Cerebrovascular Changes in Multiple Sclerosis Patient

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Abstract:

Background: Multiple sclerosis (MS) is a chronic condition that causes the central nervous system to become inflamed, demyelinated, and degenerative.

Aim of the Work: To assess cerebrovascular changes in MS patients using TCD and analyze their impact on disease progression, physical disability, and cognitive impairment in MS patients.

Patients and Methods: This research was a cross-sectional, hospital-based study conducted on 30 MS-diseased patients, according to revised MacDonald's criteria 2017, who were admitted to the Neuropsychiatry department, Assiut University Hospital from January 2020 to September 2021, and 30 healthy volunteers' age and sex-matched to cases as a control group.

Results: A significant reduction of cerebral flow was observed among patients with MS compared to matched controls. Significant different correlations were observed between the Hamilton depression rating scale, Mini-mental state examination, and Expanded disability status scale with many affected vessels, indicating that the cerebral vessel changes affected the MS-related progression and disability.

Conclusion: Cerebrovascular hemodynamic insufficiency is significantly prominent in MS-diseased patients, mainly anterior and posterior, and with lower carotid circulation affection.

Keywords: Cerebral blood flow (CBF), cerebrovascular disease, multiple sclerosis, transcranial Doppler ultrasound.

Introduction:

Multiple sclerosis (MS) is an inflammatory condition causing damage to the central nervous system, primarily affecting oligodendrocytes and myelin sheaths. It is the most common cause of non-traumatic disability in young adults[1]. The predominant histological hallmarks are demyelination and neurodegeneration. However, the exact etiology and pathophysiology are unknown [2]. Hemodynamic dysfunction in MS is a complex issue influenced by neuro-inflammatory cascades, with vascular comorbidities affecting outcomes, with an estimated 50% prevalence in the MS population [3]. Perfusion imaging studies have identified vascular characteristics associated with MS, including decreased cerebral blood flow affecting white and gray matter, as revealed by dynamic susceptibility contrast perfusion MR imaging and positron-emission tomography[4]. Cerebrovascular coupling and reactivity issues in MS patients may explain neurodegenerative processes, possibly due to cardiovascular comorbidities or elevated nitric oxide levels linked to the disease pathology [5].

The study aimed to assess cerebrovascular changes in MS patients

using TCD and analyze their impact on disease progression, physical disability, and cognitive impairment in MS patients.

Patients and Methods:

(A) Patients:

This research was a hospital-based cross-sectional study conducted on 30 MS-diseased patients, according to revised MacDonald's criteria 2017 [6], who were admitted to the Neuropsychiatry department, Assiut University Hospital from January 2020 to September 2021, and a control group of 30 volunteers who were age and sex-matched to the patients.

Patients with a history or current evidence of other central nervous system (CNS) diseases that may affect brain volume & cognition, those with endocrinal or metabolic disorders, history or current intake of any drug (antiepileptic, antipsychotic), history or current evidence of depression (according to DSM), and those with any psychiatric disorder that may affect cognitive function were excluded from the study.

The Institutional Review Board of the Faculty of Medicine at Assiut University gave its approval to the protocol (approval number: 17100649; date of approval: October 2018). Our study met all the criteria established by the Helsinki Declaration. All subjects were included after having a signed informed consent form.

(B) Methods:

All MS patients were subjected to detailed history taking and full general and neurological examination according to the sheet of the Neurology Department Assiut University Hospital and investigations. To confirm the diagnosis of MS, patients were subjected to an MRI of the brain and spinal cord by an experienced neuro-radiologist, in addition to the Visual Evoked potential (VEP) [7]. The expanded Disability Status Scale [8] was also used. This scale provides an overall rating of disabilities; higher scores indicate a greater degree of disability.

Also, we used Hamilton Depression Rating Scale [9] to exclude depression and Mini-mental State Examination [10] to assess their global cognitive performance because it can help to predict focal cognitive impairment, particularly in relapsing-remitting multiple sclerosis (RRMS) patients who also have minor physical impairments.

All studied subjects (cases and controls) underwent both trans-cranial and extra-cranial carotid duplex ultrasonography to measure [mean flow velocity (MFV), peak systolic velocity (PSV), end-diastolic velocity (EDV), pulsatility index (PI), and Intimal medial thickness (IMT)] using a high-resolution color duplex (Philips Envisor C Ultrasound System with L 12-3 MHz linear transducer probe) at neurology department. An assessment of cerebral circulation hemodynamics (for both sides) was done using the same machine.

