

Brain and skeletal muscle MRS study in patients with myotonic dystrophy type 1

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Introduction

Myotonic dystrophy type 1 (DM1) is a genetic disorder caused by an abnormal CTG expansion on chromosome 19q13.3, affecting central nervous system, skeletal muscle, heart and endocrine system.¹ Previous brain studies have showed cortical atrophy and white matter (WM) alterations, changes in cerebral metabolites, decreased glucose metabolism, and reduced blood flow.² An impaired energy metabolism of skeletal muscle was demonstrated using ³¹P-MRS.² We evaluated 14 DM1 patients in order to evaluate brain and skeletal muscle bioenergetics in this disorder.

Methods

We evaluated 14 DM1 patients (9 males, age range: 22 to 71 yrs, mean: 39; disease duration: range 4-36 yrs, mean: 15), stratified in 3 groups related to the increasing severity of molecular alteration: E1 (n=4 pts), E2 (n=7), E3 (n=3).¹ The study was carried out in a 1.5T GE Signa Horizon LX scanner. Single voxel MRS was performed using the PRESS sequence. In order to maximize the detection of lactate (Lac), a volume of interest (VOI) was selected in the lateral ventricles to include mostly the CSF (TE= 288 ms, TR= 1500 ms, NEX= 384) (Fig. 1).^{3,4} Suppressed water spectra were pre-processed with Gaussian filtering of 2 Hz followed by exponential filtering of -1Hz, and Lac fitted by the time domain semi-parametric algorithm QUEST.⁵ The amount of Lac was assessed using unsuppressed water signal as an internal standard. ³¹P spectra were acquired at rest (TR= 5s, 128-scan spectrum), during an aerobic incremental exercise of plantar flexion (12-scan spectra), and the following recovery (32 two-scan spectra).^{3,4,6} Spectra were processed by a time-domain fitting routine AMARES/MRUI (<http://carbon.uab.es/mrui>) and bioenergetic parameters were calculated as previously reported.^{3,4,6} 14 sex and age-matched healthy controls were also studied. Data are presented as mean ± SD. Informed consent was obtained from all participants to the study.

Statistical significance, determined by the Student *t* test for unpaired data, was taken as *p*<0.05.

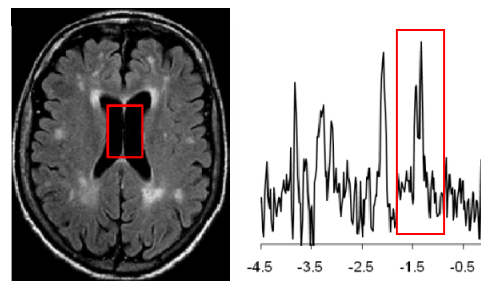


Figure 1: Flair axial image showing the volume of acquisition from lateral ventricles and the corresponding spectrum with high Lac level (Case 3).

#	Age	Disease duration	CTG Expansion	Lac/w
1	43	28	E3	1.93
2	71	36	E1	1.76
3	45	33	E3	1.06
4	34	4	E1	0.88

Table 1: Genetic and clinical characteristics in the 4 DM1 pts with high brain lactate values. All patients were male with a multi-systemic involvement.

Lac/W= Lactate/water

Group	Rest			Exercise*			Recovery
	pH	PCr/Pi	PCr/(PCr+Pi)	Duration (min)	pH	PCr/(PCr+Pi)	TC PCr (sec)
DM1 (n=14)	7.06±0.04	5.24±2.24	0.87±0.02	1.8±1.4	6.96±0.15	0.21±0.10	45±24
Controls (n=14)	7.03±0.02	7.09±1.04	0.81±0.11	4.9±1.4	6.89±0.08	0.25±0.10	22±6
p	0.038	0.012	0.044	<0.001	0.158	0.399	0.003

Table 2: ³¹P-MRS findings in patients and control subjects at rest, at the end of exercise and during post-exercise recovery. PCr = phosphocreatine; Pi = inorganic phosphate; TC = time constant of post-exercise phosphocreatine resynthesis. * Ten patients performed the exercise.

Results

Brain MRI showed the typical WM changes in 11/14 pts. A pathological increase in lactate content was detected in the lateral ventricles in 4/14 patients (Table 1). Skeletal muscle ³¹P-MRS showed increased pH, reduced PCr/Pi, and PCr/(PCr+Pi) in patients at rest indicating reduced energy reserve, while patients reached the same degree of phosphocreatine consumption and acidification at the end of the exercise but with shorter exercise duration. The rate of mitochondrial ATP synthesis measured by the assessment of time constant of post-exercise phosphocreatine resynthesis was reduced in DM 1 patients (Table 2).

Discussion

Brain ¹H-MRS showed an increase of ventricular lactate, undetectable in healthy subjects at 1.5 T, in about 30% of our DM1 patients, demonstrating an impairment of energy metabolism, as typically found in mitochondrial diseases.⁴ Moreover, the current ³¹P-MRS study has demonstrated severe alterations in skeletal muscle bioenergetics both at rest and during exercise, consistent with previous studies.² DM1 is the most common form of adult-onset muscular dystrophy, characterized by a progressive multisystem involvement, motor and cognitive function impairment, without any effective therapy.² Our data support the hypothesis of a pathogenic role of a generalized oxidative phosphorylation deficit in DM and suggest the development of therapeutic strategies targeted to metabolic levels to overcome the mitochondrial dysfunction.

References

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