

Original Research Article

An Open-Label Exploratory Study with Memantine: Correlation between Proton Magnetic Resonance Spectroscopy and Cognition in Patients with Mild to Moderate Alzheimer's Disease

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Key Words

Magnetic resonance spectroscopy · Alzheimer's disease · Activities of daily living · Image biomarker · Memantine · Cholinesterase inhibitors

Abstract

Aim: To characterize progression of Alzheimer's disease (AD) using proton magnetic resonance spectroscopy (^1H MRS). **Methods:** Eleven subjects with mild to moderate AD underwent neurocognitive testing and single-voxel ^1H MRS from the precuneus and posterior cingulate region at baseline, after 24 weeks of monotherapy with a cholinesterase inhibitor, and after another 24 weeks of combination therapy with open-label memantine and a cholinesterase inhibitor. Baseline metabolites [N-acetylaspartate (NAA), myo-inositol (ml), choline (Cho), and creatine (Cr)] and their ratios in AD subjects were compared with those of an age-matched control group of 28 cognitively normal subjects. **Results:** AD subjects had significantly higher ml/Cr and lower NAA, NAA/Cr, NAA/Cho, and NAA/ml. Baseline Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) scores significantly correlated with NAA/Cr, ml/Cr, and NAA/ml. There was an increase in ml and a decrease in NAA/ml, but no significant change in other metabolites or ratios, or neurocognitive measures, when memantine was added to a cholinesterase inhibitor. **Conclusion:** Metabolite ratios significantly differed between AD and control subjects. Baseline metabolite ratios correlated with function (ADCS-ADL). There was an increase in ml and a decrease in NAA/ml, but no changes in other metabolites, ratios, or cognitive measures, when memantine was added to a cholinesterase inhibitor.

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Introduction

One of the most pressing challenges underlying clinical trials in Alzheimer's disease (AD) is the need to validate reliable surrogate biomarkers of disease progression. Proton magnetic resonance spectroscopy (¹H MRS) allows for noninvasive in vivo detection and measurement of brain metabolites, often using the creatine (Cr) peak as a relatively stable reference [1]. N-acetylaspartate (NAA) is a marker of neuronal integrity and/or mitochondrial function. NAA concentrations [2, 3] and NAA/Cr ratios [4–7] have been reported to be lower in AD patients as compared with normal elderly subjects. Furthermore, decreased NAA/Cr levels may predict future conversion from mild cognitive impairment (MCI) to AD [8–11]. Myo-inositol (mI) is a glial cell marker, and mI/Cr ratios have been found to be elevated in AD [4] and MCI [12, 13]. Choline (Cho) is a cell membrane marker, and Cho/Cr ratios have also been found to be elevated in AD [7, 12, 14] and MCI [15].

Memantine is a low-to-moderate affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist with strong voltage dependency and rapid blocking/unblocking kinetics. While preclinical evidence suggests that memantine decreases the neuronal toxicity associated with excessive activation of NMDA receptors [16] and protects against beta-amyloid-induced toxicity [17], it is not clear whether this translates into a beneficial effect in patients with AD. Memantine has been shown to be effective for the treatment of moderate to severe AD, both as monotherapy [18] and when added to a cholinesterase inhibitor [19]. However, it has not been proven to be of benefit in mild AD, based on cognitive and functional outcome measures [20, 21].

The purpose of this study was to characterize the progression of AD using ¹H MRS and cognitive outcome measures in patients with mild to moderate AD treated with open-label memantine in addition to a stable-dose cholinesterase inhibitor. We compared baseline metabolite levels and ratios in mild to moderate AD subjects to those of age-matched cognitively normal control subjects. We examined correlations between baseline metabolites and ratios, functional status, and cognitive measures within AD subjects. In addition, we explored whether we could detect any differential longitudinal effect on either neurocognitive measures or spectroscopic biomarkers when memantine was added to a cholinesterase inhibitor.

