NeuroImage: Clinical 11 (2016) 678–685

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Relationship of white and gray matter abnormalities to clinical and genetic features in myotonic dystrophy type 1

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ARTICLE INFO

Article history:
Received 23 November 2015
Received in revised form 20 April 2016
Accepted 28 April 2016
Available online 3 May 2016

Keywords:
myotonic dystrophy type 1
DTI
TBSS
VBM
cortical thickness

ABSTRACT

Background: Myotonic dystrophy type 1 (DM1) represents a multisystemic disorder in which diffuse brain white and gray matter alterations related to clinical and genetic features have been described. We aimed to evaluate in the brain of adult patients with DM1 (i) white and gray matter differences, including cortical-subcortical gray matter volume and cortical thickness and (ii) their correlation with clinical disability, global neuropsychological performance and triplet expansion.
Methods: We included 24 adult genetically-confirmed DM1 patients (14 males; age: 38.5 ± 11.8 years) and 25 age- and sex-matched healthy controls (14 males; age: 38.5 ± 11.3 years) who underwent an identical brain MR protocol including high-resolution 3D T1-weighted, axial T2 FLAIR and DTI sequences. All patients underwent an extensive clinical and neuropsychological evaluation. Voxel-wise analyses of white matter, performed by using Tract Based Spatial Statistics, and of gray matter, with Voxel-based Morphometry and Cortical Thickness, were carried out in order to test for differences between patients with DM1 and healthy controls ($p < 0.05$, corrected). The correlation between MRI measures and clinical-genetic features was also assessed.
Results: Patients with DM1 showed widespread abnormalities of all DTI parameters in the white matter, which were associated with reduced gray matter volume in all brain lobes and thinning in parieto-temporo-occipital cortices, albeit with less extensive cortical alterations when congenital cases were removed from the analyses. White matter alterations correlated with clinical disability, global cognitive performance and triplet expansions.
Conclusion: In patients with DM1, the combined smaller overall gray matter volume and white matter alterations seem to be the main morpho-structural substrates of CNS involvement in this condition. The correlation of white matter differences with both clinical and genetic findings lends support to this notion.

1. Introduction

Myotonic dystrophy type 1 (DM1), also known as Steinert's myotonic dystrophy, is the most frequent inherited adult dystrophic myopathy due to a nucleotide expansion (CTG) in the DMPK gene mapped on chromosome 19q13.3 (Udd and Krahe, 2012). Studies regarding the pathogenetic mechanism hypothesized an accumulation of CUG-CCUG-containing transcripts within cell nuclei as ribonuclear inclusions that provoke the deregulation of numerous RNA binding factors, leading to a dysregulation of alternative splicing of several genes encoding for proteins and channels fundamental for muscle and Central Nervous System (CNS) activity (Meola and Cardani, 2015). This hypothesis is also supported by neuropathological findings and indeed the presence of CUG-containing RNA has been reported in DM1 cortical-subcortical neurons (Meola and Cardani, 2015). Moreover, neurofibrillary degeneration with intraneuronal hyperphosphorilated Tau proteins has been reported in DM1 brain specimens (Sergeant et al., 2001; Meola and Cardani, 2015).

Disease onset is typically in the adult age and muscle weakness, myotonia, and cataracts represent the main clinical features, although the disease may frequently affect other organs and systems. In particular, CNS involvement, characterized by mood and personality alterations, cognitive impairment, sleep disturbances, is quite common during disease course (Udd and Krahe, 2012; Caillet-Boudin et al.,

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http://dx.doi.org/10.1016/j.nicl.2016.04.012

2014). Previous conventional studies of magnetic resonance imaging (MRI) showed diffuse brain alterations in DM1 patients such as lateral ventricle dilatation, cortical and subcortical gray matter atrophy and leukodystrophy, prevalent in the anterior temporal lobes (Caillet-Boudin et al., 2014).

In the last decade, advanced MRI studies demonstrated across brain a widespread white matter disruption and a multifocal gray matter volume loss by using various single MRI techniques, including Diffusion Tensor Imaging (DTI), and Voxel-Based Morphometry (VBM), with correlations found between corresponding quantitative MRI parameters and triplet expansion, neuropsychological tests and the severity of muscular involvement (Antonini et al., 2004; Giorgio et al., 2006; Ota et al., 2006; Weber et al., 2010; Minnerop et al., 2011; Wozniak et al., 2011; Franc et al., 2012; Wozniak et al., 2013; Caso et al., 2014; Wozniak et al., 2014; Serra et al., 2015; Schneider-Gold et al., 2015).

The aim of our study was to evaluate the extent of white and gray matter alterations in the brain of patients with DM1 compared to healthy controls by using multimodal voxel-wise methods, such as TBSS, VBM and vertex-based cortical thickness (CT) analysis, and therefore to highlight possible correlations of these quantitative MRI measures with clinical and genetic data.

