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Cortical damage in brains of patients with adult-form of myotonic dystrophy type 1 and no or minimal MRI abnormalities

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Abstract *Objective* To evaluate, by using quantitative MRI metrics, subtle cortical changes in brains of patients with the adult form of myotonic dystrophy type I (DM1) who showed no or minimal abnormalities on MRI. *Background* DM1 is an autosomal dominant multisystem disorder caused by the expansion of CTG repeats in the myotonic dystrophy-protein kinase gene. Mild to severe involvement of the CNS can be part of the clinical features of the disease. Several MRI studies have demonstrated that both focal white matter (WM) lesions and diffuse grey matter atrophy can be found in the brains of DM1 patients. However, whether these two processes are related or may occur independently is not clear. *Design/Methods* Ten genetically-proven DM1 patients who showed no or minimal abnormalities on MRI underwent a new brain MRI examination to obtain computerized measures of total and regional brain volumes normalized to head size and regional measurements of the magnetization transfer ratio (MTr). *Results* Normalized brain volumes (NBV) were significantly ($p < 0.0001$) lower in DM1 subjects than in a group of age- and sex-matched normal controls. Normalized cortical volumes (NCV) also were lower ($p = 0.003$) in DM1 subjects than in normal controls, whereas normalized WM volumes were not different between the two groups ($p = 0.3$). In agreement with this, values of MTr in the neocortex (cortical-MTr) were significantly ($p = 0.006$) lower in DM1 patients than in normal controls and this difference was not found in the WM tissue ($p = 0.8$). *Conclusions* Neocortical damage seems to be evident in the absence of visible WM lesions suggesting that a neocortical pathology, unrelated to WM lesion formation, occurs in DM1 brains.

Key words magnetic resonance · magnetization transfer · cortical atrophy · DM1

Introduction

Myotonic dystrophy type 1 (dystrophia myotonica, DM1), the most common form of adult muscular dystrophy, is a progressive autosomal dominant disorder [18, 24]. The disease is caused by an abnormal expansion of cytosine-thymine-guanidine (CTG) repeats in the untranslated region of a gene encoding a putative serine or threonine protein kinase on chromosome 19

and leading to the defective production of myotonin [7, 15]. The clinical manifestations of DM1 can vary greatly and may include ocular, muscular, cardiac, endocrine, gastrointestinal, osseous and cutaneous abnormalities [18]. The variable phenotypic expression of the disease often includes abnormalities of the central nervous system (CNS), mainly reported as personality changes, depression and cognitive dysfunctions [1, 8, 18].

A number of neuroimaging studies have evaluated the relevance of brain involvement in DM1. In particular, MRI studies have demonstrated that focal white matter (WM) lesions can be found frequently in the brains of DM1 patients [1, 4, 9, 14, 16, 19, 26]. There is not, however, full agreement on the significance and extent of these WM lesions [14] and while some studies found a relationship between the extent of WM lesions and patients' clinical status [1, 19], most studies did not find this correlation [9, 14, 26]. Moreover, a significant number of DM1 patients seem to show no abnormalities on conventional MRI despite their clinical signs of CNS involvement [4, 9].

More recently, quantitative MR studies, using magnetization transfer (MT) imaging [28] and T_2 relaxometry [13], have demonstrated that abnormalities also can be found in the normal appearing brain suggesting that brain abnormalities are not confined to the focal areas of hyperintensity detected on conventional MRI. The notion that brain pathology can extend well beyond WM lesions in DM1 patients also is supported by recent volumetric MR studies reporting diffuse brain atrophy [2, 3, 23] and by several neuropathological studies showing diffuse neuronal damage and loss in DM1 brains [27, 33, 37].

On this basis, neurodegeneration seems to be relevant in the brains of DM1 patients, perhaps occurring with a mechanism that might be unrelated to that of focal WM lesion formation. To clarify this issue, we assessed, by using new quantitative MR methods such as MT imaging and computerized measurement of brain volumes, the extent of subtle neocortical changes in brains of DM1 patients who showed no or minimal.

