Muscle MRI findings in Facioscapulohumeral muscular dystrophy compared to other limb girdle disorders: may radiologist suggest clues for differential diagnosis?

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Aims and objectives

Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common hereditary muscular disorders with prevalence of 1 in 8,000 [1], characterized by progressive atrophy and weakness of facial, shoulder limb girdle, abdominal and anterior leg muscles [2].

FSHD muscular dystrophy is characterized by variable degree of muscular involvement. Clinical and genetic determination is sometimes difficult and clinical differentiation from other muscle disorders is debated. Lower limb muscle MRI has been proven to be a highly reliable, non-invasive tool for the diagnosis and the evaluation of progression of neuromuscular diseases, showing specific patterns of muscle involvement in a large number of myopathies [3-7]. In FSHD, muscle MRI reveals a widespread involvement of lower limb muscles, particularly hamstrings and posterior calf muscles [8-10]. However few data on muscle MRI of shoulder girdle muscles have been reported to date in patients with neuromuscular disorders, including FSHD. A recent study evaluated upper limb muscles in a wide cohort of FSHD patients showing specific muscle involvement at MRI, compared to other myopathies [11], but it was limited to the upper limbs examination.

Our aim is to delineate an MRI protocol in FSHD patients, in order to define possible specific pattern of muscle involvement in comparison to other muscular diseases.
Methods and materials

We acquired MRI imaging of 28 upper and 62 lower limb muscles (90 muscles total) in 30 patients with FSHD clinical and molecular diagnosis, as compared to a group of 23 patients affected by scapuloperoneal and limb-girdle muscular dystrophy (NFSHD).

FSHD patients' (17 males and 13 females) mean age was 41.5±15.1 years old (range 14-78) and mean disease duration was 13±10.7 years (range 6 months-40 years). All had molecular diagnosis, in particular D4Z4 fragment length ranged from 12 to 36 (normal range 41-350, FSHD < 38) [12].

NFSHD patients had a mean age at muscle MRI of 36.7±14.1 years old (range 16-65) and mean disease duration was 15.4±10.8 years (range 6 months-42 years).

MRI protocol study on a 1.5T scanner included multiplanar and multiparametric evaluation of limb girdle, pelvic girdle, upper and lower thigh and limb muscles (images were 3 mm thick, excluding when volumetric sequences were acquired). Coronal view was acquired with a whole body sequence making use of mobitrack for image fusion. (Fig. 1). Using thin slices high-resolution bilateral scans of the entire brachial plexus from nerve roots to cords were imaged, according to a previously reported protocol [13].

On muscle MRI scans distribution and quantification of muscle fatty replacement (F), atrophy (A) and edema (E) were evaluated by two expert neuroradiologists, with consensus, following a semi-quantitative scale evaluation [14-17], and total MRI muscle scores were calculated as the sum of the scores of involvement of every muscle in each patient.

We also considered asymmetric fat infiltration when the above semiquantitative scale was different in at least 3 couples of muscles of the upper girdle or 5 couples of muscles at the lower limbs (or both).

Muscle strength was assessed by neurologists through manual muscle testing (MRC scale) and each FSHD patient was also evaluated according to clinical score [18]; NFSHD group were examined by means of functional scales used for limb girdle muscle dystrophy (LGMD). Statistical analyses were performed by means of SPSS software.
Images for this section:

**Fig. 1:** T1 moby track: Whole body MRI

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Results

None of the patients in both groups had a normal muscle MRI. In FSHD patients we observed a specific pattern of upper girdle muscle involvement with some muscles more frequently and severely affected and other muscles mostly spared, whereas in NFSHD patients we observed a diffuse and more homogeneous involvement (Fig. 2 a, b, c, d). More than 80% of FSHD patients displayed fatty infiltration of trapezius, teres major and serratus anterior muscles, whereas scalenus, supraspinatus and infraspinatus muscles were rarely involved, in less than 22% of FSHD patients. Conversely, in NFSHD patients we did not observe muscles more frequently or rarely affected, but they appeared to be similarly infiltrated in 35-65% of patients (Tab 1, 2, 3, 4). In both FSHD and NFSHD patients, the more frequently involved muscles also showed a higher total fat score and vice versa, the less frequently involved muscles displayed lower fat score. At the lower limbs the difference with NFSHD patient was less evident. In FSHD the semimembranous, gluteus minimus, gluteus maximus and obliquus abdominis were the more frequently and severely infiltrated muscles (>75% patients), whereas obturator internus, iliacus, psoas and tibialis posterior were less frequently and less severely infiltrated muscles (<10%; Fig. 3). The involvement of these same muscles in NFSHD patients varied, suggesting that MRI examination for fat infiltration limited at lower limbs may be less informative to discriminate FSHD to NFSHD patients. The pattern of muscle atrophy was instead more similar in the two groups of patients, with the exception of trapezius, teres major and serratus anterior muscles, which appeared to be more frequently and severely atrophic in FSHD patients (p= 0.037; Tab. 1, 2, 3, 4). Finally we tried to identify a minimal set of muscles specifically altered in FSHD patients. If we considered only muscles in upper girdle, including trapezius, teres major and serratus anterior as muscles involved for fat infiltration and infraspinatus, supraspinatus and scalenus as spared, this pattern was observed in 18 patients, 17 out of 30 FSHD patients (57%) and only in 1 out of 23 NFSH patients (4%). On the other hand, if we considered only more infiltrated muscles (trapezius, teres major and serratus anterior) the frequency in FSHD patient rose to 76% (23 out of 30), but it also increased in NFSHD patients (52%; 12 out of 23). Instead, if we considered the pattern of muscle involvement only at lower limbs, including gluteus minimum and maximum, semimembranosus and obliquus as severely infiltrated and psoas, iliacus, tibialis posterior and obturator as spared, this pattern was present in 16 out of 30 FSHD patients (53%) and 3 out of 23 NFSHD patients (13%). When we pooled together muscles (more infiltrated and less infiltrated) of the upper girdle and lower limb, this pattern was present in 17 out of 30 FSHD patients (57%) whereas in none of NFSHD patients (p<0.001). Interestingly, in NFSHD patients we observed a significant involvement of the rotator cuff muscles (supraspinatus, infraspinatus, subscapularis and deltoids) (p<0.001) which appeared to be simultaneously fatty infiltrated in 61% of NFSHD patients, whereas only in 13% of FSHD patients. As a collateral finding, we observed the involvement of the brachial plexus (defined as T2/STIR hyperintensity of roots, trunks or cords: Fig 4) in 33% of FSHD patients. However, a similar involvement (34%) was also observed in the NFSHD
group and thus it was a non-specific finding. Moreover, we could not find any correlation between brachial plexus involvement and presence of edema in aside muscles.

Edema has been reported as inflammatory infiltration in muscle biopsies and more frequently in muscle MRI of FSHD patients [10]. We did not observe by MRI significant differences for the presence or site of edema between FSHD (16%) and NFSHD patients (17%) fig 5.

MRI findings (fat infiltration and muscle atrophy score, but not edema that was rarely observed) significantly correlated with clinical severity in both groups. Mildly affected patients (FSHD score #3 or LGMD score #2) had a significant lower mean MRI muscle score, whereas severely affected patients (FSHD score #8 or LGMD score #7) had a significant higher mean muscle MRI score, either for fat infiltration and atrophy. Furthermore, MRI muscle involvement was homogeneous between upper girdle and lower limb muscles within the same patient, thus patients severely involved in upper girdle also showed severe involvement of lower limbs, and vice versa (Pearson's correlation index FSHD fat r=0.715 p<0.001, atrophy r=0.536 p=0.003, NFSHD fat r=0.668 p<0.001, atrophy r=0.582 p=0.007). Moreover, in FSHD patients disease duration correlated with muscle atrophy and fat infiltration scores (r=0.588; p=0.003 and r=0.415, p=0.04), whereas in NFSHD it mainly correlated with fat infiltration score (r=0.640; p=0.003). Overall these results provide evidence that the two cohorts of patients have similar contribution of mild and severely affected patients and that our MRI findings correlate with clinical severity and duration of the disease. Asymmetric muscle involvement for fat infiltration was significantly more frequent in FSHD (80%; p<0.001) than in NFSHD patients (22%; Tab 5), and in mildly affected FSHD patients (score #3) this was still significantly different (p=0.02). Conversely, FSHD patients with severe phenotype (FSHD score #8) did not show significant asymmetric involvement. We could not detect a significant prevalence of side or gender. Finally, the pattern of upper limb muscle fatty involvement typical of FSHD (trapezius, serratus anterior and teres major) was observed in 40% of mild FSHD and in 80% of severe FSHD, while it was absent both in mild and severe NFSHD patients. Although the number of FSHD patients with mild or severe clinical phenotype was limited, our results suggest that the described pattern of MRI muscle involvement in the whole group of FSHD patients was consistent even in mildly and severely affected FSHD patients.
Images for this section:

![Fig. 1: T1 moby track: Whole body MRI](image)