Methods

Subjects

We enrolled 11 subjects, aged ≥ 50 years, with a diagnosis of probable AD according to NINCDS-ADRDA criteria, of mild to moderate severity based on MMSE score ≥ 15 and ≤ 26 at screening (mean MMSE score 21.9 ± 3.0), a modified Hachinski score ≤ 4 at screening, no other clinically significant neurologic, psychiatric, or medical illnesses, and an MRI scan performed as part of the screening procedures consistent with a diagnosis of AD, and without any findings that could confound spectroscopic analysis. AD subjects had been on a stable dose of a cholinesterase inhibitor (9 subjects on donepezil 10 mg daily and 2 subjects on galantamine 16 mg daily) for at least 3 months prior to study entry, and had not been previously treated with memantine. The study included a 24-week observational phase, wherein AD subjects continued stable-dose cholinesterase inhibitor treatment, followed by a 24-week open-label memantine phase, wherein AD subjects received open-label memantine treatment titrated to a dose of 20 mg per day, in addition to their ongoing cholinesterase inhibitor treatment. An age-matched control group of 28 cognitively normal subjects (mean MMSE score 28.4 ± 1.5) was used for comparison to baseline ¹H MRS metabolites and ratios in the AD subjects.

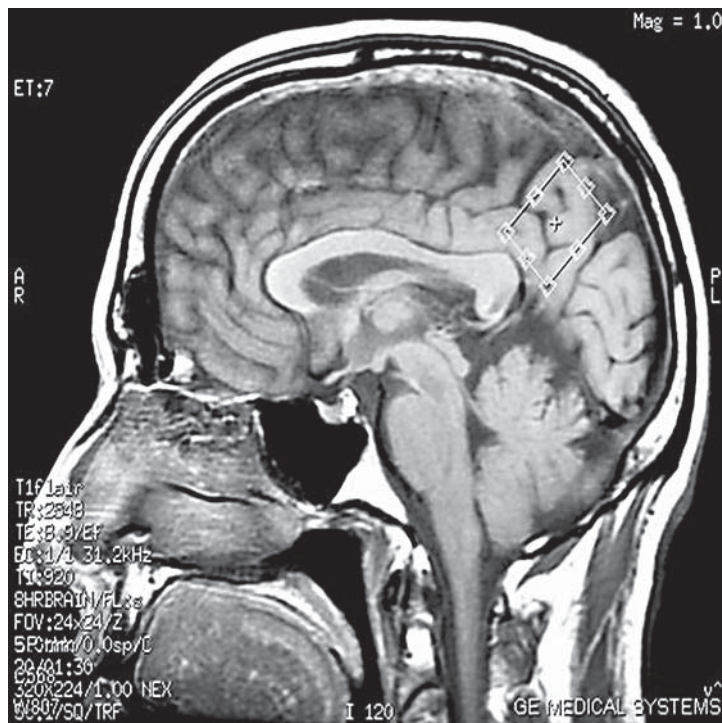


Fig. 1. Mid-sagittal precuneus and posterior cingulate region ¹H MRS voxel positioned with the long axis parallel to the parieto-occipital sulcus.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol (ClinicalTrials.gov Identifier NCT00551161) was approved by the North Shore-LIJ Health System Institutional Review Board. Written informed consent by a legally authorized representative as well as subject assent was obtained for each patient.

Neurocognitive Testing

AD subjects underwent neurocognitive testing at baseline (t_0), after 24 weeks of ongoing monotherapy with a stable-dose cholinesterase inhibitor (t_1), and after another 24 weeks of combination therapy with memantine in addition to a stable-dose cholinesterase inhibitor (t_2). The testing battery at each visit included the MMSE [22], Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog) [23], Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL) [24], Trails A and B [25], Animal Naming test and FAS verbal fluency tasks [26], logical memory and visual reproduction subtests from the WMS-R [27], Digit Span subtest from the WAIS-R [28], Rey-Osterrieth Complex Figure copying and recall [29], Judgment of Line Orientation test [30], and Buschke Selective Reminding test [31, 32].