Material and methods

Study population

Among the patients referred to the Neurometabolic Unit of the Department of Neurological and Behavioral Sciences (University of Siena), we consecutively selected 10 subjects (5 men and 5 women, mean age: 39 years, range = 25–63 years) with a genetically proven adult form of DM1 [18] who had normal appearances on their last (3 months to 3 years) conventional MRI examination. Demographic, clinical and genetic characteristics of the DM1 patients are summarized in Table 1. Three out of ten patients had no signs of clinical impairment (see Table 1), which was scored in all patients by using the Muscular Impairment Rating Scale (MIRS) [25]. None of the patients had risk factors for cerebrovascular disease, history of head trauma, hypoxic insult or any other neurological disease that might have affected the CNS. Each subject underwent brain MRI examination to obtain quantitative MR measures. Their results were compared with the MR results of 12 demographically-matched normal controls (6 men and 6 women; mean age: 39 years, range 26–60) who had normal neurological examination and no history of neurological disorders. Each DM1 patient and normal controls underwent the identical MR protocol. The MRI acquisition of all subjects involved in the study was interleaved and was done in 6 months.

The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Siena and informed consent was obtained from all participating subjects.

MR examinations

All subjects were examined using an identical MR protocol. Acquisitions of brain were obtained in a single session using a Philips Gyroscan operating at 1.5 T (Philips Medical Systems, Best, The Netherlands). A sagittal survey image was used to identify the anterior commissure (AC) and posterior commissure (PC). A dual-echo, turbo spin-echo sequence (TR/TE1/TE2 = 2075/30/90 ms, 256 × 256 matrix, 1 signal average, 250 mm field of view, 50 contiguous 3 mm slices) yielding proton density (PD) weighted and T_2-weighted (T_2W) images was acquired in the transverse plane parallel to the line connecting the AC and PC. Fluid-attenuated inversion recovery (FLAIR) images (TR = 9000 ms; TE = 150 ms; IT = 2725, 50 contiguous 3 mm slices) were acquired in the same direction. Subsequently, an MT sequence was performed acquiring two transverse T_1−weighted (T_1−W), gradient echo images, one without (No Sat) and one with (Sat) MT saturation pulses (TR/TE = 35 ms/10, 256 × 256 matrix, 1 signal average, 250 mm field of view). This sequence yielded image volumes of 50 slices, 3 mm thick, oriented to exactly match the PD/T_2-W and FLAIR acquisitions. The MT pulse was a 1.2−millisecond on-resonance, 1$\bar{2}$1 binomial pulse (radio-frequency field strength = 20 μT) placed just before each slice-selective excitation [31].

MR data analysis

In all subjects, the presence of WM lesions was visually assessed on FLAIR and PD/T_2−W images by an experienced neuroradiologist (MM) who was unaware of subject identity. Then, classification of T_2−W lesion volume (LV) was performed in each patient by a single observer (AG), unaware of subject identity, employing a segmentation technique based on user-supervised local thresholding [12]. The value of total brain LV was calculated by multiplying lesion area by slice thickness.

Normalized volumes of the brain parenchyma were measured on T_1−W gradient echo images using a method for brain volume measurement (the cross-sectional version of the SIENA software [35] [SIENAX]) (see an example of the SIENAX output in Figure 1). Reproducibility tests have resulted in a mean standard error across a group of normal subjects of less than 1% [35]. SIENAX uses a previously described method [34] to estimate the global brain volume normalized for head size (NBV). The total brain volume measurement can be optionally split into GM and WM volumes, obtaining normalized GM volume and normalized WM volume (NWMV), as previously described [12]. For selective measurement of normalized cortical volumes (NCV), a standard space mask (which includes ventricles, deep GM, cerebellum and brain stem) is used to separate segmented GM into neocortical and non-neocortical [12].

