univariate Regression			Multivariate Regression[a]		
	B	95% CI	P value	B	95% CI	P value
Age	-0.133	-0.239- -0.026	0.017*	-0.066	-0.161- 0.029	0.164
Sex	1.012	-1.003- 3.028	0.312			
Smoking	-0.261	-1.238- 0.715	0.588			
BMI	-0.061	-0.227- 0.105	0.459			
Educational level	0.949	0.490- 1.408	<0.001*	0.424	-0.122- 0.072	0.122
Disease duration	-0.290	-0.879- 0.300	0.323			
Periventricular lesion no	-0.158	-0.269- -0.046	0.007*	-0.039	-0.105- 0.072	0.473
Cortical/juxtacortical lesions	-0.920	-2.624- 0.784	0.278			
Temporal lesions	-1.000	-2.801- 0.801	0.265			
Cerebellar hemisphere lesions	-1.144	-2.890- 0.603	0.191			
Right MCP lesions	-2.300	-3.913- -0.687	0.007*	-1.309	-2.764-0.146	0.146
Left MCP lesion	-1.144	-2.890- 0.603	0.191			
T1 blackholes	-2.301	-3.868- -0.735	0.005*	-1.183	-2.631- 0.266	0.105

B: Unstandardized Coefficients, BMI: body mass index, CI: Confidence interval, MCP: middle cerebellar peduncle, MS: multiple sclerosis.
[a] All variables with P<0.05 was included in the multivariate analysis, * Statistically significant at P≤0.05.

Table 6. Regression analysis of factors affecting CVLT-II delayed free recall scores

	Univariate Regression			Multivariate Regression		
	B	95% CI	P value	B	95% CI	P value
Age	-0.220	-0.385- -0.055	0.011*	-0.107	-0.263- 0.048	0.168
Gender	2.037	-1.085- 5.160	0.192			
Smoking	-0.304	-1.840- 1.232	0.688			
BMI	-0.145	-0.402- 0.113	0.259			
Educational level	1.560	0.863 – 2.257	<0.001*	0.975	0.083-1.867	0.033*
Disease duration	-0.274	-1.209- 0.662	0.554			
Periventricular lesion no	-0.228	-0.407- -0.048	0.015*	-0.020	-0.202- 0.162	0.822
Cortical/juxtacortical lesions	0.420	-2.306-3.145	0.755			
Temporal lesions	-2.050	-4.829- 0.729	0.142			
Cerebellar hemisphere lesions	-0.498	-3.318- 2.323	0.720			
Right MCP lesions	-2.750	-5.436- -0.064	0.045*	-0.872	-3.251- 1.507	0.457
Left MCP lesions	-1.646	-4.400- 1.108	0.231			
T1 blackholes	-3.378	-5.884- -0.872	0.010*	-1.854	-4.221- 0.514	0.119

B: Unstandardized Coefficients, BMI: body mass index, CI: Confidence interval, MCP: middle cerebellar peduncle, MS: multiple sclerosis.
[a] All variables with $P<0.05$ was included in the multivariate analysis, * Statistically significant at $P \leq 0.05$.

Discussion

In this study, we investigated the impact of MCP lesions on affective and cognitive profiles in a cohort of RRMS patients. The main findings of this research were that the left MCP lesions had an independent significant impact on depression, anxiety, and stress scores, whereas none of the MCPs on either side had an impact on cognitive scores.

Cerebellum has long been reported to be involved in mood regulation, emotional responses, and affective behaviors.[23] Involvement of the cerebellum was reported to mediate depression in several neurological and psychiatric disorders such as olivopontocerebellar atrophy, hereditary ataxias, cerebellar vascular stroke, depression, and schizophrenia.[24-27] In MS, several lesion locations and volumes were reported to be correlated with depression scores such as left medial inferior prefrontal cortex, left anterior temporal volume,[28] right frontal lesion load, right temporal brain volume,[29] left arcuate fasciculus, and parietal lobes.[28-31] Cerebellar involvement was rarely reported to be correlated with depression scores in MS. In a study conducted by Lazzarotto and colleagues[32] on patients with RRMS, selective atrophy of specific cerebellar region (i.e., the lower vermis crus I) was associated with higher depression scores. In our study, the presence of left MCP lesions was associated with an almost nine-point reduction in depression, anxiety, and stress scores meaning that the lesions had a protective effect against depressive symptoms. In agreement with our finding, Schiffer et al,[33] in an old research conducted on 30 patients with MS, reported that patients with cerebellar involvement were less likely to be depressed than patients with cerebral involvement. As recent evidence exists for the emotional lateralization in the brain,[34] our finding is logical in context of the theory that the right cerebral hemisphere is specialized for perception, expression, and experience of emotion.[35] As the cortico-ponto-cerebellar pathway connects the cerebral hemisphere with the contralateral cerebellum,[36] the left MCP lesions might have disrupted the cerebellar connectivity to the right cerebral hemisphere and consequently impaired patients experience and expression of depressive emotions in our cohort of patients.

Along with emotional regulation, the cerebellum was also found to be involved in several cognitive functions such as spatial cognition, working memory, set-shifting, memory retention, verbal fluency, abstraction, and planning.[23] In MS, patients with cerebellar signs were reported to have worse cognitive performance.[37] However, no definite data could identify a correlation between specific cerebellar lesion locations and cognition.[38] Most of the MRI abnormalities that were reported to have an impact on cognition were either volumetric changes in gray or white matter or functional MRI abnormalities such as total cerebellar volume, cerebellar gray matter volume, cerebellar gray matter volume, hubs and network properties, fractional anisotropy, and voxel-based morphometry abnormalities.[39-43] Data about the impact of total lesion load in cerebellum and cerebellar peduncles on cognition were conflicting. Some authors such as Valentino and colleagues,[37] found no significant correlation between total lesion load in the cerebellum and cognition in a cohort of RRMS patients, whilst Cerasa and colleagues,[44,45] reported the reverse. Memory storage and retrieval were reported, in one study, to be corelated with cerebellar lesions number and volume.[46] Our research was in agreement with most studies that no specific lesion locations in the cerebellum correlates independently with cognitive scores.

The main limitations of this study were the relatively small sample size and the absence of volumetric analysis of whole brain volume and the MCP volume. Further studies are recommended to include further assessment of the role of MCP lesions in determination of cognitive and affective functions which include a larger sample and volumetric parameters as confounders of cognition.

Conclusion

MCP lesions might impact the patients' affective function, but do not have an independent effect on cognitive scores.

Conflict of Interest Disclosures

The authors declare no conflicts of interest.

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