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¹H MR SPECTROSCOPY IN COMMON DEMENTIAS

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Abstract

Objective—To determine the ¹H MR spectroscopic (MRS) findings and inter-group differences among common dementias: Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal lobar degeneration (FTLD).

Methods—We consecutively recruited 206 normal elderly, 121 patients with AD, 41 with FTLD, 20 with DLB, and 8 with VaD. We evaluated the ¹H MRS metabolite ratio changes in common dementias with respect to normal, and also differences among the common dementias.

Results—N-acetylaspartate/Creatine (NAA/Cr) was lower than normal in patients with AD, FTLD, and VaD. Myo-inositol (mI)/Cr was higher than normal in patients with AD and FTLD. Choline (Cho)/Cr was higher than normal in patients with, AD, FTLD, and DLB. There were no metabolite differences between patients with AD and FTLD, nor between patients with DLB and VaD. NAA / Cr was lower in patients with AD and FTLD than DLB. MI /Cr was higher in patients with AD and FTLD than VaD. MI /Cr was also higher in patients with FTLD than DLB.

Conclusions—NAA/Cr levels are decreased in dementias that are characterized by neuron loss such as AD, FTLD, and VaD. MI/Cr levels are elevated in dementias that are pathologically characterized by gliosis such as AD and FTLD. Cho/Cr levels are elevated in dementias that are characterized by a profound cholinergic deficit such as AD and DLB.

Background

Alzheimer's disease (AD) is the most common cause of dementia. Dementing illnesses that are less common, but may enter into the clinical differential diagnosis, are vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal lobar degeneration (FTLD) (1,2). ¹H magnetic resonance spectroscopy (¹H MRS) is unique among diagnostic imaging

modalities, because the signals from several different metabolites are measured within a single measurement period. Each metabolite in turn is sensitive to a different aspect of in- vivo pathologic processes at the molecular or cellular level. In principle, it may be possible to generate a disease-specific spectroscopic profile with multiple contributing components. The metabolite N-acetylaspartate (NAA) is consistently found to be lower and the metabolite myo-inositol (mI) higher in ^1H MRS studies of patients with AD than cognitively normal elderly (3-8). There are conflicting reports about choline (Cho) levels in AD. Some studies identified elevated Cho levels in people with AD, and some did not (9). NAA levels are reduced in patients with vascular dementia (VaD), and white matter NAA is lower in patients with VaD than in patients with AD (10-12). Gray matter MI /Cr levels on the other hand are normal in patients with VaD (13). ^1H MRS metabolite changes in FTLN are similar to AD, with lower NAA /Cr and higher mI /Cr levels than normal (14,15).

^1H MRS studies in common dementias are limited to comparing the ^1H MRS findings in AD to other dementias (14), FTLN (15) and VaD (11-13,16). We are not aware of any study that has compared the ^1H MRS metabolite profiles among the most common dementias. The objectives of this study were to identify the ^1H MRS metabolite changes in each of the common dementias with respect to normal, and to identify ^1H MRS metabolite differences among the common dementias.

Methods

Recruitment of Subjects

All subjects of this project were recruited through the Alzheimer's Disease Research Center (ADRC) and Alzheimer's Disease Patient Registry (ADPR) at the Mayo Clinic, Rochester (17), as part of an ongoing IRB approved MRI / ^1H MRS project. All individuals participating in the ADRC/ADPR are evaluated by a behavioral neurologist and a neuropsychologist. They undergo neurological examination, neuropsychological testing, and basic laboratory testing. At the completion of the evaluation, a consensus committee meeting is held involving the behavioral neurologists, neuropsychologists, nurses and the geriatrician who evaluate the subjects. All of the subjects undergo structural brain MRI. Subjects with structural abnormalities other than vascular disease that could produce dementia, such as tumors and subdural hematoma, as well as those who had concurrent illnesses or treatments interfering with cognitive function other than AD, VaD, DLB and FTLN were excluded from this study. We only studied patients > 40 years of age.

A diagnosis of dementia is based on DSM-III-R criteria (18). The clinical diagnoses of AD, VaD, DLB, and FTLN are made using published consensus criteria (19). Only patients meeting the criteria for one of the dementias (AD, VaD, DLB, and FTLN) were included in this study. Patients who met the criteria for two or more of the different dementias were excluded.