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Fig. 2: Findings in FSHD Patients (A,B,C) and in Non FSHD (NFSD) patient (D). A Coronal T1 W. Fat infiltration of FSHD patient: Asymmetric involvement of serratus anterior (SA), trapezius (T) and teres major (TM) with normal aspect of rotator cuff muscles. B and C) T2 weighted image: B trapezius atrophy and fatty infiltration (arrow), with asymmetric involvement of levator scapulae (arrow head) in a FSHD patient, with normal rotator cuff muscles. C: teres major atrophy and fatty infiltration (arrow), with involvement of trapezius (arrow head) and serratus anterior (yellow arrow) in a FSHD patient. D: T1 W of NFSD patient: fatty infiltration and atrophy of trapezius (T), paraspinal muscles (PS), levator scapulæ (LS) and rotator cuff muscles (RC).

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**Fig. 3:** T1W in axial view: Pelvic girdle and lower limb muscles involvement in both FSHD (A) and NFSHD (B) patients. Gm indicates gluteal muscles (gluteus maximus, gluteus medius and gluteus minimus), Abd are the abdominal muscles group, often involved in FSHD patients. A2 and B2 show thigh muscle involvement in both groups: the quadriceps (Q), biceps femoris (B), semitendinosus (St), semimembranosus (Sm), gracilis (Gr) and adductors (Add). In FSHD patient the involvement is asymmetric, in NFSHD patient it is bilateral and diffuse. A3 and B3 show asymmetric fatty replacement of the gastrocnemius (Gas) and soleus (Sol) in FSHD patient; NFSHD patient shows a lower involvement of calf muscles.

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**Fig. 4:** MRI findings in brachial plexus. Signal alteration of the brachial plexus characterized by hyperintensity of T2/STIR sequences is observed asymmetrically in FSHD patient (A, arrows), whereas signal is similar but symmetric in NFSHD patient (B, arrows).

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**Fig. 5:** Fig 5. Coronal Stir Sequence: edema in a non FSHD patient: bilateral involvement of limb girdle muscles.

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**Table 1:** Distribution of upper limb fat infiltration in the two different groups of patients.

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**Table 2:** Distribution of upper limb atrophy in the two different group of patients

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**Table 3:** Distribution of the lower limb fat infiltration in the two different group of patients.

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Table 4: Distribution of the lower limb fat atrophy in the two different group of patients.

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Table 5: Percentage of symmetric and asymmetric involvement of muscles in both groups of FSHD and NFSHD patients.

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Conclusion

MRI represents a useful tool to evaluate patients affected by muscular dystrophies and to support clinical diagnosis by detecting patterns of muscle involvement in several myopathies, including FSHD [16], usually focusing on the lower limbs.

In our study we evaluated by MRI an extensive number of muscles of upper and lower girdle and lower limbs of FSDH patients compared to NFSHD patients for the presence of edema, frequency and severity of fat infiltration and atrophy and symmetry of abnormality distribution.

Trapezius, teres major and serratus anterior were the most frequently and severely involved muscles among upper limb muscles, representing a specific MRI pattern highly suggestive of FSHD as respect to NFSHD. Most frequently affected muscles in FSHD among lower limb muscles were gluteus minimum and maximum, semimembranosus and obliquus, but their involvement was less specific because it was present in a consistent percentage of NFSHD patients as well. We also observed that the combined upper and lower limb muscle pattern makes FSHD diagnosis highly probable, instead when muscles such as scalenus, supraspinatus and infraspinatus at the upper girdle or obturator internus, liliacus, psoas and tibialis posterior at lower limbs are severely fat infiltrated, the probability of FSHD is rather low.

According to other studi(es) [11], we confirmed left/right asymmetric distribution of MRI abnormalities in FSHD patients, whereas symmetric (homogeneous) involvement of muscles in upper and lower limbs was observed. Instead we differently detected a significant involvement of the teres major muscle (mainly due to the smaller thickness of our MRI acquisitions, 3 mm thick, 0.3 mm gap), and did not confirm prevalent edema involvement in FHS patients [10,19,20], being in accordance with other authors [9,11], mainly because of different selection of the cohort of patients, which was random in our study.

In conclusion our data suggest that a precise MRI protocol can define typical pattern of involvement in subtypes of neuromuscular disorders, including FSHD. Of note, MRI in FSHD patients can also detect the involvement of non-clinical testable muscles. MRI should be considered a reliable tool to differentiate FSHD from other muscular dystrophies and to direct diagnostic molecular analysis, enabling a easier assessment of the severity of the disease and monitoring of efficacy of new therapies.
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