Proton MR Spectroscopy of Adult-onset Dentatorubral-pallidoluysian Atrophy

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Purpose: To quantify impairment of the basal ganglia (globus pallidus and thalamus) in adult-onset dentatorubral-pallidoluysian atrophy (DRPLA).

Methods: Five patients with genetically definite adult-onset DRPLA (aged 51 to 65 years, mean 55.6 years) and 5 age- and sex-matched healthy controls underwent conventional magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (MRS) of the brain in the voxels predominantly containing the globus pallidus or the thalamus.

Results: Conventional MRI studies showed apparently normal intensities in the globus pallidus and thalamus. MRS showed that the choline (Cho)/creatine (Cr) ratio for the patients' globus pallidus, the region preferentially affected in DRPLA, was significantly higher than that in the controls (p < 0.05). The N-acetylaspartate (NAA)/Cr ratio for the globus pallidus and the Cho/Cr and NAA/Cr ratios for the thalamus, the region relatively spared in this disease, did not differ significantly between the patients and controls.

Conclusions: MRS may sensitively and specifically detect biochemical alterations in susceptible regions of patients with adult-onset DRPLA.

Keywords: MRS, adult-onset DRPLA, triplet repeat disease, ataxia

Introduction

Dentatorubral-pallidoluysian atrophy (DRPLA) is an autosomal dominant spinocerebellar ataxia caused by triplet repeat expansions in the DRPLA gene.1,2 Clinical manifestations depend on the age at onset and the size of the repeat expansions. They include ataxia, choreoathetosis, and dementia for adult-onset disease and progressive myoclonus epilepsy for juvenile-onset disease. Despite distinct phenotypes in adult- and juvenile-onset DRPLA, neuropathological alterations are commonly seen in the basal ganglia (especially the globus pallidus), cerebral white matter, brainstem, and cerebellum, with more severe changes in juvenile-onset disease.3 Most affected regions can be evaluated by conventional magnetic resonance imaging (MRI), whereas assessment of the basal ganglia requires more sensitive methods.4,5 Previously, abnormalities of the basal ganglia in 3 patients with juvenile-onset DRPLA and one with adult-onset disease were detected by proton magnetic resonance spectroscopy (MRS),5 a sensitive and quantitative method that permits the use of N-acetylaspartate (NAA)/creatinine (Cr) and choline (Cho)/Cr ratios as markers of neuronal loss and gliosis, respectively. In fact, the patient with adult-onset disease showed an increased Cho/Cr ratio in the basal ganglia with normal T2 signals. However, we regard this finding to be inconclusive in that 1) it was based on the ratio from a single case, and 2) comparison with control values obtained from younger healthy individuals may have led to overestimation because the Cho/Cr ratio might increase physiologically with age.6 To better understand the MRS findings in adult-onset DRPLA, we compared the findings in the basal ganglia in 5 patients with those in age- and sex-matched controls.

Materials and Methods

Patients

Five patients with clinically definite adult-onset DRPLA (aged 51 to 65 years, mean 55.6 years; 2 men, 3 women) and 5 healthy controls well matched for age and sex were studied.7 No patient had any history of other neurological disease. Informed
consent was obtained from all patients or their guardians and from all control subjects before genetic analysis and MRS studies. The clinical features of the patients are summarized in the table.

**Magnetic Resonance Studies**

A 1.5T whole-body MR unit (Magnetom Sonata; Siemens, Enlargen, Germany) with a standard head coil was used. For conventional MRI studies, turbo spin-echo sequences were used for T1-weighted images (T1WI, repetition time [TR]/echo time [TE] = 450/9) and T2-weighted images (T2WI, TR/TE = 4000/104; echo train length [ETL] = 11). Three experienced neurologists independently evaluated atrophy of the cerebrum and cerebellum on T1WI and signal changes in the globus pallidus on T2WI according to a 4-grade scale (severity: − to +++). If the scores differed, the score agreed on by two of the neurologists was adopted. Water-suppressed MRS images were obtained by spin-echo chemical-shift imaging, a technique to obtain simultaneously spectroscopic information from multiple adjacent voxels during a single measurement. We performed global and voxel shimming before image acquisition. Water-signal suppression was performed using a chemical-shift-selective suppression pulse. Line widths (full-width at half-maximum) of 5 to 7 Hz were achieved by automatic shimming. The data were acquired in a single axial plane at a level 1 cm cranial and parallel to the anterior commissure-posterior commissure (AC-PC) line. The settings for chemical shift imaging were as follows: TR = 1,500 ms; TE = 135 ms; acquisition = 4; field of view (FOV; chemical-shift imaging [CSI] slice) = 240 × 240 mm; FOV (volume of interest) = 160 × 160 mm; matrix = 16 × 16; voxel size = 10 × 10 × 15 mm; and data acquisition time = 7 min. Gaussian fitting and baseline correction were carried out automatically in each voxel. Voxel predominantly containing the globus pallidus or the thalamus were chosen for analysis. We measured the areas of selected peaks of metabolites such as choline-containing compounds (3.2 ppm), total creatine (3.0 ppm), and NAA (2.0 ppm). The ratios of Cho/Cr and NAA/Cr for the globus pallidus and thalamus were calculated in the patients and the age- and sex-matched controls. The Mann-Whitney U test was used to compare Cho/Cr or NAA/Cr ratios between the patients with DRPLA and the control subjects. P values less than 0.05 were considered statistically significant.

