Correlation between MRI cerebral white matter changes, muscle structure and/or muscle function: a pilot study.

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Abstract

Objective: Assess the correlation between muscle structure/function and global cerebral white matter abnormalities.

Methods: Classical DM1 subjects were compared to healthy age/sex matched controls. Disease duration (DD) and muscle impairment rating scale (MIRS) were obtained. A 3T MRI was used to acquire standardized limb images. Muscle volume was derived using T1 images. T2 relaxometry was used to assess the structural organization of biological water within the muscle. Fat fraction (FF) quantification was performed using 3 point Dixon acquisition. Established protocols using a custom force measurement apparatus were used to evaluate soleus force and fatigue. A custom designed neuromuscular control evaluation system (lower extremity tracking task; LETT) was used to perform a functional weight bearing movement assessment. Diffusion weighted imaging was used to measure global cerebral fractional anisotropy (FA). Low FA measures indicate abnormalities in white matter structure.

Results: Five DM1 subjects (34-58yo, x̄ = 43.8; BMI 24.4 ± 4.9; DD 1-22yrs, x̄ = 12.6; MIRS 1-4, x̄ = 2.2) were compared to controls (34-54yo, x̄ = 42.8; BMI 24.9 ± 4.8). DM1 subjects had lower soleus muscle volume, a higher FF, and higher T2 relaxation times (T2). Besides abnormalities in muscle force/fatigue measures of DM1 subjects, abnormalities were seen in LETT which is considered to be governed by both peripheral and central mechanisms. Higher T2 correlated with lower muscle force and higher CTG repeats. Compared to controls, DM1 subjects had a lower FA. A lower global brain FA correlated with diminished muscle volume, increased FF, higher T2, decreased muscle force and quantitative muscle function measures.

Conclusions: Correlations between global cerebral FA and muscle structure/function suggests a CNS role in DM1 neuromuscular dysfunction.

Introduction

Myotonic dystrophy type I (DM1) is a progressive, multisystem, autosomal dominant disorder resulting from a CTG repeat expansion in the dystrophia myotonica protein kinase (DMPK) gene. Although the primary symptoms of classical DM1 are myotonia and muscle weakness, patients may have reduced intelligence, progressive cognitive impairment, Cluster C personality traits, attention deficit (hyperactivity) disorder and/or mood disorders. Overall, DM1 pathophysiology is complex and the origin of cognitive, psychosocial and motor impairment remains unclear. Brain MRI findings vary among DM1 patients ranging from no abnormalities to marked brain atrophy with severe white matter involvement[1-2]. MRI studies, using various techniques have shown abnormal white matter integrity in multiple tracts, including motor pathways[2-7]. Diffusion tensor imaging has shown correlations between the level of white matter abnormality (i.e. corticospinal, corticostriatal, etc.) and disease duration,[7] clinical disability,[5] muscular impairment,[2,6] and motor performance[6]. A recent study using functional MRI showed DM1 subjects with grip myotonia had greater cerebral blood oxygen level signals during a grip task in high-order cortical motor control areas (supplementary motor, dorsal anterior cingulate)[8]. Collectively, these studies lend support for CNS involvement in DM1 motor function. More importantly, CNS abnormalities may contribute to DM1 neuromuscular dysfunction. The goal of this pilot study was to assess the correlation between global cerebral white matter abnormalities, muscle structure and muscle function.

Methods/Results

Control	Myotonic dystrophy		
Age	Age	DD	MIRS
52	58	1	1
54	54	9	1
39	38	21	2
35	35	22	3
34	34	10	4

Table 1. Age matched controls were used. CTG repeat size was ~50-450, DD 1-22 years, and impairment mild to severe.

DD: years since symptom onset
DM1: x̄ = 43.8yo; BMI 24.4 ± 4.9
Control: x̄ = 42.8yo; BMI 24.9 ± 4.8

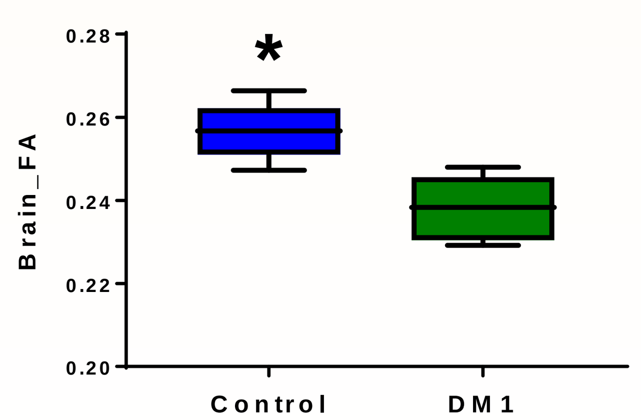

Figure 1: Brain MRI images were obtained using a Siemens 3T Trio scanner. FA measures generated by a previously reported standardized technique.[9] ***Global brain FA was lower in DM1 subjects compared to controls.*** Bars = SEM, *p = 0.004

