Magnetic Resonance Spectroscopy in the Diagnosis of Alzheimer Disease

Robert Bartha[a,b]

[a]Imaging Research Group, Robarts Research Institute, [b]Department of Medical Biophysics, University of Western Ontario, London, Ontario, CANADA, N6A 5B8

Short Title: MRS in diagnosis of AD

Corresponding Author: Robert Bartha
Centre for Functional and Metabolic Mapping (CFMM)
Robarts Research Institute
Western University
Box 5015, 100 Perth Drive
London, Ontario,
N6A 5K8
CANADA
Tel: 01 519 663 5777 x34039
Fax: 01 519 663 3403
Email: rob.bartha@imaging.robarts.ca

Word Count Manuscript (including Abstract): 1431

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 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,[21,22] scyllo-inositol,[23] and glutamate[24] have been reported. The use of magnetic resonance spectroscopy in the diagnosis and monitoring of Alzheimer disease has been described in several recent reviews.[25-33] Interested readers are directed to the review by Griffith et al (2009)[32] 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[31]) in the NMR spectrum[34]. 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.[35] Decreased NAA has been documented in subjects with AD using MRS in the occipital[36,37], temporal[38,39], parietal[22] and frontal lobes[40]. This decrease has been noted in both MRS studies and in vitro studies that are correlated with AD pathology.[41,42] 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.[38] Similarly elevated levels of mI were found in the frontal lobes of patients with frontotemporal dementia[43] and in the

basal ganglia of patients with Huntington's dementia.[3] NAA and mI change has also been noted *in the hippocampus* in AD, and this change has been associated with cognitive measures.[44]

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.[17,45] NAA/mI ratios have also been previously shown to correlate with Mini-Mental State Exam (MMSE)[45] scores and may even be predictive of MMSE decline 12 months later.[39] NAA/Cr levels have been shown to be lower in AD subjects than age matched controls.[31] NAA/Cr has also been shown to be correlated with MMSE scores in the medial temporal lobe.[44]

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,[46] paratrigonal white matter,[47] temporoparietal lobe,[48] posterior cingulate,[49,50] and posteriomedial cortex.[51] In the study by Rami et al (2007), [48] the lower NAA/Cr was observed in subjects that were classified as

prodromal AD that later converted to AD. Kantarci et al (2009)[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)[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)[49] showed that NAA/Cr <1.40 in posterior cinglulate 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)[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 ^{1}H MRS between MCI stable and MCI converters in the bilateral posterior cinglate and inferior precuneus (Kantarci 2007, Pilatus 2009)[52,53] or in the parietal white matter (Pilatus 2009).[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).[54]

3. Summary

Nine longitudinal studies have been performed to determine whether ^{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 co-ordination 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

Funding provided by the Ivey-BMO Financial Group Scientist in Brain Disorders Imaging Award.

7. Tables

		Patients	Follow-up (Months)	Converted to AD	MRI	Voxel Size	Brain Region	Results
Chao *et. al.*	2005	17 CIND	43	6	1.5T Siemens	0.9 cm^3	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 cm^3	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 cm^3	Left and right paratrigonal white matter	• Lower NAA/Cr at baseline for MCI converters compared to MCI stable
Rami et al	2007	14 MCI 28 Prodromal AD	12	3 MCI 16 Prodromal AD	1.5T GE	8 cm^3	Posterior cingulate left temporal pole left temporoparietal cortex	• Posterior cinuglate 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
Kantarci et al	2007	49 MCI	13	18	1.5T GE	8 cm^3	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 cm^3	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

							Left occipital cortex	specificity of 72%. Area under the curve was 0.82.
Pilatus et al	2009	15 MCI	42	6	1.5T Philips	8 cm^3	Posterior cingulate Parietal white matter	• Did not replicate predictive power of NAA at baseline.
Kantarci et al	2009	151 MCI	12 month evaluations	75	1.5T GE	8 cm^3	Bilateral posterior cingulate and inferior precuneus	• Multivariate analysis showed that NAA/Cr added predictive value in addition to hippocampal volume and the presence of cortical infarction.
Modrego et al	2011	71 MCI	22	27	1.5T GE	8 cm^3	Bilateral posteromedial cortex Left medial occipital lobe	• 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.

