WHITE MATTER AND CORTICAL ALTERATIONS IN MYOTONIC DYSTROPHY TYPE 1

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Introduction: Myotonic Dystrophy type 1 (DM1) is the most common form of adult-onset autosomal dominant muscular dystrophy[1], due to an expansion of a unstable CTG-repeat in the 3'-untranslated region of a gene located on chromosome 19q13.3 encoding DMPK protein (myotonic dystrophy protein kinase)[1]. The main clinical feature is myopathy, although CNS involvement has been demonstrated by clinical and neuroimaging studies[2,3]. We aimed to evaluate both white matter (WM), using Tract Based Spatial Statistics (TBSS), and cortical alterations, using both Cortical Thickness analysis (CT) and Voxel-based Morphometry (VBM) after white matter lesion load refilling.[4] We correlated TBSS, CT and VBM data with clinical and genetics severity.

Methods: 24 DM1 patients (age= 38.5±11.8 y, mean ± SD; 14 M), and 25 sex and age- matched healthy controls (38.5±11.3 y, 14 M) underwent a standardized brain MR protocol, including high resolution 3D FSPGR T1 and DTI (25 directions, b-value=900 mm^2s^{-1}) sequences on a 1.5T GE scanner. Disability and neuromuscular impairment using a validated scale[5], corrected Mini-Mental State Examination (MMSE), and triplets expansion were assessed in all patients. Patients' WM lesion load was calculated on FLAIR T2 images with the software Jim.
In order to perform comparisons between patients and controls and correlations with clinical variables, for TBSS and VBM analysis, a voxelwise General Linear Model (GLM) was applied by using nonparametric permutation methods, while for CT analysis a vertex-by-vertex GLM was performed accounting for multiple comparisons by Monte Carlo simulation. Age and sex were added for TBSS analysis as nuisance regressors, while age, sex and total intracranial volume (TIV) for VBM and CT analysis.

Results: WM lesions load (17. 2± 27.5 cm^3) correlated with age at evaluation (r = 0.644; p = 0.003) and MMSE score (r = -0.487; p = 0.48). TBSS showed a widespread WM FA values reduction and MD, AD and RD values increase in DM1 patients compared to controls with a direct correlation between DTI metrics and cognitive (MMSE), neuropsychological (NP area), motor (motricity and myotonia area) and genetic data (triplets) (Fig. 1a). Cortical thickness reduction in the bilateral parietal-occipital cortex (Fig. 1b) and diffuse voxel-based gray matter reduction in both cortical and subcortical areas were found (Fig. 1c).

White matter alterations (TBSS analysis)

