Brain Proton Magnetic Resonance Spectroscopy and Brain Atrophy in Myotonic Dystrophy

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Objectives: To evaluate by magnetic resonance spectroscopy the age-related cerebral alterations present in myotonic dystrophy (MD) and to compare these results with those obtained by magnetic resonance imaging.

Design: Twenty-one patients (aged 16-63 years) with MD were compared with 16 age-matched healthy control subjects.

Results: In magnetic resonance spectroscopy, the mean (± SD) ratio of N-acetylaspartate to creatine and phosphocreatine in the patients with MD (1.09 ± 0.32) was significantly lower than that in the control subjects (1.93 ± 0.43) (P<.001). The mean ratio of N-acetylaspartate to choline-containing compounds in the patients with MD (1.70 ± 0.44) was also significantly lower than that in the control subjects (2.75 ± 0.53) (P<.001).

These changes could be observed already in the younger patients. In magnetic resonance imaging, the mean brain area was significantly decreased and the mean ventricular space was significantly increased in patients with MD compared with the control subjects. Although we have confirmed brain atrophy in patients with MD in previous reports, a regression analysis indicated that the brain shrinks progressively with age in patients with this disorder and in control subjects, resulting in overlapping values for younger subjects.

Conclusion: Magnetic resonance spectroscopy indicates that the cerebral abnormalities in patients with MD may be present at an early stage, when the results of magnetic resonance imaging studies are still equivocal.

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Myotonic Dystrophy (MD) is an autosomal dominant, multisystem disease. It is caused by an abnormal expansion of CTG repeats in the untranslated region of a gene encoding a putative serine or threonine protein kinase on chromosome 19.1,2 In addition to the characteristic muscular symptoms and CTG amplification, patients with MD frequently show central nervous system symptoms, including apathy, hypersomnia, and mild mental impairment.3,4 Similarly, brain abnormalities such as ventricular dilatation detected by computed tomographic scans,6 brain atrophy and white matter lesions (WMLs) detected by magnetic resonance imaging (MRI),7,8 hypoperfusion detected by single photon emission computed tomography,9 and a low uptake of glucose detected by positron emission tomography11 have been documented. On histological examination, the MD brain sometimes contains neural inclusion bodies, a disordered cortical cellular arrangement, abnormally frequent neurofibrillary tangles, and tau protein.12-15 These results strongly indicate significant brain involvement in MD.

The N-acetylaspartate (NAA) content of the brain can be measured by proton magnetic resonance spectroscopy (MRS) and is a noninvasive indicator of neuronal status because this molecule is present exclusively in neurons and in glial cells.16-18 Decreases in the NAA content were correlated with a loss in the neuronal number during experimental ischemia.19 Decreases in the brain NAA levels have also been associated with neuronal loss or pathological changes in human postmortem studies.20,21 Because of the inherent problems in estimating the absolute NAA levels by in vivo MRS, comparisons are usually made relative to the ratios of NAA to phosphocreatine (Cr) and to choline (Cho). Magnetic resonance spectroscopy has successfully detected metabolic derangements in diseased brain of a variety of disorders.22-24

Using MRI, some reports on MD have noted the occurrence of WMLs and cerebral atrophy, particularly in the
SUBJECTS AND METHODS

PATIENTS

Twenty-one patients with MD were subjected to their informed consent to proton MRS and MRI. Table 1 shows the clinical profiles of these patients. There were 12 men and 9 women from 18 families, aged 16 to 63 (37.0 ± 13.6 [mean ± SD]) years. To estimate the intellectual status, either or both the Mini-Mental State Examination (MMSE)25,26 and the Hasegawa Dementia Scale (HDS)27,28 were used. In addition to the characteristic neuromuscular symptoms, 8 patients showed other neurologic or neuropsychological symptoms (Table 1). No specific common neuropsychological symptoms were noted in these patients, however.

In all patients, a definite diagnosis was established by a combination of the family history and the results of a neurologic examination, electromyography, and histological analysis of a muscle biopsy specimen. All of the patients had percussion or grip myotonia and myotonic discharges on electromyography. They also had muscle weakness in their distal extremities, scored as grade 4 or less in 1 or more of the muscles.29 The CTG expansion was confirmed by Southern blotting in 3 of the patients, who showed no apparent systemic manifestation of their disease. The other patients had frontal baldness, cataracts, gonadal atrophy, or endocrine abnormalities (Table 1). None of the patients had proximal dominant muscle weakness that was suggestive of proximal myotonic myopathy.30 The age-matched healthy control subjects (n = 16; 8 men and 8 women; age range, 23-62 [39.0 ± 15.0] years) had no central nervous system disorders, hypertension, diabetes mellitus, or abnormal MRI findings. All of the experiments were approved by the ethics committee of Kyoto University, Kyoto, Japan.

