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MRI/MRS evaluation of a female carrier of Duchenne muscular dystrophy

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Abstract

The purpose of this study was to evaluate skeletal muscle composition of lower extremity muscles in a manifesting female carrier of Duchenne muscular dystrophy (MFC_{DMD}) using magnetic resonance imaging (MRI) and spectroscopy (MRS). MRI/MRS was performed on the lower extremities and heart of a MFC_{DMD} (47 years, 51 kg) on four occasions within 21 months and in a control subject. Heterogeneity and asymmetry among muscles in the MFC_{DMD} was observed in lipid fraction and mean transverse relaxation time (T_2) of lower extremity muscles with some muscles presenting as unaffected (e.g., rectus femoris) and others showing substantial deterioration and lipid infiltration (e.g., vasti muscles). There was an association of abnormal MRI findings and strength and motor function. Over the 21 months a small decrease in CSA_{max} and increase in lipid fraction and T_2 was observed in the MFC_{DMD} in some muscles. In summary, this MFC_{DMD} revealed significant imaging evidence of pathologic heterogeneity among muscles. Furthermore, this study shows the feasibility of combining various quantitative MRI and MRS approaches to monitor skeletal muscle involvement.
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Keywords: Female carrier; Duchenne muscular dystrophy; Magnetic resonance imaging; Magnetic resonance spectroscopy; Skeletal muscle; Biomarker

1. Introduction

Duchenne muscular dystrophy (DMD) is a genetic disease that is caused by mutations in the dystrophin gene [1]. DMD has a prevalence of 1 in 3600–6000 male births, and is characterized by progressive muscle weakness, deteriorating functional capabilities, loss of independence, and early death [2]. Although DMD is an X-linked recessive

Abbreviations: AL, adductor longus; AM, adductor magnus; BFl, biceps femoris-long head; BFs, biceps femoris-short head; Con, control; CSA_{max}, maximal cross sectional area; CSI, chemical shift imaging; DMD, Duchenne muscular dystrophy; EDL, extensor digitorum longus; GE, gradient echo; Gra, gracilis; ^1H, hydrogen; ^1H_2O, water; LG, lateral gastrocnemius; m, meter; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MG, medial gastrocnemius; N m, newton meter; NNLS, non-negative least squares; Per, peroneas longus and brevis; Rt, right; RF, rectus femoris; Sar, sartorius; SM, semimembranosus; Sol, soleus; SPIR, spectral presaturation by inversion recovery; ST, semitendinosis; T_1, spin lattice relaxation time; T_2, transverse relaxation time; TA, tibialis anterior; TE, echo time; TP, tibialis posterior; TR, repetition time; VI, vastus intermedius; VL, vastus lateralis; VM, vastus medialis

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disease, it is not uncommon for female carriers of DMD to report symptoms, including muscle pain [3], cramping [4], weakness [4] and cardiac dysfunction [5,6]. Hoogerwaard et al. [4] reported 22% of female carriers manifested symptoms, with 19% demonstrating muscle weakness measured by handgrip strength and manual muscle testing and 8% presenting with dilated cardiomyopathy. A similar prevalence of females with symptoms was observed by Grain et al. [14], with 12% presenting with muscle weakness and 7% displaying cardiomyopathies. Onset of symptoms typically occur in early adulthood but in some cases have been reported in children [7,8]. Muscle weakness of the proximal muscles, such as the shoulder and pelvic girdle musculature, is common and usually presents in an asymmetrical manner [4]. The specific muscles affected are variable [4], with a range of severity from no muscle weakness to being wheelchair bound [7].

The signs and symptoms of a manifesting female carrier of Duchenne muscular dystrophy (MFC_{DMD}) have been suggested to be due to X-autosomal translocations leading to skewed X-inactivation of the normal dystrophin gene [9]. Alternatively, there may be impaired production of the dystrophin protein due to other, still unknown, genetic factors altering the protein levels [10]. A mosaic pattern of dystrophin-positive and dystrophin-negative fibers has previously been reported in MFC_{DMD} [11], and elevated levels of creatine kinase are commonly observed [12].