As for the analysis of MT data, we used here a fully automated procedure (see an example of the output in Figure 2). Saturated (Sat) images were registered to No-Sat images using a registration

Table 1 Demographic, clinical and genetic data of the DM1 patients

Patients	Age (years)	Gender	Dis. Dur. (years)	MIRS	CTGn
1	49	F	4	2	325
2	53	F	5	5	400
3	25	M	13	3	700
4	63	M	39	2	350
5	35	M	23	3	1500
6	25	F	15	2	750
7	25	M	11	2	350
8	55	M	0	1	70
9	33	F	0	1	400
10	30	F	0	1	400

Dis. Dur. = Disease duration (from presentation of first symptom)
MIRS = Muscular Impairment Rating Scale; CTGn = cytosine-thymine-guanidine number of repeats

method previously described [34]. The brain was extracted from both Sat and No-Sat images using a previously described method [34] and MT ratio (MTr) images were then calculated using the formula MTr = 100 * (No-Sat –Sat)/No-Sat [30]. The extracted No-Sat images were then segmented into different tissue types (GM, WM and CSF) using a previously described segmentation method [34], thresholding the resulting probabilistic tissue-class images to retain voxels where the tissue-class probability was equal to or greater than p = 0.75. This gives fairly conservative GM and WM binary images which were applied to the MTr image to produce GM-MTr and WM-MTr images. To select identical brain regions in each subject, standard space WM and GM masks were automatically applied in native space to the WM-MTr and GM-MTr images by using the MNI152-to-native brain space transformation derived during registration. For a conservative measurement of the WM-MTr, we used a thresholded (> 60% of the intensity) standard space WM mask, made on the MNI152 average normal brain (McConnell Brain Imaging Centre, Montreal Neurological Institute). For selective MTr measurement of neocortical brain regions, a standard space mask (made on the MNI152 average normal brain and including ventricles, deep GM, cerebellum and brain stem) was used to separate segmented GM-MTr into neocortical and non-

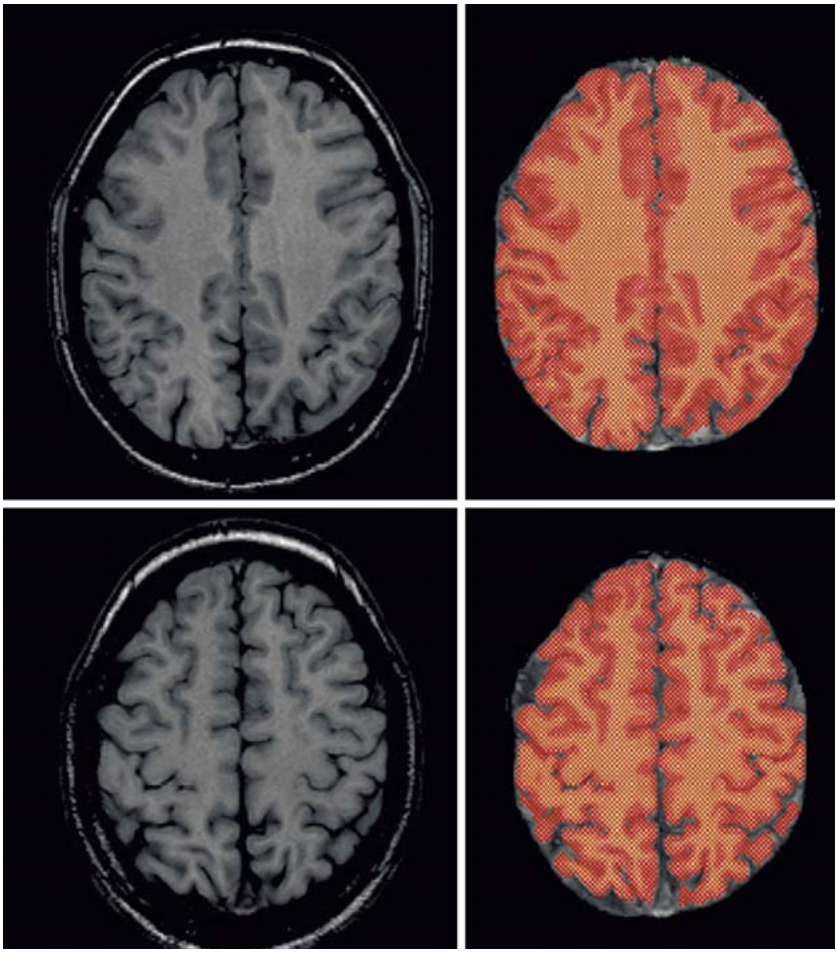

Fig. 1 Typical transverse T_1 weighted MR images (*left panels*) and illustrative example of the SIENAX output (*right panels*) for neocortex and white matter assessment of a normal control. The normalized brain volumes include only segmented brain parenchyma (*light and dark red color*) and discard CSF and other non-brain tissues (*in black and white*, e.g., superior sagittal sinus, falx cerebri, dura mater), yielding an estimate of total and regional brain tissue volume (see *Methods* for details)

