Serial Concentration of N-acetlyaspartate in Young Healthy Adults

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Introduction:

Proton MR Spectroscopy (^{1}H-MRS) is a noninvasive, quantitative imaging procedure frequently used to augment information obtained from MRI, by providing information about the underlying biochemistry. One key ^{1}H-MRS-detectable metabolite is *N*-acetylaspartate (NAA), which is almost exclusive to neurons and therefore considered a good marker for their concentration and health (1,2). Since many diseases studied with ^{1}H-MRS are chronic, it is frequently part of a serial study of one to two years. Therefore, it is necessary to establish the individual temporal behavior of NAA in healthy subjects. Unfortunately, most ^{1}H-MRS studies to date have concentrated on single voxel (SV) or multi-voxel volumes of interest (VOI), located, usually, at sites of gross pathology throughout the brain, a method that usually misses 80-99% of the brain, leads to misregistration errors, and precludes studies close to the skull to prevent lipid contamination (3,4). This study addresses these problems by measuring the total NAA throughout the brain serially, at 2-3 time points, over a period of one to two years. The whole-brain *N*-acetylaspartate concentration (WBNAA) enables one to determine the overall stability of the neurons in the brain, at a total loss of localization (5).

Methods:

Absolute whole-brain NAA amount was obtained with non-localizing proton MR spectroscopy from 14 healthy subjects (5 men, 9 women) 29.6±8.6 years old. The amount was converted into WBNAA dividing by their brain's parenchymal volume obtained from MRI image segmentation (5). Temporal variations in this cohort were determined with a second WBNAA measurement 20±6 months later (N=14) and a third measurement 21±3 months after the second (N=7). Restricted maximum likelihood (REML) was used to estimate variance components within a mixed model analysis of variance framework that modeled WBNAA as a function of subject ID and imaging session, each represented as a random classification factor. Likelihood ratio tests were used to compare time points with respect to the between-subject variance of WBNAA and to determine if its within-subject variation depended on whether observations were taken within 28 months or were separated by least 33 months. A paired sample *t* test was used to compare each pair of time points with respect to the mean level of WBNAA.

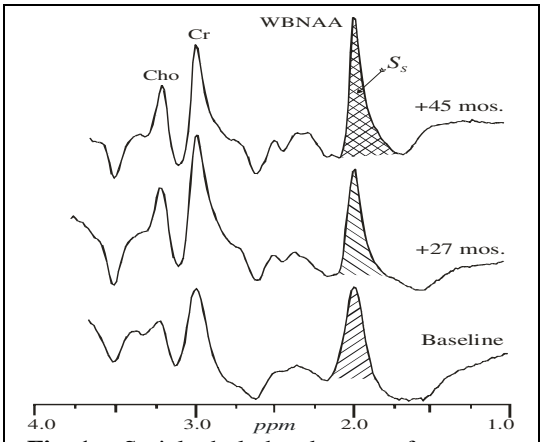

Fig. 1. Serial whole-head spectra from one subject at baseline, +27 and +45 months later. The peak areas (S_s) are within ±7%.

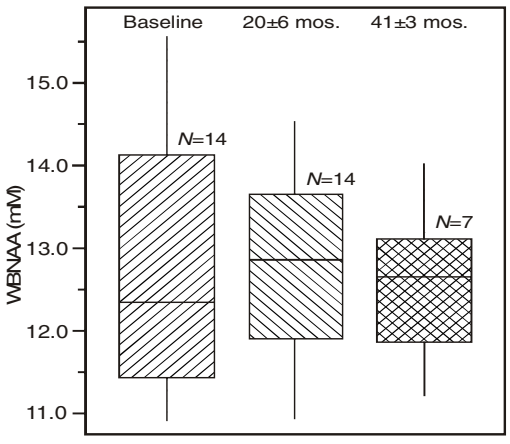

Fig. 2. Box plots showing the 1st, 2nd (median) and 3rd quartiles (box), ±95% (whiskers) of the WBNAA distributions at baseline, first, and second follow-up time points (7 subjects at third are a subset of the 14). WBNAA differences are statistically indistinguishable (p>0.6).

Results:

Sample whole-head ^{1}H-spectra from three serial scans of one subject at baseline, +27 and +45 months are shown in Fig 1. Box plots of the WBNAA concentrations of the entire cohort are shown in Fig. 2. They exhibit similar median WBNAA between the three time points with average±std of 12.5±1.4, 12.8±1.4 and 12.6±1.2 mM. Additionally, the inter-subject distribution of WBNAA values at baseline was not significantly different from the second or third follow-up time points with respect to mean (p>0.5) or between-subject variation (p>0.3). The mean intra-subject WBNAA concentration changes were 1.7±9.0% between baseline and first follow up (N=14), -0.3±9.0% between 2nd and 3rd time points (N=7) and 0.5±12% between baseline and 3rd time points (N=7).

Discussion:

The global NAA concentration a young healthy adult brain is stable, to within the ±6% precision of the measurement, over the 1 – 3 years periods common to many follow-up clinical trials. The fact that the WBNAA is stable is also reflected in the fact that the variations between measurements taken one day or one year apart are not significantly different. Therefore, any detectable decline in WBNAA is likely to reflect some sort of neurodegeneration.

References:

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