Magnetic Resonance Spectroscopy in the Diagnosis of Alzheimer Disease

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**Short Title:** MRS in diagnosis of AD

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Abstract

The role of in-vivo magnetic resonance spectroscopy (MRS) in the prediction of progression from mild cognitive impairment (MCI) to dementia is described. This evidence-based review determines whether there is sufficient evidence to recommend the use of magnetic resonance spectroscopy by family physicians or specialists in Canada to make or differentiate a diagnosis of dementia in people presenting with mild cognitive impairment.

Keywords: Alzheimer disease, magnetic resonance spectroscopy, mild cognitive impairment
1. Methods

The literature review used the PubMed database including articles in English that involved human subjects from January 2002 to January 2012. Search terms included Alzheimer, mild cognitive impairment, and magnetic resonance spectroscopy. A separate search used the same parameters but restricted it to review articles to identify recent evidence-based reviews. Case studies were not included. The search produced a total of 10 review papers and 30 original articles meeting the search criteria. Of the 30 original articles, 22 articles described cross-sectional comparisons of MRS measured metabolite levels between normal elderly subjects, subjects with mild cognitive impairment and subjects with Alzheimer disease. The remaining 8 articles describe longitudinal studies to assess the utility of MRS measured metabolite levels in predicting conversion from mild cognitive impairment to dementia. One additional paper describing longitudinal studies was found in the references of the review papers.

2. Magnetic Resonance Spectroscopy

\( ^{1}H \text{ Magnetic Resonance Spectroscopy in Alzheimer Disease:} \) Magnetic resonance spectroscopy (\(^{1}H\) MRS) is a non-invasive technique used to measure the concentration of low molecular weight metabolites in-vivo, with a detection threshold of approximately 1 mmol/L (mM) from a volume of interest (VOI) typically between 1 to 8 cm\(^3\). Detectable in-vivo brain metabolites including \(N\)-Acetylaspartate (NAA), glutamate (Glu), glutamine (Gln), choline-containing compounds (Cho), creatine compounds (Cr) and myo-inositol (mI) have a typical concentration between 1 and 10 mM. Reduced NAA levels have been found in diseases such as Huntington’s,\(^{1-9}\) Parkinson’s disease\(^{3,10-14}\) as well as Alzheimer Disease.\(^{15-20}\) Altered levels of NAA or NAA/Cr
is the most common finding reported in subjects with Alzheimer disease and mild cognitive impairment although alterations in other metabolites including myo-inositol, scyllo-inositol, and glutamate have been reported. The use of magnetic resonance spectroscopy in the diagnosis and monitoring of Alzheimer disease has been described in several recent reviews. Interested readers are directed to the review by Griffith et al (2009) for a detailed description of MR spectroscopy findings in the dementias.

NAA is an amino acid present primarily within neurons in the central nervous system. The concentration of NAA is among the highest of the free amino acids in the brain (8-10 mM in brain tissue) and it normally produces the largest peak (a large uncoupled singlet resonance at 2.01ppm) in the NMR spectrum. NAA is considered a marker of neuronal density and/or viability. Therefore, reduced NAA may imply neuronal death, or it may imply neurometabolic impairment based on the established correlation between the rate of mitochondrial activity and NAA synthesis. Decreased NAA has been documented in subjects with AD using MRS in the occipital, temporal, parietal and frontal lobes. This decrease has been noted in both MRS studies and in vitro studies that are correlated with AD pathology. The level of depletion of NAA has not been found to be proportional to the severity of dementia, as the decline has been found to be approximately 10-15% across different brain regions (mostly gray matter and to a lesser degree, white matter). Several MRS studies in dementia have also noted an increase in mI levels by 15-20% in the gray matter regions of patients with AD. Elevated mI has also been noted in the posterior cingulate regions in subjects with MCI. Similarly elevated levels of mI were found in the frontal lobes of patients with frontotemporal dementia and in the
basal ganglia of patients with Huntington’s dementia. NAA and mI change has also been noted in the hippocampus in AD, and this change has been associated with cognitive measures.

While NAA alone tends to have poor clinical specificity to AD, the combination of NAA and mI increases the accuracy of these biomarkers as diagnostic tools. The ratio of NAA/mI has been shown in several studies to be the most robust marker for discriminating AD patients for age-matched normal elderly controls. NAA/mI ratios have also been previously shown to correlate with Mini-Mental State Exam (MMSE) scores and may even be predictive of MMSE decline 12 months later. NAA/Cr levels have been shown to be lower in AD subjects than age matched controls. NAA/Cr has also been shown to be correlated with MMSE scores in the medial temporal lobe.

