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Cognitive impairment in adult myotonic dystrophies: a longitudinal study

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Abstract The clinical relevance and extent of cognitive impairment in adult myotonic dystrophy type 1 (DM1) and 2 (DM2) is still unclear. The aim of this study was to determine whether previously reported cognitive abnormalities progress over time and if this occurs in DM2 as it does in DM1. Fifty-six patients with DM1 and 29 patients with DM2 were subjected to muscle strength assessment, and to a complete battery of neuropsychological tests. Repeated assessment was performed in 20 DM1 and 13 DM2 over time (DM1 mean follow-up: 7.3±2.7 years; DM2 mean follow-up: 9.5±2.4 years). Muscle strength and test scores for frontal lobe functions worsened significantly over time ($p<0.01$), in both DM1 and DM2. DM2 is a progressive muscle disorder, although less severe than DM1. In both DM1 and DM2 frontal cognitive impairment (attentional) worsens over time but does not extend to additional areas of cognition.

Key words Myotonic dystrophy type 1 • Myotonic dystrophy type 2 • Dysexecutive syndrome • Follow-up • Dementia

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Introduction

Multisystem involvement in myotonic dystrophies includes the brain [1, 2]. Neuropsychological tests [3–9], neuropsychiatric interviews [10], neuroimaging [11, 12], neuropathology [13–16] and biomolecular studies [17, 18] all support this statement. More specifically, there is growing evidence that cognitive impairment in adult myotonic dystrophies is characterised by an impairment in frontal lobe functions resulting in a dysexecutive syndrome [19], both in myotonic dystrophy type 1 (DM1) and in myotonic dystrophy type 2 (DM2), which is not correlated to the degree of cortical atrophy or white matter hyperintense lesions on brain MRI but rather to a reduced cerebral perfusion in the frontal and temporal lobes by H_2O PET scans [20]. Despite the growing body of evidence of cognitive involvement in these disorders [21–24], what is less clear is the clinical relevance of these abnormal findings, including neuropsychological test scores, white matter hyperintense lesions, cortical atrophy [3–9, 25, 26], neurofibrillary tangles, the characteristic tau protein pattern [14–16] or the toxicity of abnormal ribonuclear inclusions found in specific brain regions of these patients [17]. Whether these brain abnormalities culminate in a dementia syndrome is yet to be determined. The crucial point here is to determine whether brain involvement in adult myotonic dystrophies progresses over time. Whereas several reports describe follow-up studies of muscle strength deterioration [27] or progression of cardiac conduction arrhythmias [28], there are limited studies on the progression of cognitive decline [29, 30].

In this study we wish to determine whether previously reported visual-spatial impairment and dysexecutive frontal lobe syndrome progress over time in DM1 and DM2 and whether patients develop dementia. We also wish to determine whether there is a distinct rate of progression between patients with DM1 compared to DM2.

Materials and methods

Patient selection

Sixty-seven patients with genetically determined DM1 and 34 patients with genetically determined DM2 referred to the Neuromuscular Clinic of the University of Milan at the IRCCS Policlinico San Donato were considered in the initial study population. Congenital and juvenile myotonic dystrophy patients; patients with a positive medical history of stroke, diabetes, dementia, mental retardation, head trauma, alcohol or drug abuse; patients with MMSE scores below 24 and with a positive Epworth Sleep Scale (score ≥9); and patients with finger flexor strength weaker than 3+ were excluded from the study. The selected sample at the beginning of the study resulted in 56 patients with CTG expansion ranging between 500 and 700 repeats and 29 patients with CCTG expansion in the ZNF9 gene. All patients were ambulatory. Activity of daily living disability was defined as needing help in at least one of the following: walking across a small room, taking a shower, toileting, using the toilet, dressing and eating.

