Dilated Perivascular Spaces in the Basal Ganglia Are a Biomarker of Cerebral Small Vessel Disease in a Very Elderly Dementia Population

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Target Audience – Researchers and clinicians interested in cerebral small vessel disease (SVD)

Purpose –SVD is common in older individuals and is the most common cause of vascular dementia (VaD) and mixed dementia. Patients with Alzheimer's disease (AD) commonly have coexistent SVD and it is increasingly recognised that many patients have mixed pathology, particularly in older dementia patients   Although MRI is commonly used to study SVD, the presence of white matter hyper intensity, which is the most commonly used biomarker, has been found to be non-specific. Improved specificity has been demonstrated for scoring systems that document the frequency of dilated peri-vascular spaces. Patankar et al [1] originally described scoring systems for the recognition of dilated PVS but the original scoring system was designed for sensitive detection of early disease. Later workers described an alternate scoring system designed to allow categorisation of patients with more severe SVD by the use of numerical counting of dilated PVS [2]. This study was designed to examine the utility of PVS scoring systems in very elderly patients with dementia.

Methods –Patients with clinical Alzheimer's disease (AD), VaD, or mixed AD and VaD were recruited from secondary care old age psychiatry services in greater Manchester, United Kingdom. An independent clinician classified patients into probable or possible AD or VaD categories using the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for AD and the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria for VaD . Patients with severe dementia (Mini-Mental State Examination (MMSE) score <10) {Folstein, 1975 #6} , mixed AD and VaD and those receiving anticoagulant treatment were excluded {Purandare, 2006 #36}. Control subjects were age-matched to the dementia group. Neuroimaging- included FLAIR (TR 11000, TE 140, TI 2600) and T1-weighted inversion recovery (TIR; TR 6850, TE 18, TI 300) images. White matter intensities were scored using an established rating scale [3]. PVS were scored using both previously described scoring systems. The first, (PVS-1) is based on number and location of PVS. The second scoring system (PVS-2) was adapted from Doubal et al 2010 and is based on counts of PVS in the most heavily affected slice of the basal ganglia and centrum semiovale: 0 = no PVS, 1 = 1-10 etc.

Results: The final study group consisted of 117 subjects; 47 AD (mean age 74.1 ± 8.5 yrs); 39 VaD (mean age 76.9 ± 7.7yrs) and 3) Norm (mean age 78 ± 5.3 yrs). Inter and Intra-observer variation studies showed good to very good agreement for modified Schelten's, PVS-1 and PVS-2 scores (Table 1). The modified Schelten's score was higher in VaD than in AD (p<0.05) or Norm (p<0.01) but there was no significant difference between AD and Norm (Fig 1A). The PVS-1 score showed no significant differences across groups. However, the PVS-2 in the basal ganglia was higher in VaD than in AD (Fig 1B; p<0.01) or Norm (p<0.01; Fig 1). Modelling demonstrated PVS-2 and Modified Schelten's score as the only imaging parameters with independent significant

Inter-observer agreement							
White Matter Score				PVS-1		PVS-2	
Rater	1 vs 2	0.82	Very Good	0.79	Good	0.92	Very Good
	1 vs 3	0.91	Very Good	0.84	Very Good	0.89	Very Good
	2 vs 3	0.88	Very Good	0.82	Very Good	0.83	Very Good
Intra-observer agreement							
Rater	1	0.82	Very Good	0.87	Very Good	0.92	Very Good
	2	0.	Very Good	0.96	Very Good	0.84	Very Good

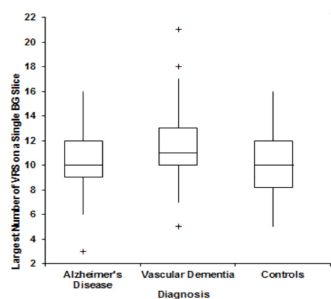Table 1: Inter and Intra observer agreements assessed by calculation of weighted Cohen's kappa

Figure 1: Distribution of PVS-2

discriminative power (p<0.01 and p< 0.01 respectively) to distinguish dementia patients (VaD and AD combined) from normal controls. The area under the ROC curve was 0.798. Modelling of AD against Norm demonstrated no discrimination between groups. Modelling of VaD against Norm showed PVS-2 (p<0.01) and modified Schelten's score (p<0.05) contributed significant, independent discriminatory power accounting for 32% and 12% of the variance in the model respectively. The resulting model produced an area under the ROC of 0.91. Finally modelling of VaD against AD demonstrated that PVS-2 (0.05) and modified Schelten's score (p<0.05) contributed significant, independent discriminatory power accounting for 28% and 14% of the variance in the model respectively producing an area under the ROC of 0.771.

Conclusions: This study has demonstrated that PVS scores retain discriminatory power for SVD even in a very elderly population with dementia.

1.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. **2.** Doubal, F.N., et al., *Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease.* Stroke. **41**(3): p. 450-4. **3.** Scheltens, P., et al., *A semiquantitative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging.* J Neurol Sci, 1993. **114**(1): p. 7-12.