Hippocampal NAA Differences Despite Similar Atrophy Between Subcortical Ischemic Vascular Dementia and Alzheimer's Disease

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INTRODUCTION: Alzheimer's disease (AD) is associated with neuron loss, especially in the hippocampus (HP), while subcortical ischemic vascular dementia (SIVD) is thought to be primarily related to ischemia of subcortical gray and white matter, leading to cortical/HP deafferentation, but without frank cortical/HP neuron loss. Consistent with this picture, many structural MRI studies show extensive HP atrophy in AD and disproportionately high prevalence of white matter lesions in SIVD. Recently, however, we found autopsy-confirmed HP atrophy in cases of pure SIVD, without concomitant AD [1]. This implies that HP atrophy is not specific for AD. Therefore, HP volume measurements alone may not be helpful to differentiate between AD and IVD.

Using ^{1}H MRSI, we previously reported reduced NAA in HP of AD [2]. Moreover, when HP NAA from ^{1}H MRSI and HP volume from MRI were used together, the discrimination between AD and elderly controls was better than when using HP volume alone. This implies that NAA contributes useful information about AD beyond what is available from structural changes. In this study, we sought to measure HP NAA in addition to HP volume in order to improve discrimination between AD and SIVD. Our specific hypothesis was that *for similar dementia severity there would be less hippocampal NAA loss in SIVD than in AD, because of the different pathologies involved.*

M**ETHODS:** This study included the first 9 SIVD, 27 AD, and 19 elderly control (CN) subject with complete quantitative MRI and PRESS ^{1}H MRSI analysis from a larger sample of a prospective study on SIVD and AD. The demographic data is listed in the table. All studies were performed on a 1.5 T MR scanner. All subjects had axial PD and T2 double spin echo, and volumetric gradient echo (MP-RAGE) MRI scans, followed immediately by PRESS ^{1}H MRSI in the HP region. MRIs were semi-automatically tissue-segmented and the HP surfaces were manually outlined on MP-PRAGE and normalized to the total intracranial volume. Furthermore, the outlined HP masks were added to the tissue-segmented MRIs, which were then blurred to the spatial resolution of MRSI to determine the tissue composition enclosed in each MRSI voxel. In addition, a hippocampal tissue index (HTI = HP tissue/total tissue in a voxel) was computed to measure partial volume effects. The voxel with maximum HTI in each subject was selected for further analysis. Intensities of NAA, Cho and Cr were obtained using fully automated spectral fitting software [3], corrected for tissue-volume, and finally normalized to the intensity of CSF. Between group differences were tested using ANOVA, with adjustments for HTI.

RESULTS: The Table lists the results for volume, NAA, Cho, Cr, and NAA/(Cho+Cr), as well as HTI from the right HP. Similar results were obtained for left HP (data not shown). When the HP volumes were compared both, SIVD and AD had about 23% ($p < 0.001$) smaller volumes than CN. SIVD and AD had similar HP volumes ($p > 0.7$). When HP NAA was compared, AD showed about 30% ($p < 0.03$) lower HP NAA levels than CN. In contrast, SIVD compared with CN had only 11% ($p > 0.2$) lower HP NAA levels. However, HP NAA differences between SIVD and AD were not significant. Cr was also lower in AD compared with both, SIVD and CN, but this was not significant. Cho and NAA/(Cho+Cr) values were not significantly different between the groups. Finally, HTI of CN was significantly ($p < 0.001$) larger than in SIVD or AD, indicating that the MRSI data from HP of CN contained more HP tissue than the data from the other groups.

	CN	SIVD	AD
N	19	9	27
Age	71 ± 9	76 ± 4	75 ± 9
MMSE	29.0 ± 0.7	20.8 ± 3.9	19.3 ± 6.2
Hippocampus			
Volume[a]	2.67 ± 0.52	2.04 ± 0.36†	2.02 ± 0.38†
NAA[b]	2.0 ± 0.7	1.8 ± 0.6	1.4 ± 0.5‡
Cr[b]	1.4 ± 0.3	1.5 ± 0.4	1.2 ± 0.4
Cho[b]	0.6 ± 0.2	0.5 ± 0.2	0.4 ± 0.2
NAA/(Cho+Cr)	1.0 ± 0.3	0.9 ± 0.2	0.8 ± 0.2
HTI	44. ± 14	36 ± 8	33. ± 13

† $p < 0.001$; ‡ $p < 0.03$; AD or SIVD versus CN.
[a] in cubic centimeters;
[b] in arbitrary units;

DISCUSSION: Different magnitude of HP NAA loss despite similar degree of HP atrophy in SIVD versus AD supports our hypothesis. In SIVD, cognitive impairment is thought to be related to neuronal disconnection rather than neuron loss, while in AD, neuron loss is well documented. Our MRI finding of similar HP atrophy in SIVD and AD implies that volume measurements alone cannot distinguish between the different processes. In SIVD, disconnection of the hippocampus may cause shrinkage of both neurons and glia. Alternatively, primary ischemia of the hippocampus may cause drop-out of both neurons and glia. In both scenarios, neuronal loss in SIVD would be proportional to tissue loss. In contrast, volume loss in AD may be attenuated because reactive gliosis replaces neurons. Therefore, in AD neuronal loss may be disproportionate to tissue loss. Because NAA concentration is not reduced by loss of glial cells or other non-neuronal tissue, NAA measurements when corrected for tissue-atrophy can in principle differentiate between neuron loss that is proportional vs. disproportional to tissue loss. Our NAA findings imply that there is disproportionately greater neuron loss in HP of AD than in SIVD. Finally, the finding of prominent HP NAA loss in AD but not in SIVD cannot be explained to be simply an artifact of structural differences between the groups, because NAA was tissue corrected and furthermore, HP partial volume effects were accounted for.

In summary, our findings provide further support that atrophy-corrected measures of NAA may be useful for the differential diagnosis of SIVD and AD.

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