It was possible to administer the neuropsychological tests in 20 of 56 patients with DM1 and 13 of 29 patients with DM2 at the beginning of the study and in 14 of 20 patients with DM1 and 11 of 13 patients with DM2 on follow-up. A high proportion of patients included in the initial assessment (36 DM1=64% and 16 DM2=55%) refused neuropsychological follow-up because they claimed good cognitive performance (refusals, n=22 DM1 and 9 DM2); they died (5 DM1 patients, 2 due to cardiac arrest, 3 to respiratory insufficiency; 1 patient with DM2 due to cardiac arrest); they never returned to the Neuromuscular Clinic, for unknown reasons (unreachable, 7 DM1 and 5 DM2 patients); or they developed long finger flexor weakness below 3+ MRC range (2 DM1 and 1 DM2 patients) and were thus excluded from the study.

Patients were subjected to follow-up assessments without any *a priori* scheduling, according to the patients' availability and not on the basis of subjective neuropsychological worsening. In any case, the mean follow-up period was considered sufficient to detect both neuromuscular and neuropsychological potential progression of disease.

Muscle strength assessment

Muscle strength assessment was determined in all patients in the initial (56 DM1 and 29 DM2) and follow-up (20 DM1 and 13 DM2) study population. Assessment was made using the modified 5-point MRC scale (Medical Research Council, Aids to the examination of the peripheral nervous system, Memorandum 45. 1976, Pendragon House, London) testing 15 muscles on the right and left and considering a total score (Megascore) of 150 for normal muscle strength. All patients with long finger flexor weakness scoring less than 3+ MRC were excluded to make sure that distal muscle weakness did not impair performance in those neuropsychological tests requiring visual scanning associated with motor speed and agility (Divided Attention Test, Alertness and Trail Making Test). This criterion was applied at initial and at follow-up assessment to avoid bias due to potential worsening of muscle dexterity over time. To make sure that motor dexterity would not influence time-related scores alertness in attentional tasks, performance was calculated in trial making test (TMT) B-A, in addition to TMT A and B considered separately. TMT B-A reflects only cognitive resource employment because it is calculated subtracting the TMT A score (pure attentional task) from the TMT B score (visuo-spatial planning).

The same neurologists (VS and GM) evaluated muscle strength on initial and follow-up assessments. Repeated muscle strength testing and neuropsychological assessment were performed 2–10 years after initial assessment (mean 7.3±2.7 for DM1 and 9.5±2.4 for DM2) (Fig. 1).

Neuropsychological assessment

The neuropsychological test battery administered was the one previously described [19, 20]. It included a screening test for dementia (Mini-Mental State Examination, MMSE) and tests of nonverbal reasoning (Raven's Progressive Colored matrices, RPM), auditory language comprehension (Token test), verbal fluency with phonemic and semantic cues, verbal and spatial short-term memory (Digit Span forward and Spatial Span), verbal and spatial long-term memory (Story Recall and Rey Recall), constructional abilities (Rey's complex copy) , and attention and executive function (Trail Making A and B, Alertness and Divided Attention (TEA) and Tower of London Test (TLT)) [31]. The tests were administered by an experienced examiner in a quiet environment at the hospital site. Approximately 60–90 min were needed to administer the battery of tests required. Thirty-seven patients with DM1 and 17 patients with DM2 were subjected to the complete battery of neuropsychological tests on initial assessment. Follow-up was possible in 14 patients with DM1 and 11 patients with DM2.

The same neuropsychologist (MC) performed the tests on initial and final assessment.

Data analysis

In order to compare clinical and demographic characteristics at baseline between DM1 and DM2 patients we performed a Mann–Whitney *U*-test.

Non parametric intra-group comparisons for initial assessment were performed using the Mann–Whitney *U*-test for each variable considered (muscle strength and neuropsychological performances).

To assess follow-up evolution, nonparametric intra-group comparisons were employed (Wilcoxon test) for each variable considered.

