CARDIOVASCULAR RISK FACTORS AFFECT BRAIN VOLUME IN YOUNG MS PATIENTS

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INTRODUCTION and PURPOSE

Cardiovascular (CV) risk factors (RF) have been associated with changes in clinical and MRI outcomes in patients with multiple sclerosis (MS):

- The presence of vascular risk factors, coronary heart disease or peripheral arterial disease is associated with a substantially increased risk of disability progression in MS [1].
- MS patients with migraine, hyperlipidemia or a high comorbidity burden (≥ 3 among CV RF and psychiatric comorbidities) had an increased relapse rate over 2 years [2].
- Better lipidic profile (higher HDL cholesterol) was associated with lower gadolinium+ lesion volume [3].
- An increase in typical MS lesions was mainly seen in smokers; this CV RF is most likely to be present from onset of MS, whereas other CV RF effects may be partly mitigated by treatment [4].

Previous studies have not set an age-limit, but older patients may be affected by cerebral small vessel disease-related damage in addition to MS. Neither have previous studies assessed the presence vs absence of CV RF, without attempting to grade strength of exposure (e.g., pack-years for smoking, time and control of individual CV RF).

In this study, we aimed to investigate the impact of CV RFs on T2-hyperintense lesion volume and brain atrophy in patients with MS under age 50 years

METHODS

Subjects: 124 MS (79 relapsing-remitting, 45 progressive) patients and 95 healthy controls (HC).

Neurological assessment: Expanded Disability Status Scale rating and CV RF assessment at time of MRI acquisition.

Traditional CV risk factors were assessed:

- having smoked ≥5 pack-years
- hypertension
- dyslipidemia
- diabetes/prediabetes

"*Stringent*" CV risk factors were assessed:

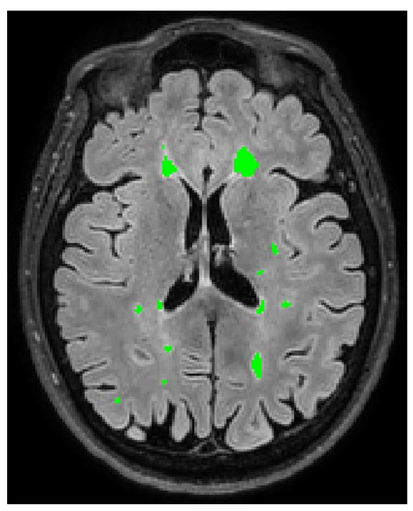
- having smoked ≥10 pack-years
- hypertension under treatment
- dyslipidemia under treatment
- diabetes under treatment**Figure 1B**)

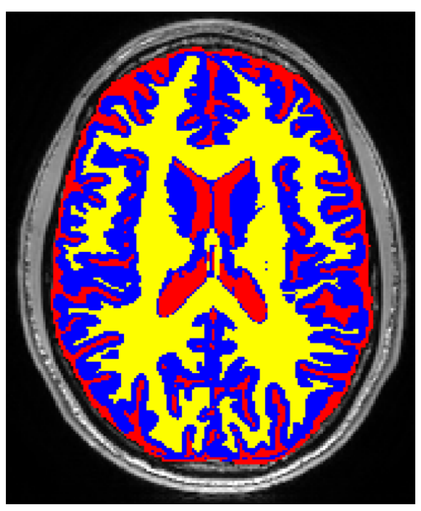
MRI acquisition (3.0 Tesls scanner): brain and cervical SC pulse sequences for the assessment of lesions and atrophy.

MRI analysis:

- T2-hyperintense LV quantification (T2LV) on 3D T2-weighted and FLAIR images (**Figure 1A**)
- SIENAX 2.0 for quantification of normalized WM (nWMV), GM (nGMV) and total brain (nBV) volumes on 3D T1-weighted images (**Figure 1B**)

Figure 1. MRI analysis

A) 

B) 

Statistical analysis:

- Fisher exact test, Mann-Whitney and t student test for demographic and clinical variables
- **Linear models adjusted for age, sex, disease duration, phenotype (RRMS vs PMS) and treatment** were used to determine the impact of CV risk factors on MRI variables

RESULTS

Demographic and clinical variables of study participants (Table 1).

