Is a Progressive Increase in the Number of Microhemorrhages in the Aged an Earlier Sign of Alzheimer's Disease?

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Introduction:

Vascular dementia has been long recognized as one mechanism in Alzheimer's disease. This may be brought on by the development of cerebral amyloid angiopathy (CAA), not surprisingly, related to beta amyloid and reduction of blood flow to tissue. Two key questions are: "What is the progression of this disease?" and "How prevalent is it as a form of Alzheimer's disease?" It is known that CAA manifests in imaging as a large number of micro-hemorrhages (MH) at the arteriole level. To date, little evidence exists as to its development over time in the aging. Susceptibility weighted imaging (SWI)(1), a high resolution gradient echo imaging technique, is sensitive to hemosiderin even at the level of an arteriole bleed (2). Our research goal is to determine if an increase in the number of MH corresponds to a progression of AD.

Methods:

A series of 107 patients, 28 controls and 78 mild cognitively impaired (MCI), were evaluated in a longitudinal study of the aging (informed consent was obtained in all cases). All subjects were scanned at least on an annual basis over a period of 4 years. Apart from conventional imaging methods (T1 and T2), SWI was also done. SWI acquisition parameters were: in-plane resolution 0.5mm x 1.0mm; TH = 2mm, FOV = 256mm x 256mm; Nx = 512; Ny = 256; Nz = 48; TE = 40ms; TR = 57ms; FA = 20 degrees. The phase images were high pass (HP) filtered and an SWI magnitude image created. The images were reviewed for the presence of MH. All of the original magnitude images, SWI filtered phase images and the contrast enhanced SWI magnitude images were used in the data review process. Local minimum intensity projections (mIPs) over 3 slices were used to ensure that a MH was not connected to a major vessel but rather was isolated from the macro-vasculature. Volume was determined by counting the number of voxels in each slice associated with the MH. Finally, phase was measured in each MH to estimate the product of overall magnetic moment and volume content.

Results:

Out of 78 MCI subjects, 16 progressed to probably AD. In a blinded fashion, all the 78 cases were reviewed for the presence of MH and for an increase in the presence of MH over time. We found that there were 6 such cases. All 6 of these were later found to belong to the group 16 subjects who had probably AD. The change in the number of MH is shown in Figure 1. Clinical Dementia Rating (CDR) test was done almost at the same time points for each subject before or after the scan. An increase in the number of MH correlates to an increase in the (CDR). MH were observed in both gray matter and white matter. Figure 2 shows an example slice from study two and four of single subject.

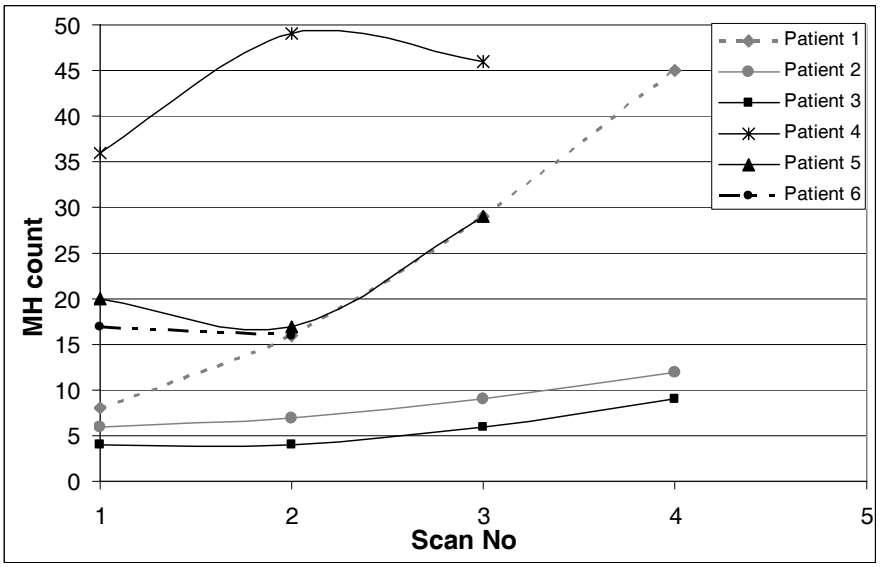

Figure 1: Plot of MH count at different time points

Discussion:

The sensitivity of SWI to the presence of local MH opens the door to evaluating micro-vascular disease in the aging. From this study, it appears as if the percentage of vascular dementia to the total number of AD cases (6 out of 16) is higher than originally thought. However, numerous papers today are beginning to focus more on the role of micro-vascular disease, the damage caused by free iron from micro-bleeds, and the role amyloid deposition plays in the degradation of blood vessel walls in diseases like CAA. Although our results are still preliminary, there is some evidence that a continued increase in the number of MH may correspond to the rapid development of reduced perfusion to the tissue and an onset of vascular dementia.

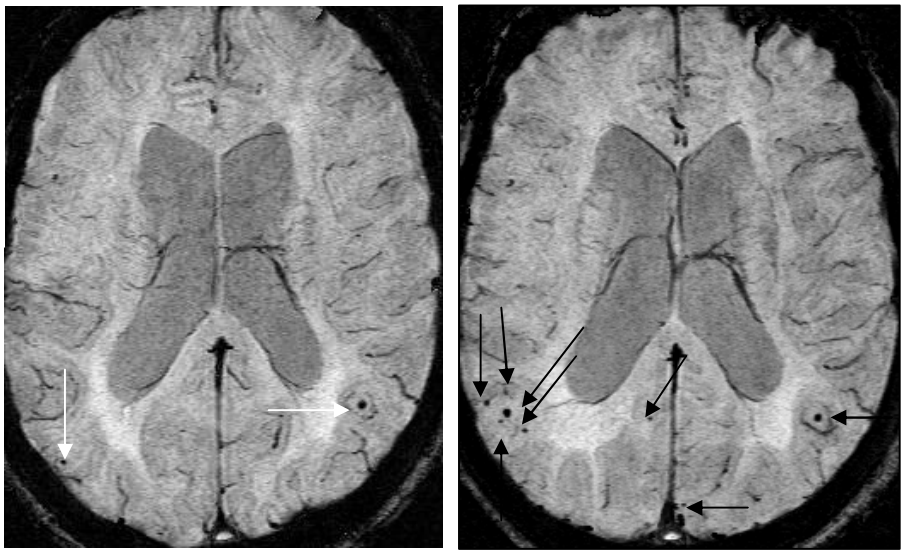

Figure 2: Same slice (each 8mm thick) from two different scans of the same subject, two years apart. An increase in Microhemorrhages is observed in second scan.

Reference:

1- Haacke EM, Xu Y, Cheng YC, Reichenbach JR. Susceptibility Weighted Imaging (SWI). Magn Reson Med 2004;52:612-618.

2- Walker, D.A., Broderick, D.F., Kotsenas, A.L.,Rubino, F.A. Routine use of gradient-echo MRI to screen for cerebral amyloid angiopathy in elderly patients. AJR Am J Roentgenol. 2004 Jun;182(6): 1547-1550