Normals are individuals who; 1) are independently functioning community dwellers 2) do not have active neurological or psychiatric conditions, 3) have no cognitive complaints, 4) have a normal neurological exam, 5) are not taking any psychoactive medications in doses that would impact cognition.

Single Voxel ^1H MRS

^1H MRS studies were performed with the LX system automated single voxel ^1H MRS package: PROBE /SV (General Electric Medical Systems, Milwaukee, WI) (20). An eight cm^3 ($2 \times 2 \times 2$ cm) voxel was placed on a mid-sagittal T1-weighted image covering right and left posterior cingulate gyri and inferior precune (Figure 1). Point resolved spectroscopy (PRESS) pulse sequence with TR = 2000 ms, TE=30 ms, 2048 data points and 128 excitations were used for

the examinations. The prescan algorithm of PROBE automatically adjusts the transmitter and receiver gains and center frequency. The local magnetic field homogeneity is optimized with the three-plane auto-shim procedure, and the flip angle of the third water suppression pulse is adjusted for chemical-shift-water suppression (CHESS) prior to PRESS acquisition. The single voxel ^1H MRS scan time is about 6 min. Metabolite intensity ratios are automatically calculated at the end of each PROBE /SV acquisition. ^1H MRS variables that were analyzed for this study are NAA /Cr, Cho /Cr, and mI /Cr ratios.

Statistical Analysis

Gender differences among the clinical groups (normal, AD, FTL, DLB, and VaD) were tested with the chi squared test. ANOVA was used to compare clinical groups with respect to age, Clinical Dementia Rating (CDR), Dementia Rating Scale (DRS), Mini-Mental State Exam (MMSE), and the three metabolite ratios. In order to control the experiment-wise error rate, we first tested for differences in each metabolite ratio among the five groups (ie. including normals) using a one-way ANOVA. If the test was significant at the 0.05 level, we tested which groups differed from normals using Dunnett's test. We then performed a one-way ANOVA excluding the normals. If this dementia-group ANOVA was significant at the 0.05 level, we used Fisher's Least Significant Difference (LSD) procedure to make pairwise comparisons of metabolite ratios among the groups. All tests were two-sided. The effects of age on metabolite ratios were tested by linear regression analysis and the gender effects were tested with student's t-tests in normal subjects only, as the data in normals should be free of the confounding effects of disease.

Results

Demographic Aspects

We consecutively recruited 206 cognitively normal elderly volunteers, 121 patients with AD, 41 patients with FTL, 20 patients with DLB, and 8 patients with VaD, from October 2001 until January 2003. We excluded 36 patients from this study who fulfilled the diagnostic criteria for more than one dementia, because they constitute a clinically and pathologically heterogeneous group, and there are no accepted research criteria available to classify the different mixed dementia subtypes. Demographic aspects of the study groups are listed in table 1. There were no gender differences between the clinical groups (chi square $p=0.06$). Mean ages of clinical groups were different (ANOVA $p<0.0001$). Patients with VaD were older than patients with DLB ($p=0.04$). Patients with FTL were younger than all other clinical groups (normals, AD, VaD, DLB) ($p<0.01$ for all comparisons). We did not find any association between age and metabolite ratios in the normals, probably due to the older age range of our subject group (Supplemental data). Because there was no association between age or gender ($p>0.05$) and metabolite ratios in normals, metabolite measurements were not adjusted for age or gender in normals or patients. The DRS and MMSE scores of patients with different dementias were lower than the normals ($p<0.0001$ for all comparisons). There were no differences between the CDR, DRS, and MMSE scores of patients with different dementias on ANOVA, indicating that clinical dementia severity was similar between the dementia groups. Ninety one out of 121 patients with AD, 16 /41 patients with FTL, and 17 /20 patients with DLB were being treated with cholinesterase inhibitors.

All patients with vascular dementia had leukoaraiosis on MRI. In addition, four had cortical and four had subcortical infarctions. None of the lesions involved the posterior cingulate gyri and inferior precune. The ^1H MRS voxel included only the normal appearing brain tissue on MRI in all subjects.