8. References

1. Davie CA, Barker GJ, Quinn N, Tofts PS, Miller DH. Proton MRS in Huntington's disease. Lancet 1994;343(8912):1580.

2. Harms L, Meierkord H, Timm G, Pfeiffer L, Ludolph AC. Decreased N-acetyl-aspartate/choline ratio and increased lactate in the frontal lobe of patients with Huntington's disease: a proton magnetic resonance spectroscopy study. J Neurol Neurosurg Psychiatry 1997;62(1):27-30.

3. Hoang TQ, Bluml S, Dubowitz DJ, *et al.* Quantitative proton-decoupled 31P MRS and 1H MRS in the evaluation of Huntington's and Parkinson's diseases. Neurology 1998;50(4):1033-40.

4. Jenkins BG, Koroshetz WJ, Beal MF, Rosen BR. Evidence for impairment of energy metabolism in vivo in Huntington's disease using localized 1H NMR spectroscopy. Neurology 1993;43(12):2689-95.

5. Jenkins BG, Rosas HD, Chen YC, *et al.* 1H NMR spectroscopy studies of Huntington's disease: correlations with CAG repeat numbers. Neurology 1998;50(5):1357-65.

6. Reynolds GP, Pearson SJ. Glutamate in Huntington's disease. Lancet 1994;344(8916):189-90.

7. Sanchez-Pernaute R, Garcia-Segura JM, del Barrio Alba A, Viano J, de Yebenes JG. Clinical correlation of striatal 1H MRS changes in Huntington's disease. Neurology 1999;53(4):806-12.

8. Taylor-Robinson SD, Weeks RA, Bryant DJ, *et al.* Proton magnetic resonance spectroscopy in Huntington's disease: evidence in favour of the glutamate excitotoxic theory. Mov Disord 1996;11(2):167-73.

9. Taylor-Robinson SD, Weeks RA, Sargentoni J, *et al.* Evidence for glutamate excitotoxicity in Huntington's disease with proton magnetic resonance spectroscopy. Lancet 1994;343(8906):1170.

10. Axelson D, Bakken IJ, Susann Gribbestad I, Ehrnholm B, Nilsen G, Aasly J. Applications of neural network analyses to in vivo 1H magnetic resonance spectroscopy of Parkinson disease patients. J Magn Reson Imaging 2002;16(1):13-20.

11. Bowen BC, Block RE, Sanchez-Ramos J, *et al.* Proton MR spectroscopy of the brain in 14 patients with Parkinson disease. AJNR Am J Neuroradiol 1995;16(1):61-8.

12. Clarke CE, Lowry M. Systematic review of proton magnetic resonance spectroscopy of the striatum in parkinsonian syndromes. Eur J Neurol 2001;8(6):573-7.

13. Griffith HR, den Hollander JA, Okonkwo OC, O'Brien T, Watts RL, Marson DC. Brain N-acetylaspartate is reduced in Parkinson disease with dementia. Alzheimer Dis Assoc Disord 2008;22(1):54-60.

14. Summerfield C, Gomez-Anson B, Tolosa E, *et al.* Dementia in Parkinson disease: a proton magnetic resonance spectroscopy study. Arch Neurol 2002;59(9):1415-20.

15. Chen JG, Charles HC, Barboriak DP, Doraiswamy PM. Magnetic resonance spectroscopy in Alzheimer's disease: focus on N-acetylaspartate. Acta Neurol Scand Suppl 2000;176:20-6.

16. Dixon RM, Bradley KM, Budge MM, Styles P, Smith AD. Longitudinal quantitative proton magnetic resonance spectroscopy of the hippocampus in Alzheimer's disease. Brain 2002;125(Pt 10):2332-41.

