Correlation of Global N-Acetyl Aspartate With Cognitive Impairment in Multiple Sclerosis

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Background: Whole-brain N-acetyl aspartate (NAA), a measure of neuronal function, can be assessed by multislice echo-planar spectroscopic imaging.

Objective: To test the hypothesis that the global brain NAA/creatine (Cr) ratio is a better predictor of cognitive dysfunction in multiple sclerosis than conventional magnetic resonance imaging measures.

Design: Survey.

Setting: Research-oriented hospitals.

Patients: Twenty patients, 16 women and 4 men (mean age, 36 years), with early relapsing-remitting multiple sclerosis (mean Expanded Disability Status Scale score, 2.5).

Main Outcome Measures: Correlation between the global NAA/Cr ratio and a cognitive dysfunction factor comprising 16 measures from an extensive neuropsychological test battery that best distinguished patients with multiple sclerosis from healthy control subjects.

Results: A significant partial correlation between the global NAA/Cr ratio and the cognitive dysfunction factor was found (partial r = 0.62, P = .01), and 9 cognitively impaired patients had significantly lower global NAA/Cr ratios than 11 unimpaired patients (P = .04). No significant correlations were found between the cognitive dysfunction factor and conventional magnetic resonance imaging measures (ie, brain parenchymal fraction and lesion volume).

Conclusions: Multislice echo-planar spectroscopic imaging provides global metabolic measures that distinguish between cognitively impaired and unimpaired patients with multiple sclerosis and correlate with a global cognitive measure. Standardization of the technique is needed, and largerscale studies that include healthy controls are suggested.

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Cognitive impairment occurs in approximately 50% of patients with multiple sclerosis (MS),1-3 with increasing incidence during the course of the disease. Some cognitive functions are more frequently impaired than others, such as memory, attention, verbal fluency, executive functions, and information processing.4 Slowed speed of information processing seems to be an important aspect of overall cognitive dysfunctioning in MS.5 The pathophysiology of the cognitive deficits is unclear. The presence of MS lesions affecting the interhemispheric and intrahemispheric white matter tracts connecting cortical areas seems to be an important factor, but undetected pathologic changes in normal-appearing brain might also play a relevant role. It is hypothesized that the overall cognitive dysfunction in MS is related to the overall disease burden of the brain. To assess pathologic features in gray and white matter, which appears normal on conventional magnetic resonance (MR) imaging, techniques with higher pathologic specificity such as MR spectroscopy are needed. Multislice echo-planar spectroscopic imaging (EPSI) is a flexible and fast spectroscopic imaging method that is able to cover most of the brain rapidly and to provide reproducible global and local metabolite measures.6 Measurements of N-acetyl aspartate (NAA) provide information on neuronal loss or dysfunction. Few previous studies have evaluated MR spectroscopy and cognitive dysfunction in MS. Gadea et al7 demonstrated that axonal damage of the right locus coeruleus relates to selective attention impairment in early relapsing-remitting MS. Results of other studies8,9 suggest that focal NAA levels may relate to cognitive variables, and Christodoulou et al10 found correlations between metabolic measures and cognitive dysfunction in a single-slice multivoxels study of a 2-cm-thick slice through corpus callosum. Our present study tested the hypothesis that the global brain NAA/creatine (Cr) ratio differs in cognitively impaired and unimpaired patients with MS and correlates with a global measure of cognitive dysfunction.
chymal fraction was calculated by dividing this volume by the total volume of gray and white matter. The brain parenchyma was evaluated by the same observer (H.K.M.), who was unaware of clinical and neuropsychological findings. Written informed consent was obtained from all subjects. The study was approved by the local ethics committee.

METHODS

PATIENTS

Twenty patients, 16 women and 4 men, with newly diagnosed clinically definite early relapsing-remitting MS and disease duration of less than 5 years were included. The mean±SD age was 36±8 years (age range, 22-48 years), the educational index (years at school and educational status) was 15±2 years (range, 12-17 years), and the Expanded Disability Status Scale (EDSS) score was 2.5±1.1 (range, 0-4.5). None of the patients had experienced a relapse or received corticosteroid treatment 6 months before the study. None had upper limb impairment or visual deficits interfering with neuropsychological test performance. Fifteen patients received immunomodulatory therapy. The study was approved by the local ethics committee. Written informed consent was obtained from all subjects.

