Biomarkers of Cerebral Microvascular Angiopathy in Healthy Subjects at Risk of Stroke

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Background: The mechanisms by which atheroma produces end organ damage in the brain are multifactorial and include indirect effects of systemic vascular disease such as embolism and systolic hypertension and direct atheromatous involvement of the cerebral arteries and arterioles; a pathological process referred to as microvascular angiopathy (MVA). Although MVA is common there are few reliable imaging markers of its presence. MVA is characterised by histological changes including thickening of the walls of arterial vessels and dilatation of the Virchow-Robin spaces (VRS). We have previously described two novel biomarkers of MVA based on magnetic resonance imaging (MRI), VRS dilatation and abnormalities in the transfer of systolic arterial pulsation to the ventricular CSF, which occur as a result of decreased cerebral arterial compliance[2, 3]. These are associated with vascular dementia and treatment resistant late onset depression. We studied a group of normal elderly subjects at risk of stroke to determine if these biomarkers are present in patients who have no evidence of symptomatic vascular disease.

Methods: Patient participants were identified as having at least three clinical risk factors for stroke (hypertension, atrial fibrillation, coronary artery disease, left ventricular hypertrophy, cigarette smoking, diabetes mellitus, dyslipidaemia and peripheral vascular disease). A careful clinical history was taken to exclude any symptoms that might suggest a history of transient ischaemic attack (TIA) or stroke, a history of cerebral injury, or cognitive impairment. Control participants had only one or no vascular risk factors and no history or symptoms to suggest previous stroke or TIA. All subjects were scanned using a Philips 3 Tesla ACS-NT scanner. The imaging protocol included Axial Fluid Attenuated Inversion Recovery and Axial T1 weighted inversion recovery images. Arterial blood flow and CSF flow in the cerebral aqueduct were measured using quantitative single-slice phase-contrast angiography (PCA) ECG gated with 16 cardiac phases. The assessment of white matter lesion load was based on the Scheltens' scale [1]. Virchow Robin spaces (VRS) were scored using a locally developed scoring scheme [2, 3]. PCA images were analysed to produce estimates of: 1) Aqueduct systolic peak width (aqWSP); 2) Aqueduct systolic stroke volume (sysV); 3) Aqueduct diastolic stroke volume (diasV) ;4) Aqueduct average stroke volume (SV) and Arterial-aqueductal delay (AAD).

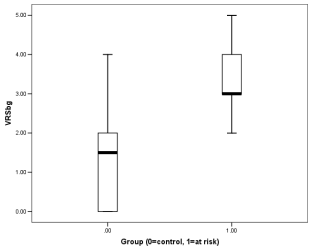
Results: The final study group consisted of 16 males (mean age 63+/-8.0yrs) and 15 females (mean age 60.5 +/- 7.4 yrs). Of these there were 15 control subjects (mean age 59.5 yrs +/- 6.2 yrs, 4 male) and 16 subjects at risk of stroke (mean age 65.0 +/- 6.8 yrs). Although there was a trend to increased DWMH and PVH in the at risk group univariate ANOVA using age and gender as cofactors demonstrated no significant differences in in individual regional scores or summary total scores. There were significant inter-group differences in the VRSbg, VRSex, VRSov and VRSm (Table 1 and 2, Figure 1). Unvariate ANOVA using age and gender as cofactors demonstrated significant differences in atWSP (control 0.472 +/-0.030; at risk 0.430 +/- 0.049; p=0.015; Figure 3). No other measured flow variable demonstrated significant intergroup differences. There was a significant positive correlation between aqWSP and AAD (rho=0.529; p<0.01). In addition both atWSP and systolic BP correlated with all measurements of aqueductal flow volume: sysV(atWSP: rho= 0.45, p<0.05; BP: rho=0.01, p<0.05), diasV (atWSP: rho= 0.52, p<0.05; BP: rho=0.42, p<0.05)and SV (atWSP: rho= 0.49, p<0.05, BP: rho=0.42, p<0.05, Figure 4). Binary logistic regression analysis included the following variables and factors: 1) total DWMH, 2) total PVH, 3) VRSbg, 4)VRSm, 5) VRSov ,6) VRSext,7) atWSP, 8) AAD, 9) age and 10) gender. Only VRSbg (p<0.001) and total PVH (p<0.05) demonstrated independently significant correlations with subject group accounting respectively for 37% and 14% of the variance between the groups

	Control	At Risk	Significance
PVH (total)	1.00 (1.30)	1.7 (1.79)	0.092
DWMH (total)	2.86 (2.85)	4.58 (5.23)	0.099
BG VRS	1.29 (1.32)	3.29 (0.77)	<0.001

Table 2: Group differences between variables demonstrating normal distribution. Probability values calculated using Univariate ANOVA with age and gender as cofactors and were used to select variables for binary logistic regression

	Control	At Risk	Significance
Vertex VRS	2	12	<0.05
Midbrain VRS	1	8	<0.05
Lacunes	0	4	0.79
Ext capsule VRS score = 1	3	11	
Ext capsule VRS score = 2	0	2	P<0.01

Table 3: Group differences in categorical variables. Numbers represent number of positive cases in the class. Probability values calculated using chi squared test and were used to select cofactors for binary logistic regression analysis.



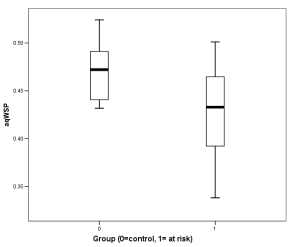


Figure 1: Right: Boxplot showing distribution of VRSbg scores in control and at risk subjects (p<0.001)
Left Boxplot showing distribution of aqWSP scores in control and at risk subjects (p<0.05)

Conclusions: This study demonstrates that imaging biomarkers, specific for the presence of MVA, demonstrate abnormality in elderly normal subjects who are considered at risk for stroke. This confirms the sensitivity of these biomarkers for the presence of MVA even in the early stages of microvascular cerebral injury.

References:

1.Scheltens, P., et al., A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. J Neurol Sci, 1993. 114(1): p. 7-12.; 2.Patankar, T.F., et al., Dilatation of the Virchow-Robin space is a sensitive indicator of cerebral microvascular disease: study in elderly patients with dementia. AJNR Am J Neuroradiol, 2005. 26(6): p. 1512-20.
3.Patankar, T.F., et al., Virchow-Robin space dilatation may predict resistance to antidepressant monotherapy in elderly patients with depression. J Affect Disord, 2007. 97(1-3): p. 265-70.