Combined ^{31}P MRSI and MRI shows distinct abnormalities in affected muscles in facioscapulohumeral muscular dystrophy

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Background. Facioscapulohumeral muscular dystrophy (FSHD) is the third most common muscular dystrophy (MD), characterized by asymmetric dysfunctioning of individual muscles (8). In patients with FSHD, atrophy and fatty infiltration of muscles and loss of force occurs in the face and shoulder region first, while muscles in the legs are affected later. Currently, it is unknown why specific muscles are affected before others and muscle pathophysiology of both affected and non-affected muscles is poorly understood. To elucidate energy metabolism and pathophysiology of MD, ^{31}P MRS has been applied in several MD types but not FSHD (1). ^{31}P MRS is commonly applied with only surface coil localization, making it difficult to differentiate between affected and non-affected muscles. Clinically, individual muscle involvement is not always easy to assess due to the presence of unaffected synergistic muscle groups. In patients with FSHD, T1 weighted images show clear differences between affected and non-affected muscles (7). A combination of MRI to differentiate affected and non-affected muscles and ^{31}P MRSI to study energy metabolism would provide an ideal approach to study MD. The aim of this study was to characterize anatomic and metabolic differences between affected muscles in patients with FSHD and healthy muscles in volunteers. Additionally, non-affected muscles in patients were compared with healthy volunteers.

Methods. Nine patients with diagnosed FSHD (age 49 ± 16 years) and seven healthy age and sex matched volunteers (49 ± 15 years) were measured in a 3T magnet (Magnetom trio, Siemens Medical Solutions). A home-built, 16 leg birdcage coil was used for imaging (length 18 cm, inner diameter 25 cm), together with a circularly polarized, anatomically shaped surface coil (diameter 14 cm) for ^{31}P MRS that fitted closely around the calf. At ~13 cm below the tibial head, T1 weighted images (TR=552 ms, TE=16 ms, 17 slices of 4 mm, FOV=135*180 mm) were recorded. Subsequently, 3D ^{31}P MRSI (FOV 15x15x25 cm, matrix 10x10x8, TR=1s, 45° bir4 pulse for excitation, 12 averages, Hamming weighted acquisition, Waltz 16 decoupling) (voxel volume 20.8 ml) was applied to all patients. Signal intensity on T1 weighted images was assessed for a differentiation between affected (>20 % of muscle volume shows hyperintensity) and non-affected muscles. Eight different muscles: gastrocnemius medialis and lateralis (GM, GL); soleus medialis and lateralis (SM, SL), tibialis posterior and anterior (TP and TA), peronei muscles (PB) and extensor digitorum longus (EDL) were assessed. In the analysis of ^{31}P MRSI data, representative voxels of all muscles of the middle two slices were manually selected on the co-registered MR images. MR spectra of these voxels were analyzed using jMRUI. Relative signal intensities of phosphocreatine (PCr/ATP), inorganic phosphate (Pi/ATP) and tissue pH were compared intra-individually (affected and non-affected muscle) and between the same muscles in matched healthy volunteers and patients with a paired t-test.