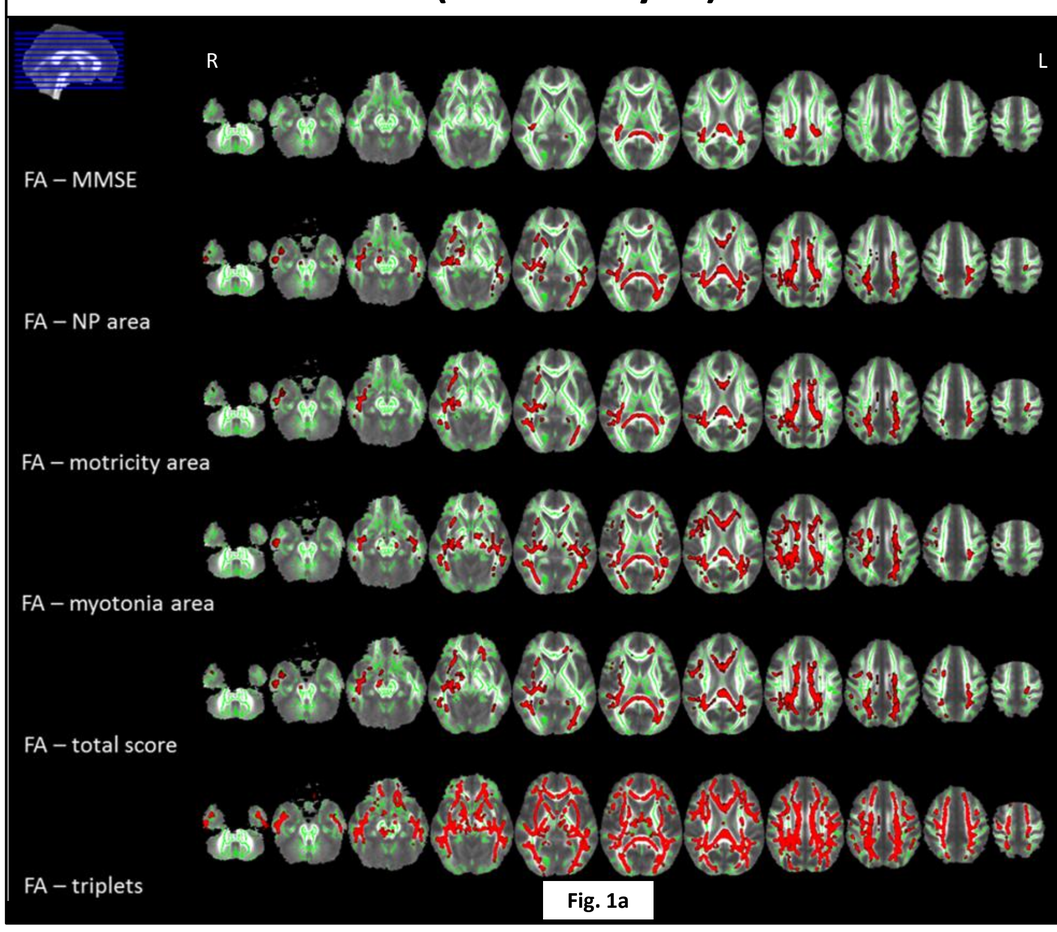

Fig. 1a

Cortical and subcortical alterations (CT and VBM analysis)