**Longitudinal Studies in Subjects with Mild Cognitive Impairment:** The value of MR spectroscopy as a prognostic indicator of impending dementia in subjects with mild cognitive impairment can only be answered by longitudinal studies. Since 2005, there have been nine longitudinal MR spectroscopy studies performed in subjects with cognitive impairment. Subjects were typically followed for 1-3 years to identify a cohort that converted to dementia. The results from these studies are summarized in Table 1.

To summarize, the most consistent finding reported in MCI subjects that convert to dementia compared to MCI subjects that remain stable is lower NAA or NAA/Cr. Lower levels of NAA/Cr have been noted in several brain regions including occipital cortex, paratrigonal white matter, temporoparietal lobe, posterior cingulate, and posteriomedial cortex. In the study by Rami et al (2007), the lower NAA/Cr was observed in subjects that were classified as
prodromal AD that later converted to AD. Kantarci et al (2009)\textsuperscript{50} demonstrated that NAA/Cr measured from the posterior cingulate added predictive value for conversion to dementia when combined with hippocampal volume. Furthermore, of the studies listed above, three have included ROC analysis. Modrego et al (2005)\textsuperscript{46} demonstrated that ROC analysis for NAA/Cr<1.61 predicted conversion with 100% sensitivity and 75% specificity. Area under the curve was 0.91 with positive predictive value of 83% and negative predictive value of 100%. Similarly, Feyed et al (2008)\textsuperscript{49} showed that NAA/Cr <1.40 in posterior cingulate predicted conversion of MCI to probably AD with sensitivity of 82% and specificity of 72% with area under the curve of 0.82. Finally, Modrego et al (2010)\textsuperscript{51} showed that NAA/Cr<1.43 in posteromedial parietal cortex predicted conversion to probable AD with 74% sensitivity and 84% specificity with area under the curve of 0.84.

Despite the consistency of the studies listed above, two studies reported no baseline differences in \textsuperscript{1}H MRS between MCI stable and MCI converters in the bilateral posterior cingulate and inferior precuneus (Kantarci 2007, Pilatus 2009)\textsuperscript{52,53} or in the parietal white matter (Pilatus 2009).\textsuperscript{53} Another study showed no differences in the medial temporal lobe in cognitively impaired not demented (CIND) stable and CIND converters in the medial temporal lobe (Chao 2005).\textsuperscript{54}

3. Summary

Nine longitudinal studies have been performed to determine whether \textsuperscript{1}H MR spectroscopy can predict conversion to dementia examining multiple brain regions including occipital cortex, paratrigonal white matter, temporoparietal lobe, posterior cingulate, and posteriomedial cortex.
All studies have been performed at a single centre using 1.5 Tesla MRI scanners and incorporating a variety of methodologies for spectral quantification. Cohorts sizes range from <20 to >100 subjects and studies followed subjects from one year to more than three years. In all but two studies, lower NAA or NAA/Cr was observed in MCI subjects who converted to dementia compared to MCI subjects who remain cognitively stable. ROC analysis in a subset of studies showed 82-100% sensitivity and 72-85% specificity for NAA/Cr cutoff ranging from 1.4-1.61. Although current studies show an emerging trend of lower NAA/Cr in MCI subjects that convert to dementia compared to MCI subjects that remain stable, further study is needed.

Variability in participant selection, the criteria for conversion to dementia, and methodological inconsistencies in the brain region studied, the spectroscopy acquisition protocol, and the spectroscopy analysis procedures limits the generalizability of the current studies.

4. Draft Recommendations

Clinical Recommendations:

1. Magnetic resonance spectroscopy shows promise for predicting which people with mild cognitive impairment are likely to progress to dementia. However, it is not currently recommended for clinical use to make or differentiate a diagnosis of dementia in people presenting with mild cognitive impairment (Grade 2B; the quality of current evidence is moderate).

Research Recommendations:

1. $^1$H MRS remains a promising technique for the identification of subjects with mild cognitive impairment who will convert to dementia. Further multi-site longitudinal
studies should be conducted to establish normative values. Such studies should utilize standardized enrollment criteria, diagnosis criteria, data acquisition methods, and include automated analysis of spectra that incorporates proper prior-knowledge of metabolite lineshapes.

