Outcome measures for CNS symptoms in adult-onset myotonic dystrophy: insights from a case-control study

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Background

- Myotonic dystrophy type 1 (DM1) is a complex, inherited multi-system condition
- Symptoms due to the effects of DM1 on the central nervous system (CNS), such as fatigue, excessive sleepiness and cognitive deficits, are commonly reported and greatly impact quality of life
- With the advent of clinical trials in DM1, there is a need to identify valid outcome measures for central symptoms
- We set out to evaluate cognitive tests and self-reported symptom questionnaires commonly used in DM1, with regard to their specificity for brain involvement and thus suitability for use as CNS outcome measures

Study protocol

Cohort
- 46 DM1-affected subjects recruited from outpatient review clinic
- 20 age – matched controls

Clinical assessment
- Participants completed a battery of cognitive assessments and self-reported symptom questionnaires, including those recommended by the Outcome Measures in Myotonic Dystrophy (OMMYD) working group

MRI brain

Diffuse brain atrophy and presence of white matter hyperintensities are hallmarks of DM1 on structural MRI. MRI brain sequences were therefore analysed with respect to the total volume of white matter lesions and global grey matter volume

Performance in complex cognitive tests is hampered by a basic speed limitation

- DM1 subjects gained lower scores on average in Stroop, trailmaking and block design tests compared with controls
- However, correction of scores in these complex tests for basic speed attenuated the effect sizes, especially in Stroop and trailmaking tests (Table 1)
- This limitation of basic speed may reflect slowing of simple processing, but could also be influenced by peripheral effects of DM1 (dysarthria and upper limb weakness respectively), thus undermining specificity of these tests for brain involvement

Cognitive test	Cohen's D effect size (DM1-affected vs. controls)	*p*
Stroop colour-word test	1.276	< 0.001
Adjusted Stroop score	0.636	0.017
Trailmaking test (number-letter switching)	1.000	0.001
Adjusted trailmaking score	0.105	0.268
Block design test	1.591	< 0.001
Adjusted block design score	1.458	< 0.001

Table 1: Difference between mean scores of DM1-affected participants and control participants (expressed as Cohen's D) in cognitive assessments. A correction step was applied to adjust for basic reading speed (Stroop test) or basic motor speed (trailmaking and block design tests), giving the adjusted score.

Low mood is strongly associated with self-reporting of central symptoms

- 30% of DM1-affected subjects met clinical threshold for at least mild depression (Beck Depression Inventory II score > 13)
- Depression scores correlated strongly with self-reported cognitive impairment (adj R^2 = 0.613) and impaired social performance (adj R^2 = 0.412), measured by the Myotonic Dystrophy Health Index

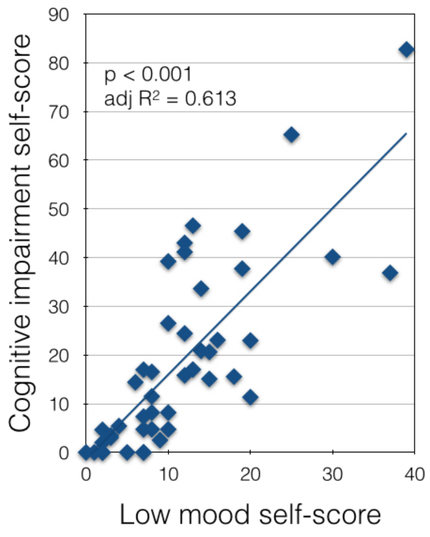

Figure 1: Low mood score (Beck Depression Inventory II) plotted against self-reported cognitive impairment (Myotonic Dystrophy Health Index cognitive impairment subscale).

Individuals with milder white matter change tend to report more cognitive problems

- There was a trend towards higher depression and cognitive impairment self-scores in patients with milder white matter change on MRI (Figure 2)
- Whether this reflects increased acceptance of symptoms or reduced insight in those with more severe brain changes is unclear
- However, executive symptoms rated by a relative, friend or carer (DEX questionnaire) showed a positive relationship with white matter lesion volume (p = 0.001, adj R^2 = 0.254)

