Decrease in secondary neck vessels and cerebral aqueduct enlargement in multiple sclerosis: a 5-year longitudinal MRI study

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Disclosures

- Dejan Jakimovski, Maria Marcella Lagana, and Niels Bergsland have nothing to disclose.
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Background

- In addition to multiple genetic and environmental factors, cardiovascular health has been recently recognized as a contributor to worse clinical and radiological MS outcomes. ^{1,2}
- On the other hand, several intracranial CSF flow studies of MS patients demonstrate some cross-sectional differences when compared to HCs.³



MS – multiple sclerosis, CSF – cerebrospinal flow, AoS – aqueduct of Sylvious, LV – lesion volume, WM –white matter

Vaughn et al. 2019 Nat Rev Neurol; Jakimovski et al. 2019 Expert Rev Neurother, Sundstorm et al. 2010 Ann Neurol; Magnano et al. J Magn Reson Imaging 2012.

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Preliminary results – extracranial vasculature

	MS (n	MS (n = 193)		HC (n = 193)			
Arterial (CCA/ICA,							
C2/C3		55.1	55.1 (16.4)		60.9 (17.9)		
C4		60.8	60.8 (15.7)		63.4 (16.3)		
C5/C6		50.1 (10.1)		53.9 (12.5)		.026 ^b	
C7/T1		47.6 (9.8)		52 (9.9)		.005 ^b	
	N	o. of Vessels	of Vessels		CSA (mm ²)		
	MS (n = 193)	HC (<i>n</i> = 193)	P Value	MS (n = 193)	HC (n = 193)	<i>P</i> Value	
Secondary vessels							
C2/C3	12.9 (5.4)	10 (4.2)	<.001 ^b	92.1 (40.6)	81.6 (35.5)	.016 ^b	
C4	9.1 (4.2)	7.5 (3.3)	<.001 ^b	71.0 (33.7)	65.3 (28.7)	.022 ^b	
C5/C6	7.8 (3.9)	6.8 (3.4)	.012 ^b	61.9 (32.2)	57.2 (28.2)	.028 ^b	
C7/T1	8.8 (4.9)	6 (3.5)	<.001 ^d	71.1 (40.5)	56.7 (32.5)	<.001 ^d	



¹Belov et al. AJNR Am J Neuroradiol 2018, ²Pelizzari et al. AJNR Am J Neuroradiol 2018

- Cross-sectionally, RRMS patients have smaller arterial vessel size and higher number of secondary neck vessels.¹
- Longitudinal analysis of the major arterial vessels demonstrated further vessel narrowing in MS patients when compared to HCs. ²
- What are the longitudinal changes in secondary neck vessels and in CSF flow dynamics?

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METHODS AND MATERIALS

- Recruitment and eligibility
- MRA and PC-cine imaging
- Statistical analysis







Study population and criteria

• Study subjects were recruited from ongoing prospective 5-year longitudinal cardiovascular, environmental, and genetic study in MS (CEG-MS).¹

Inclusion criteria:

- Age 18-75 at baseline
- 3T MRI availability both at baseline and follow-up
- Sub-study acquisition of PC cine imaging

Exclusion criteria:

- Clinically-defined relapse or use of intravenous corticosteroids within 30 days of blood sample collection
- Pregnant or nursing mothers





MRI acquisition and analysis

- Study specific sequences acquisition and analysis include:
 - High resolution T1 brain volumes determined with SIENAX.
 - Magnetic Resonance Angiography (MRA) semi-automated thresholding/contouring secondary vessel segmentation by JIM software.
 - Phase contrast (PC) cine imaging AoS measures derived with Segment software







Statistical analysis

- Differences between MS and HCs in the number and total CSA of secondary vessels was performed by Mann Whitney U test.
- For longitudinal analyses, non-parametric repeated measure (Wilcoxon) was performed and respective z-change scores were derived.
- FDR-corrected q-values were reported.

Sub-study analysis

- Cross-sectional differences in AoS-measures were derived by age and sex-adjusted ANCOVA, whereas longitudinal changes were derived by paired t-tests.
- Associations between brain volumes and AoS measures were derived with Spearman's correlation.