¹H MRS

AD subjects underwent MRI with single-voxel ¹H MRS at baseline (t_0), after 24 weeks of ongoing monotherapy with a stable-dose cholinesterase inhibitor (t_1), and after another 24 weeks of combination therapy with memantine in addition to a stable-dose cholinesterase inhibitor (t_2). A 10.8 cm³ (2 × 2 × 2.7 cm) mid-sagittal oblique precuneus and posterior cingulate region ¹H MRS voxel was prescribed, with the long axis parallel to the parieto-occipital sulcus (fig. 1). Double-spin-echo (PRESS) spectra were acquired on a GE Twinspeed 3T MRI scanner with HDx technology, using an 8-channel-phased array head coil (GE Healthcare), with 128 excitations acquired at TR = 1,600 ms and TE = 30 ms (fig. 2). Metab-

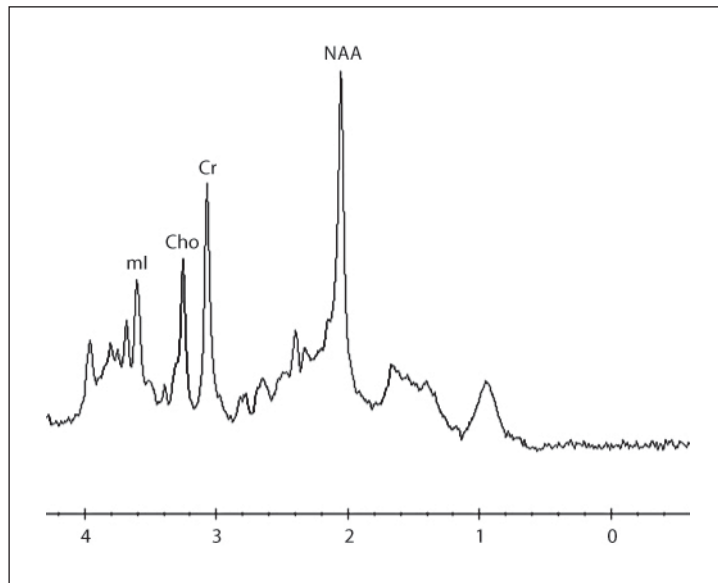


Fig. 2. ¹H MRS spectrum acquired at TR = 1,600 ms and TE = 30 ms.

olite ratios were quantified automatically with vendor-supplied software. Another 128 excitations were acquired at TR = 1,600 ms and TE = 144 ms. This allowed use of the water signal intensity at TE = 144 ms (W144) to correct the water signal intensity at TE = 30 ms (W30) for T2 losses as follows: (1) $W30 = W0 * e^{(-30/T2)}$; (2) $W144 = W0 * e^{(-144/T2)}$; (3) $T2 = 114 / \ln(W30/W144)$, and (4) $W0 = W30 * e^{(30/T2)}$, where W0 is the water signal intensity extrapolated to TE = 0 ms. Individual metabolite levels were calculated as the ratio of the metabolite signal intensity to the water signal intensity corrected for T2 losses (W0). These metabolite/T2-corrected water ratios were multiplied by a scaling factor of 10^6 to derive the individual metabolite levels reported herein.

Statistical Analysis

Comparisons between AD patients and normal control subjects were made using the Mann-Whitney test for continuous factors and Fisher's exact test for gender. For each measurement, the Wilcoxon signed-rank test was used to examine whether there was a change in that measurement between visits, and between the first and last visit (t_1 vs. t_0 , t_2 vs. t_1 , and t_2 vs. t_0). The Wilcoxon signed-rank test was also used to examine whether the change between t_0 and t_1 differed from the change between t_1 and t_2 [$(t_2 - t_1) - (t_1 - t_0)$]. This analysis was carried out in order to examine whether the rate of change differed while on monotherapy as compared with combination therapy. Spearman correlation coefficients were computed in order to determine the degree of correlation between each neurocognitive measurement and each ¹H MRS metabolite level and metabolite ratio at baseline. For the changes in measurements between visits, as described above, Spearman correlation coefficients were computed in order to determine the degree of correlation between the changes in each neurocognitive measurement and the changes in each metabolite level and ratio. Due to the exploratory nature of these analyses, no adjustment for multiple testing was made; hence, $p < 0.05$ was considered significant. Although it would have been preferable to carry out an omnibus analysis, due to the small sample size, the descriptive approach described above was used.

