Progression of fatty infiltration after muscle inflammation in FSH muscular dystrophy

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Target audience: persons interested in neuromuscular dystrophies, non-invasive MR biomarkers in dystrophic muscle, muscle inflammation, Facioscapulohumeral muscular dystrophy

Purpose: With a prevalence of 1:20,000 Facioscapulohumeral dystrophy (FSHD) is one of the most common muscular dystrophies. This incurable disease is progressive and characterized by asymmetric involvement of specific muscles with muscle weakness and fatty infiltration. FSHD is associated with contraction of D4Z4 microsatellite repeats on chromosome 4q35, which causes DNA exposure that may lead to a stabilized distal DUX4 transcript[1], a toxic product for muscular tissue. In a large cohort of patients we recently established several MR detectable biomarkers for FSHD, with muscular fat fraction as the most valuable one[2]. We also discovered that only a small subpopulation of the investigated muscles occur in a phase of rapid disease progression, which may be related to the average low number of detectable DUX4. Currently, the trigger for the synthesis of this protein is not known. We hypothesize that inflammation plays an important role in this initiation process of disease progression.
The *aim of this study* was to investigate if progression of fatty infiltration in muscles of FSHD patients is related to the presence of muscle inflammation.

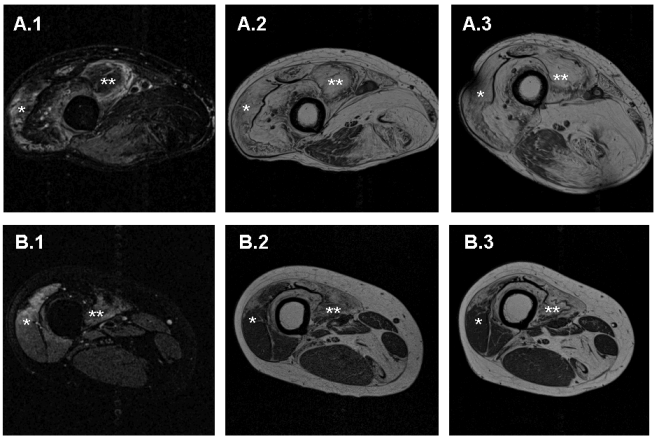

Figure 1: Typical MR images of two FSHD patients (A and B) showing signs of inflammation based on hyperintesities on TIRM images (panels 1). Baseline and follow up T1 weighted images are displayed in panels 2 and 3 respectively. Especially in patient B an increase of fatty infiltration is apparent in the vastus lateralis (*) and vastus intermedius (**) muscles.

Methods: *Recruitment:* Ten genetically proven FSHD patients were included (7 male/ 3 female), with an average age of 55 (range 34-76).
MR protocol: All patients underwent a baseline MR measurement (at time T0), and a follow up exam after 4 months in which the patient was instructed to maintain usual care. MR was performed on a Siemens Trio 3T system using a ^{1}H volume coil to measure the upper leg of the patient. A marker was positioned at 1/3 of the distance between spina iliaca anterior superior and patella for slice matching between the baseline and follow up measurements. T1-weighted images were acquired with a spin-echo sequence (TR/TE: 530 ms/16 ms, 23 slices, slice thickness/gap: 4 mm/0.4 mm, FOV 175 mm x 175 mm). Turbo Inversion Recovery Magnitude (TIRM) images were collected with nulled fat signals to visualize inflammation associated edema. (TR/TE/IT 4000 ms/41 ms/ 22 ms, 23 slices slice thickness/gap: 4mm/0.4 mm, FOV 175 x 175 mm)
Analysis: To assess fatty infiltration by a 2 compartment analysis based on different T2 values is not suitable in the case of inflammation as it has an intermediate T2 value. Therefore we used a different approach in this study based on T1 weighted images. First we visually inspected TIRM images for hyperintensities that indicate inflammation. The slice with the highest TIRM signal intensity (SI) was chosen for further analyses. T1 SI and TIRM SI were determined for every muscle by carefully drawing regions of interest on the T1 weighted images in Image J and normalized to the SI of the bone marrow.

Results: Among the ten patients, two showed hyperintensities on the TIRM images at baseline (figure 1.1). In both patients the vastus lateralis and vastus medialis showed signs of inflammation, and in one of the patients (A) also the vastus intermedius and rectus femoris had signs of inflammation based on the TIRM images. The difference in SI between the baseline and follow up exam of the T1 weighted images was significantly different in the muscles with hyperintense signal on the baseline TIRM images compared to the muscles with normal TIRM signal ($p<0.01$), see figure 2. The difference in T1 SI was calculated by subtracting the SI of the follow up measurement from the baseline measurement, the negative values thus indicate an increase in SI (brighter signal), which corresponds to signal from fatty infiltration.
Linear regression analysis showed a trend between the TIRM SI and the difference in T1 SI ($p<0.1$, $R^2=0.1$), see figure 3.

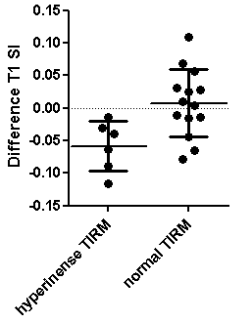

Figure 2: Difference between the SI of the weighted images between the baseline and follow up measurements is significantly different for muscles that have a hyperintense TIRM SI (-0.059±0.038) compared to muscles having a normal TIRM SI (0.008±0.051), p<0.01.

Discussion: The genetic cause of FSHD has recently been uncovered, involving specific chromosome "stripping" that may lead to DUX4 production. How this production is initiated remains elusive, but several possibilities related to the progression of fatty infiltration as seen by MR may be considered. One hypothesis is that inflammation plays an important role in the initiation of this progression in FSHD. Indeed, by assessing fatty infiltration as seen on T1 weighted images, we observed that muscle inflammation as reflected in TIRM images precedes increased progression in fatty infiltration in muscles of FSHD patients. Whether inflammation promotes transcription of the DUX4 gene or is a consequence of , or sustains early initiation processes remains to be investigated.

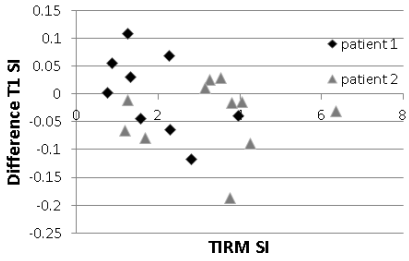

Figure 3: Difference between baseline and follow up T1 SI of the individual muscles as function of baseline TIRM SI. Linear regression analyses revealed a trend (p<0.1).

Conclusion: Visual inspection of T1 weighted images and a quantitative comparison of signal intensities of baseline and follow up measurements supports the hypotheses that fatty infiltration is promoted by inflammation in muscles of FSHD patients.

References: 1. Lemmers R, van der Vliet P, Klooster R, *et al*., A unifying genetic model for facioscapulohumeral muscular dystrophy, Science 2010;329(5999):1650-1653; **2** Janssen B, Arts R, Voet N, *et al*., ISMRM annual meeting 2011;
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