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RESULTS



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Demographic and clinical characteristics

	MS (n=83)	HCs (n=25)	p-value			Baseline	
Female, n (%)	59 (71.1)	20 (80)	0.449		HCs	MS	HCs vs
Age, mean (SD)	49.2 (12.3)	44.3 (14.5)	0.095				MS
Time of follow-up, mean (SD)	5.4 (0.5)	5.5 (0.5)	0.125	Sex (F/M)	15/5	22/15	0,383
BMI at baseline, mean (SD)	27.9 (5.6)	26.7 (6.8)	0.421	Age, mean±SD	47.3±12.9	51.9±9.2	0.133
BMI at follow-up, mean (SD)	27.6 (4.9)	26.7 (6.0)	0.481			• • • • • •	0,200
Hyperlipidemia at baseline, n (%)	16 (19.3)	4 (16)	1.000	Excluded (N)	5	2	
Hypertension at baseline, n (%)	10 (12)	4 (16)	0.734				
Heart disease at baseline, n (%)	5 (6)	1 (4)	1.000				
Diabetes, n (%)	2 (2.4)	1 (4)	0.55	• 3 CIS patients were excluded			
Disease duration, mean (SD)	15.1 (11.3)	-	-	form the analysis		8	
CIS/RRMS/PMS	13/41/29	-	-	torini ule anarysis			20
Annualized relapse rate, mean (SD)	0.192 (0.423)	-	-	• Additional exclusion of PC			
EDSS at baseline, median (IQR)	2.5 (1.5-5.38)	-	-	- cine scans		o substa	ntial
EDSS at follow-up, median (IQR)	3.0 (1.9-6.0)	-	-	image noise			
EDSS change, mean (SD)	0.33 (1.0)	-	-	ininge i			

• No statistical difference in any demographic characteristics between MS and HCs.

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Change in number and size of secondary neck vessels

	MS (1	n=83)	HCs (n=25)					
	Z-change	q-value	Z-change	q-value				
Number of secondary vessels								
C2-C3	-5.425	<0.001	-2.486	0.090				
C3-C4	-4.533	<0.001	-2.122	0.095				
C4	-5.000	<0.001	-1.107	0.342				
C4-C5	-4.840	<0.001	-2.356	0.086				
C5-C6	-3.273	0.001	-1.414	0.275				
C6-C7	-3.556	<0.001	-1.337	0.282				
C7-T1	-4.055	<0.001	-2.138	0.114				
Cross-sectional area of secondary vessels								
C2-C3	-4.735	< 0.001	-2.650	0.113				
C3-C4	-4.000	< 0.001	-1.762	0.182				
C4	-3.799	< 0.001	-0.821	0.480				
C4-C5	-5.230	<0.001	-1.224	0.309				
C5-C6	-4.036	< 0.001	-0.067	0.946				
C6-C7	-4.517	<0.001	-1.466	0.285				
C7-T1	-2.864	0.004	-0.740	0.495				



Longitudinal change in the number of secondary neck vessels measured at C4-C5.





Longitudinal changes in Aqueduct of Sylivius measures

	AoS Variable	Baseline	Follow-up	p-value
	Vmean systolic peak (cm/s)	5.46±2.16	5.43±1.73	0,939
	Vmean diastolic peak (cm/s)	4.22±1.32	4.06 ± 1.20	0,415
_	Vmax systolic peak (cm/s)	9.85±3.56	9.54±2.97	0,53
Г	Vmax diastolic peak (cm/s)	7.23 ± 2.00	7.86 ± 2.76	0,037
L	Average Area (mm ²)	3.12 ± 1.07	3.69±1.55	0.001*
	Flow rate systolic peak (ml/min)	10.36 ± 5.53	12.16 ± 7.30	0.051
L	Flow rate diastolic peak (ml/min)	7.76±3.51	9.33±5.64	0.023
	Net vol caudal (µl/beat)	46.93±27.31	50.49±34.4	0,391
	Net vol cranial (µl/beat)	41.13±23.56	45.86±32.22	0,208

- The MS patients had average AoS CSA increase from 3.1mm² to 3.7mm², q=0.001,increase in diastolic peak flow rate from 7.8ml/min to 9.3ml/min, p=0.023, and increase in diastolic peak velocity from 7.2cm/s to 7.8cm/s, p=0.037.
- The change in AoS CSA was not associated with the change in secondary vessels, but with global ventricular CSF expansion ($r_s=0.457$, p=0.025).