17. Parnetti L, Tarducci R, Presciutti O, *et al.* Proton magnetic resonance spectroscopy can differentiate Alzheimer's disease from normal aging. Mech Ageing Dev 1997;97(1):9-14.

18. Rapoport SI. Hydrogen magnetic resonance spectroscopy in Alzheimer's disease. Lancet Neurol 2002;1(2):82.

19. Shonk TK, Moats RA, Gifford P, *et al.* Probable Alzheimer disease: diagnosis with proton MR spectroscopy. Radiology 1995;195(1):65-72.

20. Stoppe G, Bruhn H, Pouwels PJ, Hanicke W, Frahm J. Alzheimer disease: absolute quantification of cerebral metabolites in vivo using localized proton magnetic resonance spectroscopy. Alzheimer Dis Assoc Disord 2000;14(2):112-9.

21. Siger M, Schuff N, Zhu X, Miller BL, Weiner MW. Regional myo-inositol concentration in mild cognitive impairment Using 1H magnetic resonance spectroscopic imaging. Alzheimer Dis Assoc Disord 2009;23(1):57-62.

22. Miller BL, Moats RA, Shonk T, Ernst T, Woolley S, Ross BD. Alzheimer disease: depiction of increased cerebral myo-inositol with proton MR spectroscopy. Radiology 1993;187(2):433-7.

23. Griffith HR, den Hollander JA, Stewart CC, *et al.* Elevated brain scyllo-inositol concentrations in patients with Alzheimer's disease. NMR Biomed 2007;20(8):709-16.

24. Rupsingh R, Borrie M, Smith M, Wells JL, Bartha R. Reduced hippocampal glutamate in Alzheimer disease. Neurobiol Aging 2011;32(5):802-10.

25. Loos C, Achten E, Santens P. Proton magnetic resonance spectroscopy in Alzheimer's disease, a review. Acta Neurol Belg 2010;110(4):291-8.

26. Kantarci K. 1H magnetic resonance spectroscopy in dementia. Br J Radiol 2007;80 Spec No 2:S146-52.

27. Lehericy S, Marjanska M, Mesrob L, Sarazin M, Kinkingnehun S. Magnetic resonance imaging of Alzheimer's disease. Eur Radiol 2007;17(2):347-62.

28. Modrego PJ. Predictors of conversion to dementia of probable Alzheimer type in patients with mild cognitive impairment. Curr Alzheimer Res 2006;3(2):161-70.

29. Jones RS, Waldman AD. 1H-MRS evaluation of metabolism in Alzheimer's disease and vascular dementia. Neurol Res 2004;26(5):488-95.

30. Burns A, Zaudig M. Mild cognitive impairment in older people. Lancet 2002;360(9349):1963-5.

31. Valenzuela MJ, Sachdev P. Magnetic resonance spectroscopy in AD. Neurology 2001;56(5):592-8.

32. Griffith HR, Stewart CC, den Hollander JA. Proton magnetic resonance spectroscopy in dementias and mild cognitive impairment. Int Rev Neurobiol 2009;84:105-31.

33. Fayed N, Modrego PJ, Salinas GR, Gazulla J. Magnetic Resonance Imaging Based Clinical Research in Alzheimer's Disease. J Alzheimers Dis 2012.

34. Pouwels PJ, Frahm J. Regional metabolite concentrations in human brain as determined by quantitative localized proton MRS. Magn Reson Med 1998;39(1):53-60.

35. Bates TE, Strangward M, Keelan J, Davey GP, Munro PM, Clark JB. Inhibition of N-acetylaspartate production: implications for 1H MRS studies in vivo. Neuroreport 1996;7(8):1397-400.

36. Mori S, Crain BJ, Chacko VP, van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol 1999;45(2):265-9.

37. Moats RA, Ernst T, Shonk TK, Ross BD. Abnormal cerebral metabolite concentrations in patients with probable Alzheimer disease. Magn Reson Med 1994;32(1):110-5.

