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Evaluation of Automated MR Spectroscopy: Application in Alzheimer Disease

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Summary: In a trial involving 21 patients with dementia and 3 healthy control subjects, a comparison between the major cerebral metabolite ratios obtained with an established manually optimized proton MR spectroscopic examination and those obtained with an automated proton MR spectroscopic procedure shows that the two techniques provide very comparable results.

Index terms: Dementia; Magnetic resonance, spectroscopy

The accuracy of antemortem diagnosis of Alzheimer disease, based largely on neuropsychologic testing, varies from 70% to 100% depending on the expertise of the clinician and the patient population sampled; however, at most centers the accuracy is likely to be approximately 80% (1). The neurochemical changes seen with magnetic resonance (MR) spectroscopy in patients with probable Alzheimer disease (2, 3) have been reported. In a more recent clinical trial we have evaluated the utility of MR spectroscopy for the diagnosis of Alzheimer disease in a population of patients with dementia (Ross BD, Moats RA, Shonk T, Miller BL, Gifford P. Sensitivity and specificity of ^{1}H MRS for diagnosis of probable AD [abstr]. *Radiology* 1993;189[P]:297) (4). The spectroscopy results obtained from occipital gray matter indicated that an increase in *myo*-inositol/creatine (mI/Cr) helps distinguish other dementias from Alzheimer disease with a negative predictive value of 80%, whereas *myo*-inositol/*N*-acetylaspartate (mI/NAA) gives a sensitivity and positive predictive value of 95% to 98% for patients with Alzheimer disease versus healthy elderly (4). The most sensitive criterion of Alzheimer disease is mI/NAA. It is our clinical experience that abnormalities in ratios are often seen when the images are judged to be normal. Although these results reflect studies in 200 patients, larger patient numbers involving multicenter studies are called for to confirm the utility of MR spectroscopy for the diagnosis of Alzheimer disease and to fully delineate its clinical utility. Expanded uses for this test could include, for example, defining patient populations for prospective clinical trials, comparing MR spectroscopy with other imaging modalities, and defining the benefit of combined MR imaging and MR spectroscopy examinations.

Because the MR spectroscopy examination technique in our studies were performed by skilled clinical spectroscopists using software developed at our institute, its use is limited to a small number of specialized MR spectroscopy sites. A new test consisting of an automated short-echo-time MR spectroscopy examination (proton brain examination, PROBE), which can easily be run by MR technicians, is available for use on any General Electric high-field (1.5-T) MR scanner (5). We have evaluated PROBE for its ability to reproduce the mI/NAA ratio. We tested the method in 3 control subjects and 21 patients in whom mI/NAA was expected to be increased. The results indicate a high degree of correlation for both NAA/Cr and mI/Cr, indicating that PROBE can reliably be used in future clinical trials.

Subjects and Methods

Patients and Control Subjects

Twenty-one patients with dementia whose diagnoses were not yet completed were referred by physicians at Huntington Memorial Hospital. Three healthy volunteers (two men and one woman 28 to 34 years old) were also recruited. Informed consent was obtained from patients and healthy subjects as approved by the Internal Review Board of Huntington Memorial Hospital. Ultimately, but not

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reported herein, a clinical diagnosis of probable Alzheimer disease, or other dementia, was made by the referring physician following National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.

Methods

Spectroscopy examinations with both MR spectroscopy and PROBE used in the same session and from an identical location were performed in patients and controls using a General Electric Signa unit. MR spectroscopy parameters included 1500, 3000/30/128 (repetition time/echo time/excitations). Specifically, an axial locator (with no obliquity) was used with 5-mm spacing to place the desired gray matter voxel of 21 mm (x), 27 mm (y), and 20 mm (z) (size, 11.34 cm^3) across the posterior interhemispheric fissure with the center of the voxel carefully centered at the level of the posterior horns of the lateral ventricles (6). Particularly important details concerning the use of PROBE and not emphasized in the manual (Kohler S, *Signa Advantage PROBE/SV: Single-voxel Proton Brain Exam Applications Guide,* Vol 5, General Electric Medical Systems, 1993) are discussed below. A typical PROBE examination would be completed in 12 minutes. The voxel must be positioned so as to maximize the gray matter it contains, to minimize the contamination of signal from out-of-voxel fat, and to avoid inconsistencies caused by a tendency of the operator to place the voxel below the desired location. The position must be recorded, because this information is not stored on the Signa unit. Autoprescan of PROBE is used to set all parameters but sometimes requires that autoprescan be repeated until convergence is reached (5). Only the echo time, mixing time, repetition time, and the number of excitations should be adjusted; all other parameters should be left at their default values, because changes may cause PROBE to fail. Spectra are displayed by PROBE on the Signa unit. However, for numerical analysis the raw data for both the PROBE and MR spectroscopy examinations were transferred to the SUN (Sun Microsystems, Mountain View, Calif) workstation and processed off-line using the method previously described to obtain values of NAA/Cr, choline (Cho)/Cr, mI/Cr, and glutamine and glutamate (α and β γ-Glx) (6).

