

Pontine Hyperintensities are a Sensitive Indicator of Small Vessel Disease in Elderly Patients with Dementia

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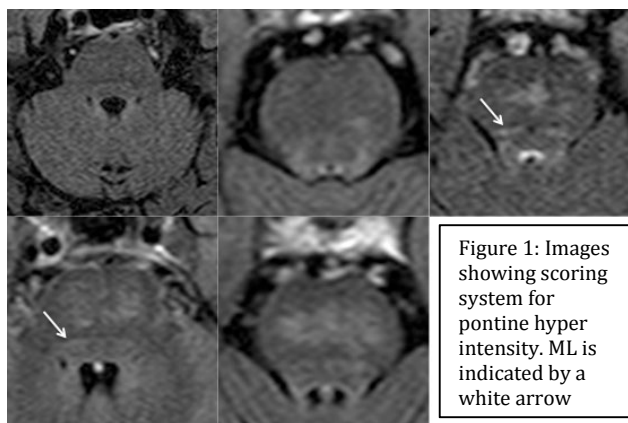
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Target Audience – Researchers and clinicians interested in cerebral small vessel disease (SVD)

Purpose –A recent international consensus review on imaging features of SVD [1] highlighted areas requiring further study including the need for the development of scoring systems to integrate the many imaging findings for small vessel disease. This review identified differing opinions as to whether brainstem hyperintensities should be routinely classified as white-matter hyper intensities, and the consensus was that lesions in the brainstem should not be included unless explicitly stated [1]. Recently, Erbay and colleagues have identified the presence of high signal in the medial lemniscus (ML) as specific indicator of SVD [2]although they provide no data to document whether or not ML hyperintensity provide useful data over and above existing white-matter scoring systems. The purpose of this study is to examine the discriminative power of high signal intensities within the brain stem in the identification of STD in a very elderly population of normal volunteers and patients with dementing disease.

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) [3] , mixed AD and VaD and those receiving anticoagulant treatment were excluded. 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. Scoring of white matter disease was performed using a modified version of the Schelten’s scoring scheme from which brainstem components were omitted. Medial meniscus hyper intensity (ML) was scored as 0 equals absent; 1 equals present. White matter hyperintensity in the brainstem was scored using a novel alternate system. Pontine and mesencephalic hyperintensities were scored 0 = none; 1= a single area of hyperintensity, 2 = more than one hyperintensity involving < 25% of the cross sectional area on the worst affected slice; 3 = more than 25% but less than 50% of the cross sectional area on the worst affected slice and 4 = more than 50% of the cross sectional area on the worst affected slice. In addition the presence of established hemispheric stroke, lacuna infarct and dilated perivascular spaces (PVS) were recorded.



Results: The final study group consisted of 117 subjects; 47 AD (mean age 74.1 ± 8.5 yrs); 39 VaD (mean age 76.9 ± 7.7 yrs) and 3) Norm (mean age 78 ± 5.3 yrs). Intra and inter-observer agreement were very good for medial lemniscus hyperintensity ($\kappa = 1.0$) and the new pontine score ($\kappa = 0.82$) but remained moderate for the new mesencephalon score ($\kappa = 0.46$). Hyperintensities in the brainstem showed strong correlations with a number of other

imaging features (Table 1). ML, pons and midbrain scores all showed strong correlation with each other ($p < 0.001$). Linear regression modeling showed brainstem components to have no independent discriminative power to separate dementia from normal subjects, VaD from control subjects or AD from VaD. Modeling of VaD vs AD demonstrated that pons ($p < 0.001$), ML ($p < 0.01$) and the presence of lacunar infarcts ($p < 0.01$) all contributed significant, independent discriminatory power accounting for 48%, 12% and 8% of the variance in the model respectively. The resulting model ($\text{Diagnosis} = 1.218 \times \text{pons} - 3.708 \times \text{ML} + 2.329 \times \text{lacunar}$) produced an area under the ROC of 0.833.

Conclusions: We demonstrate that white matter hyperintensity in the brainstem provides greater discriminative power for the separation of VaD and AD in a very elderly population than other imaging features. White matter hyperintensity in the brainstem is an important biomarker of SVD in the presence of advanced microvascular disease and should be included in standard scoring systems.

1. Wardlaw, J.M., et al., *Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration*. Lancet neurology, 2013. **12**(8): p. 822-38.

2. Erbay, S.H., et al., *T2 hyperintensity of medial lemniscus is an indicator of small-vessel disease*. AJR. American journal of roentgenology, 2012. **199**(1): p. 163-8.

3. Folstein, M.F., S.E. Folstein, and P.R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research, 1975. **12**(3): p. 189-98.

Feature	Pons	Midbrain	Lacunar Infarct	PVS	Schelten's
ML	0.633***	0.290***	ns	0.299***	0.396***
Pons		0.291***	0.136**	0.336***	0.537***
Midbrain			ns	ns	0.190*
PVS					0.347***

Table 1: Correlation between imaging features of SVD