Limitations

- Low HCs sample size for inferring normal "aging" trajectories of secondary neck vessel changes.
- Lack of PC-cine imaging with high velocity encoding (for arterial and venous flow measurement).

Conclusions

- MS patients experience greater longitudinal decrease in secondary neck vessels when compared to HCs.
- Concurrently, MS patients demonstrate greater AoS enlargement, potentially reflecting local brain atrophy changes.
- Larger multimodal studies should determine the interrelationship between vascular and CSF longitudinal changes.



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Thank you! Any questions?

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Supplement Slides

	CIS (n=13)		RRMS	(n=41)	PMS (n=29)		
	Z-change	p-value	Z-change	p-value	Z-change	p-value	
Number of secondary vessels							
C2-C3	-2.784 ^b	0.005	-4.056 ^b	<0.001	-2.430 ^b	0.015	
C3-C4	-1.899 ^b	0.058	-4.272 ^b	<0.001	-1.103 ^b	0.270	
C4	-1.843 ^b	0.065	-3.684 ^b	<0.001	-2.857 ^b	0.004	
C4-C5	-2.620 ^b	0.009	-3.395 ^b	0.001	-2.468 ^b	0.014	
C5-C6	-2.808 ^b	0.005	-1.753 ^b	0.080	-1.610 ^b	0.107	
C6-C7	-1.531 ^b	0.126	-3.056 ^b	0.002	-1.310 ^b	0.190	
C7-T1	352 ^b	0.725	-3.135 ^b	0.002	-2.77 ^b	0.005	
Cross-sectional area of secondary vessels							
C2-C3	-2.970 ^b	0.003	-3.726 ^b	<0.001	-1.546 ^b	0.122	
C3-C4	-2.341 ^b	0.019	-3.052 ^b	0.002	-1.806 ^b	0.071	
C4	-1.433 ^b	0.152	-2.844 ^b	0.004	-2.346 ^b	0.019	
C4-C5	-3.040 ^b	0.002	-3.415 ^b	0.001	-2.562 ^b	0.010	
C5-C6	-2.341 ^b	0.019	-2.430 ^b	0.015	-2.173 ^b	0.030	
C6-C7	-1.852 ^b	0.064	-3.713 ^b	<0.001	-1.762 ^b	0.078	
C7-T1	035 ^b	0.972	-2.831 ^b	0.005	-1.594 ^b	0.111	





Supplement Slides

		RRMS (N=15)			PMS (N=14)	
	Baseline	Follow-up	Baseline vs follow-up	Baseline	Follow-up	Baseline vs follow-up
Vmean systolic peak (cm/s)	5.38±2.59	5.55±1.78	0,77	5.54±1.67	5.31±1.74	0,525
Vmean diastolic peak (cm/s)	-4.22±1.69	-4.32±1.31	0,718	-4.21±0.84	-3.78 ± 1.04	0,128
Vmax systolic peak (cm/s)	10.1±3.9	9.69±3.14	0,626	9.58±3.27	9.37±2.89	0,708
Vmax diastolic peak (cm/s)	-7.13±2.17	-8.03±2.73	0,053	-7.33±1.88	-7.69±2.89	0,386
Average Area (mm2)	3.02±0.89	3.44±1.31	0,078	3.24±1.27	3.96±1.78	0.004*
Flow rate systolic peak (ml/min)	9.5±4.51	11.8±7.34	0,16	11.27±6.5	12.54 ± 7.51	0,144
Flow rate diastolic peak (ml/min)	-7.41±3.2	-9.35±5.85	0,113	-8.14±3.9	-9.31±5.62	0,075
Net vol caudal (µl/beat)	42.56±23.42	50.21±37.35	0,298	51.61±31.15	50.78±32.34	0,826
Net vol cranial (µl/beat)	-36.96±21.01	-46.26±35.71	0,167	-45.6±26.05	-45.44±29.37	0,959