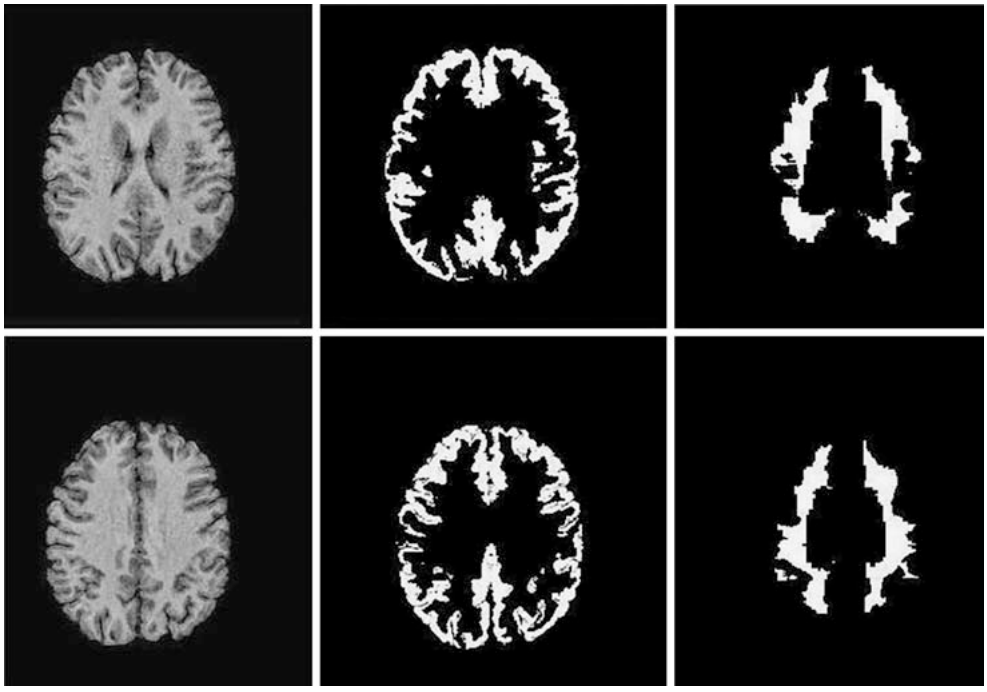

Fig. 2 Illustrative examples of the MTr images of a normal control (left panels), segmented cortical (central panels) and white matter regions (right panels). Note that the fully automated procedure does not select the whole segmented tissue region (allowing a more conservative measurement of each tissue-class probability image) and gives comparable results across subjects or groups (see *Methods* for details)

neocortical tissues. To avoid contamination of image noise, all voxels of the neocortical regions with values <10% of the GM-MTr mean were excluded. Finally, mean values (averaging all voxels contained in the given region) from cortical-MTr and WM-MTr, which now gave comparable results across subjects or groups, were evaluated.

Statistical analysis

Values of NBV, NCV, NWMV, WM-MTr and cortical-MTr of the DM1 patients were compared with those of the normal control group using the non-parametric Mann-Whitney test. Correlations between MR and clinical and genetic indices were assessed in each patient by using the Spearman rank order correlation (SROC). Analyses allowed for age and sex correction and were considered significant at the 0.05. The SYSTAT software version 9 running on Windows (copyright SPSS Inc. 1998) was used to perform statistical calculations.

Results

On FLAIR images, we detected small, hyperintense abnormalities in the WM in 4/10 patients: patient 2, 4 and 7 showed punctuate, periventricular and subcortical WM lesions; patient 5 showed 2 bilateral lesions in the WM of the anterior poles of the temporal lobes. In these 4 DM1 patients, the WM lesion load was minimal, with a LV ranging from 0.08 to 0.9 cm^3 (see Table 2) The remaining 6 DM1 patients showed no abnormalities at visual inspection. No dilation of Virchow-Robin spaces was found in the 10 patients. No abnormal findings were found in the normal control group. Quantitative MR results of the DM1 patients are summarized in Table 2.