CONVENTIONAL MR IMAGING

Brain scans were obtained using a 1.5-T whole-body scanner (Siemens Vision, Erlangen, Germany) with a standard circular polarized head coil. To assess the total lesion volume and the total intracranial volume, T2-weighted images were obtained using fluid-attenuated inversion recovery. Thirty 5-mm axial slices centered 10 mm above a transversal tangent plane at the top of the mesencephalon covered the brain (repetition time, 9000 milliseconds; inversion time, 2500 milliseconds; echo time, 110 milliseconds; 2 acquisitions; echo train length, 11 echoes; with a 0.9×0.9×0.9-mm3 matrix). The scanning time was 13 minutes. The global NAA/Cr ratio was calculated to correct for cerebrospinal fluid content, coil sensitivity variations, and edema. Brain parenchyma unsuitable for evaluation because of poor shim or cerebrospinal fluid was excluded. Areas near the inner ear, the nasal cavity, and the frontal and sphenoid sinuses were typically excluded, as these are areas that cause problems in MR spectroscopy because of considerable magnetic field inhomogeneity (Figure). Manual editing added consistency in the choice of regions. The adapted brain mask covers approximately 60% of the brain parenchyma. However, the exclusion of brain areas that would have degraded the spectra improves the quality and reproducibility of the technique. All images were evaluated by the same observer (H.K.M.), who was unaware of clinical and neuropsychological findings.

SPECTROSCOPIC IMAGING

The multislice EPSI sequence and analysis used in this study are described in detail elsewhere (repetition time, 4300 milliseconds; echo time, 144 milliseconds; with a 32×32×32-mm3 matrix). Eight 10-mm axial slices covered most of the cerebrum with 1-mm3 isotropic voxels. The scanning time was 20 minutes. The global NAA/Cr ratio was calculated to correct for cerebrospinal fluid content, coil sensitivity variations, and edema. Brain parenchyma unsuitable for evaluation because of poor shim or cerebrospinal fluid was excluded. Areas near the inner ear, the nasal cavity, and the frontal and sphenoid sinuses were typically excluded, as these are areas that cause problems in MR spectroscopy because of considerable magnetic field inhomogeneity (Figure). Manual editing added consistency in the choice of regions. The adapted brain mask covers approximately 60% of the brain parenchyma. However, the exclusion of brain areas that would have degraded the spectra improves the quality and reproducibility of the technique. All images were evaluated by the same observer (H.K.M.), who was unaware of clinical and neuropsychological findings.

NEUROPSYCHOLOGICAL EVALUATION

The neuropsychological test battery consisted of 18 tests, resulting in 29 measures covering a broad range of cognitive functions (Table). Each of the 29 cognitive variables was normalized and transformed to z scores based on the combined distributions of the 20 patients and 75 healthy control subjects. The normalized z scores were standardized to t scores, with a mean±SD of 50±10 in the control group.

A cognitive dysfunction factor (CDF) measuring global cognitive dysfunction (ie, primarily the information-processing aspect) was constructed by summing the t scores for 16 test variables with high intercorrelations (Cronbach α=.76) and with mean t scores less than 50. To assess possible cognitive impairment, the expected (premorbid) CDF scores were calculated from a regression analysis based on the control group and included sex, age, age squared, and educational index as predictor variables (Table). A CDF residual score (the difference between the expected and obtained t scores) of −15 was used to differentiate between cognitively impaired and unimpaired patients. This cutoff point of −1.5 SDs was chosen because residual scores represent more precise measures of dysfunction than t scores and because sensitivity was given higher priority than specificity. This