Results

Both studied groups were matched for age, sex, and educational level, with no significant difference between them (P>0.05), **Table 1**.

Table (1): General characteristics of the studied patients (n=60)

Measured scales	Cases (n=30)	Controls (n=30)
Age (years)	34.5 ± 5.3	25.7 ± 2.4
Sex		
• Male • Female	9 (30%) 21 (70%)	9 (30%) 21 (70%)
Education		
• University • Secondary school • Illiterate	13 (43.3%) 10 (33.3%) 7 (23.3%)	11 (36.7%) 10 (33.3%) 9 (30%)

Quantitative data are presented as mean ± SD; qualitative data are presented in numbers (percentage).

Table 2 shows that the total mean value of the MMSE score and all its subcategories (except for coping strategy) were significantly lower in the MS cases compared to the control group ($P < 0.001$ for all). Additionally, the mean value of HDRS in the MS group was significantly higher than the control group ($P < 0.001$).

Table (2): Measured scales among the studied group (n=60)

Measured scales	Cases (n=30)	Controls (n=30)	P value
MMSE	24.2 ± 1.5	29.1 ± 0.8	<0.001
• Orientation	8.17 ± 0.7	10.0 ± 0.0	<0.001
• Recall	2.7 ± 0.4	3.0 ± 0.0	0.001
• Registration	2.6 ± 0.4	3.0 ± 0.0	<0.001
• Language	3.9 ± 0.7	7.5 ± 0.5	<0.001
• Coping	1.0 ± 0.0	1.0 ± 0.0	-------
• Attention	4.6 ± 0.4	5.9 ± 0.7	<0.001
HDRS	24.8 ± 2.8	10.2 ± 1.3	<0.001

MMSE: Mini-mental state examination; **HDRS**: Hamilton depression rating scale.
Quantitative data are presented as mean ± SD. Significance defined by $p < 0.05$

There was a significant difference between the cases group and control group regarding MMSE, Orientation, Recall, Registration, Language, Coping, Attention, and HDRS **(Table 3).**

Table (3): Transcranial Doppler results of the anterior-posterior circulation among both studied groups (n=60)

	Cases (n=30)	Controls (n=30)	P value
Anterior circulation			
• Rt MCA sv	39.2 ± 2.1	70.5 ± 2.8	<0.001
• Rt MCA dv	20 ± 1.7	49.1 ± 3.7	<0.001
• Rt MCA mv	40 ± 2	217.3 ± 912	0.291
• Rt MCA pi	0.4 ± 0.03	0.7 ± 0.05	<0.001
• Lt MCA sv	51.4 ± 2.3	60.5 ± 2.9	<0.001
• Lt MCA dv	25.3 ± 2	32.3 ± 1.5	<0.001
• Lt MCA mv	44.5 ± 1.5	51.4 ± 2.3	<0.001
• Lt MCA pi	0.5 ± 0.03	0.6 ± 0.04	<0.001
• Rt ACA sv	-40.4 ± 1.6	70.6 ± 1.8	<0.001
• Rt ACA dv	-16.9 ± 0.8	37.2 ± 1.4	<0.001
• Rt ACA mv	36.3 ± 1.2	58.7 ± 2.2	<0.001
• Rt ACA pi	0.5 ± 0.06	0.7 ± 0.08	<0.001
• Lt ACA sv	-45.5 ± 1.8	71.2 ± 2	<0.001
• Lt ACA dv	-22.2 ± 1.5	38.7 ± 1.3	<0.001
• Lt ACA mv	35.9 ± 1.2	59.6 ± 1.8	<0.001
• Lt ACA pi	0.5 ± 0.08	0.7 ± 0.07	<0.001
• Rt PCA sv	48.6 ± 2.2	59 ± 1.8	<0.001

Table (3): Transcranial Doppler results of the anterior-posterior circulation among both studied groups (n=60) *(Cont.)*