¹H MRS differences between different dementias and normal elderly

The ¹H MRS metabolite differences from normal in patients with AD, FTLD, DLB, and VaD, are listed in table 2. NAA /Cr ratios were lower than normal in patients with AD ($p<0.001$), VaD ($p=0.08$), and FTLD ($p<0.001$), but not different from normal in patients with DLB. Cho /Cr ratios were higher than normal in patients with AD ($p=0.05$), DLB ($p=0.001$), and FTLD ($p=0.02$), but not different from normal in patients with VaD. MI /Cr ratios were higher than normal in patients with AD and FTLD ($p<0.001$ for both comparisons), but not different from normal in patients with DLB and VaD. Examples of ¹H MRS from each of the clinical groups are shown in Figure 2.

¹H MRS differences between the dementias

The ¹H MRS metabolite ratios, NAA /Cr ($p=0.009$) and mI /Cr ($p=0.008$) were different between the dementia groups on ANOVA. Cho /Cr was not different between dementia groups. ¹H MRS metabolites that differed between dementias are summarized in Table 3. NAA /Cr was higher in patients with DLB than AD and FTLD ($p<0.01$ for both comparisons). MI /Cr was higher in patients with AD than VaD ($p=0.02$), and higher in patients with FTLD than DLB ($p=0.02$) and VaD ($p=0.003$). There were no differences between patients with AD and FTLD, nor between VaD and DLB.

Discussion

The objective of this study was to identify ¹H MRS metabolite signatures of common dementias, in order to determine if ¹H MRS may be useful in differentiating them. While the literature on neuroimaging findings in people with AD is extensive, the neuroimaging literature on other common dementias is limited. Cross-sectional studies like this one are required as the first step towards identifying neuroimaging markers that might be useful bio-markers for dementing disorders.

Our data indicates that posterior cingulate NAA /Cr levels were decreased in all dementias studied except in patients with DLB. Normal NAA /Cr levels were previously reported in this region in patients with DLB (21). NAA is a neuronal metabolite and NAA levels correlate with neuronal and axonal density (22,23). Decreased NAA levels normalize with the recovery of cognitive performance after head trauma (24), or termination of seizures after epilepsy surgery (25), therefore NAA is also regarded as a marker for neuronal function. Patients with DLB have preserved neuronal numbers at autopsy (26), and have normal limbic cortical volumes on voxel based morphometry, which distinguishes them from patients with AD (27). The normal NAA /Cr levels observed in our study suggest integrity of neurons in the posterior cingulate gyrus of patients with DLB, and are consistent with other studies in this respect.

Patients with VaD had a trend toward lower NAA /Cr levels than normal. All of the patients with VaD in this study had subcortical vascular disease, and none of them had large hemispheric strokes. The posterior cingulate voxel contained mostly gray matter with a small amount of subcortical white matter, which did not have elevated intensity on T2-weighted MRI. Thus MRI changes related to vascular pathology were not included in the ¹H MRS voxel in patients with VaD. We attribute this trend of depressed NAA /Cr in VaD to retrograde Wallerian degeneration or neuronal dysfunction in the posterior cingulate gyri from vascular disease located elsewhere in the brain. One limitation of this data is that there were only eight patients with dementia who fulfilled the NINDS-AIREN criteria for VaD during the 15 month period of patient recruitment. Because of the small sample size, our findings in patients with VaD should be regarded as preliminary, and should be confirmed in a larger VaD sample.

Donepezil HCL, a cholinesterase inhibitor has been reported to increase NAA /Cr levels in people with AD (28). This effect, if present in our data, would only decrease the NAA /Cr differences between AD, FTLD and normal subjects. This effect would have negligible impact on our data concerning differentiating the AD and DLB from each other, because most of the patients with AD and DLB were taking cholinesterase inhibitors. However it is possible that the NAA/Cr differences between AD and FTLD were obscured because the proportion of AD subjects taking cholinesterase inhibitors was greater than FTLD subjects.

Cho /Cr ratios were elevated in patients with degenerative dementias compared to normals, but not in patients with VaD. Normal Cho /Cr levels in the cortical gray matter of patients with VaD is in agreement with previous studies (11-13). The largest amount of choline in the brain is in the choline bound membrane phospholipids. Among the cytosolic choline-containing species, free choline and acetylcholine is very low in abundance in brain tissue. The Cho peak in the ^1H MRS spectra of the brain is thought to be composed of cytosolic glycerolphosphocholine and phosphocholine, which are the products of membrane phosphatidylcholine breakdown, and precursors of choline and acetylcholine synthesis (29). One possible explanation for the elevation of Cho in AD and FTLD is increased membrane turnover due to dying back of the neuropil. It has also been postulated that the elevation of Cho peak is the consequence of membrane phosphatidylcholine catabolism in order to provide free choline for the chronically deficient acetylcholine production in AD (11,30).