Figure. Corresponding spectrum (A) and brain areas (white areas) suitable for global N-acetyl aspartate-creatine ratio measurements (B). Cerebrospinal fluid and areas degrading the spectral quality because of considerable magnetic field inhomogeneity are excluded.
Cognitive impairment is common in MS and may profoundly disrupt social and occupational functioning. Neuropsychological testing is often time consuming, and simple ways of screening for possible cognitive dysfunction are needed. Although the subject has been addressed in numerous projects, no unambiguous relationship exists between MR imaging measures and cognitive impairment. In previous work, correlations between T2-weighted lesion load and neuropsychological measures have been weak, probably because of the lack of pathologic specificity, and findings correlating lesion location or lesion volume in specific brain areas with specific cognitive deficits have been contradictory. Brain plasticity and redundancy in the neural functional systems might confound the interpretations, and although lesion location is considered, it is also significant whether edema, gliosis, demyelination, or axonal dysfunction and loss dominate in each lesion. Results of MR imaging techniques with known higher correlation with physical disability (eg, EDSS), such as atrophy measures, magnetization transfer imaging, and T1-weighted hypointense lesions, have shown slightly better correlations with cognitive dysfunction. Although the correlation between cognitive impairment and metabolic changes has been described in patients with neurological and neuropsychiatric disorders and in healthy subjects, the topic has gained little attention in MS. Howver, MR spectroscopy has the potential to improve the pathologic specificity of MR imaging. With multislice EPI, a novel MR spectroscopic method in the field of MS, information on metabolic changes and on neuronal loss or dysfunction can be obtained from local and global measurements. Measurements of global or diffuse pathologic features might be important in assessing the overall cognitive function of patients, as suggested by the significant correlation found in this study. Investigating relationships between metabolism in specific brain areas and specific cognitive domains would require larger patient samples and rigorous definitions of which neuropsychological measures are associated with specific cognitive domains.

The minimal effects of age, treatment, EDSS, and educational index on the relationship between the global NAA/Cr ratio and the CDF may be due to the limited sample size. Furthermore, the role of Cr or metabolite relaxation

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**Results**

The mean ± SD global NAA/Cr ratio was 1.55 ± 0.10 (range, 1.35-1.69), and the CDF was −9.74 ± 12.25 (range, −28 to 16). Nine patients had CDF residual scores less than −15 and were considered cognitively impaired, while the remaining 11 patients (with CDF residual scores of −15 or higher) were considered cognitively unimpaired. Seven of the 9 cognitively impaired patients had a global NAA/Cr ratio less than 1.55, compared with 2 of 11 cognitively unimpaired patients. Cognitively impaired patients had significantly lower global NAA/Cr ratios than unimpaired patients (P = .04). The Pearson product moment correlation between the global NAA/Cr ratio and the CDF was 0.67, while a regression analysis controlling for sex, age, treatment, EDSS, and educational index revealed a significant partial correlation of 0.62 (P = .01). In contrast to this result, the conventional MR imaging measures, such as the mean ± SD brain parenchymal fraction (0.89 ± 0.03 [range, 0.83-0.95]) and lesion volume (9.58 ± 13.63 mL [range, 0.10-58.70 mL]), did not show any significant correlation with the CDF.
times in the metabolite ratio is unknown. These data support the fact that the global NAA/Cr ratio measures aspects of MS pathologic features, as exemplified by cognitive dysfunction, that are independent of age, atrophy, and clinical disability. The significant correlation found in this work does not elucidate causality. Our working hypothesis remains that the global NAA/Cr ratio measured by multislice EPSI represents a measure of the neuronal capacity of the brain, including possible neuronal death, decreased neuronal metabolism, or reduced volume of dendrite arborization, and might be a useful screening instrument in detecting cognitive impairment in patients with MS. The presented data need confirmation in larger-scale studies.

CONCLUSIONS

Multislice EPSI using a standard brain template with a corresponding standard volume of interest might become a simple yet important tool in screening for possible cognitive impairment. Screening with EPSI may result in earlier neuropsychological assessment and medical treatment and delay the progression of cognitive deterioration in patients with MS.

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