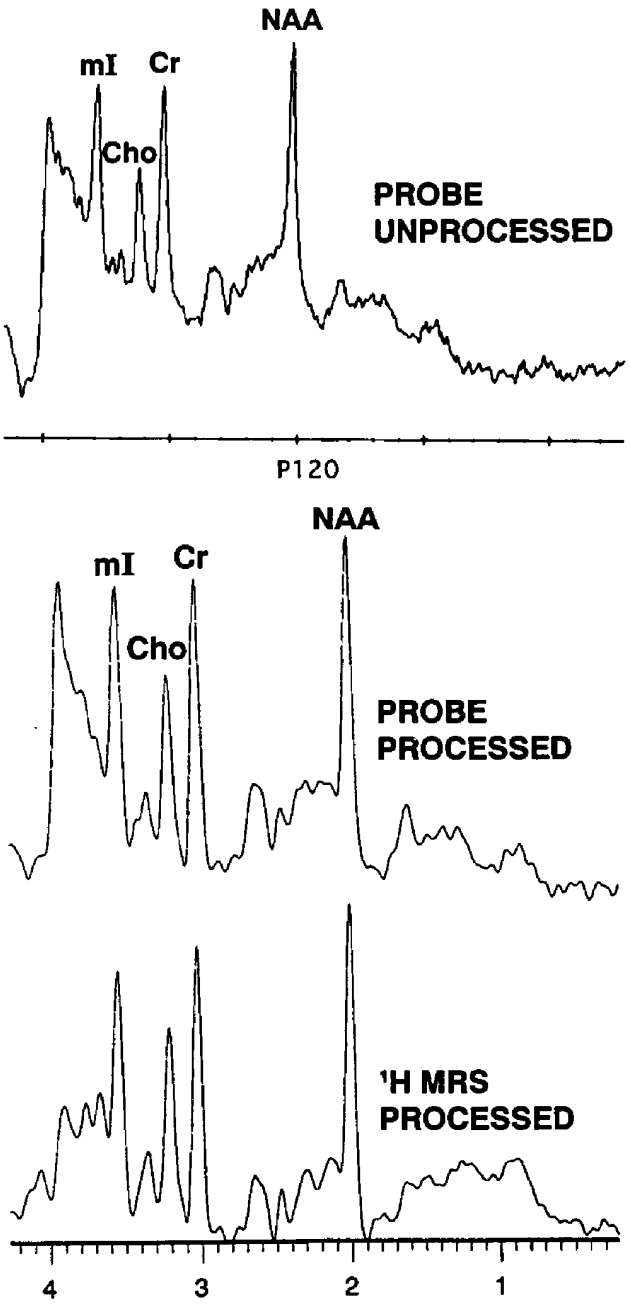

Fig 1. Spectra of a patient with probable Alzheimer disease. *Top*, The unedited PROBE examination; *middle*, the PROBE data processed; and *bottom*, MR spectroscopy obtained during the same examination and processed.

Results

In all spectra the water linewidth was between 3 and 5 Hz. Figure 1 shows the occipital gray matter spectra from a patient with probable Alzheimer disease. The data indicate that PROBE readily reproduces the salient features of the MR spectroscopy spectrum of Alzheimer disease. Good agreement between PROBE and MR spectroscopy (Fig 2A) in patients was achieved, except for β,γ-Glx, which gave significantly lower values in PROBE (paired t tests, P not significant; β,γ-Glx, $P = .04$).

