Pathophysiology of cerebral small vessel disease: cerebral collateral efficiency and markers of small vessel disease

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Background

Cerebral small vessel disease (CSVD) is a microvascular process with distinct MRI markers: white matter hyperintensities (WMH), cerebral microbleeds (CMB), lacunes, and enlarged perivascular spaces (EPVS). It is a common cause of cognitive decline and gait problems especially in the elderly. While each of the markers are associated with cardiovascular risk factors, there is mounting evidence that they may be pathophysiologically distinct[1], though classically cerebral hypoperfusion has been thought to play a central role. We undertook this analysis to explore the association between cerebral collateral circulation status and CSVD burden.

Methods

A retrospective cohort of 142 consecutive patients who presented to a single academic center with anterior circulation large vessel occlusions on CT angiography was analyzed. MRI images obtained in the acute stroke phase were independently examined for markers of CSVD in the contralesional hemisphere using previously published criteria[2] by investigators blinded to risk factors or demographic data. Patients were excluded if MRI images unavailable for review. The degree of WMH was quantified using the Fazekas scale. The total CSVD burden score was calculated based on severity of the Fazekas score, presence of CMB or lacunes, and severity of EPVS[1]. We used a previously described collateral score (CS) to characterize the degree of collateral supply[3]. Univariable and multivariable adjusted analyses were performed to explore the association between CS and CSVD.

Results

A total of 127 patients (63.5±17.7 years, 49% female) were included in the study. HTN was the most common vascular risk factor and was present in 69% of patients. The median collateral score was 2 (IQR 1-2). Among the CSVD markers, WMH was the most prevalent marker (76%) followed by basal ganglia EPVS (61%) and lacunes (21%). Lower mean CS was associated only with presence of WMH (4.19±1.98 vs 5.19±2.54, p=0.02). This association was maintained in multivariable logistic regression (OR 0.75, 95% CI: 0.58-0.95, p=0.01). There was no significant association between CS and lacunes or EPVS. Older age had the most potent association with individual CSVD markers and higher total CSVD burden (p=<0.0001). Of the typical vascular risk factors, HTN showed the most significant association with CSVD burden (p=0.006). Ipsilateral large vessel stenosis was also associated with higher CSVD burden (p=0.02).

Discussion

Lower CS is associated with WMH presence, but not other CSVD markers or total CSVD burden. This suggests that while WMH may be associated with chronic ischemia, other markers of CSVD, especially lacunes, may have a different pathophysiology. The current literature is mixed with this regard[4,5], at least partially due to the fact that different terms and definitions have been used to study CSVD[2]. While further work in human studies of WMH is needed to elucidate the underlying mechanism, our work suggests that better collaterals may be protective against development of WMH.

Table 1 Study population characteristics

Age Mean +/- SD)	63.5 +/- 17.7
Female sex N(%)	62 (49)
White race, N(%)	87 (74)
Left MCA, N(%)	53 (42)
Tan Score, median (IQR)	2 (1-2)
Expanded Tan Score, median (IQR)	5 (2-6)
Hypertension, n (%)	87 (69)
Hyperlipidemia, n (%)	64 (50)
Diabetes, n(%)	33 (26)
Current smoking, n (%)	22 (18)
Admission SBP, mean +/- SD	140.7+/- 25.3
Admission NIHSS, median IQR	16 (11-20)
Significant carotid stenosis (>50%), n (%)	9 (7)
Intracranial large artery stenosis, n (%)	6 (5)
Any large artery atherosclerotic stenosis, n (%)	14 (11)

Table 2 Markers of CSVD

CMB, n(%)	7 (6)
Lacunes, n (%)	27 (21)
EPVS basal ganglia, n(%)	76 (61)
Severe BG EPVS (grades 2-4)	8 (6)
EPVS CSO, n(%)	64 (51)
Severe CSO EPVS (grades 2-4)	9 (7)
Deep WMH, n (%)	
Grade 0	65 (51)
Grade 1	35 (28)
Grade 2	16 (13)
Grade 3	11 (8)
"Severe" Deep WMH (Grades 2/3)	27 (21)
Periventricular WMH, n(%)	
Grade 0	31 (24)
Grade 1	65 (51)
Grade 2	21 (17)
Grade 3	10 (8)
"Severe" PVWMH (Grade 3)	10 (8)
Total CSVD burden	
Grade 0	78 (62)
Grade 1	29 (23)
Grade 2	16 (13)
Grade 3	3 (2)
Grade 4	0

Table 3 Association between CS and CSVD markers

	Present	Not present	p value
Lacunes			
Age	70.2+/- 15.2	61.7+/-17.8	0.03
Expanded CS	4.1+/-0.4	4.5+/-0.2	0.38
CMBs			
Age	70.7+/-16	63.1+/-17.8	0.27
Expanded CS	5.28+/- 2.13	4.38+/-2.16	0.29
WMH			
Age, mean,(SD)	66.8+/-16.9	53.1+/-16.1	0.0001
Expanded CS	4.19 +/-1.98	5.19+/-2.54	**0.02**
Multivariate analysis	*OR*	*95% CI*	
Age	1.04	1.01-1.08	0.003
Expanded CS	0.75	0.58-0.95	0.01
EPVS (basal ganglia)			
Age	68.8 +/-16.9	55.1 +/- 15.8	<0.0001
Expanded CS	4.34+/-1.99	4.49+/-2.4	0.71

Table 4 Total CSVD load and associated risk factors

Risk factors	β	Std error	p value
Age	0.018	0.004	<0.0001
CS	-0.08	0.1	0.39
Expanded CS	-0.02	0.03	0.41
Risk factors			
Female sex			0.74
HTN			0.006
HLD			0.05
DM			0.03
Smoking			0.85
Ipsilateral large vessel stenosis			0.02

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