**Results**

Conventional MRI studies showed different degrees of diffuse white matter abnormalities and cerebral and cerebellar atrophy in all patients (Table). High signals of the globus pallidus on T2-weighted images were seen in only one of the 5 patients. The Cho/Cr ratio in the voxel predominantly containing the globus pallidus was significantly higher in the patients with DRPLA than in the controls (p < 0.05) (Figs. 1, 2). The NAA/Cr ratio for the globus pallidus and the Cho/Cr and NAA/Cr ratios in the voxel predominantly containing the thalamus did not differ significantly between the patients and controls (Fig. 2). The Cho/Cr ratio for the globus pallidus did not correlate with either disease duration or expanded triplet repeat size.

**Discussion**

In this study, MRS revealed a significantly increased Cho/Cr ratio in the voxel predominantly containing the globus pallidus in 5 patients with adult-onset DRPLA. Previous pathological studies of the globus pallidus have demonstrated that gliosis and neuronal loss are mild to moderate in adult-onset DRPLA, but severe in juvenile-onset DRPLA of similar duration. Because choline resonance reflects increased cell membrane turnover or progressive gliosis, our MRS data and the results of pathological studies indicate that gliosis is progressive in adult-onset disease. By
Fig. 2. (A) N-acetylaspartate (NAA)/creatine (Cr) and (B) choline (Cho)/Cr ratios of the globus pallidus and (C, D) those of thalamus in patients with dentatorubral-pallidoluysian atrophy (DRPLA) and controls. The Cho/Cr ratio in the globus pallidus of the patients was significantly higher than that of the controls, whereas the NAA/Cr ratio did not differ. The bars represent means ± standard deviation (SD). *p < 0.05 by Mann-Whitney U test.
contrast, absent or mild increase in Cho/Cr ratios in the basal ganglia of patients with juvenile-onset disease may indicate that gliosis is already severe and, thus, almost stable. So, the increased Cho/Cr ratio may reflect the dynamics of neurodegeneration, a finding not discernible on pathological studies alone. In contrast to MRS, conventional MRI revealed abnormal intensities of the globus pallidus in only one of 5 patients, suggesting that MRS is more sensitive for the detection of neurodegeneration. Negative results on MRS of the thalamus, the region showing minimal pathological changes in DRPLA, may suggest that MRS specifically detects abnormalities in the region preferentially affected by disease. However, confirmation awaits further study because of the small number of patients considered. Nevertheless, this assumption is supported by findings in Huntington disease, another triplet repeat disease, in which the Cho/Cr ratio was markedly increased in the basal ganglia, the region preferentially affected in that disease. Collectively, available evidence suggests that MRS may sensitively and specifically detect the regional gliosis occurring in triplet repeat diseases.

A previous MRS study showed that the NAA/Cr ratio was significantly lower in the basal ganglia of 3 patients with juvenile-onset DRPLA than in controls. In adult-onset DRPLA, the NAA/Cr ratio in the basal ganglia was normal in one previously described patient and all five of our patients. This difference probably reflects more severe neuronal loss in juvenile-onset DRPLA, as suggested by the results of pathological studies. Although there was no significant change in the NAA/Cr ratio, neuronal loss in adult-onset disease may be present but still too mild to significantly reduce this ratio. This speculation is based on our findings that the mean NAA/Cr ratio was lower than the control value and that the Cho/Cr ratio had increased, reflecting gliosis in response to neuronal loss. The significantly decreased NAA/Cr ratio in juvenile-onset DRPLA may also be attributed in part to loss of the physiological increase in this ratio during childhood; consequently, earlier onset of neurodegeneration probably produces a greater reduction in the NAA/Cr ratio.

In conclusion, we believe that this is the first study to compare MRS findings in multiple patients with adult-onset DRPLA and in well-matched controls. Our findings suggest that increased Cho/Cr ratios and unchanged NAA/Cr ratios reflect mild neuronal loss with progressive gliosis. Possible limitations of this study include the small number of patients evaluated and the relatively large voxel size used; partially contained regions may thus have affected our results. Despite these limitations, our results suggest that MRS analysis may sensitively and specifically detect biochemical alterations in regions susceptible to the effects of DRPLA as well as other triplet repeat diseases.

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References