MRS AND MRI

Proton MRS was performed using a 1.5-T whole-body MRI device (Signa) (General Electric, Milwaukee, Wis) with a routine bird-cage imaging head coil. For localized proton spectroscopy, the dry steam (vapor produced by volume-localized, solvent-attenuated proton nuclear magnetic resonance) technique was used. The repetition time (TR) was 2500 milliseconds, the echo time (TE) was 19 milliseconds, and the middle interval time was 5.7 milliseconds. To reduce contamination by signals from outside the volume of interest, an 8-step 0/180-phase cycle was used for 3-slice, selective radiofrequency pulses. The duration of the dephasing gradient pulses for solvent suppression was 2, 4, and 2 milliseconds, respectively. The spectra were obtained with a sweep width of 4000 Hz and 2048 data points, and exponential multiplication with a 3-Hz line broadening was applied before the Fourier transformation. When water suppression was incomplete, an additional baseline correction using polynomial interpolation was applied. The data were randomly extracted and processed by one of us (R.K.), who was unaware of the clinical diagnosis, using a computer workstation (Sun Microsystems, Mountain View, Calif) with Omega software (General Electric). The proton MRS of the brain showed 3 major peaks corresponding to NAA at 2.0 ppm, creatine plus phosphocreatine (Cr) at 3.0 ppm, and choline derivatives (Cho) at 3.2 ppm (Figure 1). Although other peaks due to glutamine or glutamate at 2.2 to 2.4 ppm and myoinositol at 3.5 ppm were visible, they were subject to a baseline correction caused by incomplete water suppression and were excluded from the present study. The peak areas were calculated by automatic curve fitting with the Simplex method using software programmed in our laboratory.31

Based on the axial T1-weighted magnetic resonance images (TR/TE 600/20 milliseconds, 3-mm slice thickness with a 2.5-mm intervening gap), the region of interest was selected at 20 to 30 mm above the nasion line, parallel to the orbitomeatal line, where the interventricular space was visible. The coordinates of the volume of interest, a 27-ml cube of 3 × 3 × 3 cm, were in the insular cortex and included the frontal, temporal, and parietal opercula. These regions, previously indicated by single photon emission computed tomographic and positron emission tomographic scans, were the most affected by MD (Figure 2).30,31 The number of acquisitions was 256, and the time required for the accumulation of a spectrum was 10 to 20 minutes. The total time required for the examination was 30 to 40 minutes per subject.

The MRI studies were performed in a 1.5-T magnetic field. The axial brain images were obtained using T1-weighted pulse sequences with a TR of 2500 milliseconds, a TE of 30 milliseconds, and a slice thickness of 5 mm. The areas of the brain and ventricle were measured with imaging analysis software (Adobe Photoshop, Version 3.0, Adobe Systems Incorporated, Mountain View, Calif) at the same level as the MRS study. T1-weighted images were divided into the brain parenchyma, ventricles, and subarachnoid space by thresholding segmentation. The number of pixels in these segments was then counted.

STATISTICAL ANALYSIS

Statistical comparisons were performed using commercial software (StatView; Abacus Concepts, Inc, Berkeley, Calif), and comparisons between 2 values were made with the Student t test. Differences were considered to be significant when P < .05. For linear correlations, a least-squares method was used, and the correlation coefficient was then determined. The F distribution and its associated significance level were computed from the ratio of the regression and a residual mean sum of squares.

In the present study, we investigated the NAA/Cr and NAA/Cho ratios in patients with MD to evaluate the neuronal alterations present. In addition, we quantified the brain atrophy present in these patients with MRI, paying particular attention to the age-related changes in control subjects and patients with MD.
RESULTS

MAGNETIC RESONANCE SPECTROSCOPY

Table 2 shows the results of the MRS study. Figure 3 shows the relationship between the NAA/Cr or NAA/Cho ratio and age in both groups. There was no correlation between the NAA/Cr, NAA/Cho, or Cho/Cr ratios and patients’ age. The mean NAA/Cr, NAA/Cho, and Cho/Cr ratios of the patients with MD with subnormal scores on MMSE or HDS were not statistically different from those of the patients with MD with normal scores on these mental tests (data not shown).

MAGNETIC RESONANCE IMAGING

Three patients had WMLs in their subcortical or periventricular regions, and 5 had brain atrophy, ventricular dilatation, or both, that could be observed by visual inspection alone. Table 2 summarizes the ratios of the brain and ventricular areas against the cranial space. Figure 4 shows a regression analysis between these ratios scored by MRI and the patients’ age. In the patients with MD, the brain–cranial space ratio was inversely correlated with age (r = −0.666; P = .001), whereas the ventricle–cranial space ratio was positively correlated with age (r = 0.442; P = .04). In the control subjects, the brain–cranial space ratio was inversely correlated with age (r = −0.767; P = .002), and the ventricle–cranial space ratio was positively correlated with age (r = 0.803; P = .001).