The only measurement that was different from normal in patients with DLB was the Cho /Cr ratio. The activity of choline acetyltransferase, the enzyme responsible for acetylcholine synthesis from free choline, is reduced earlier and more severely in the disease course of DLB than AD (31). Furthermore, patients with DLB who were treated with cholinesterase inhibitors have shown substantial cognitive improvement (32), revealing the functional significance of acetylcholine deficiency in DLB. Although the basis for the elevation of Cho /Cr in AD and DLB is not completely understood, down regulation of choline acetyltransferase activity may be responsible for this change in both pathological processes. The fact that Cho /Cr levels decrease with cholinergic agonist treatment in AD (33), raises the possibility that Cho /Cr levels could be a biomarker of therapeutic efficacy in AD and DLB drug trials. This would however require further validation with longitudinal studies.

MI /Cr levels were elevated in patients with AD and FTLD, and were not different from normal in patients with DLB and VaD. MI is primarily isolated from glial cells (34). MI levels correlate with glial proliferation in inflammatory CNS demyelination (23). Our findings of elevated mI levels in AD and FTLD are in agreement with others (4,6,8,15), and support the hypothesis that mI may be a marker for glial cell activity in these neurodegenerative diseases. Since there is no evidence that glial proliferation is a characteristic of DLB pathology, normal mI /Cr levels would be expected in DLB. Our observation of normal posterior cingulate mI /Cr in patients with VaD is not surprising because the portion of the brain with vascular pathology evident on structural MRI was not included in the ^1H MRS voxel. Our data do not address whether ^1H MRS acquired directly from the ischemic brain areas would reveal elevated mI /Cr levels.

The metabolite measurements in this study were obtained from a single region in the brain; right and left hemispheric posterior cingulate gyri and inferior parietal lobules. It would seem intuitive at first that ^1H MRS imaging (^1H MRSI), in which ^1H MRS data is simultaneously acquired from multiple voxels, would be a more appropriate way to comprehensively study different dementias. We chose to use single voxel ^1H MRS for several technical reasons related to data quality. Achieving uniform water suppression across the entire volume and removal of signal contributions from subcutaneous lipids is difficult with short echo time ^1H MRSI (35,36). Using short echo time (30ms) in ^1H MRS acquisitions was critical to this study, because mI has a relatively short transverse relaxation time and can only be quantified at short echo times.

The single voxel ^1H MRS acquisition in this study was included as part of a comprehensive longitudinal MR protocol. Due to time constraints, we were only able to perform one single voxel ^1H MRS acquisition per exam. While acquiring single voxel data from several locations in the brain would have been useful, such an approach would require an excessively long acquisition protocol that could produce unwanted subject attrition from the longitudinal study. We acknowledge that single voxel ^1H MRS measurements from other regions in the brain could have improved differentiating among the dementias, and we might have observed inter-group differences of greater magnitude had we sampled different regions. Furthermore, while many reports have shown Cr to be stable in AD (9), it is not known if this holds true for other dementias. It is possible that absolute quantitation of metabolite concentrations (37) may differentiate the clinical groups better than ratios.

Overall, our in vivo ^1H MRS data are consistent with the biochemical changes that would be expected based on the known pathology in each of the dementias studied. However, we used clinical diagnoses for dementia classification. Correlations with neuropathology would more firmly validate the biological significance of ^1H MRS changes in common dementias. Our data indicates that ^1H MRS metabolite profiles may be useful biochemical imaging markers in common dementias. This however, needs to be tested with longitudinal studies and in therapeutic trials.

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Figure 1. Placement of the ^1H MRS voxel on a mid-sagittal T1 weighted image. The 8 cm^3 ($2 \times 2 \times 2\text{ cm}$) voxel is covering right and left hemispheric posterior cingulate gyri and inferior precuneus.

NAA

Figure 2.

Examples of proton spectra obtained from the posterior cingulate voxel with an echo time of 30 ms. in a normal subject (a), a patient with AD (b), FTLD (c), DLB (d), and VaD (e). The NAA /Cr ratio is lower in patients with AD, FTLD and VaD than both the DLB and the normal subjects. The Cho /Cr ratio is higher in patients with AD, FTLD and DLB than the normal subject. The mI /Cr ratio is higher in the patients with AD and FTLD than both the VaD and the normal subjects. All spectra are scaled to the height of the reference peak Cr, which is held constant across Figures 2a-2e.