ANCOVA adjusted for age, disease duration and follow-up years was used to assess differences between groups at initial

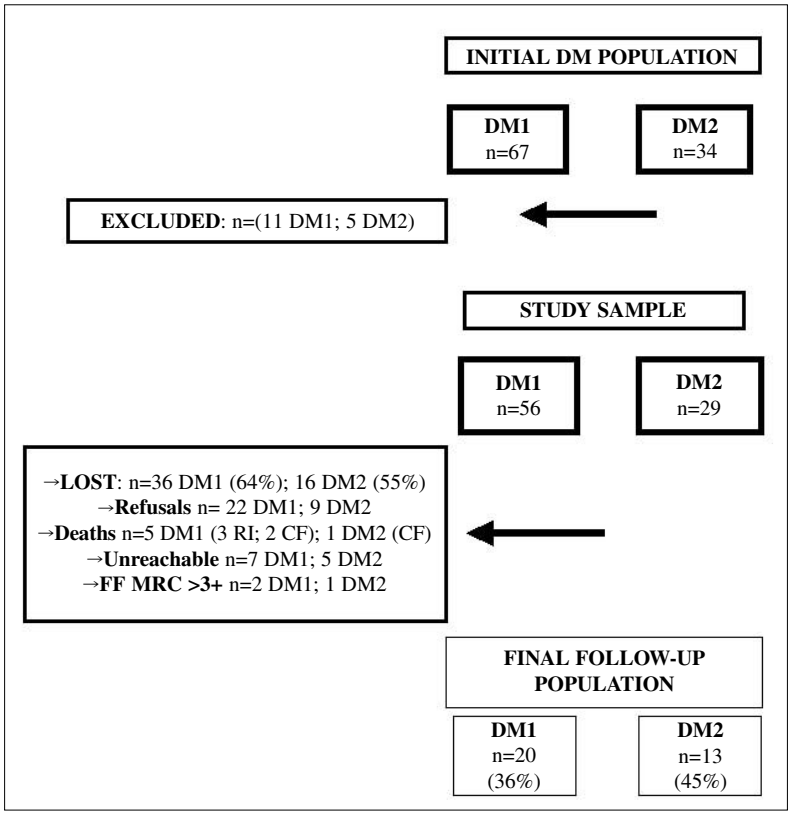

Fig. 1 Diagram illustrating initial and follow-up DM1 and DM2 study population. *CF*, cardiac failure; *RI*, respiratory insufficiency

assessment for muscle strength, in order to take into account the influence of these covariates.

Results are expressed as means and standard deviations, if not otherwise indicated. Significance was set when $p<0.05$.

Results

Results are expressed as means and standard deviations. Significance was set when $p<0.05$.

Table 1 indicates clinical characteristics, muscle strength and cognitive results in the initial study population. Figure 2 indicates initial and follow-up muscle strength assessment. Tables 2 and 3 indicate neuropsychological test results in the follow-up population.

No difference for disease duration and age between groups was found (for details see Table 1). No difference in activities of daily living (ADL) scores was observed over time. Patients were totally independent at baseline and remained totally independent at follow-up.

Muscle strength

Initial assessment

ANCOVA adjusted for age and mean disease duration did not show any significant difference ($p>0.05$) between the two groups (56 DM1 and 29 DM2) for muscle strength (Table 1).

Follow-up assessment (20 DM1 and 13 DM2)

Mean muscle strength in DM1 (MMRC) decreased significantly from 134.5 (±9.0) on initial examination to 124.6

Table 1 Clinical, neuromuscular and general intelligence profiles of 56 patients with DM1 (23 women and 33 men) and 29 patients with DM2 (15 women and 14 men) subjected to muscle strength assessment and neuropsychological tests on initial assessment

	DM1 (n=56)	DM2 (n=29)	*p*
Age	44.9±14.8	55.1±12.5	ns
Disease duration	18.3±13.5	17.9±12.6	ns
MMRC	134.2±13.6	136.9±15.2	ns
MMSE	27.3±1.4	27.6±1.1	ns

MMRC, megaMRC. In the DM1 population 45 patients had paternal transmission; in the DM2 population 15 patients had paternal transmission. See text for details