Measures of NBV were significantly ($p < 0.0001$) lower in DM1 subjects than in normal controls (DM1 = 1573 ± 45 cm^3, normal controls = 1685 ± 44 cm^3). On regional volume measurements, NCV loss was significantly ($p = 0.001$) more pronounced in DM1 subjects than in normal controls (DM1 = 646 ± 62 cm^3, normal controls = 724 ± 31 cm^3), whereas no differences were found between the two groups in the NWMV (DM1 = 725 ± 59, normal controls = 739 ± 43, $p = 0.5$).

In agreement with volumetric data, cortical-MTr values were significantly ($p = 0.006$) lower in DM1 patients than in normal controls (DM1 = 22.0 ± 1.2, normal controls = 23.1 ± 0.5), whereas this difference was not found in the WM-MTr (DM1 = 35.4 ± 0.9, normal controls = 35.6 ± 0.8; $p = 0.6$).

When the 4 DM1 patients with minimal WM lesions on conventional MRI were excluded, NCV and cortical-MTR decreases were still more evident in patients than in normal controls (NCV in DM1 = 663 ± 61 cm^3, NCV in normal controls = 724 ± 31 cm^3; cortical-MTr in DM1 = 22.3 ± 0.8, cortical-MTr in normal controls = 23.1 ± 0.5; $p < 0.05$ for both).

None of the quantitative MR indices correlated closely with patients' clinical scores and number of CTG repeats. However, a trend towards a correlation was found between disease duration and NCV ($r = -0.52$, $p = 0.1$) and a close relationship was

Table 2 Quantitative MR results in the DM1 patients

Patients	WM-LV	NBV	NCV	NWMV	WM-MTr	Cortical-MTr
1	-	1505	562	762	34.0	20.7
2	0.95	1561	664	704	34.7	22.7
3	-	1667	707	757	35.7	22.3
4	0.32	1568	528	866	33.9	18.9
5	0.57	1554	641	719	36.0	22.2
6	-	1568	679	681	36.4	22.0
7	0.08	1556	656	688	36.7	22.6
8	-	1532	615	728	36.2	23.0
9	-	1616	699	686	34.9	22.9
10	-	1606	717	661	35.7	22.6
Control mean		1685	724	739	35.6	23.1
Control SD		44	31	43	0.8	0.5

WM-LV = white matter lesion volume
NBV = normalized brain volume
NCV = normalized cortical volume
NWMV = normalized white matter volume
WM-MTr = magnetization transfer ratio in the white matter
Cortical-MTr = magnetization transfer ratio in the neocortex

found between disease duration and cortical-MTr ($r = -0.75$, $p = 0.01$) (see Figure 3). This correlation was still significant when data from patient 4 (an outlier in whom potential segmentation error cannot be excluded, see Table and Figure 3) were omitted from the analysis ($r = -0.60$, $p = 0.03$).

Discussion

A number of *in vivo* [1, 4, 9, 14, 16, 19, 26] and *ex vivo* [1, 27] studies have stressed the importance of WM pathology in DM1 and this has been interpreted as due to increases of interfascicular space, cellular infiltrates and breakdown of myelin sheaths [1, 27]. However, several studies also have shown that abnormalities can extend well beyond the focal areas of hyperintensity detected on conventional MRI [13, 28] and that diffuse brain atrophy can occur in patients with DM1 [2], with similar involvement of WM and GM [3]. In agreement with this, the importance in DM1 of a diffuse pathology that significantly involves the GM has been stressed by several neuropathological studies showing specific signs of neuronal damage such as neurofibrillar tangles and hyperphosphorylated tau proteins in the cerebral cortex [33, 37, 38].

By showing, with respect to normal controls, lower cortical-MTr and higher cortical atrophy in DM1 patients with no or minimal WM abnormalities on conventional MRI, the results presented here strongly support the hypothesis of the presence of neocortical pathology in DM1. The absence of significant differences between DM1 patients and normal controls in both WM-MTr and NWMV values further supports this hypothesis and suggests that cortical abnormalities may occur with a mechanism that is not related to that of focal WM lesion formation.

