Clinical variability in myotonic dystrophy type 1: a 5-categories disease classification fits clinical but not brain complexity

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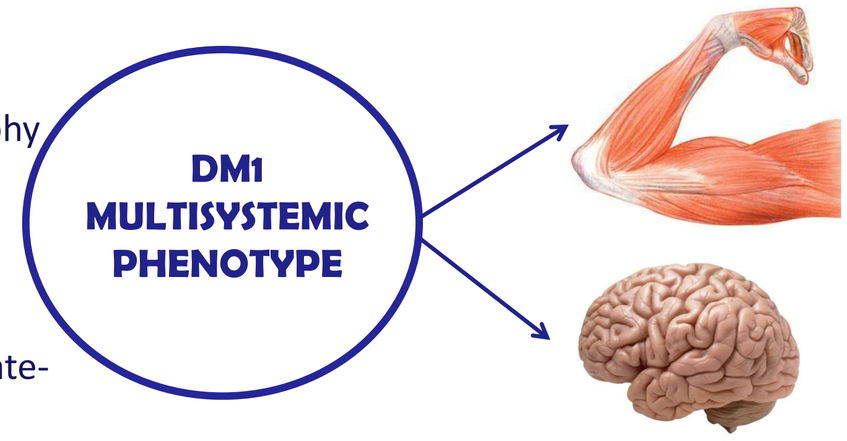
BACKGROUND

The clinical presentation of myotonic dystrophy type 1(DM1) is characterized by **high phenotypical variability**.
In literature, a classification into five main clinical categories according to age at onset (congenital, infantile, juvenile, adult-onset, late-onset), has been proposed (De Antonio et al.2016) but it is still under debate.



TRIAL READINESS

European Reference Network
for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

METHODS

We enrolled **73 DM1 patients** also included in the Italian Registry of Myotonic Dystrophies Project. Each patient was evaluated on the basis of a comprehensive clinical protocol and a **subgroup of 31 patients with cognitive impairment** also underwent neuropsychological evaluation and **brain MRI**.

MULTISYSTEMIC EVALUATION

- Neurological
- Cardiological
- Pneumological
- ORL
- Psychological
- Gastrointestinal
- Ocular
- Blood parameters

	[CTG]n		
	E1 (%)	E2 (%)	E3 (%)
Congenital	0	66.7	33.3
Infantile	0	75	25
Juvenile	12.5	75	12.5
Adult-onset	10.7	82.1	71
Late-onset	18.2	81.8	0

RESULTS

- Motor impairment assessment revealed high prevalence of cases with moderate disability. Multisystem involvement was characterized **mainly by cardiac, respiratory and central nervous system** involvement with 52.3% of patients carrying cardiac conduction defects, 50 % has respiratory involvement and 65,2 % showing cognitive impairment.
- We also observed that:

→ Sleepiness and dyslipidemia are more frequent in adult and late-onset forms compared to juvenile form.
→ Dysphagya is more frequent in adult form compared to juvenile and late-onset form
→Cataract and costipation/diarrhea are more frequent in late-onset form compared to juvenile and adult form

- Typical neuropsychological profile was characterized by visuo-spatial and executive dysfunction associated, in 51,2% of cases of adult-onset patients to disease unawareness, and was significantly related to cortical damage expressed by calculation of MRI brain parenchymal fraction. Tract-based spatial statistics results indicate involvement of normal appearance WM, beyond the signal changes detected with conventional MR imaging, this in turn associated to neuropsychological alterations. fMRI with self-awareness elicitation task showed, compared to normal controls, putative mid-line-structures correlates of disease unawareness.

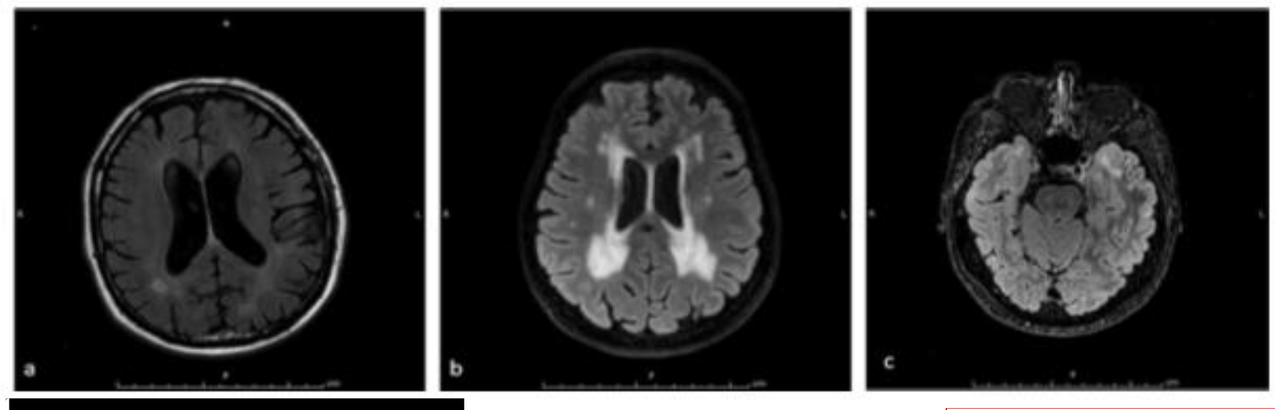
	Frequency	Sesso (M, F)	
Congenital	3 (4.1%)	3 (100%)	0 (0%)
Infantile	4 (5.5%)	3 (75%)	1 (25%)
Juvenile	16 (21.9%)	10 (62.5%)	6 (37.5%)
Adult-onset	28 (38.4)	17 (60.7%)	11 (39.3%)
Late-onset	22 (30.1)	12 (54.5%)	10 (45.5%)
Total	73 (100)	45 (61.6%)	28 (38.4%)

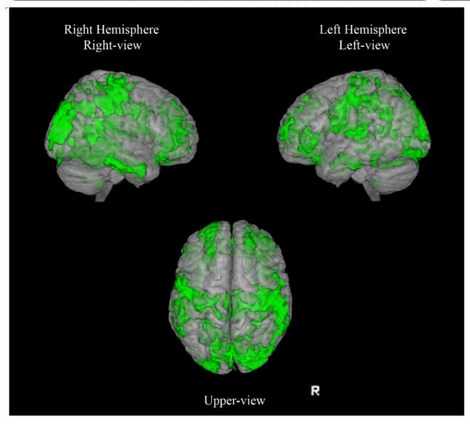
CTG → MIRS			
	N	Mean	SD
E1	9	2.33	1.118
E2	58	2.47	0.821
E3	6	3.83	0.753
Total	73	2.56	0.928

MRI imaging evaluation **failed to reveal distinctive features of the brain for each clinical form**, thus strengthening the statement that **multisystem and brain involvement do not fit the same disease severity time-elapsed trajectory in DM1.**

	HEART	RESPIRATORY	COGNITIVE	ESS	CATARACT	DYSLIPIDEMIA	ENDOCRINE SYSTEM	Constipation / Diarrhea
CONGENIT FORM (3)	1 (1,5%)	1 (1,6%)	3 (4,3%)	1 (1,4%)	0	0	0	1 (1,4%)
INFANTILE FORM (4)	2 (3%)	2 (3%)	4 (5,7%)	1 (1,4%)	0	1 (1,4%)	1 (1,4%)	1 (1,4%)
JUVANILE FORM (16)	7 (10,5%)	6 (9,7%)	12 (17,4%)	1 (1,4%)	3 (4,4%)	0	3 (4,3%)	3 (4,3%)
ADULT FORM (28)	13 (19,5%)	12 (19,4%)	15 (21,7%)	9 (13%)	11 (16,2)	7 (11,3%)	9 (13%)	8 (11,6%)
LATE-ONSET (22)	12 (17,9%)	10 (16,1)	11 (15,9%)	8 (11,6%)	14 (20,6%)	7 (11,3%)	8 (11,6%)	1 (1,4%)

Lesion load (LL%) assessment through ROI technique. a) parietal lobe subcortical WM hyperintensities; b) periventricular WM hyperintensities; c) insular WM hyperintensities





VBM revealed several clusters of reduced cortical GM in DM1 patients compared to healthy controls (TFCE $p<0.001$ corrected for multiple comparisons).
- BPF value in DM1 subjects was 0.760 ± 0.035.
- Atrophy was diffuse in both cerebral hemispheres and in particular in perirolandic, orbitofrontal, dorsolateral frontal, insular, temporo occipital, parietomesial, anterior and posterior cingulated areas.

DISCUSSION

Even if these data suggest that disrupted neuronal networks can underlie cognitive-behavioural dysfunctions in DM1, MRI evidences **failed to reveal distinctive features of brain involvement for each clinical form**, maybe because multisystem and brain involvement do not fit the same disease severity time-elapsed trajectory. The **fine achievement of peculiar brain phenotypic features in each clinical form** may be a key step for better comprehension of DM1 natural history as well as for patient stratification in clinical trials.