qMT imaging to assess brain tissue modifications in patients with Miotonic Dystrophy type-1.

INTRODUCTION

Miotonic dystrophy type 1 (MD1), the most common form of adult muscular dystrophy, is an autosomal dominant progressive multisystem disorder characterized by muscular atrophy, myotonia, frontal baldness, cataract, gonadal atrophy, cardiac disorders, and endocrine abnormalities [1]. A number of neuroimaging studies have evaluated the relevance of brain involvement in MD1. In particular, MRI studies have demonstrated that focal white matter (WM) lesions can be found frequently in the brains of MD1 patients. There is no, however, full agreement on the significance and extent of these WM lesions and while some studies found a relationship between the extent of WM lesions and patients’ clinical status, most studies did not find this correlation. Moreover, a significant number of MD1 patients seem to show no abnormalities on conventional MRI despite their clinical signs of CNS involvement. A number of in vivo and ex vivo studies have stressed the importance of WM pathology in MD1 and this has been interpreted as due to increases of interfascicular space, cellular infiltrates and breakdown of myelin sheaths. However, several studies also have shown that abnormalities can extend well beyond the focal areas of hyperintensity detected on conventional MRI and that diffuse brain atrophy can occur in patients with MD1, with similar involvement of WM and GM. In agreement with this, the importance in MD1 of a diffuse pathology that significantly involves the GM has been stressed by several neuropathological studies showing specific signs of neuronal damage such as neurofibrillary tangles and hyperphosphorylated tau proteins in the cerebral cortex [2]. More recently, Giorgio et al. [2] using magnetization transfer (MT) imaging showed, with respect to normal controls, lower cortical-MT ratio and higher cortical atrophy in MD1 patients with no or minimal WM abnormalities on conventional MRI, supporting the hypothesis of the presence of neocortical pathology in MD1. They also showed absence of significant differences between MD1 patients and normal controls in both WM-MT ratio and normal-appearing white values (NMWW) further supporting this hypothesis and suggesting that cortical abnormalities may occur with a mechanism that is not related to that of focal WM lesion formation. MT generates contrast dependent upon the exchange rate, or RM

METHODS

We recruited 21 MD1 patients [F/M=10/11; mean (SD) age=40.0 (9.2) years] with no or minimal abnormalities visible on conventional MRI, and 21 sex- and age-matched healthy controls [HS, F/M=10/11; mean (SD) age=37.4 (9.8) years]. All subjects underwent a neuropsychological examination and an MRI acquisition at 3.0T. The MRI session included for every subject: (1) a Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR=1338 ms, TE=2.4 ms, Matrix=256 x 224, n. slices=176, thick. 1 mm); (2) a series of 12 MT-weighted 3D FLASH sequences (TR=35 ms, TE=7.4, flip angle=7º) with various combinations of amplitude and offset frequency of the MT pulse, optimised according to [6]; (3) three 3D FLASH sequences with variable flip angle for T1 mapping [7]; (4) three 3D FLASH sequences with near-180º flip angles for B1 mapping [8]. Images from sequences (2)-(4) were used to compute the qMT parameters on a voxel-by-voxel basis [8]; T1; and B0 maps were obtained as described in [7] and [8]; respectively; then, we fitted Ramani's model [10] of MT to the data of sequence (2) to compute maps of R0, F, T1, and RM0, where R0 is the longitudinal relaxation rate of the liquid pool, F, is the forward exchange rate, and RM0 is the relative size of the macromolecular pool, TR, is the transverse relaxation time of the macromolecular pool, and RM0 is the forward exchange rate). The largest flip angle scan from sequence (3) was used to compute the transformation from native to MNI space, which was then applied to all qMT parameter maps. qMT maps were smoothed with a 6 mm Gaussian kernel. To assess between groups differences in the normalized and smoothed RM0, F and T1 maps, we performed two different ANCOVA analysis for each qMT map, one confined in GM and the other in WM, using SPM8 (www.fil.ion.ucl.ac.uk/spm).

RESULTS

The only qMT parameter which showed significant differences between MD1 patients and normal controls was RM0, in GM. These differences were located bilaterally in the cingulum, in right and left thalamus, in the right postcentral cortex and in the right temporoparietal cortex (Fig1). No other significant results were obtained.

DISCUSSION

Our results show that among qMT parameters, RM0 is the most sensitive to MD1 pathology. Data reported in the present study support the hypothesis that cortical damage can be significant in MD1 patients even when they have no or minimal abnormalities visible on conventional MRI. In contrast, signs of subtle and/or diffuse WM abnormalities are not found in these patients [2]. In conclusion these results support the notion that significant neocortical damage can be evident even in the absence of WM lesions and can proceed in parallel with disease duration, suggesting that a neocortical pathology, unrelated to WM lesion formation, occurs and is clinically relevant in the brains of patients with MD1.

References: