

Adding MRS to ADNI Criteria for Drug Monitoring Will Reduce Group Size for Clinical Trials

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Background: Drug development for treatment of Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) has been both expensive and unsuccessful, using currently recognized clinical endpoints (MMSE, etc). While drug discovery needs additional thought, FDA, NIA and Pharma now recommend use of objective disease end points ("biomarkers") in place of clinical diagnosis as a means of reducing group size and therefore cost of trials. The Alzheimer's Disease Neuroimaging Initiative (ADNI) [1] harnesses the well known reduction in brain volume (3 – 3.5% per year) during evolution of AD, which is now recommended along with CSF biomarkers, beta-amyloid, Tau protein. Another readily accessible AD and MCI biomarker, short-echo time proton MRS ratio NAA/ml [2], also falls by 3.5% each year. We ask why MRS is not currently included in the ADNI protocols?

Methods: Literature survey to establish the longitudinal progression, specificity and sensitivity of NAA/ml of MRS for diagnosis of AD and MCI. Experiments completed on GE 1.5 and 3.0 Tesla clinical MRI scanners to test-retest errors for an automated standard operating procedure (SOP) in MRS acquisitions. Cohort size established in a potential clinical trial of a drug slowing the progression of AD or MCI, plotting standardized difference (D/sd) vs Power graphically [3]. Subjects were examined using automated sequences PROBE-P TE 35ms. In each subject, 5 spectra were acquired as test, retest I, retest II, shim and retest III and newly prescribe voxel IV (Fig 1).

Results: Maximum variance for NAA/Cr = 0.6 % +/- 0.5; NAA/ml = 2.6 % +/- 1.0. For definition of 'progression' after 1 year, D/sd = 1.34; N=20. Using short TE MRS NAA/ml to monitor a drug effect of 50% per year, D/sd = 0.7; N= 60 per Group.

Discussion: Group size for monitoring of Clinical Drug size using SOP of MRS metabolic ratio NAA/ml is very comparable to that claimed for brain MRI. The commonest stated reason for omission of MRS from drug trials is the absence of a SOP for MRS and indeed the published literature offers little guidance. Sample size for clinical assays of drugs falls from the N=600 predicted by Schott et al [4] to N=60 when NAA/ml error was improved by definition of an SOP. A second reason for inclusion of NAA/ml in ADNI criteria might emerge if the reductions in brain volume and brain chemistry were independent of one another (Figure 3) [5].

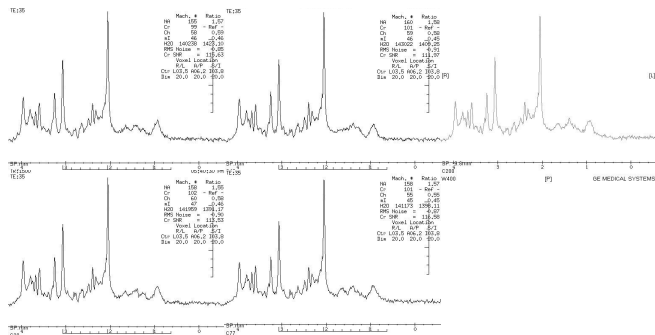


Figure 1. Five 1H MRS (PRESS, TE35) spectra acquired from posterior cingulate gyrus in healthy volunteer on a clinical MR scanner.

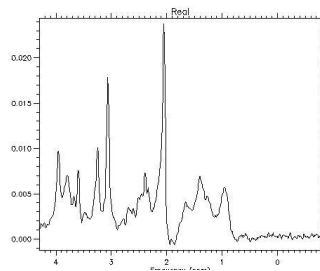


Figure 2. Unoptimized 1H MRS (STEAM, TE35) spectrum acquired from posterior cingulate gyrus of a healthy volunteer. Previous studies showed STEAM>PRESS for AD diagnosis [6].

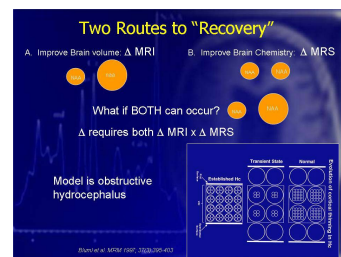


Figure 3. Changes in brain volume and brain chemistry are independent of each other [Bluml et al, 7].

We suggest there are at least three ways in which this may be so: brain locations (hippocampus for MRI; posterior cingulate gyrus for MRS) differ; reduced cell volume or cell number contributes to falling brain volume in MRI; reduced neuronal activity and increased glial activity or both may contribute. Third, MRS changes defined several years earlier than the MRI brain volume changes (Figure 4).

Conclusion: MRI and MRS biomarkers may be un-related and thereby amplify the ADNI signal to reduce sample sizes for future clinical drug trials in AD. Optimization will improve MRS SOP (e.g. STEAM vs PRESS) with further reduction in sample size.

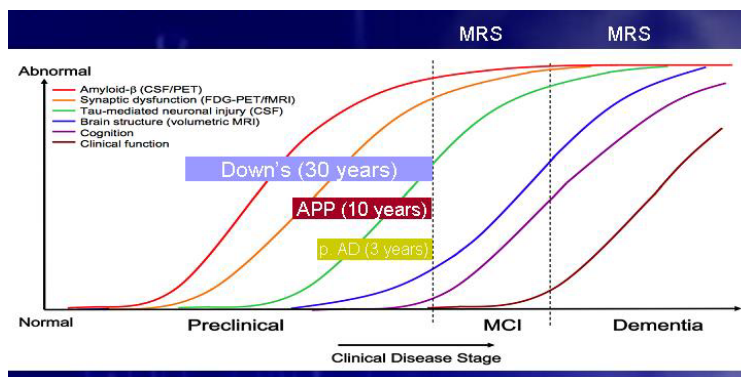


Figure 4. Neurochemical changes are defined earlier than changes in brain volume. (Image modified from Clifford R. Jacks)

References: (1) <http://adni.loni.ucla.edu>. (2) Ross et al. TAMU NMR Newsletter 1993. (3) Douglas G. Altman. Practical Statistics for Medical Research; Chapman & Hall, London 1990, p. 456. (4) Schott et al. Brain 2010; doi: 10.1093/brain/awq208. (5) Ross BD, Tran T, Lin AP, Sailasuta N. NIA Advisory Workshop: Maryland, 2010. (6) Enriquez et al. Proc ISMRM 2003, p2001. (7) Bluml et al. MRM 1997; 37(3):395-403.

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