Dilated Virchow Robin spaces (VRS) on MRI predict treatment resistance in patients with late onset depression

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Introduction: There is increasing evidence that cerebral microvascular disease may predispose to, trigger or perpetuate depression in later life [1]. In hospital-treated depression, research with magnetic resonance imaging (MRI) shows unexpectedly high numbers of white matter lesions [2]. However, existing white matter rating scales have not proved sufficiently sensitive or specific to be of use with the individual patient. Virchow-Robin spaces (VRS) are perivascular spaces which surround perforating arteries that enter the brain. In pathological studies abnormal dilatation of VRS is most commonly associated with the cerebral microvascular angiopathy (MVA) which results from atheromatous disease of cerebral arteries and arterioles [3]. Abnormal dilatation of VRS therefore offers a theoretical alternative biomarker of cerebral small vessel disease. This study tests the hypothesis that abnormal dilatation of VRS will be seen in patients with late onset depressive disorder and will be more extensive in patients who exhibit treatment resistance.

Material and Methods: 50 patients with late-onset major depressive disorder (29 who were responders to antidepressant monotherapy and 21 who were non-responders) and 35 age matched controls were recruited. The imaging protocol on a Philips 1.5T ACS-NT scanner included Axial FLAIR (TR 11000, TE 140, TI 2600, matrix 256^2, field of view (FOV) 230mm^2 , slice thickness 3.0mm, Axial T1W Inversion recovery (IR TR 6850, TE 18, TI 300, slice thickness 3.0 mm, matrix 256^2, FOV 230mm^2, reconstructed as real images) and axial high-resolution 3D T1 weighted Fast Field Echo[FFE] sequences (TR 24,TE 18, matrix 256^2, FOV 230mm^2,slice thickness 0.89 mm, Flip angle 30°). Deep White Matter and Periventricular Hyperintensities assessment was performed on matched T1WIR and T2W FLAIR images using a scoring system based on the Scheltens' scale [4]. VRS visibility was greatest on IR images (Contrast to noise ratio for VRS vs normal white matter was: IR = 64.1, FFE = 24.8) scoring was therefore performed using IR images . VRS were scored separately in centrum semiovale (0 = none; 1= less than 5 per side; 2 = more than 5 on one or both sides), mesencephalon (0 = none, 1 = VRS present), and sub-insular region lateral to the lentiform nucleus (0 = none, 1 = less than 5 on either side, 2 = more than 5 on one or both sides). VRS in the basal ganglia were scored using two separate scoring schemes, the first of these (BG1: 0= VRS only in the substantia innominata and <5 VRS on either side/side; 1= >5 VRS in the substantia innominata on either side or any VRS in the lentiform nucleus; 2= VRS in caudate nucleus on either side) reflects the anatomical distribution of basal ganglia VRS and the second (BG2: 0= VRS only in the substantia innominata and <5 VRS on either side/side, 1= VRS only in the substantia innominata, >5 dilated VRS on either side; 2= <5 in lentiform nucleus on either side, 3=5-10 VRS in lentiform or <5 in caudate nucleus on either side, 4=> 10 in lentiform nucleus and <5 in caudate nucleus on either side, 5=>10 in lentiform nucleus and >5 in caudate nucleus on either side) reflects the distribution and number. Statistical group comparisons used ANOVA with *a posteriori* Tukey test and Kruskal Wallis test with *a posteriori* Mann-Whitney U test for non-parametric data. Multiple regression analyses, using a forward stepwise method, were performed to identify the proportion of inter-group variance, which can be accounted for by individual variables

Results: Significant group differences were seen in the total Schelten's score, the white matter hyperintensity score and the periventricular hyperintensity score. This reflects a trend towards higher scores in all of the parameters in the treatment resistant group. However, none of the group-to-group comparisons reached significance. The simpler BG1 score showed a non-significant trend to higher values in the treatment resistant group. The BG2 score shows a highly significant group statistic ($p < 0.001$) and pairwise tests shows significantly higher values in treatment resistant patients than in treatment responsive patients ($p < 0.01$) or normal volunteers ($p < 0.001$). Multiple regression analysis in the depression group showed that the BG2 VRS score accounted for 38% of the variance in the regression model and that the Schelten's PVH score acted as an independent predictive factor accounting for an additional 6%. In this study a BG2VRS score>2 would have provided sensitivity and specificity of 80% and 63% respectively in separating treatment resistant depression patients within the depression group and BG2VRS >4 would decrease the sensitivity to 30% but improve the specificity to 89%.

Conclusion: VRS gives important biological information about cerebral microvascular disease in patients with late onset depressive disorder. Dilatation of VRS may play a role in identifying patients with a high risk of treatment resistance at the time of diagnosis

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