	Cases (n=30)	**Controls (n=30)**	**P value**
Posterior circulation			
• Rt PCA dv	21.5 ± 1.8	35.2 ± 1.6	<0.001
• Rt PCA mv	40.2 ± 1.6	38.3 ± 1.3	<0.001
• Rt PCA pi	0.6 ± 0.06	0.7 ± 0.06	<0.001
• Lt PCA sv	42.6 ± 1.3	58.4 ± 1.7	<0.001
• Lt PCA dv	22.6 ± 0.9	36.3 ± 1.3	<0.001
• Lt PCA mv	39.7 ± 1.3	43.6 ± 2	<0.001
• Lt PCA pi	0.6 ± 0.06	0.6 ± 0.07	0.487
• Rt verteb.A sv	-31 ± 23.6	48.9 ± 1.4	<0.001
• Rt verteb.A dv	-15.2 ± 11.5	22.7 ± 0.9	<0.001
• Rt verteb.A mv	36.8 ± 0.9	36.8 ± 0.9	0.889
• Rt verteb. A pi	0.6 ± 0.06	0.6 ± 0.06	0.770
• Rt verteb.A IMT	0.06 ± 0.01	0.06 ± 0.01	0.876
• Lt verteb.A sv	-29.5 ± 1.4	48.5 ± 3	<0.001
• Lt verteb.A dv	-9.9 ± 9.4	20.9 ± 2.2	<0.001
• Lt verteb.A mv	22.2 ± 1	36.9 ± 0.9	<0.001
• Lt verteb.A pi	0.6 ± 0.07	0.6 ± 0.06	0.686
• Lt verteb.A IMT	0.06 ± 0.01	0.6 ± 0.01	0.620
• Rt basilar A sv	36.8 ± 0.9	49.1 ± 1.6	<0.001
• Rt basilar A dv	6.7 ± 12.7	20.4 ± 1.3	<0.001
• Rt basilar A mv	33.9 ± 1.3	45.9 ± 1.5	<0.001
• Rt basilar A pi	0.5 ± 0.06	0.6 ± 0.06	<0.001
• Lt basilar A sv	35.8 ± 1.1	49.3 ± 1.5	<0.001
• Lt basilar A dv	12.9 ± 0.7	21.9 ± 1.6	<0.001
• Lt basilar A mv	35.2 ± 1.2	44.2 ± 1.8	<0.001
• Lt basilar A pi	0.5 ± 0.05	0.6 ± 0.07	<0.001
Carotid Circulation			
• Rt distal CCA sv	48.1 ± 38.5	77.9 ± 2.7	<0.001
• Rt distal CCA dv	20.9 ± 1.8	20.1 ± 1.7	0.090
• Lt distal CCA sv	66.6 ± 4	70.7 ± 1.5	<0.001
• Lt distal CCA dv	20.8 ± 2.2	20.5 ± 1.7	0.638
• Rt proximal ICA sv	43.8 ± 1.9	43.8 ± 1.9	0.987
• Rt proximal ICA dv	17.3 ± 0.9	17.4 ± 0.9	0.947
• Lt proximal ICA sv	46.2 ± 1.3	46.2 ± 1.3	1.000
• Lt proximal ICA dv	19.7 ± 1.7	19.7 ± 1.7	0.974

MCA: Middle cerebral artery; **ACA**: Anterior cerebral artery; **PCA**: Posterior cerebral artery; **CCA**: Common carotid artery. Quantitative data are presented as mean ± SD. Significance defined by $p < 0.05$.

Table 4 shows a significant negative correlation between HDRS and Rt & Lt ACA pi, respectively. Another significant negative correlation was observed between EDSS and Rt ACA pi. There was also a significant positive correlation between EDSS and Rt MCA dv and Rt ACA mv.

Table (4): Correlation between the studied scales and anterior circulation TCD results parameters among the studied Patients with MS