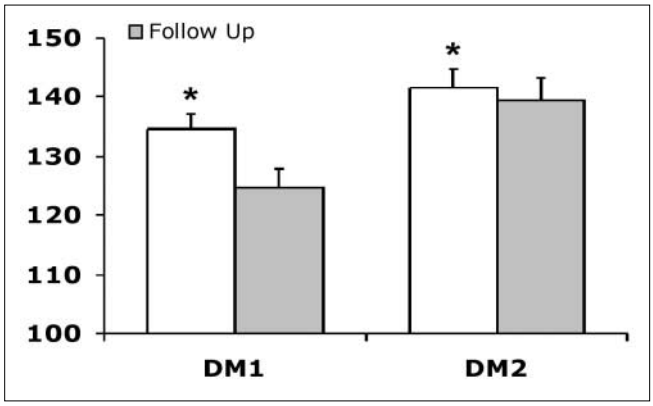

Fig. 2 Muscle strength at initial and follow-up examination in DM1 and DM2 study population. On the *y* axis: mean MMRC values; standard errors are indicated on the bar charts. MMRC significantly decreased over time for both groups (*), but muscle strength for DM1 patients decreased greater than DM2 (see text for further details)

(±14.0) on final assessment (Z=3.31, p<0.01). A significant decrease in muscle strength (MMRC) was also observed in DM2 over time (141.8±14.4 initially *vs.* 139.4±14.0 on final assessment, Z=2.93, p<0.01). We then calculated, for each patient, the MMRC decline per year dividing the total MMRC decline for the follow-up time. Average values of MMRC decline per year were compared between groups using the Mann–Whitney U-test. DM1 patients showed a significantly greater MMRC decline per year (–1.23±1.43) than DM2 patients (–0.26±0.19) (Z=–1.95, p=0.05).

We further performed an ANCOVA (adjusted for age, education, duration of disease, years of follow-up) on the amount of MMRC decrease as dependent variable (MMRC at follow-up minus initial MMRC) for DM1 and for DM2. Over time, decline in muscle strength for DM1 was significantly greater than for DM2 (F(1, 28)=7.93, p<0.05). See Figure 2 for details.

Neuropsychological evaluation

Initial assessment (37 DM1 and 17 DM2)

In agreement with our previous findings [19, 20], patients with DM1 and DM2 showed an impairment in tests measuring frontal function (alertness with and without warning signal, divided attention and the Tower of London Test) and showed an impairment of visual-spatial recall (Rey Recall) and visual-spatial construction (Rey copy). Nonparametric comparison showed no significant difference between DM1

Table 2 Initial and final neuropsychological test results in 14 DM1 patients of the follow-up study population

	Initial evaluation Raw score		Follow-up Raw score		*p* values
	Mean	SD	Mean	SD	
Screening test for dementia					
MMSE (cut-off: 24)	27.43	1.74	28.07	1.59	ns
Nonverbal reasoning					
CPM Raven (cut-off: 18)	27.77	4.3	25.50	5.63	ns
Language					
Token test (cut-off: 26.5)	35.83	0.39	32.93	1.71	<0.01[#]
Controlled association letters test (cut-off: 17)	34.64	11.58	32.21	11.04	ns
Controlled association categories test (cut-off: 25)	42.79	7.08	3936	8.26	ns
Memory					
Digit Span (cut-off: 3.75)	5.15	0.55	5.54	0.97	ns
Spatial Span (cut-off: 3.75)	4.92	0.76	4.86	1.03	ns
Story Recall (cut-off: 8)	10.46	3.26	15.46	3.27	<0.01[#]
Rey Recall figure (cut-off: 9.47)	12.69	7.43	15.14	7.97	ns
Constructional abilities					
Rey Copy figure (cut-off: 28.88)	29.29	8.7	28.57	8.59	ns
Attentional and executive functions					
Trial Making test A (cut-off: 93)	49.43	22.45	56.07	28.43	ns
Trial Making test B (cut-off: 282)	113.43	68.7	191.07	207.77	<0.01
Trial Making test B-A (cut-off: 186)	64.00	49.42	135.00	182.22	<0.01
Alertness without auditory warning signal (TEA) (ms)	228.77	21.64	264.89	37.95	<0.05
Alertness with auditory warning signal (TEA) (ms)	228.53	29.99	260.11	42.38	<0.05
Divided attention (TEA) (ms)	704.41	83.29	768.71	154.69	ns
Omission (divided attention) (TEA)	4.79	5.15	5.21	4.28	ns
Tower of London test (TOL) (%)	94.14	82.56	80.82	40.89	ns