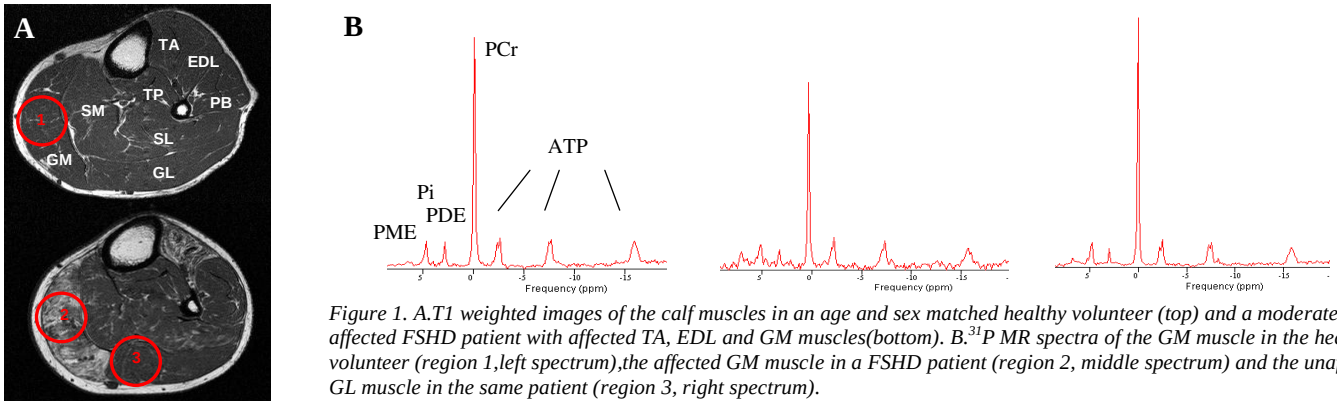

Figure 1. A.T1 weighted images of the calf muscles in an age and sex matched healthy volunteer (top) and a moderately affected FSHD patient with affected TA, EDL and GM muscles(bottom). B.^{31}P MR spectra of the GM muscle in the healthy volunteer (region 1,left spectrum),the affected GM muscle in a FSHD patient (region 2, middle spectrum) and the unaffected GL muscle in the same patient (region 3, right spectrum).

Results. Of all patients, 7 showed moderate to severe muscle involvement on MRI, denoted by an increased signal intensity in one or more muscles (Fig 1A). Most affected muscles were the GM (6/7), TA (4/7) and EDL (4/7). In the ^{31}P MRSI data, on average 27 ±11 voxels were analyzed per subject. When compared to the same muscle in an age and sex matched healthy volunteer, affected muscles in FSHD patients showed a significantly lower PCr/ATP ratio (3.9 ± 0.5 in patients vs 4.8 ± 0.5, uncorrected for T1 effects) and a significantly elevated tissue pH (7.07 ± 0.04 vs 7.01 ± 0.02) (Fig 1B). Interestingly, muscles that appeared unaffected on T1 weighted images did not show any changes compared to the same muscles in healthy volunteers (PCr/ATP = 4.9 ± 0.3 and 5.0 ± 0.7, Pi/ATP= 0.3 ± 0.1 and 0.2 ± 0.1 and tissue pH =7.04 ± 0.1 and 7.04 ± 0.05 respectively).

Conclusion and discussion. Our results show that T1 weighted muscle MRI together with ^{31}P MRSI is a valuable combination in the characterization of individual muscle involvement in patients with FSHD. Although ^{31}P MRSI of human muscle has been reported previously (e.g. 3,4) this is the first application in patients with FSHD and this enabled for the first time, to our knowledge, a separation between affected and non-affected muscles using *in vivo* ^{31}P MRSI during the same acquisition in patients with MD. In this way, the need of multiple biopsies for this purpose is avoided. The observed elevation in tissue pH and decrease in PCr/ATP in the affected muscles of FSHD patients has been shown before in some but not all other MDs (e.g. 2, 5, 6). Assuming unchanged ATP levels, the decrease in PCr is an indication for impaired energy metabolism and increased ADP levels while the reason for the increased tissue pH remains unknown (1). In unaffected muscles, no abnormalities were observed in patients with FSHD, suggesting that these muscles have unaltered metabolism. This could indicate that affectedness in FSHD truly progresses in a muscle specific way, without abnormalities in preclinical muscles, and stresses the importance of image guided biopsies to avoid false negative results. It is currently unknown if ^{31}P MRS of unaffected muscles in other MDs also appears normal, as these have only been studied by unlocalized ^{31}P MRS. Applying our approach to other MDs could elucidate this issue and could also be useful in the assessment of muscle involvement during disease progression.

References. *[1]Argov Z*, et al. Muscle Nerve *23: 1316-1334, 2000.[2]Heerschap A*, et al. Muscle Nerve *16: 367-373, 1993.[3]Houtman CJ*, et al. J Appl Physiol *91: 191-200, 2001.[4]Jeneson JA*, et al. Am J Physiol *263: C357-364, 1992.[5]Kemp GJ*, et al. J Neurol Sci *116: 201-206, 1993.[6]Lodi R*, et al. Neuromuscul Disord *7: 505-511, 1997.[7]Olsen DB*, et al. J Neurol *253: 1437-1441, 2006. [8]Upadhyaya M*, et al. *In:* FSHD: Clinical medicine and molecular cell biology, *p. 1-16, 2004.*