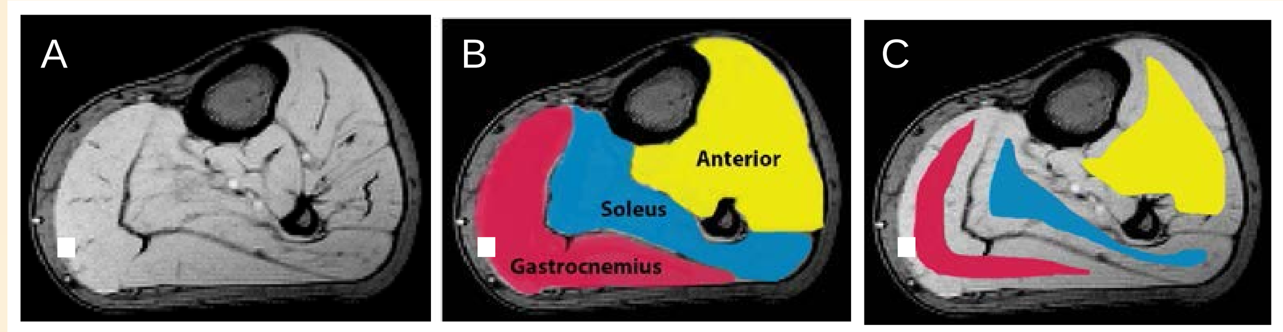

Figure 2a: Lower leg MRI was performed on Siemens 3T Trio scanner using an acquisition protocol previously reported[10]. MRI-based assessment included: T1 for volume measures, T2, and FF quantification with 3-point Dixon imaging. For muscle volume measures, T1 images (A) were used to trace the surface area of a standardized slice then multiplied by the slice thickness (7mm). B. Regions of interest (ROI). C. Eroded ROI were used for T2 measures.

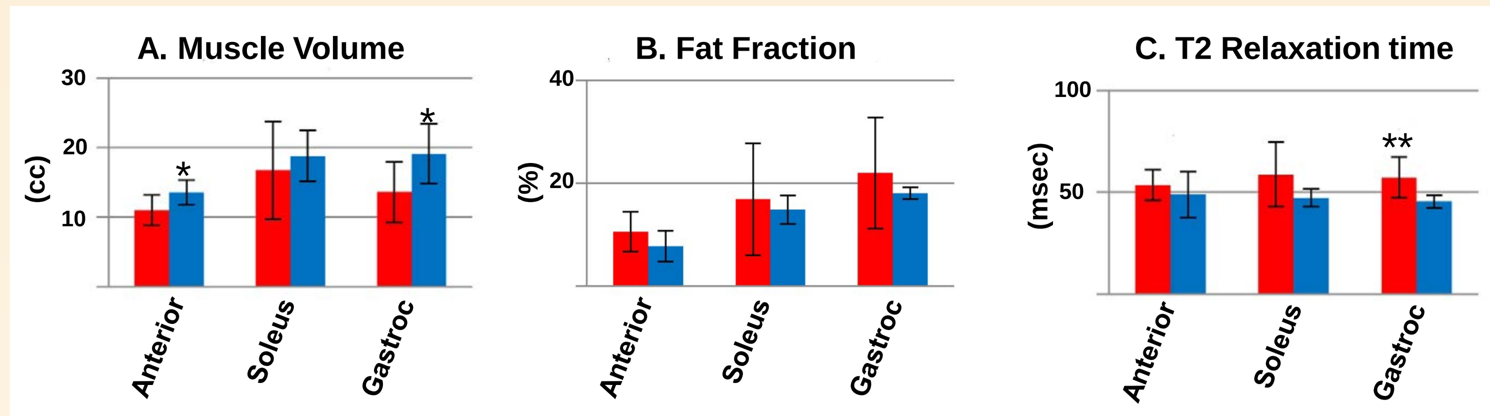

Figure 2b: ***DM1 patients** (red) **had lower muscle volume** (A), **higher FF** (B) **and higher T2** (C) **compared to controls** (blue).* Variability was likely attributed to mild (MIRS 1) versus severe (MIRS 4) impairment. Groups compared using ANOVA. Bars = SD. *p<0.07, **p<0.03