Overall, skeletal muscle involvement in MFC_{DMD} appears to be variable among individuals and muscles. Previous studies have mainly utilized self-reports [13], manual muscle testing [14], hand-held dynamometry strength tests [4], and muscle biopsies of single muscles [15]. Also, magnetic resonance imaging (MRI) has been used to provide a qualitative assessment of thigh muscles [16] and to examine proton spin lattice relaxation time (T_1) in female carriers at a low magnetic field strength [17]. In that study T_1 was elevated in the gluteals, vastus lateralis (VL), and gastrocnemius of MFC_{DMD} relative to controls, and this was attributed to an increase in edema [17]. However, in general, the use of MR to evaluate skeletal muscles of MFC_{DMD} has been limited.

A more comprehensive assessment of numerous muscles in the legs and thighs of MFC_{DMD} could provide additional insight regarding this population. Therefore, the purpose of this study was to evaluate a MFC_{DMD} using MRI and magnetic resonance spectroscopy (MRS) to examine structure and composition of multiple muscle groups of the lower extremities, as related to functional abilities and bilateral lower extremity strength, and to follow progression of lower extremity MRI measures over 21 months.

2. Methods

A MFC_{DMD} (47 years, 51 kg, 161.5 cm) who reported symptoms of muscular weakness and a female control subject (Con) of similar age and body size (45 years, 50 kg, 158.0 cm) volunteered to participate in this study. The Con was not involved in any sport specific training. The study was approved by the University of Florida Institutional Review Board and an informed written consent was obtained from the subjects prior to participation in the study.

2.1. Subject history

The MFC_{DMD} reported that she first noticed lower extremity weakness approximately 10 years prior to the initial time point, and that at first the weakness was most prominent in the right thigh/quads region. She was able to perform recreational activities, such as skiing, into her 30s. She reported that her left anterior leg muscles were increasingly becoming weak, and shortly prior to her final testing session received a prescription for an ankle foot orthosis to address foot drop, which became more evident with fatigue. Her medications included deflazacort (6 mg/day) and calcium supplements (500 mg/day) during the study. Her son has typical features of DMD; both have the same dystrophin mutation caused by a premature termination codon at exon 61 (9100C>T, R3034X).

Longitudinal MRI/MRS measures were acquired on the lower extremity muscles at three time points over 21 months and in the heart on one occasion. The right lower extremity was studied at baseline (T0), 9 months (T9), and at 21 months (T21). The cardiac scan was performed at 13 months (T13) and the left lower extremity was scanned at T21. Strength testing of the lower extremities and functional testing was also performed at T21. MRI and MRS were performed on the right lower extremity of the Con at one time point.

2.1.1. MR data acquisition

MR scans were performed using a 3T Philips Achieva system (Philips Medical Systems, R2.6.3). Initially, the subjects were placed supine in the bore of the magnet with the leg secured using foam padding and weighted rice bags. An 8-channel SENSE volume knee coil (Invivo corp.) was used for the lower leg and a 2-channel FLEX surface coil (Invivo corp.) was used for the thigh.

Lower extremity skeletal muscles were evaluated using T_1-weighted 3-D gradient echo (GE) images with spectral presaturation by inversion recovery (SPIR) fat suppression (lower leg: FOV $120 \times 120 \times 146$ mm, TR 17 ms, TE 1.9 ms, and 20° flip angle; upper leg: FOV $170 \times 170 \times 146$ mm, TR 24 ms, TE 1.8 ms, 20° flip angle) and without fat suppression (lower leg: FOV $120 \times 120 \times 146$ mm^3, TR 4.9 ms, TE 1.9 ms, and 20° flip angle; upper leg: FOV $170 \times 170 \times 146$ mm^3, TR 6.1 ms, TE 1.4 ms, and 20° flip angle). Three-point (3Pt) Dixon images were acquired on both the lower leg and thigh (25 axial slices, TR 430 ms, 20° flip angle) and T_2-weighted SE images (18 axial slices, TR 3 s, 5 TE's: 20–100 ms) were acquired on the lower leg. Also, a ^{1}H-MRS scan was performed at each time point to test the feasibility of these measures; these measures were