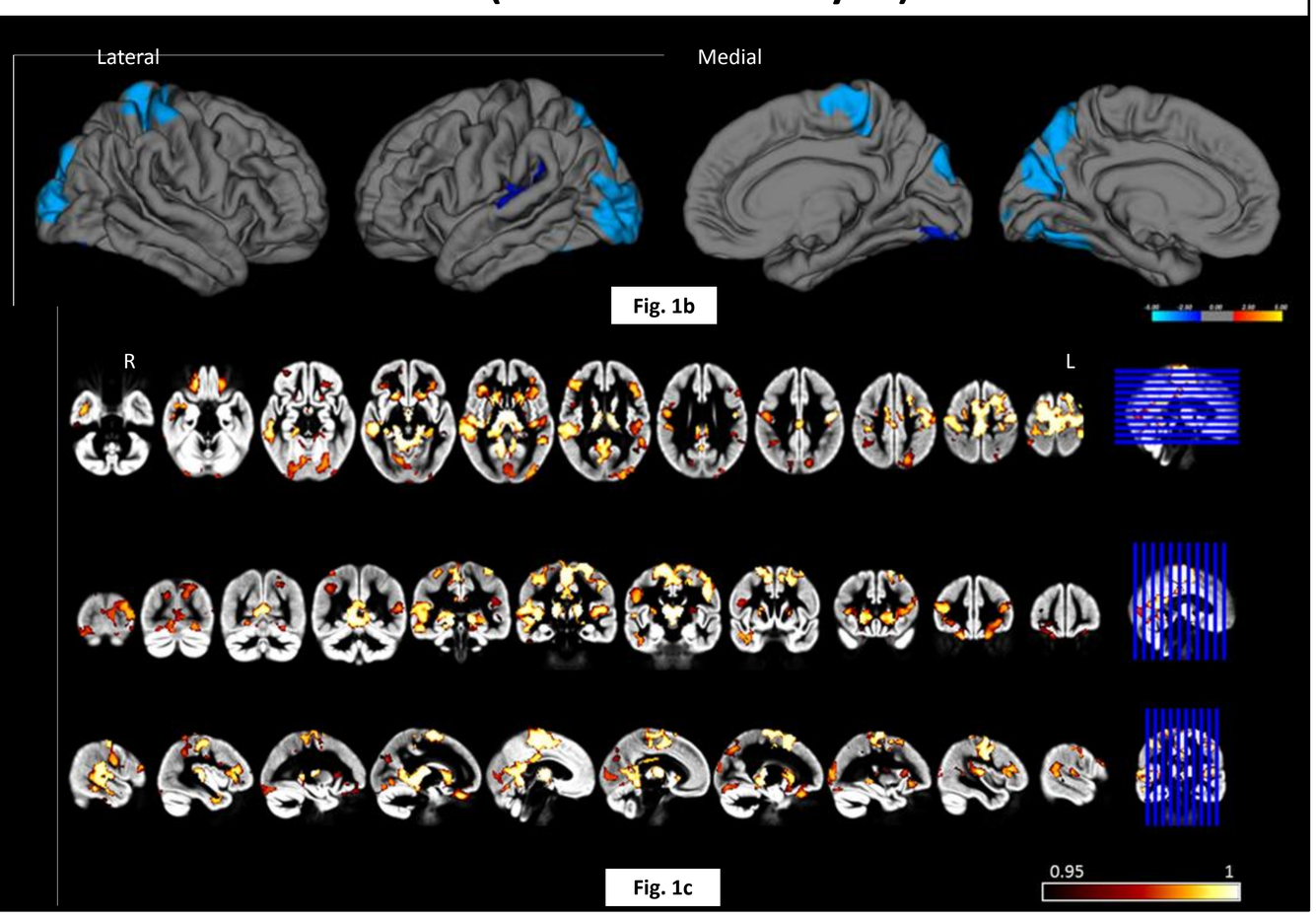

Fig. 1b

Fig. 1c

Fig.1a Tract-based spatial statistics (TBSS) significant correlation results (*red*) between FA values and clinical or genetic scores superimposed to mean FA and skeleton masks (*green*) and shown in radiological convention. Correlation between MMSE score and FA values were found in the splenium and the posterior part of the body of the corpus callosum (CC), posterior corona radiata and posterior thalamic radiations, **bilaterally????** and the right retrolenticular part of the internal capsule. FA values in the genu, body and splenium CC, in the supero-posterior corona radiata, in the posterior thalamic radiations, external capsule and superior longitudinal fasciculus **and????** were correlated to neuropsychological, motor, myotonia area score and with the total score[4].
A correlation between triplet expansion size and white matter DTI parameters, diffuse to all white matter tracts in supra- and infratentorial compartments was found *(p < 0.05, corrected).*

Fig.1b Group comparison results of **Cortical Thickness (CT)** analysis. Whole brain vertex-wise differences of CT between DM1 patients and healthy controls are displayed with -log10(p) values. Areas of grey matter thinning are overlaid on a reference grey matter surface; left hemisphere is shown on right and right hemisphere on left; lateral view on top and medial view at bottom. Compared to controls, DM1 patients presented a reduced CT in lateral-occipital cortex bilaterally, in the right precentral and in the left superior-parietal, superior-temporal and fusiform cortices (*p < 0.05, corrected)*.
No correlations between CT results and clinical/genetic variables were found.

Fig.1c Voxel-based morphometry (VBM) group comparison. Voxel-wise differences between DM1 patients and healthy controls are displayed with (1-p) values in red-to-white. Areas of grey matter atrophy are overlaid on the group grey matter template and shown in radiological convention. Compared to healthy controls, DM1 patients presented a bilateral significant reduction of gray matter quantity in subcortical regions such as thalamus, hippocampus, putamen and caudate, and in cingulate, frontal, parietal, occipital, insular and temporal cortices *(p < 0.05, corrected).*
No correlations between VBM results and clinical/genetic variables were found.

Conclusions

This multimodal MR study demonstrated diffuse white matter alterations in DM1 patients that correlated with cognitive performances, motor impairment and triplets expansion. Cortical thickness reduction was detected in the parietal-occipital cortex and grey matter volume loss in cortical (frontal, parietal, occipital, temporal, insular and cingulate cortices) and sub-cortical regions (hippocampus, thalamus, putamen and caudate nuclei).

References

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