Table 2. Muscle structure vs brain FA**

	Ms Volume	Fat Fraction	T2
Anterior	0.657 (0.05)	-0.267 (0.48)	-0.466 (0.21)
Soleus	0.424 (0.26)	-0.326 (0.39)	-0.631 (0.07)
Gastroc	0.735 (0.02)	-0.301 (0.43)	-0.822 (0.01)

**Pearson partial correlation coefficient (p-value)

Table 2: This table represents the correlation between Brain FA and MRI leg measurements (muscle structure). ***Brain FA tended to correlate with lower muscle volumes and higher T2.*** It is important to highlight that these are correlations and do not prove causality. These measures may both be related to underlying DM1 pathology but not directly related to each other.

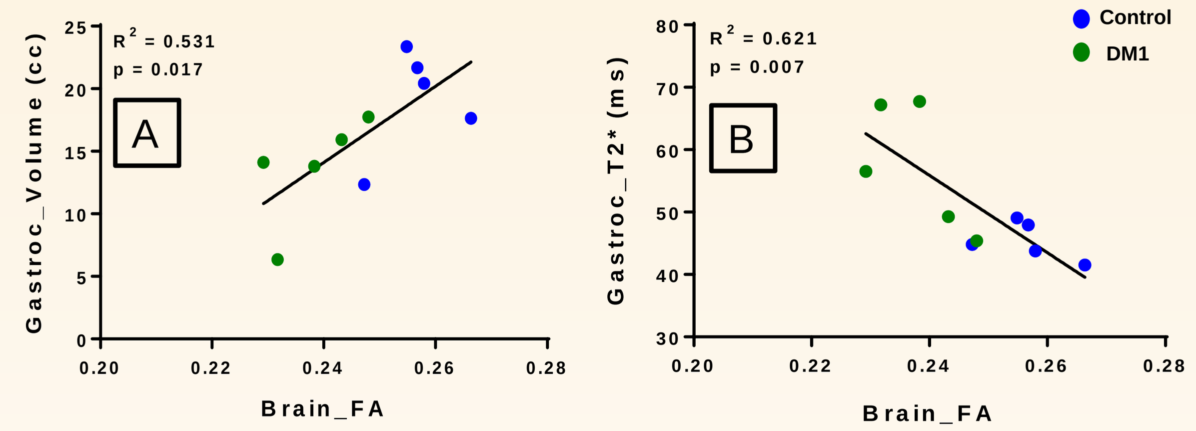

Figure 3a: Linear regression analysis comparing gastrocnemius muscle volume to global brain FA. ***Brain FA (greater white matter abnormality) highly correlates with lower muscle volume.***

Figure 3b: Linear regression analysis comparing gastrocnemius muscle T2 to global brain FA. ***Brain FA (greater white matter abnormality) highly correlates with higher T2 (greater muscle abnormality).***

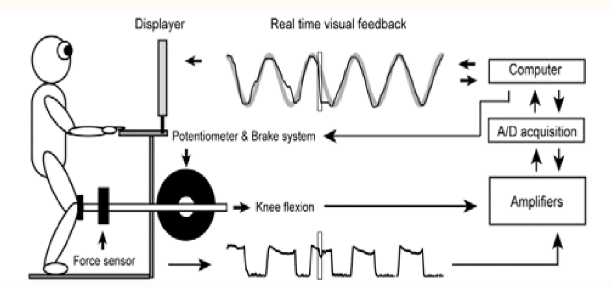

Figure 4. Using surface electromyography, soleus force, fatigue and a functional weight bearing movement assessing neuromuscular control were evaluated[11-13]. The schematic of neuromuscular control evaluation system above of a single leg squat bearing task (i.e. LETT) utilizes both centrally mediated feedforward control as well as peripheral nervous system feedback control. The mean coherence index depicts how subjects track a target signal with their volitionally generated target signal. The mean cycle error delineates the absolute error involved in performing the task.

