Regional myo-inositol concentration in mild cognitive impairment and Alzheimer disease using 1H magnetic resonance spectroscopic imaging

M. Siger[1,2], N. Schuff[1], X. Zhu[1], and M. Weiner[1]

[1]Center for Imaging of Neurodegenerative Diseases, Veterans Administration Medical Center, San Francisco, CA, United States, [2]Department of Neurology, Medical University of Lodz, Lodz, Lodz, Poland

Background: Clinical observations show that patients with mild cognitive impairment (MCI) have a higher risk of conversion to Alzheimer's disease (AD) than cognitively normal elderly subjects of similar age consistent with the view that MCI is a prodromal stage of AD. In this study, we used spectroscopic imaging (MRSI) to determine whether both MCI and AD show systematic regional patterns of metabolite abnormalities in white matter and gray matter Specifically, we tested the following hypotheses:

1) MCI and AD are associated with increased myo-inositol (mIn) and decreased (N-acetyl-aspartate (NAA) in gray matter (GM) and normal appearing white matter (NAWM) compared with healthy, age related control group

2) The most prominent metabolite abnormalities in MCI and AD occur in the parietal lobe. In addition, we determined the extent to which vascular pathology, expressed as white matter hyperintensities (WMH) on MRI, can explain metabolite abnormalities.

Methods: Fourteen amnestic MCI (6 women, 8 man, mean age 77.1 ±6.3 years) were studied using MRI and MRSI and compared with 16 healthy control (HC) (11 women, 5 men, mean age 72.5±5.2 years) and 17 AD patients (7 women, 10 men, mean age 74.5 ±7.7 years). Multislice MRSI data (TR/TI/TE=1800/170/25 msec, 30 min total acquisition) were acquired from axially oblique, 15-mm-thick slices, with a nominal in-plane resolution of 7.8x 7.8 mm^2. Structural MRI were used for brain tissue segmentation into GM, NAWM, CSF and WMH and analyzed together with registered MRSI too estimate metabolite concentrations separately of "pure" gray matter and white matter in the left and right frontal and parietal lobes

Statistics: Metabolites (from ^{1}H MRSI) were analyzed within a linear model, accounting for the effects of diagnosis and WMH, which was expressed as an index for each subject, defined as the volumes of all regions classified as WMH on MRI divided by the total volume of normal appearing WM and WMH. Age, gender, WMH index as well as voxel tissue composition of MRSI were added into the model as covariates. *F*-tests were used to determine if factors added explanatory power and were therefore appropriate for inclusion in the model. Regional variations were tested using repeated measures ANOVA and post-hoc Scheffe tests. An alpha of 0.05 was used as level of significance for all tests.

Results: After accounting for age, gender and WMH index, MCI patients showed in comparison to HC higher mIn concentrations ($F_{3,26} = 4.5$, $P < 0.05$) in the right parietal white matter and a trend in left parietal white matter ($F_{3,26} = 3.9$, $P = 0.058$), while differences in the frontal white matter as well as in gray matter were not significant (all $p > 0.2$) (table 1). Surprisingly, the mIn levels of parietal white matter in MCI were not significantly different from those in AD ($P > 0.13$). However, mIn levels of frontal white matter in MCI were markedly lower than those in AD (right $F_{3,27} = 4.8$ $P < 0.04$; left $F_{3,27} = 4.8$ $P < 0.04$). AD patients had in comparison to HC substantially higher mIn concentrations in both frontal and parietal white matter (right frontal: $F_{3,29} = 9.9$, $P < 0.004$; left frontal $F_{3,29} = 13.6$, $P < 0.001$; right parietal: $F_{3,29} = 12.6$, $P < 0.002$; left parietal: $F_{3,29} = 7.0$, $P < 0.02$). AD patients had also higher mIn concentrations in frontal gray matter compared to HC, primarily on the right side ($F_{3,29} = 4.4$,$P < 0.05$) and a trend on the left side ($F_{3,29} = 3.3$, $P = 0.09$) but no significant elevations of mIn in parietal gray matter. In contrast to mI, MCI subjects had similar NAA concentrations in both GM and WM than controls (table 2). Differences in NAA concentrations between AD and controls or MCI were also not significant. Finally, mIn and NAA variations were not significantly associated with WMH in any of the groups ($p > 0.5$ for all tests)

Table 1 Myo-inositol and NAA concentration[*] in all groups

Group	Region	mIn gray matter	mIn white matter	NAA gray matter	NAA white matter
Control	RF	14.34 (3.58)	15.84 (2.58)	24.68 (4.13)	29.36 (4.55)
MCI	RF	13.87 (3.18)	16.91(2.18)#	22.05 (4.89)	29.02 (4.14)
AD	RF	15.56(3.16)[**]	18.59 (2,6)[‡‡]	22.48 (4.39)	29.53 (4.17)
Control	LF	14.91 (3,96)	16.97 (2.65)	26.59 (4.81)	30.31 (4.98)
MCI	LF	15.19 (3.01)	18.43(2.66)#	25.35 (5.41)	29.74 (5.50)
AD	LF	16.70(3.03)[*]	20.88(3.99)[‡‡]	26.31 (4.19)	30.31 (6.03)
Control	RP	14.87 (3.99)	16.59 (2.15)	27.85 (5.17)	29.47 (3.51)
MCI	RP	14.97 (2.05)	18.70 (2.59)[††]	25.81 (5.06)	29.33 (4.95)
AD	RP	15.08 (2.83)	19.80 (2.95)[‡‡]	22.11 (4.48)	28.94 (5.21)
Control	LP	14.55 (3.67)	14.52 (2.00)	27.97 (4.83)	26.11 (3.25)
MCI	LP	15.28 (2.07)	15.57 (1.85)[†]	25.35 (4.93)	25.50 (4.87)
AD	LP	15.19 (2.54)	16.17 (3.16)[‡‡]	23.12 (4.91)	24.66 (3.74)

[*]concentrations in arbitrary units , listed are mean and standard deviation in parenthesis, MCI-mild cognitive impairment, AD-Alzheimer's disease, RF- right frontal, LF- left frontal, RP-right parietal, LP-left parietal l [††] $p < 0.05$ MCI vs control, [†] $p = 0.058$ MCI vs control, # $p < 0.04$ MCI vs AD, [‡‡] $p < 0.05$ AD vs control, [**] $p < 0.05$ AD vs control. [*] $p = 0.09$ AD vs control

Conclusion: This study suggests vulnerability of white matter in the pathology of AD and MCI as indicated by widespread increased mI in white matter regions. Furthermore, increased mIn may be an even more robust and sensitive marker for MCI and AD than NAA, which was not significantly reduced in white matter compared to aging. Moreover, the dissociation between mI and NAA alterations could provide important information regarding the role of glial and neuronal damage in MCI and AD