Table 1. Baseline demographics and ¹H MRS metabolites (normalized to T2-corrected water signal intensity) and metabolite ratios for AD subjects as compared with cognitively normal control subjects

	Controls (n = 28)	AD (n = 11)	p value
Gender (M/F)	10/18	7/4	0.1582 (n.s.) ^a
Age, years	75.2 ± 2.8	76.1 ± 7.5	0.4613 (n.s.) ^b
MMSE	28.4 ± 1.5	21.9 ± 3.0	<0.0001 ^a
NAA	697 ± 50	651 ± 68	0.0351 ^a
Cr	462 ± 32	452 ± 45	0.674 (n.s.) ^a
Cho	275 ± 26	285 ± 31	0.629 (n.s.) ^a
mI	258 ± 34	280 ± 48	0.230 (n.s.) ^a
NAA/Cr	1.51 ± 0.09	1.44 ± 0.09	0.0287 ^a
Cho/Cr	0.60 ± 0.06	0.63 ± 0.06	0.0602 (n.s.) ^a
mI/Cr	0.56 ± 0.07	0.62 ± 0.07	0.0115 ^a
NAA/Cho	2.55 ± 0.23	2.30 ± 0.29	0.0169 ^a
NAA/mI	2.74 ± 0.33	2.37 ± 0.35	0.0063 ^a

Data represent mean ± SD.

^a Mann-Whitney test; ^b Fisher's exact test. n.s. = Nonsignificant.

Results

Baseline demographics and ¹H MRS metabolites and metabolite ratios for AD subjects as compared with control subjects are summarized in table 1. As compared with control subjects, AD subjects had significantly higher baseline mI/Cr ($p = 0.0115$) and significantly lower baseline NAA ($p = 0.0351$), NAA/Cr ($p = 0.0287$), NAA/Cho ($p = 0.0169$), and NAA/mI ($p = 0.0063$). There was a trend towards increased Cho/Cr in AD subjects as compared with normal controls ($p = 0.0602$). In the AD subjects, baseline ADCS-ADL scores were significantly correlated with baseline NAA/Cr (Spearman $r = 0.80$, $p = 0.0032$; fig. 3a), mI/Cr (Spearman $r = -0.73$, $p = 0.0115$; fig. 3b), and NAA/mI (Spearman $r = 0.83$, $p = 0.0014$; fig. 3c), but not with individual metabolite levels. Baseline cognitive measures were not significantly correlated with baseline metabolite levels or ratios.

Metabolites and metabolite ratios for AD subjects at each time point as well as changes in metabolites and metabolite ratios are summarized in table 2. There was an increase in mI ($p = 0.032$) and a decrease in NAA/mI ($p = 0.042$) over the 24-week phase of combination therapy as compared with the 24-week phase of cholinesterase inhibitor monotherapy. There were no significantly different changes in the other metabolites or metabolite ratios. Also, there was no significantly different change in neurocognitive test performance over the 24-week phase of combination therapy as compared with the 24-week phase of cholinesterase inhibitor monotherapy.

Discussion

This is a small, exploratory study, and the findings may be limited by the sample size of AD subjects. Despite the relatively small number of subjects and the relatively high mean baseline MMSE score (21.9 ± 3.0) in our mild to moderate AD subjects, we were able to demonstrate significant differences in ¹H MRS metabolite ratios as compared with cognitively normal age-matched control subjects. All of the differences in metabolite ratios were in the expected directions based on prior cross-sectional studies (higher baseline mI/Cr and Cho/Cr, and lower baseline NAA/Cr, NAA/Cho, and NAA/mI) [4–7, 12–15].

