Combining voxel-based morphometry and 1H magnetic resonance spectroscopy in myotonic dystrophy type 2 and type 1

K. Schiltz[1], J. Kaufmann[2], H. G. Niessen[3], and S. Vielhaber[4]

[1]Department of Psychiatry, University of Magdeburg, Magdeburg, Sachsen-Anhalt, Germany, [2]Department of Neurology II, University of Magdeburg, Magdeburg, Sachsen-Anhalt, [3]Department of Neurology II, University of Magdeburg, Magdeburg, Sachsen-Anhalt, Germany, [4]Department of Neurology II, Universitiy of Magdeburg, Magdeburg, Sachsen-Anhalt, Germany

Introduction

Myotonic dystrophy type 1 (DM1; MIM 160900) and type 2 (DM2, proximal myotonic myopathy, PROMM; MIM 602668) are multisystem diseases characterized by neuromuscular symptoms and a range of potential systemic manifestations.[1] In clinically advanced DM1 stages significant brain involvement has been shown by magnetic resonance imaging (brain atrophy, white matter lesions).[2] However, knowledge about brain involvement in mildly affected DM1 patients and genetically proven DM2 is more limited.[1] To evaluate early subtle cortical and subcortical abnormalities associated with DM 1 and DM2, we assessed gray and white matter atrophy using optimized voxel-based morphometry and conducted ^{1}H magnetic resonance spectroscopic (MRS) analyses in different brain regions in matched adult patient groups.

Subjects and Methods

Patients with mild DM1 (n=14), DM2 (n=14) and 13 healthy age-matched volunteers underwent three-dimensional spoiled gradient-recalled sequence scanning. Voxel-based morphometry was conducted applying the optimized protocol according to Good et al.,[4] to detect regions of gray or white matter atrophy in the DM groups relative to the control group. Proton MRS was performed on a 1.5 T whole-body MRI GE scanner with a neuro-optimized imaging head coil. A PRESS sequence (TR 1500 ms, TE 135 ms, 256 averages) was chosen for volume selective spectroscopy and performed in two cortical regions: midoccipital gray matter (GMO; 4.8 cm^3) and temporoparietal gray matter (GTP; 6 cm^3). In addition, a voxel was placed in the frontal white matter (WF; 4.8 cm^3).

Results DM1 but not DM2 patients showed areas of local gray matter amount reduction that were most distinct in the motor cortex bilaterally ($p<0.05$), indicating a pronounced focal cortical atrophy specific to DM1 (Figure 1). No significant differences of local white matter amount were detected between between the disease groups or compared to controls (data not shown). By contrast, in both patients groups the concentration of *N*-acetylaspartate – a major neuronal metabolite – was significantly reduced relative to healthy subjects in subcortical frontal white matter as well as occipital and temporoparietal cortical gray matter (Figure 2). Neither grey or white matter volumes nor cerebral metabolites correlated with the clinical or the genetic characteristics of the patients.

Figure 1

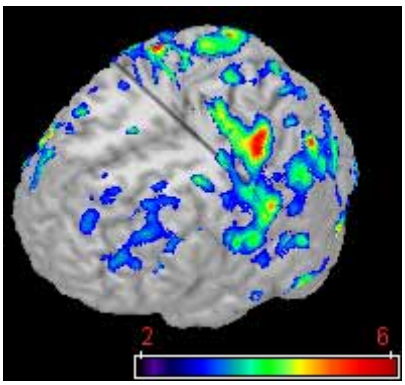

Figure 2

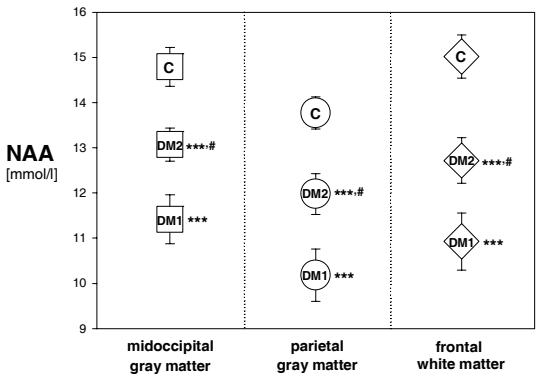

***Figure 1**: Voxelwise comparison of local gray matter amount between healthy controls and DM1 patients. Shown are voxels where controls display a significantly higher local gray matter (LGM) than DM1 patients. Thresholded at $p < 0.05$ (False discovery rate corrected for multiple comparisons), cluster size >100 voxels. Color: T-values from 2 to 6. **Figure 2**: NAA concentrations in cortical and subcortical regions of patients with DM1 and DM2 in comparison to controls. *** - $p < 0.001$ significant different to the controls; # - $p < 0.05$ significant different to DM1.*

Conclusions

Multimodal MR imaging revealed a complex pattern of structural brain changes in genetically confirmed myotonia patients. While voxel-based morphometry analysis revealed pronounced focal cortical atrophy in motor areas in DM1 patients, no such changes were evident in matched DM2 patients. By contrast, in vivo ^{1}H-MRS showed that the decline in NAA concentration was impaired in DM1 as well as DM2 patients, being more distinct in the former. The NAA decline differed between regions and, for both groups was most pronounced in the frontal white matter. Gray matter NAA reduction was more pronounced in temporoparietal than midoccipital areas. Remarkably, NAA levels of DM2 patients fell between the values of the control subjects and DM1 patients, indicating intermediate levels of neurocellular pathology. Our results demonstrate the presence of spatially widespread metabolic changes in DM1 and DM2. Only in DM1 patients these metabolic changes are accompanied by detectable focal gray matter atrophy in bilateral motor areas.

References

1. Udd B, Meola G, Krahe R, Thornton C, Ranum L, Day J, et al. Report of the 115th ENMC workshop: DM2/PROMM and other myotonic dystrophies. Neuromuscul Disord 2003;13:586-589.

2. Kornblum C, Reul J, Kress W, Grothe C, Amanatidis N, Klockgether T, et al. Cranial magnetic resonance imaging in genetically proven myotonic dystrophy type 1 and 2. J Neurol 2004;251:710-714.

3. Harper PS. Myotonic dystrophy. London: WB Saunders; 2001. 139 p.

4. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage. 2001;14:21-36