Table 1

Demographic aspects of the subjects

	Normal	AD	FTLD	DLB	VaD
n	206	121	41	20	8
Age (mean $\pm$ SD) *	76.7 $\pm$ 8.6	76.0 $\pm$ 8.2	65.2 $\pm$ 9.8	72.8 $\pm$ 8.4	80.0 $\pm$ 7.9
(range)	(40 - 99)	(46 - 92)	(44 - 81)	(56 - 89)	(71 - 96)
Male/Female	91 / 115	56 / 65	24 / 17	15 / 5	4 / 4
CDR 0 (no. (%))	206 (100)	0	2 (5)	0	0
CDR 0.5 (no. (%))	0	56 (46)	21 (51)	12 (60)	4 (50)
CDR 1 (no. (%))	0	42 (35)	8 (20)	6 (30)	4 (50)
CDR $\geq$ 2 no. (%))	0	23 (19)	10 (24)	2 (10)	0
DRS (mean $\pm$ SD) *	137.7 $\pm$ 4.9 **	108.4 $\pm$ 19.1	105.7 $\pm$ 25.1	119.7 $\pm$ 20.1	114.29 $\pm$ 9.9
(range)	(115 - 144)	(28 - 139)	(42 - 140)	(67 - 138)	(104 - 128)
MMSE (mean $\pm$ SD)	28.4 $\pm$ 1.4 **	18.8 $\pm$ 6.6	17.9 $\pm$ 8.4	22.0 $\pm$ 6.6	20.9 $\pm$ 4.4
(range)	(25 - 30)	(3 - 30)	(2 - 30)	(8 - 29)	(14 - 26)
Patients treated with cholinesterase inhibitors (n (%))	0	91 (75)	16 (39)	17 (85)	0

* Mean age of patients with FTLD is lower than the mean ages of normals, patients with AD, DLB, and VaD ($p < 0.01$ for all comparisons). Mean age of the patients with VaD is higher than the mean ages of patients with DLB ($p = 0.04$).

** The DRS and MMSE scores of patients with different dementias are lower than normal ($p < 0.0001$).

¹H MRS metabolite ratios (mean ± SD) in normals and patients with AD, DLB, VaD, and FTL

	Normal	AD	FTLD	DLB	VaD
n	206	121	41	20	8
NAA /Cr (range)	1.53 ± 0.13 (1.07 - 1.93)	1.42 ± 0.12 (1.11 - 1.67)	1.43 ± 0.15 (1.13 - 1.78)	1.53 ± 0.13 (1.23 - 1.78)	1.43 ± 0.13 (1.27 - 1.69)
Cho /Cr (range)	0.66 ± 0.08 (0.49-0.95)	0.69 ± 0.08 (0.45-0.91)	0.70 ± 0.08 (0.55-0.92)	0.73 ± 0.10 (0.61-0.92)	0.69 ± 0.11 (0.52-0.90)
MI /Cr (range)	0.65 ± 0.08 (0.32 - 0.89)	0.73 ± 0.11 (0.40 - 0.97)	0.76 ± 0.09 (0.56 - 1.00)	0.69 ± 0.11 (0.55 - 0.92)	0.64 ± 0.08 (0.51 - 0.79)

Metabolite ratios were different from normal on Dunett's test:

- * (p=0.08)
- ** (p= 0. ≤ 0.05)
- *** (p≤ 0.01)
- **** (p<0.001)

Table 3¹H MRS metabolites that were different between dementia groups

¹ H MRS Metabolite Ratio	ANOVA - <i>P</i> value [*]	Between-group difference	Pairwise LSD test <i>P</i> -value ^{**}
NAA /Cr	0.009	DLB > AD DLB > FTLD	<0.001 0.009
Cho /Cr	0.12		
MI /Cr	0.008	AD > VaD FTLD > VaD FTLD > DLB	0.02 0.002 0.02

* ANOVA - *P* value is derived from ANOVA comparing all four dementia groups

** LSD test - *P* value is derived from pair-wise between dementia group comparisons of metabolite ratios significant on ANOVA