There were no correlations between the presence of WMLs, brain atrophy, dilatation of the ventricles, and subnormal scores on the MMSE or HDS in the patients with MD (data not shown).

COMMENT

Mental defects have been found in approximately 24% to 50% of patients with MD.7,9,32,33 In our study, 5 (24%) of 21 patients with MD had scores in the subnormal range on the MMSE or HDS. The low NAA/Cr ratio in the younger patients with MD and the slow decline of the NAA/Cr regression line with age were consistent with a clinical profile indicating that the cognitive deficits were mainly congenital or developmental and were relatively stable.12,34,35 Histological studies in patients with MD have also shown alterations suggestive of congenital brain involvement; for example, Rosman and Kakulas12 demonstrated the presence of pachygyria and neuronal heterotopia, particularly in the frontal and temporal lobes. Some acquired or presenile changes may be present, however, such as thalamic inclusions, a high incidence of neurofibrillary tangles,14 and the tau-variant protein.15 Culebras and Chang36 suggested that pachygyria and cortical heterotopia could account for the congenital varieties of stable mental retardation, whereas thalamic damage would explain the progressive forms of acquired cognitive deficits.

The NAA/Cr ratio in the patients with MD was 46% lower than that in the control subjects. A previous pos-
tron emission tomographic study also indicated a substantial (20%) reduction in glucose uptake in the temporal lobe of patients with MD. Even patients with MD who have a normal IQ tend to show a lack of attention, personality changes, and hypersomnia or sleep apnea. Our patients also showed a variety of central nervous system symptoms, as indicated in Table 1. The reduction in the NAA/Cr ratio in patients with MD with a normal score on their mental tests may be related to changes other than overt dementia.

On the MRI study, 5 of our patients with MD showed brain atrophy or ventricular dilatation on visual inspection alone, and the quantitative MRI study confirmed that brain shrinkage was present. Although we have confirmed the presence of brain atrophy in MD in previous reports, regression analysis indicated that the brain shrinks progressively with age in patients with MD and in control subjects, thus resulting in overlapping values in the younger subjects. Characteristic lesions in the subcortical white matter of the temporal lobe have been reported in 23% or more of patients with MD. Our study found WMLs in 3 patients (14%); however, our results did not confirm this preferential localization in the temporal lobe. Furthermore, several reports have indicated a correlation between the presence of WMLs on MRI and mental impairment, but no association was found between the MRI abnormalities and low MMSE or HDS scores in our study.

This discrepancy may be because the previous studies included patients with congenital MD, in whom severe mental retardation almost always accompanies WMLs. The origin of the WMLs in the brain of patients with congenital MD is sometimes attributed to perinatal hypoxia. The decreased NAA/Cr ratio in the brains of patients with congenital MD is most likely due to an asphyxic episode during uterine development or birth. Our patients did not have congenital MD, however, and did not suffer from respiratory distress at birth. In addition, another study of MD only found no association between the presence of WMLs and intellectual deficits. One possible cause of the WMLs in patients with MD could be cortical heterotopia, which is found on histological examination of the brains of patients with MD.

Magnetic resonance imaging fails to measure selective neuronal loss. For example, in patients infected with the human immunodeficiency virus, cognitive impairments due to the infection are rarely manifested on an MRI scan as abnormal anatomy. However, the results of MRS suggest substantial neuronal damage. Postmortem studies of brains of persons infected with the human immunodeficiency virus indicated a reduction in the neuronal density of the frontal cortex by 18% or 38%, with minimal atrophy partly due to the replacement of neurons with glia. Magnetic resonance spectroscopy is also superior to MRI for detecting neuronal dysfunction in hypoxic encephalopathy and can detect specific involvement of the cortex in supranuclear palsy or corticobasal degeneration. Therefore, although the brain atrophy of younger patients with MD was not conspicuous, the obvious decrease in the NAA/Cr ratio may indicate cerebral dysfunction in these patients.
The Cho/Cr ratio is increased in patients with adrenoleukodystrophy \(^47,48\) and those with multiple sclerosis,\(^49\) reflecting an increased turnover of choline-containing compounds in the myelin. In our study, the Cho/Cr ratio was not increased in patients with white matter hyperintensities. This result suggests the minimal involvement of demyelination in the WMLs observed in MD.

The reduction in the NAA/Cr and NAA/Cho ratios in the present study may indicate a decrease in NAA, an increase in Cr and Cho, or a combination of both. After the submission of this article, Chang et al\(^ {50} \) reported the results of a proton MRS study in MD. They noted increased absolute values for Cr and Cho without an alteration in the absolute NAA content, thus resulting in a decrease in the NAA/Cr and NAA/Cho ratios. Moreover, myoinositol levels were elevated. These findings of increased Cr, Cho, and myoinositol suggested an increased glial content and cell membrane abnormalities in the MD brain.\(^ {20} \) Our present results confirmed their observations of cerebral abnormalities in patients with MD, although we did not measure the absolute values.

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