	HC (n=95)	MS (n=124)	MS vs HC p value
Men/Women	48/47	50/74	0.17
Mean age (SD) [years]	35 ± 8 (18 - 50)	36 ± 8 (18 - 50)	0.37
Phenotype RRMS/PMS	-	79/45	-
Median disease duration (IQR) [years]	-	8 (2-17)	-
Median EDSS score (IQR)	-	2.5 (1.5-5.5)	-
DMT none/1st/2nd line	-	22/61/41	-

Table 2. Burden of CV RF in HC and MS patients

	HC (n=95)	MS (n=124)	MS vs HC p value
Classic RF (1/≥2)	19 (20%) / 4 (4%)	48 (39%) / 15 (12%)	<0.001
Smoked ≥5 pack-years	16 (17%)	42 (34%)	0.005
Hypertension	4 (4%)	14 (11%)	0.08
Dyslipidemia	8 (8%)	19 (15%)	0.15
Diabetes/prediabetes	2 (2%)	5 (4%)	0.70
Stringent RF (1/>1)	10 (11%) / 3 (3%)	30 (24%) / 8 (6%)	0.01
Smoked ≥10 pack-years	8 (8%)	23 (19%)	0.05
Hypertension on treatment	3 (3%)	12 (10%)	0.06
Dyslipidemia on treatment	4 (4%)	10 (8%)	0.28
Diabetes on treatment	1 (1%)	4 (3%)	0.39

By using linear models, we performed the below reported group comparisons.

Table 3. Presence (RF+) vs absence (RF-) of at least one traditional CV RF

	HC RF- (n=72)	HC RF+ (n=23)	HC RF- vs RF+ p value	MS RF- (n=61)	MS RF+ (n=63)	MS RF- vs RF+ p value
Median T2-LV (IQR) [mL]	0.00 (0.00 – 0.15)	0.00 (0.00 - 0.07)	0.76	2.10 (0.88 – 4.51)	3.00 (0.90 – 7.14)	0.27
nBV [mL]	1582 ± 34	1563 ± 40	0.34	1531 ± 66	1508 ± 64	0.06
nGMV [mL]	892 ± 35	880 ± 31	0.79	863 ± 42	845 ± 39	0.09
nWMV [mL]	690 ± 27	683 ± 28	0.11	668 ± 39	664 ± 35	0.26

Table 4. Presence (RF+) vs absence (RF-) of at least two traditional CV RFs

	HC RF- (n=91)	HC RF+ (n=4)	HC RF- vs RF+ p value	MS RF- (n=109)	MS RF+ (n=15)	MS RF- vs RF+ p value
Median T2-LV (IQR) [mL]	0.00 (0.00 – 0.12)	0.28 (0.00 - 0.48)	0.30	2.17 (0.87 – 6.22)	3.23 (1.64 – 6.86)	0.27
nBV [mL]	1580 ± 34	1553 ± 65	0.08	1524 ± 65	1481 ± 68	**0.003**
nGMV [mL]	890 ± 33	868 ± 54	0.10	856 ± 42	836 ± 35	**0.01**
nWMV [mL]	689 ± 27	671 ± 29	0.14	668 ± 37	645 ± 40	**0.03**

Table 5. Presence (RF+) vs absence (RF-) of at least one stringent CV RF

	HC RF- (n=82)	HC RF+ (n=13)	HC RF- vs RF+ p value	MS RF- (n=86)	MS RF+ (n=38)	MS RF- vs RF+ p value
Median T2-LV (IQR) [mL]	0.00 (0.00 – 0.13)	0.00 (0.00 - 0.26)	0.45	1.90 (0.77 – 4.31)	5.73 (1.73 – 8.29)	**0.03**
nBV [mL]	1581 ± 34	1551 ± 45	0.27	1534 ± 62	1484 ± 64	**<0.001**
nGMV [mL]	891 ± 33	870 ± 39	0.67	863 ± 40	833 ± 39	**0.006**
nWMV [mL]	690 ± 27	681 ± 23	0.16	671 ± 37	651 ± 34	**0.003**

For all tables, variables are mean ± SD unless otherwise specified.

CONCLUSIONS

- The presence of **CV RFs** is associated with **brain atrophy**, involving both the GM and WM, **in MS patients, even under age 50**
- **CV RFs** seem to have **synergistic effects**, determining brain atrophy even for levels of exposure that may often be overlooked by clinicians, when present in combination

REFERENCES. [1] Marrie et al., *Neurol* 2010; [2] Kowalec et al., *Neurol* 2010; [3] Weinstock-Guttman et al., *Journal of Neuroinflammation* 2011; [4] Geraldes et al., *JNNP* 2020.