38. Kantarci K, Jack CR, Jr., Xu YC, *et al.* Regional metabolic patterns in mild cognitive impairment and Alzheimer's disease: A 1H MRS study. Neurology 2000;55(2):210-7.

39. Doraiswamy PM, Steffens DC, Pitchumoni S, Tabrizi S. Early recognition of Alzheimer's disease: what is consensual? What is controversial? What is practical? J Clin Psychiatry 1998;59 Suppl 13:6-18.

40. Deicken RF, Zhou L, Schuff N, Fein G, Weiner MW. Hippocampal neuronal dysfunction in schizophrenia as measured by proton magnetic resonance spectroscopy. Biol Psychiatry 1998;43(7):483-8.

41. Klunk WE, Xu C, Panchalingam K, McClure RJ, Pettegrew JW. Quantitative 1H and 31P MRS of PCA extracts of postmortem Alzheimer's disease brain. Neurobiol Aging 1996;17(3):349-57.

42. Mohanakrishnan P, Fowler AH, Vonsattel JP, *et al.* An in vitro 1H nuclear magnetic resonance study of the temporoparietal cortex of Alzheimer brains. Exp Brain Res 1995;102(3):503-10.

43. Ernst T, Chang L, Melchor R, Mehringer CM. Frontotemporal dementia and early Alzheimer disease: differentiation with frontal lobe H-1 MR spectroscopy. Radiology 1997;203(3):829-36.

44. Jessen F, Block W, Traber F, *et al.* Decrease of N-acetylaspartate in the MTL correlates with cognitive decline of AD patients. Neurology 2001;57(5):930-2.

45. Rose SE, de Zubicaray GI, Wang D, *et al.* A 1H MRS study of probable Alzheimer's disease and normal aging: implications for longitudinal monitoring of dementia progression. Magn Reson Imaging 1999;17(2):291-9.

46. Modrego PJ, Fayed N, Pina MA. Conversion from mild cognitive impairment to probable Alzheimer's disease predicted by brain magnetic resonance spectroscopy. Am J Psychiatry 2005;162(4):667-75.

47. Metastasio A, Rinaldi P, Tarducci R, *et al.* Conversion of MCI to dementia: Role of proton magnetic resonance spectroscopy. Neurobiol Aging 2006;27(7):926-32.

48. Rami L, Gomez-Anson B, Sanchez-Valle R, *et al.* Longitudinal study of amnesic patients at high risk for Alzheimer's disease: clinical, neuropsychological and magnetic resonance spectroscopy features. Dement Geriatr Cogn Disord 2007;24(5):402-10.

49. Fayed N, Davila J, Oliveros A, Castillo J, Medrano JJ. Utility of different MR modalities in mild cognitive impairment and its use as a predictor of conversion to probable dementia. Acad Radiol 2008;15(9):1089-98.

50. Kantarci K, Weigand SD, Przybelski SA, *et al.* Risk of dementia in MCI: combined effect of cerebrovascular disease, volumetric MRI, and 1H MRS. Neurology 2009;72(17):1519-25.

51. Modrego PJ, Fayed N, Sarasa M. Magnetic resonance spectroscopy in the prediction of early conversion from amnestic mild cognitive impairment to dementia: a prospective cohort study. BMJ Open 2011;1(1):e000007.

52. Kantarci K, Weigand SD, Petersen RC, *et al.* Longitudinal 1H MRS changes in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 2007;28(9):1330-9.

53. Pilatus U, Lais C, Rochmont Adu M, *et al.* Conversion to dementia in mild cognitive impairment is associated with decline of N-actylaspartate and creatine as revealed by magnetic resonance spectroscopy. Psychiatry Res 2009;173(1):1-7.

54. Chao LL, Schuff N, Kramer JH, *et al.* Reduced medial temporal lobe N-acetylaspartate in cognitively impaired but nondemented patients. Neurology 2005;64(2):282-9.