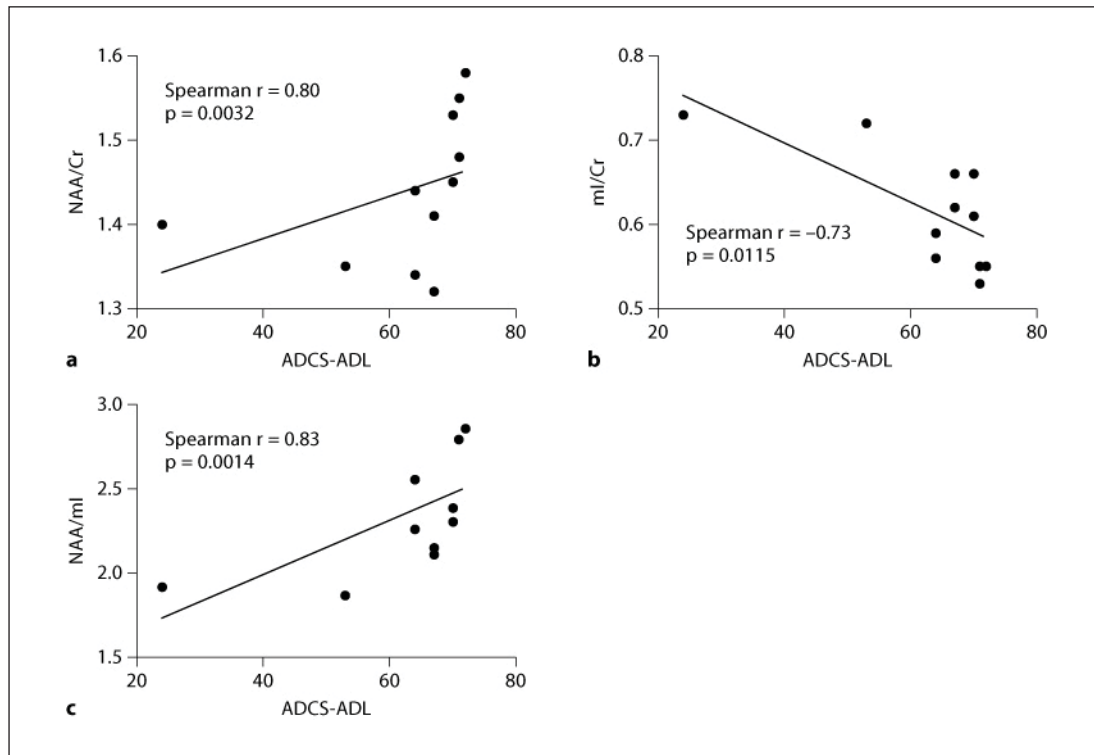


Fig. 3. Baseline ADCS-ADL scores correlated with baseline NAA/Cr (a), mI/Cr (b), and NAA/mI (c) ratios.

Table 2. Mean (\pm SD) metabolite levels (normalized to T2-corrected water signal intensity) and metabolite ratios for AD subjects at t_0 , t_1 , and t_2