	HDRS		MMSE		EDSS	
Anterior circulation	**R**	**P-value**	**R**	**P-value**	**R**	**P-value**
• Rt MCA sv	-0.127	0.503	0.245	0.191	-0.143	0.540
• Rt MCA dv	0.028	0.855	0.121	0.524	0.399	0.029
• Rt MCA mv	0.161	0.396	0.284	0.111	0.293	0.116
• Rt MCA pi	-0.161	0.396	-0.300	0.108	-0.122	0.519
• Lt MCA sv	0.006	0.975	0.338	0.067	-0.242	0.198
• Lt MCA dv	-0.104	0.583	0.034	0.859	-0.090	0.635
• Lt MCA mv	-0.026	0.890	0.010	0.958	0.012	0.950
• Lt MCA pi	-0.031	0.869	0.029	0.881	-0.260	0. 166
• Rt ACA sv	-0.107	0.575	0.032	0.868	0.173	0.359
• Rt ACA dv	0.046	0.809	0.159	0.402	0.100	0.600
• Rt ACA mv	0.215	0.254	0.331	0.074	0.383	0.037
• Rt ACA pi	-0.552	0.002	-0.241	0.214	-0.406	0.026
• Lt ACA sv	0.093	0.624	0.012	0.948	0.253	0.178
• Lt ACA dv	0.023	0.903	0.115	0.545	-0.008	0.967
• Lt ACA mv	0.227	0.227	0.231	0.231	-0.323	0.082
• Lt ACA pi	-0.399	0.029	-0.180	0.175	-0.042	0.825

MCA: Middle cerebral artery; **ACA**: Anterior cerebral artery. **R:** Correlation coefficient. Significance defined by $p < 0.05$.

Table 5 shows a significant negative correlation between HDRS and Rt PCA sv, Rt vertebral A IMT, Rt basilar A dv, and Rt basilar A pi, and a significant positive correlation between HDRS and Lt vertebral A dv. MMSE shows a significant negative correlation with t vertebral mv, Rt Basilar mv, and Lt basilar A dv, and a significant positive correlation between MMSE and Lt PCA edv and Lt basilar A pi. Another significant positive correlation was observed between EDSS and left vertebral a. IMT.

Table (5): Correlation between the studied scales and posterior circulation TCD results parameters among the studied Patients with MS.

	HDRS		MMSE		EDSS	
Posterior circulation	**R**	**P-value**	**R**	**P-value**	**R**	**P-value**
• Rt PCA sv	-0.411	0.024	-0.204	0.324	-0.089	0.641
• Rt PCA dv	-0.310	0.095	0.052	0.784	-0.382	0.037
• Rt PCA mv	-0.105	0.582	0.152	0.423	-0.290	0.120
• Rt PCA pi	-0.016	0.935	0.075	0.693	0.207	0.273
• Lt PCA sv	-0.241	0.199	0.209	0.268	0.081	0.670
• Lt PCA dv	-0.219	0.245	0.438	0.011	-0.053	0.872
• Lt PCA mv	-0.013	0.947	-0.037	0.846	0.024	0.899
• Lt PCA pi	-0.148	0.434	-0.137	0.469	0.067	0.724
• Rt verteb.A sv	0.360	0.051	0.194	0.124	0.220	0.242

Table (5): Correlation between the studied scales and posterior circulation TCD results parameters among the studied Patients with MS. *(Cont.)*

	HDRS		MMSE		EDSS	
Posterior circulation	**R**	**P-value**	**R**	**P-value**	**R**	**P-value**
• Rt verteb.A dv	0.336	0.070	0.201	0.109	0.207	0.272
• Rt verteb.A mv	-0.224	0.234	-0.331	0.046	-0.051	0.791
• Rt verteb. A pi	-0.136	0.474	0.070	0.713	-0.299	0.108
• Rt verteb.A IMT	-0.412	0.024	-0.184	0.331	-0.198	0.293
• Lt verteb.A sv	0.006	0.974	0.240	0.202	-0.154	0.416
• Lt verteb.A dv	0.379	0.039	0.254	0.282	0.239	0.203
• Lt verteb.A mv	-0.179	0.345	-0.088	0.644	0.045	0.814
• Lt verteb.A pi	-0.357	0.053	0.094	0.620	-0.213	0.259
• Lt verteb.A IMT	0.116	0.541	0.003	0.989	0.379	0.039
• Rt basilar A sv	0.224-	0.234	-0.152	0.243	0.051-	0.791
• Rt basilar A dv	-0.372	0.043	-0.211	0.110	-0.339	0.067
• Rt basilar A mv	0.275	0.141	-0.510	0.003	0.078	0.683
• Rt basilar A pi	-0.472	0.008	-0.075	0.765	-0.250	0.182
• Lt basilar A sv	0.240	0.202	0.244	0.194	0.269	0.151
• Lt basilar A dv	-0.016	0.932	-0.322	0.041	0.231	0.220
• Lt basilar A mv	0.173	0.361	-0.113	0.551	0.087	0.646
• Lt basilar A pi	0.129	0.498	0.421	0.027	-0.211	0.264

PCA: Posterior cerebral artery; **R:** correlation coefficient. Significance defined by $p < 0.05$.