[#]*p* value <0.05 but within normal range. Available cut-off values are indicated in brackets. For TEA and Tower of London Test where no cut-off is available, baseline and follow-up results are used to determine improvement or worsening

Table 3 Initial and final neuropsychological test results in 11 DM2 patients of the follow-up study population

	Initial evaluation Raw score		Follow-up Raw score		*p* values
	Mean	SD	Mean	SD	
Screening test for dementia					
MMSE (cut-off: 24)	28.36	1.80	29.00	1.00	ns
Nonverbal reasoning					
CPM Raven (cut-off: 18)	30.55	3.01	30.09	4.30	ns
Language					
Token test (cut-off: 26.5)	35.30	1.34	33.23	2.33	<0.05[#]
Controlled association letters test (cut-off: 17)	32.00	7.29	31.00	8.01	ns
Controlled association categories test (cut-off: 25)	39.73	7.95	38.64	8.15	ns
Memory					
Digit Span (cut-off: 3.75)	5.45	0.52	5.44	0.73	ns
Spatial Span (cut-off: 3.75)	4.64	0.67	5.45	0.93	<0.05[#]
Story Recall (cut-off: 8)	11.95	4.30	13.05	3.49	ns
Rey Recall figure (cut-off: 9.47)	15.18	7.28	15.36	6.07	ns
Constructional abilities					
Rey Copy figure (Cut-off: 28.88)	31.68	4.58	33.36	2.98	ns
Attentional and executive functions					
Trial Making test A (cut-off: 93)	54.60	22.40	52.00	19.41	ns
Trial Making test B (cut-off: 282)	107.90	30.93	178.50	71.04	<0.01
Trial Making test B-A (cut-off: 186)	53.30	17.52	126.50	61.51	<0.01
Alertness without auditory warning signal (TEA) (ms)	227.00	28.68	254.35	56.40	ns
Alertness with auditory warning signal (TEA) (ms)	218.61	13.54	249.80	89.05	ns
Divided attention (TEA) (ms)	704.72	79.16	753.90	46.78	ns
Omission (divided attention) (TEA)	3.56	2.07	4.00	2.11	ns
Tower of London test (TOL) (%)	73.22	45.06	45.53	27.49	ns

[#]*p* value <0.05 but within normal range. Available cut-off values are indicated in brackets. For TEA and Tower of London Test where no cut-off is available, baseline and follow-up results are used to determine improvement or worsening

and DM2 except for alertness with auditory warning signal (TEA). Reaction time was 246±40.5 ms for DM1 compared to 219.9±12.5 ms for DM2 (Z=–2.52, p<0.05). ANCOVA adjusted for age, education and disease duration confirmed the same results.

Follow-up assessment (14 DM1 and 11 DM2)

In DM1, nonparametric intra-group comparisons showed significant worsening over time for alertness without auditory warning signal (Z=2.40, p<0.05), alertness with auditory warning signal (Z=2.16, p<0.05), TMT B (Z=2.92, p<0.01) and TMT B-A (Z=3.11, p<0.01). A statistically significant worsening was also found for the Token Test (Z=3.48, p<0.01), while a significant improvement was found for Story recall (Z=2.94, p<0.01). Despite the changes described over time for these two tests [32], the scores were within normal ranges in initial and final assessments, and therefore clinically irrelevant. For details see Table 2.