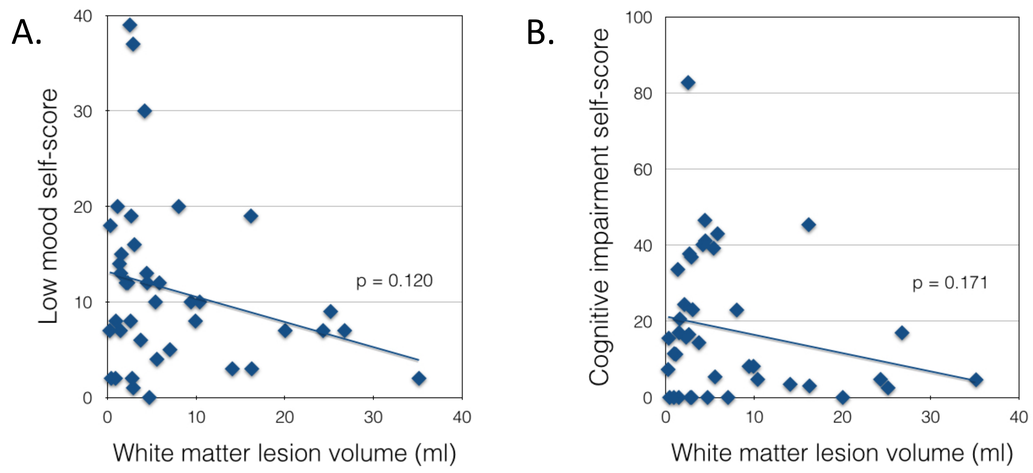

Figure 2: Scatterplots demonstrating trends towards increased self-rating of depression (A) and cognitive impairment (B) symptoms in DM1-subjects with milder white matter change on MRI.

Grey matter volume changes are influenced by age and gender

- Grey matter volume tended to be lower in male DM1-affected subjects compared with females of a similar age (Figure 3), despite the groups being well matched for genetic repeat size
- Inclusion of age and gender as co-factors considerably improved correlations of grey matter volume with several neuropsychology assessments (data available on request)
- Group comparison suggests atrophy of subcortical structures drives grey matter volume loss in DM1. This is compatible with the cognitive profile observed, including slowing of basic processing, and provides a plausible link to excessive sleepiness (Figure 4)

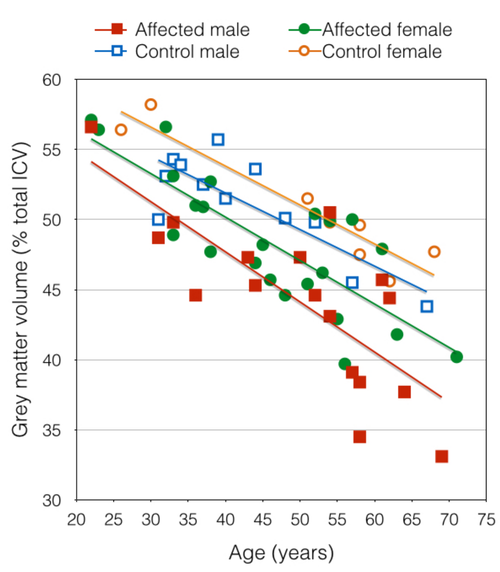

Figure 3: Grey matter volume plotted against age, demonstrating an apparent gender effect that was exaggerated in DM1-affected subjects

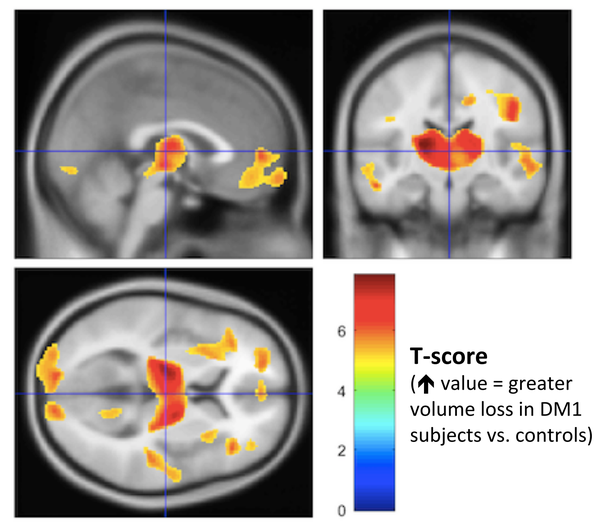

Figure 4: Group comparison of grey matter volume in DM1-affected versus control subjects using Statistical Parametric Mapping software (SPM12). Results demonstrate an excess of grey matter loss affecting subcortical regions in the DM1-affected group.

Conclusions

Identification of valid CNS outcome measures in DM1 is challenging, since performance in complex cognitive tasks may be affected by muscle weakness, and self-reported symptom scales are influenced by mood and insight. Large, longitudinal studies are required to identify and validate both imaging biomarkers and cognitive tests that are not influenced by muscle weakness.

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