Plotting mI/NAA for PROBE versus that for MR spectroscopy gives a correlation coefficient of 0.86 and slope of 1.0 (Fig 2B), which, considering the narrow range of the data, is good. Thus, mI/NAA can be equally well defined by

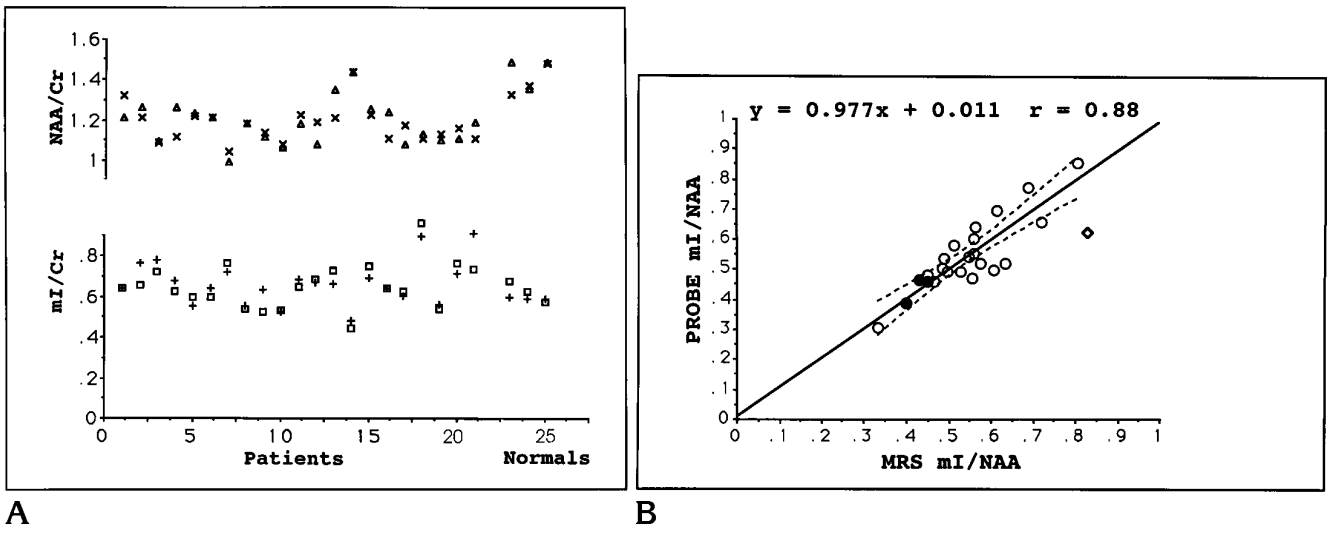

Fig 2. *A*, MR spectroscopy values for NAA/Cr (*x*) and mI/Cr (+); PROBE values for NAA/Cr (△) and mI/Cr (□).
B, mI/NAA for PROBE versus mI/NAA for MR spectroscopy: ○ indicates patients and control subjects; ●, excluded point; and ◇, $r = .83$ when included.

the use of a rapid automated examination (PROBE). Excluding the control subjects from the analysis did not affect the conclusion. Another important difference between the PROBE spectra and those obtained with MR spectroscopy was noted: in cases in which narrow linewidth was achieved, PROBE tended to oversuppress the water, which is manifest in the baseline sloping down toward the water resonance.

Discussion

A fully automated image-guided proton MR spectroscopy examination accurately reproduces the changes in mI/Cr and NAA/Cr observed previously in patients with Alzheimer disease, using the more elaborate and time-consuming method of conventional proton MR spectroscopy. In the prior trial of MR spectroscopy, the division between Alzheimer disease and other dementia was achieved with a value for mI/NAA greater than 0.52. Although this was not tested in the present trial, the slope of approximately 1 for the mI/NAA plotted for PROBE versus MR spectroscopy suggests the value will be similar at various other sites using PROBE. This likelihood is further increased by the robustness exhibited by PROBE in a previous trial involving healthy subjects and a white matter location (5).

A PROBE can be performed in 13 minutes at repetition time of 1.5 seconds with minimal expertise. This time period is not much larger than that required for many commonly used MR sequences. Those centers with a significant population of patients with probable Alzheimer disease may be encouraged to use PROBE and to test the diagnostic utility of the increase of mI/Cr and the decrease in the NAA/Cr ratios.

At present, numerical data may be obtained using a software package for data processing (6); future versions may become available that will contain numerical results, making the increase of mI/Cr and the decrease in the NAA/Cr ratios easier to determine. At present, PROBE is available only for General Electric scanners, but automation of a short-echo MR spectroscopy sequence using any high-field system should achieve the same result.

Although the examination described above has proved useful in our clinical setting, we recognize that room for improvement exists in the diagnostic application of MR spectroscopy in dementia and invite studies refining its usefulness. The significant differences in the β,γ-Glx region are under investigation.

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