2. Standardized $^1$H MRS data acquisition and analysis methods should be developed in coordination with recommendations from the International Society of Magnetic Resonance in Medicine.

3. Future $^1$H MRS studies to demonstrate clinical effectiveness should utilize 3 Tesla MRI where available to increase data quality.

5. Author Disclosures

Robert Bartha is co-founder and Chief Scientific Officer of Bioscape Imaging Solutions Inc.

6. Acknowledgements

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7. Tables

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Follow-up (Months)</th>
<th>Converted to AD</th>
<th>MRI Type</th>
<th>Voxel Size</th>
<th>Brain Region</th>
<th>Results</th>
</tr>
</thead>
</table>
| Chao et al.          | 2005 | 17 CIND  | 43                 | 6               | 1.5T Siemens | 0.9 cm³   | Medial Temporal Lobe          | - CIND converters had less medial temporal lobe NAA than controls.  
- No difference between CIND stable and controls.  
- No significant difference between CIND converters and CIND stable                                                                 |                                                                                                                                 |
| Modrego et al        | 2005 | 55 MCI   | 36                 | 29              | 1.5T GE   | 8 cm³      | Left hippocampus Right parietal cortex Left occipital cortex | - Occipital cortex NAA/Cr predicted conversion to dementia.  
- ROC analysis for NAA<1.61 predicted conversion with 100% sensitivity and 75% specificity. Area under the curve was 0.91 with positive predictive value of 83% and a negative predictive value of 100% |                                                                                                                                 |
| Metastasio et al     | 2006 | 25 MCI   | 12                 | 5               | 1.5T GE   | 8 cm³      | Left and right paratrigonal white matter | - Lower NAA/Cr at baseline for MCI converters compared to MCI stable                                                                                                                                 |                                                                                                                                 |
| Rami et al           | 2007 | 14 MCI   | 12                 | 3 MCI 16 Prodromal AD | 1.5T GE   | 8 cm³      | Posterior cingulate left temporal pole left temporoparietal cortex | - Posterior cingulate had higher Cho/Cr at baseline in MCI converters compared to MCI stable  
- Temperoparietal lobe showed lower NAA, Cho, and Cr at baseline in prodromal AD converters compared to non-converters                                                                 |                                                                                                                                 |
<p>| Kantarci et al       | 2007 | 49 MCI   | 13                 | 18              | 1.5T GE   | 8 cm³      | Bilateral posterior cingulate and inferior precuneus | - No baseline 1H MRS differences between MCI stable and MCI converters.                                                                                                                                 |                                                                                                                                 |
| Feyed et al          | 2008 | 119 MCI  | 29                 | 54              | 1.5T GE   | 8 cm³      | Bilateral posterior cingulate | - NAA/Cr less than 1.40 in posterior cingulate predicted conversion of MCI to probable AD with a sensitivity of 82% and a specificity of 75% |                                                                                                                                 |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Group Size</th>
<th>Age</th>
<th>Follow-up</th>
<th>MRI Field Strength</th>
<th>MRI Coil</th>
<th>Pathological Abnormalities</th>
<th>Imaging Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilatus et al 2009</td>
<td>15 MCI</td>
<td>42</td>
<td>6</td>
<td></td>
<td>1.5T Philips</td>
<td>8 cm³</td>
<td>Posterior cingulate and parietal white matter</td>
<td>specificity of 72%. Area under the curve was 0.82.</td>
</tr>
<tr>
<td>Kantarci et al 2009</td>
<td>151 MCI</td>
<td>75</td>
<td>12 month evaluations</td>
<td>8 cm³</td>
<td>1.5T GE</td>
<td>Bilateral posterior cingulate and inferior precuneus</td>
<td>Did not replicate predictive power of NAA at baseline.</td>
<td></td>
</tr>
<tr>
<td>Modrego et al 2011</td>
<td>71 MCI</td>
<td>22</td>
<td>27</td>
<td></td>
<td>1.5T GE</td>
<td>8 cm³</td>
<td>Bilateral posteromedial cortex and left medial occipital lobe</td>
<td>Decreased NAA/Cr in converters compared to non-converters in posteromedial cortex and occipital lobe. NAA/Cr ratio less than or equal to 1.43 in posteromedial parietal cortex predicted conversion to probably AD at 74.1% sensitivity and 83.7% specificity. Area under curve was 0.84. In left occipital lobe, 85.2% sensitivity, 61.4% specificity. Area under the curve of 0.8.</td>
</tr>
</tbody>
</table>
8. References