2. Materials and methods

2.1. Subjects

We enrolled 24 genetically confirmed DM1 patients (14 males; age [mean ± SD]: 38.5 ± 11.8 years; age at onset: 22.3 ± 12.8 years, range: 0–53 years; disease duration: 16.2 ± 10.8 years, range: 1–36 years) and 25 age- and sex-matched healthy controls (14 males; age: 38.5 ± 11.3 years). Demographic and clinical features of patients and controls are reported in Table 1.

Patients were enrolled at the neuromuscular outpatients unit of the U.O. Clinica Neurologica, IRCCS Istituto delle Scienze Neurologiche di Bologna, by neurologists expert in neuromuscular disorders (RoL). Controls, matched to patients for age and sex, were selected among a sample of healthy volunteers, enrolled among University and Hospital workers and their relatives, that underwent brain MRI in order to obtain normative values for quantitative MRI parameters for clinical and research purposes.

Clinical diagnosis was genetically confirmed and CTG triplet expansion sizes were determined in all patients. Depending on the number of repeat expansions, patients were divided into classes E1 (mild phenotype, 50–150 CTG repeats), E2 (adult classical form, 150–1000 CTG repeats) or E3 (congenital disease, more than CTG 1000 repeats) (Contardi et al., 2012).

An extensive neurological examination and a disability scale for DM1 created by Contardi and colleagues, investigating neuropsychological (maximum score = 20), motor (maximum score = 35), myotonia (maximum score = 12) and daily life activity (maximum score = 15) areas were performed in all patients, with a total score ranging from 0 (normal) to 82 (worst condition) (Contardi et al., 2012).

Moreover, all patients underwent a neuropsychological assessment including Mini Mental State Examination (MMSE) (Folstein et al., 1975; Measso et al., 1993), Wechsler Adult Intelligence Scale (WAIS) 3rd edition (Wechsler, 1997) with Verbal Intelligence score (VIQ) and non-verbal performance score (PIQ), Brief Mental Deterioration Battery (BMDB) (Gallassi et al., 1986) including Rey's 15 word test, Immediate

Table 1
Demographic and clinical features of study sample.

	Myotonic dystrophy 1 patients (n = 24)	Controls (n = 25)	p
Age (years) (mean ± SD)	38.5 ± 11.8	38.5 ± 11.3	n.s.
Sex (M)	14	14	n.s.
Age at onset (years) [mean ± SD (range)]	22.3 ± 12.8 (0–53)		
Disease duration (years) [mean ± SD (range)]	16.2 ± 10.8 (1–36)		
Education (years) (mean ± SD)	10.0 ± 2.8		
CTG triplet expansion size category			
E1	4		
E2	13		
E3	7		
Clinical scale scores [median (range)]			
Neuropsychological area	3 (0–16)		
Motor area	11 (0−23)		
Myotonia area	7 (0−12)		
Daily-life activities area	2.5 (0–9)		
Total score	23 (1–59)		

Neuropsychological evaluation	N	Score (mean ± SD)	Normal values cut offs	% of patients with pathological scores
Corrected MMSE score	21	27.0 ± 2.7	>23.8 Measso et al. (1993)	9.5%
BMDB final result	20	1.6 ± 0.9	>0 Gallassi et al. (1986, 2002)	0%
- Rey's 15 word test (short term)	20	45.8 ± 8.9	>28.53 Carlesimo et al. (1996)	0%
- Rey's 15 word test (long term)	20	9.8 ± 2.3	>4.69 Carlesimo et al. (1996)	0%
- Immediate Visual Memory test	20	17.9 ± 3.0	>13.85 Carlesimo et al. (1996)	10.0%
- Barrage Test	20	11.0 ± 2.0	>9 Carlesimo et al. (1996)	10.0%
- Simple analogies	20	16.4 ± 2.6	>15.1 Gallassi et al. (1986, 2002)	20.0%
Total WAIS score	17	81.6 ± 20.6	> 70 Wechsler (1997)	29.4%
- Verbal Intelligence score	17	83.9 ± 18.8	>70 (Wechsler, 1997)	29.4%
- Non-verbal performance score	17	82.9 ± 19.8	>70 Wechsler (1997)	29.4%
Verbal Fluency test	20	33.4 ± 12.8	>17.35 Carlesimo et al. (1996)	10.0%
Stroop Test (reaction time - seconds)	20	30.4 ± 22.5	<36.91 Caffarra et al. (2002)	20.0%
Wisconsin Card Sorting Test	19			
- Corrected perseverative responses	19	23.8 ± 29.7	<42.60 Laiacona et al. (2000)	15.8%
- Corrected non-perseverative errors	19	18.3 ± 16.8	<29.90 Laiacona et al. (2000)	26.3%
- Categories completed	19	4.2 ± 2	No cut-off	
- Learning to learn	19	−0.6 ± 5.7	>0.00 Tarter (1973)	50.0%
- Corrected total score	19	67.4 ± 40.1	<90.50 Laiacona et al. (2000)	36.8%

Legend. SD: standard deviation; M: males; MMSE: Mini Mental State Examination; BMDB: Brief Mental Deterioration Battery; WAIS: Wechsler Adult Intelligence Scale – 3rd edition; WCST: Wisconsin Card Sorting Test.