	t_0	t_1	t_2	$t_1 - t_0$	$t_2 - t_1$	$[(t_2 - t_1) - (t_1 - t_0)]$	p value ¹
NAA	651 \pm 68	678 \pm 94	651 \pm 81	27 \pm 41	-26 \pm 76	-54 \pm 102	0.240 (n.s.)
Cr	452 \pm 45	452 \pm 48	450 \pm 63	0 \pm 13	-2 \pm 33	-2 \pm 36	0.831 (n.s.)
Cho	285 \pm 31	282 \pm 32	289 \pm 39	-2 \pm 14	6 \pm 17	9 \pm 12	0.067 (n.s.)
mI	280 \pm 48	277 \pm 49	289 \pm 57	-3 \pm 23	13 \pm 21	16 \pm 23	0.032
NAA/Cr	1.44 \pm 0.09	1.50 \pm 0.10	1.46 \pm 0.17	0.06 \pm 0.06	-0.04 \pm 0.14	-0.09 \pm 0.15	0.106 (n.s.)
Cho/Cr	0.63 \pm 0.06	0.63 \pm 0.06	0.64 \pm 0.05	-0.01 \pm 0.03	0.02 \pm 0.04	0.02 \pm 0.06	0.246 (n.s.)
mI/Cr	0.62 \pm 0.07	0.61 \pm 0.09	0.64 \pm 0.08	-0.01 \pm 0.05	0.03 \pm 0.04	0.04 \pm 0.08	0.142 (n.s.)
NAA/Cho	2.30 \pm 0.29	2.42 \pm 0.37	2.28 \pm 0.26	0.11 \pm 0.17	-0.14 \pm 0.30	-0.26 \pm 0.39	0.083 (n.s.)
NAA/mI	2.37 \pm 0.35	2.53 \pm 0.59	2.32 \pm 0.51	0.15 \pm 0.34	-0.20 \pm 0.31	-0.35 \pm 0.50	0.042

¹ The Wilcoxon signed-rank test was used to examine whether the change between t_0 and t_1 differed from the change between t_1 and t_2 $[(t_2 - t_1) - (t_1 - t_0)]$. n.s. = Nonsignificant.

We found that baseline ¹H MRS metabolite ratios in the precuneus and posterior cingulate region correlated with function as measured by the ADCS-ADL. Functional imaging studies have suggested that the precuneus/posterior cingulate cortex is a pivotal node in the default network [33] and plays a central role in a wide spectrum of highly integrated tasks [34]. This region is affected relatively early in AD [35]. Since the operative definition of AD

dementia, in contradistinction to MCI, hinges upon the presence of functional impairment, it is plausible that biochemical changes in this region, as reflected by altered ¹H MRS metabolite ratios, would correlate with reduced functional performance.

We did not observe any overall significant change in neurocognitive performance when open-label memantine was added to stable-dose cholinesterase inhibitor treatment. There was an increase in mI and a decrease in NAA/mI over the 24-week phase of combination therapy as compared with the 24-week phase of cholinesterase inhibitor monotherapy. The clinical significance of these findings is questionable in the absence of concomitant changes in the other metabolite ratios. Given the unidirectional crossover design of the study, this tendency towards worsening mI and NAA/mI during the second phase of the study could be due to the natural history of disease progression rather than an effect of medication.

Our inability to demonstrate a differential effect of memantine does not necessarily exclude the utility of ¹H MRS as a surrogate longitudinal biomarker in clinical trials of AD, as memantine has not been proven to have any clinical benefit in patients with mild AD [20, 21]. An open-label study of donepezil found that lower baseline parietal NAA/Cr predicted a clinical response to donepezil over 3 months, and that changes in parietal NAA/Cr correlated with changes in ADAS-Cog scores [36]. A non-randomized controlled study of rivastigmine found that changes in metabolite ratios in the frontal cortex correlated with changes on clinical scales [37]. A randomized rater-blinded parallel-group 6-month trial of memantine versus donepezil in mild to moderate AD patients found no significant differences between memantine and donepezil in clinical scales or metabolite levels, although changes in posterior cingulate region NAA/Cr significantly correlated with changes in ADAS-Cog scores [38]. A recent double-blind placebo-controlled pilot study of memantine treatment in mild to moderate AD patients also failed to demonstrate a benefit of memantine on the inferior parietal region NAA/Cr ratio, or any secondary outcome measures [39].

¹H MRS can reproducibly distinguish between relatively early AD patients and normal subjects. Further studies will be needed to replicate whether changes in precuneus/posterior cingulate metabolite ratios reliably correlate with measures of function, and whether they may yet prove useful as longitudinal biomarkers in clinical trials of disease-modifying therapies. As previously suggested [40], the precuneus and posterior cingulate region NAA/mI ratio may be a particularly sensitive spectroscopic surrogate outcome parameter for validation in future studies.

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