Table 3a. Muscle Function and Physiology Measures	DM1 (n=5)	Control (n=3)	F (p)*
1. Doublet Force Pre: Peak force from 2 stimulation pulses (160Hz)	2.56	6.83	22.13 (0.005)
2. Doublet Force Post: Same as #1, but after 3 Hz fatigue protocol	2.70	7.71	21.16 (0.005)
3. Singlet Force Pre: Peak force from 1 stimulation pulse.	1.39	3.68	10.90 (0.02)
4. Singlet Force Post: Same as #3, but after 3 Hz fatigue protocol	1.46	4.37	15.16 (0.01)
5. Double Single Ratio: Ratio of doublet force/singlet force.	2.14	1.80	1.28 (0.30)
6. Double Single Ratio Post: Same as #5, but after 3 Hz fatigue protocol	2.32	1.61	3.56 (0.11)
7. Time-To-Peak Pre: Time in ms to peak force for the singlet	0.177	0.186	0.79 (0.41)
8. Time-To-Peak Post: Same as #7, but after 3 Hz fatigue protocol	0.178	0.179	0.03 (0.87)
9. Maximum Force 3Hz: Peak force during 3 Hz stimulation	1.72	4.61	7.36 (0.04)
10. Final Force 3Hz: Final force during 3 Hz stimulation.	1.46	4.05	9.77 (0.02)
11. Fatigue Index: Final force of 3 Hz protocol/Peak force.	0.796	0.919	20.78(0.005)
Table 3b. Single Leg Squat Weight Bearing Task (LETT) (Figure 4)			
1. Mean Coherence: X-correlation of target and user err. during 1 leg squat.	0.362	0.777	8.3 (0.02)
2 Mean Cycle AE: Absolute Err associated with performing 1 leg squat.	0.471	0.192	11.13 (0.02)

*ANCOVA controlling for Age. X = cross, Err = error

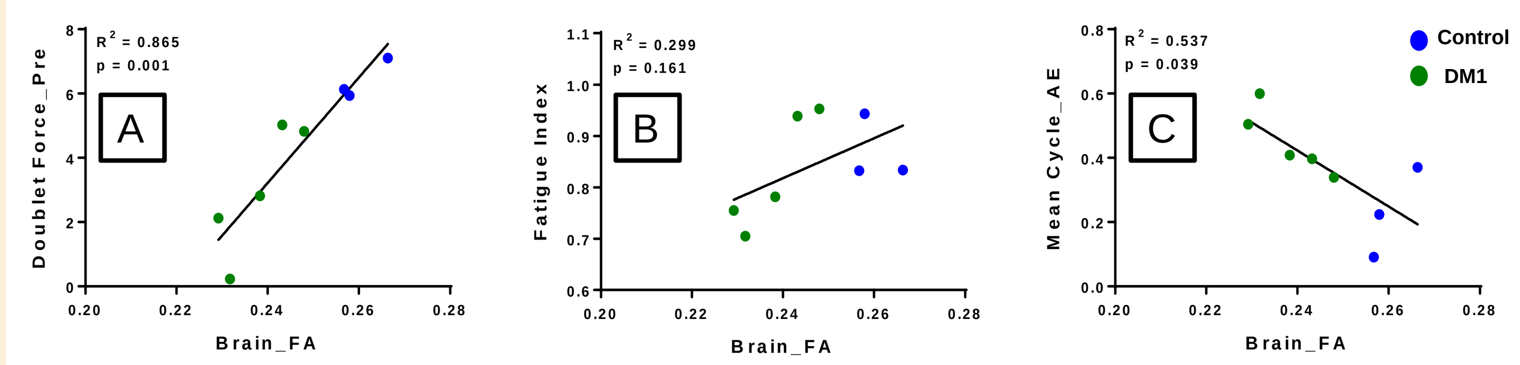

Figure 5. Linear regression analysis comparing brain FA to muscle functional measurements. ***Brain FA highly correlates with both force*** (A) ***and error rate in the lower extremity tracking task*** (C). Lower Brain FA (higher white matter abnormality) correlates with lower muscle force and higher error rate.

Conclusions

Consistent with previous studies[3-7], DM1 brain FA was significantly lower than controls indicating global abnormalities in cerebral white matter. Overall, DM1 subjects had lower calf muscle volume, higher FF and higher T2. These were large effect sizes in a small sample (n=5) with some measures reaching significance, thus supporting sensitivity to changes from DM1 pathology with MRI lower leg imaging. With muscle function/physiology testing, DM1 subjects had lower force, increased fatigue, and increased error when performing the LETT which is governed by both peripheral and central mechanisms. Brain FA correlated with many measures in this pilot study. Low brain FA was associated with lower muscle volume, higher T2, lower force, increased fatigue, and increased error when performing the LETT. Although it is important to highlight that these correlations do not prove causality, they suggest the CNS may contribute to DM1 neuromuscular dysfunction.

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