MT imaging of the brain is based on the interactions between the free water protons and protons attached to macromolecules [17]. Low MTr indicates a reduced capacity of the protons in the brain tissue matrix to exchange magnetization with the surrounding water protons, which seems to be strongly associated with the degree of tissue (matrix) damage

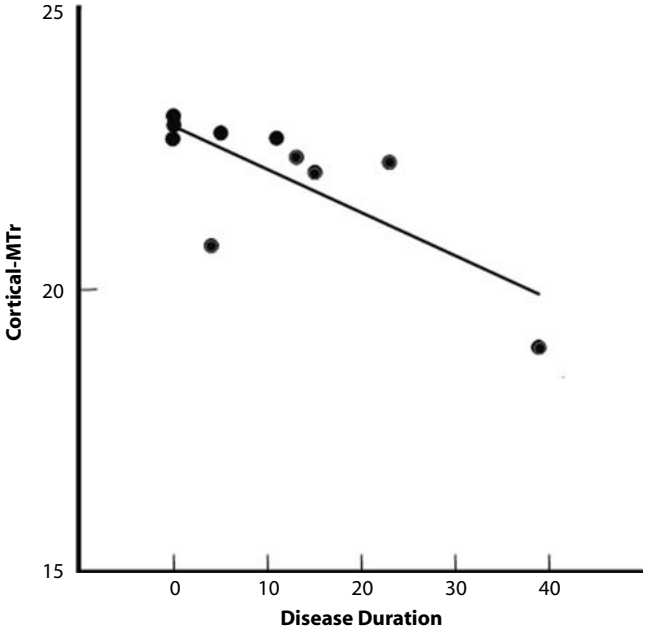

Fig. 3 Scatter plots illustrating the close relationship between cortical-MTr and disease duration in DM1 subjects (Spearman rank correlation = −0.75, p = 0.01)

[17, 30]. Several recent studies have demonstrated marked MTr reductions in lesional and normal-appearing tissues of a number of neurological disorders [5, 20, 21, 30, 36]. As these reductions have been interpreted as the expression of subtle microscopic pathology possibly occurring in both myelin and axons [32], the low cortical-MTr found in our patients is likely to reflect a diffuse underlying structural pathology occurring in the cortex of DM1 brains.

Several recent studies have indicated the quantitative assessment of brain atrophy as a reliable index of tissue damage in several neurological disorders [6, 10, 11, 29, 35]. Computerized methods to evaluate total and regional brain volumes allow estimations of changes that go well beyond visual inspection and are able to detect unrevealed early brain pathological changes [10, 35]. These changes are detected with higher sensitivity in isotropic voxels. In the present study, although MR images were non-isotropic, significant changes were selectively found in the neocortex of DM1 patients. Thus, the presence of significant NCV decreases in DM1 patients with apparently normal conventional MRI pattern adds to the low cortical-MTr in suggesting that diffuse cortical damage can be present in DM1 brains even when no changes can be detected at MRI visual assessment. While methodological insensitivity may have obscured some changes in NWMV, the results indicate that disease effects on NWMV are smaller, if not entirely absent, when compared with disease associated NCV reductions.

In general, in the present study, clinical and genetic indices did not correlate with MR metrics. Unfortunately, we were not able to assess the correlation between MR indices of cortical damage and the degree of patients' mental impairment as it was not possible to perform neuropsychological tests in all patients. Interestingly, however, disease duration showed a trend towards correlation with NCV measures and did correlate strongly with cortical-MTr values. This suggests that disease progression and increase in cortical damage may proceed in parallel. Longitudinal studies using these and other quantitative approaches to imaging analysis should be carried out to better clarify this aspect as well as the time-dependent nature of cortical changes and their progressive importance on cognition in DM1.

In conclusion, data reported in the present study show that cortical damage can be significant in DM1 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. Although these results need to be confirmed in a larger patient population, the notion that significant neocortical damage can be evident even in the absence of WM lesions and can proceed in parallel with disease duration suggests that a neocortical pathology, unrelated to WM lesion formation, occurs and is clinically relevant in the brains of patients with DM1. Whether this is due to an alteration of tau expression leading to a peculiar taupathy [37], to a toxic gain-of-function by mutant RNA [22] or to other unknown causes needs to be clarified.

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