Discussion

In the current study, the mean age of the studied MS patients was 34.5±5.3 years. This comes in accordance with Hassab et al. [11] study, which reported that the mean age of MS patients was 32±11 years. In our study, females represented 70% of the MS cases, which is consistent with MS epidemiology in general [12].

In the present study, the mean value of MMSE in the cases group was 24.2±1.5, which was significantly lower than the control group (P<0.001). On regression analysis, we found that neither age, sex, disease duration, nor VEP are considered risk factors for total cognition deterioration among MS cases. Contrary to other investigations, the majority of cross-sectional and longitudinal studies on adult-onset MS have linked aging to an increase in the frequency and severity of cognitive impairment [13]. On the other hand, a cohort of pediatric MS patients followed up for five years revealed that younger age at MS onset was a risk factor for cognitive impairment (CI) and decreased intelligence quotient (IQ) [14]. The mean value of HDRS in the MS group was 24.8 ± 2.8, which is significantly higher than the controls group in our study. In the anterior circulation, the mean value of all vessels in patients with MS shows significantly less blood flow than in the control group except for the Rt MCA mv. In the posterior circulation, the mean value of all results in vessels in patients with MS illustrated significantly less blood flow than the controls group except for the Lt PCA pi, Rt vertebral A mv, pi, IMT, and Lt vertebral A pi, IMT. For the carotid circulation, the mean values of results of only Rt distal CCA sv and Lt distal CCA sv showed significantly less blood flow in the cases group than the controls group. All these changes illustrated significant affection of cerebral flow among patients with MS.

Ranadive et al. [15] showed that patients with MS exhibited different patterns of vascular morphology in the neck with respect to aging when they were compared to the healthy population. In MS, the arteries supplying the CNS may be more vulnerable to atherosclerotic damage. They found that

patients with MS had dramatically altered arterial function compared to the control group, as seen by lower carotid artery compliance, without change in structure. However, according to recent research by Belov et al. [16], the common, internal, and external carotid arteries, as well as the vertebral artery, appear to have a decreased arterial cross-sectional area in patients with MS. The cross-sectional area of the carotid and vertebral arteries (CSA) is also reduced.

In 5-year follow-up research, 2-dimensional (2D) neck MRI angiography was used to monitor the neck vascular CSA in patients with MS and healthy controls. They found no change in CSA between the groups at the beginning. The monitoring showed a decline in the CSA of the common carotid artery, internal carotid artery, vertebral artery, and internal jugular vein, regardless of the disease profile [17].

In the present study, there is a significant negative correlation between HDRS and Rt ACA pi, Lt ACA pi, and Rt PCA sv, also with Rt vertebral A IMT, Rt basilar A pi, and Rt basilar A dv. And significant positive correlation between HDRS and Lt vertebral A dv. In addition, there is a significant negative correlation between MMSE and Rt vertebral mv, Rt basilar mv, and Lt basilar A dv. While there is a significant positive correlation between MMSE and Lt PCA edv and Lt basilar A pi. There is also a significant negative correlation between EDSS and Rt ACA pi. There is also a significant positive correlation between EDSS and Rt MCA dv, Rt ACA mv, and left vertebral a. IMT.

This is in harmony with Adhya et al. [18], who investigated this association in 11 controls and 22 MS patients using 3 Tesla (3T) MRI. They discovered a stronger connection between EDSS and periventricular CBF in primary progressive MS (PPMS) compared to RRMS ($r = 0.48$ and $p = 0.0016$).

Conclusion

Cerebrovascular hemodynamic insufficiency is significantly prominent in patients with MS in mainly anterior and posterior circulation, while the carotid circulation shows less affection. The different significant correlations that were observed between the studied scales (HDRS, MMSE, and EDSS) with many affected vessels among patients with MS indicated that the cerebral vessel changes affected the progression and disability related to MS.

Competing interests:

The authors declare that they have no competing interests.

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