In DM2 patients, a statistically significant worsening in test scores over time was found for: TMT B (Z=2.76, p<0.01) and TMT B-A (Z=2.76, p<0.01). A statistically significant worsening was also found for the Token test (Z=2.50, p<0.05) while a significant improvement in test scores was found for the spatial span test (Z=2.26, p<0.05). As in DM1, despite the changes described over time for the Token test, the score was within normal ranges in initial and final assessments, and therefore clinically irrelevant. For details see Table 3.

Discussion

Follow-up studies of muscle strength [27] and cardiac involvement [28] in DM1 have demonstrated the progression of the disease over time and have provided important clinical information on the most frequent causes of morbidity and mortality [27] in patients with this disorder. Regarding brain involvement, so far there has been no clear demonstration of the clinical relevance of the abnormal neuropsychological test scores and neuroimaging findings in patients with DM1. Longitudinal studies in cognitive function in adult DM1 are still limited [29, 30, 33] and controversial. The progressive decline in working capacity and

physical activity in patients with DM1 has in general been attributed to the progression of muscular symptoms and respiratory insufficiency [34, 35]. Very limited information, mainly on muscle strength and cardiac conduction disturbances, is as yet available as natural history data of patients with DM2 [19].

To our knowledge this is the first longitudinal study of patients with DM2 that provides natural history data on muscle and brain disease. The study is limited by the relatively small number of patients available for follow-up. We cannot rule out that a number of patients who refused follow-up did so because they felt they had cognitively deteriorated. If so, however, the remaining sample, although small, would underestimate cognitive decline observed over time in our sample population. We can also state the reasons for drop-out (18 out of 56 refusals for DM1: 32%, and 8 out of 29: 28% refusals for DM2). We emphasise the reluctance of these patients to perform regular out-patient follow-up neurology visits, in agreement with the behavioural abnormalities previously demonstrated in these patients [19, 24].

Although based on a small number of patients, our data confirm selective progressive frontal lobe function (attentional) involvement and demonstrate that, over time, there is no progression to additional areas of cognition, and there is no progressive interference in ADL as in patients with dementia associated with other medical conditions. Interestingly, the involvement of frontal, temporal and parietal cortical areas is in agreement with neuropathological and biomolecular data [16, 18], demonstrating expanded CUG and CCUG repeats by FISH in these same areas, suggesting that CNS symptoms in DM1 and DM2 are triggered by RNA inclusions, having a deleterious gain-of-function. In contrast to the extent and progression of CNS involvement in other expansion disorders like Huntington's disease, the clinical picture of myotonic dystrophies, although including specific brain areas, is predominantly one of muscle involvement. We may speculate that this may be related to the fact that in myotonic dystrophy patients, splicing abnormalities are less frequent and severe in the cerebral cortex than in skeletal muscle; in contrast a diffuse neuronal dysfunction related to the diffusion of polyglutamine proteins is observed in Huntington's disease. This less unexpectedly gives rise to the typical cognitive and behavioural abnormalities that characterise patients with Huntington's disease.

Our results also demonstrate that, over time, muscle strength progresses in both DM1 and in DM2, but with a faster rate in DM1 as compared to DM2, irrespective of age, disease duration and years of follow-up. The slower progression of muscle weakness in DM2 suggests a more favourable prognosis for patients with DM2, although caution is needed in interpreting these results because they are only representative of a small group of patients with DM2. There was no correlation between the neuropsychological test scores considered and the degree of muscle weakness.

Conclusions

We can conclude that adult myotonic dystrophies, and specifically DM2, like DM1, although to a minor degree, are progressive muscle disorders. From a cognitive point of view these disorders are also characterised by specific and progressive frontal cognitive impairment (attentional), without extension to additional areas of cognition. The awareness of cognitive and behavioural symptoms, although not progressive, may help to understand why patients with DM1 and DM2 may not function as well in their work-related and family-related activities as expected by their muscle disability. When muscle strength is impaired, as in patients with DM1 and DM2, the efficacy of a specific treatment whose target is muscle strength improvement, may be underestimated by the coexistence of a dysexecutive syndrome. We recommend that both aspects of muscle and CNS involvement should be considered when planning a clinical trial.

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