Quantitative MRI in lower limb muscles and heart of patients with limb-girdle muscular dystrophy type R9: preliminary results of a natural history study

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Background & Aim

✓ **Limb-girdle muscular dystrophy type R9 (LGMD R9)** is an autosomal recessive rare neuromuscular disorder caused by a mutation in the fukutin-related protein gene ***FKRP***[1]. Respiratory and cardiac involvement is common and can occur independently of skeletal muscle involvement[2]. The disease is heterogeneous with age of onset, degree of severity and rate of progression, which was earlier confirmed by assessment of muscle fat fraction (FF) using **quantitative magnetic resonance imaging (MRI)[3].**

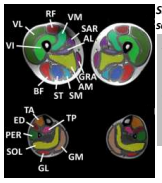
✓ Quantitative **MRI-based outcome measures**, including **FF, water T_2** and **water T_1** (which reflect disease activity mechanisms such as inflammation/edema/…) are used in many longitudinal studies in neuromuscular diseases[4]. Besides skeletal muscle MRI, **MRI-based cardiac outcome measures** are also assesed in muscle diseases with cardiac involvement[5].

✓ Here, we investigated preliminary MRI data in skeletal and cardiac muscle in the Généthon natural history study in LGMD R9.

Materials & Methods

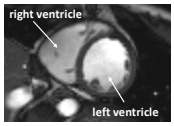
✓ **Study information:**
- ✓ GNT-015-FKRP study: NCT03842878
- ✓ three sites in Europe → here, data from:
  - ✓ 26 patients (site 1)
  - ✓ 17 patients (site 2)

✓ **MRI:**
- ✓ Exams: performed on a **3-T** clinical system (Siemens)
- ✓ quantitative MRI protocol skeletal muscle (left and right thighs/legs):
  - **water-fat imaging** (Dixon: 64 axial slices, 3 echo times) → **FF (%)**[6]
  - **T_2 relaxometry** (MSE: 9 axial slices, 17 echo times) → **water T_2 (ms)**[6]
  - **T_1 relaxometry** (MRF: 9 axial slices) → **water T_1 (ms)**[7], only at site 2
  - → manual segmentation **individual muscles** (mean value of 5 central slices)[8]
  - → post-processing using in-house code[6,7]



Skeletal muscle MRI lower limbs – manual segmentation of individual muscles

Abbreviations: AL/AM = adductor longus/magnus, BF = biceps femoris, ED = extensor digitorum, GL/GM = gastrocnemius lateralis/medialis, GRA = gracilis, PER = peroneus, RF = rectus femoris, SAR = sartorius, SM = semimembranosus, SOL = soleus, ST = semitendinosus, TA/TP = tibialis anterior/posterior, VI/VM/VL = vastus intermedius/medialis/lateralis



Cardiac MRI - short-axis view

Abbreviations of MRI sequences: MSE = multi-spin-echo, MRF = magnetic resonance fingerprinting, bSSFP = balanced steady-stat-free-precession, MOLLI = modified Look-Locker inversion recovery

✓ Quantitative MRI protocol cardiac muscle[5] (only at site 2):
- **CINE MRI** (bSSFP: stack of short axis **oriented slices covering left ventricle) → ejection fraction, EF (%)**
- **T_2 relaxometry (bSSFP: basal/mid-ventricular levels of short axis oriented slices, 2 preparation times) → water T_2 (ms)**
- **T_1 relaxometry (MOLLI: basal/mid-ventricular levels of short axis oriented slices, 3 inversion times), before and after contrast agent → water T_1 (ms) and extracellular volume, ECV**
- → post-processing using Segment software (**17-segment model**)

✓ **Analysis:**
- ✓ **Student's *t*-test were** used to assess differences between sites and visits (statistical significance: ***P*<0.05**).
- ✓ **Standardized response means (SRM)** values were calculated to assess sensitivity to change (**SRM>0.8 considered as sensitive**).
- ✓ Control values (stem from 12 age and sex matched volunteers): 90th percentile is indicated in red in the plots.

Results

1. Demographics

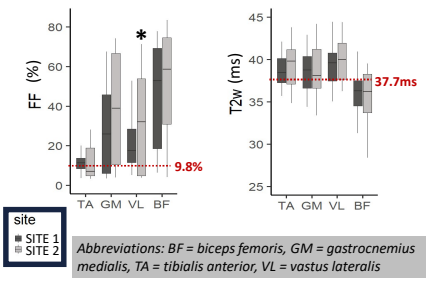
	site 1	site 2	*P*
sex (female/male)	14/12	17/1	<0.001
age at baseline (years)	33.9±13.1	38.7±12.2	0.11
years since onset symptoms at baseline	9.4±6.2	9.7±5.8	0.43
BMI at baseline (kg/m²)	24.8±4.6	23.8±6.0	0.29

Data are expressed as mean±standard deviation.

✓ Besides the male/female ratio, no significant differences were observed between the two sites for age, years since onset symptoms and body-mass index (BMI). Patients were younger in site 1 as compared to site 2 (but this was not significant).

Results

2. Baseline FF and water T_2: site 1 vs. site 2



Abbreviations: BF = biceps femoris, GM = gastrocnemius medialis, TA = tibialis anterior, VL = vastus lateralis

✓ There were no left-right differences (*P*>0.10). Mean left-right values are shown here.

✓ FF was abnormal in all muscles (*P*<0.001), demonstrating a strong heterogeneity in disease severity, especially in posterior muscles.

✓ Water T_2 (T2w) was abnormal (>37.7ms), predominantly in anterior muscles. Water T_1 was abnormal (>1266ms), predominantly in medial-posterior muscles.

✓ Significant differences in FF (but not for water T_2) were found between the 2 sites for several thigh muscles, such as vastus lateralis.

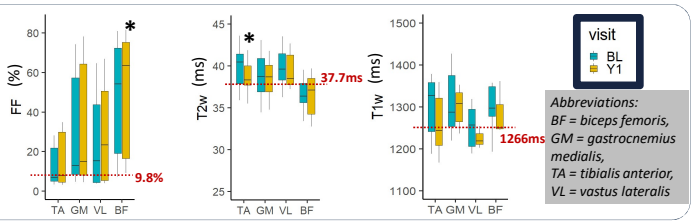
Results

3. One-year changes in FF, water T_2 and water T_1 (site 2 only)

✓ Posterior thigh muscles, such as biceps femoris, demonstrated significant one-year changes in FF.

✓ High SRM values (>0.8) were also found for the posterior thigh muscles.

✓ With the exception of tibialis anterior water T_2 (T2w), water T_2 (T2w) and water T_1 (T1w) values in other muscles did not change between baseline and year-1.



Abbreviations: BF = biceps femoris, GM = gastrocnemius medialis, TA = tibialis anterior, VL = vastus lateralis

Results

4. Cardiac MRI (site 2 only)

Data are expressed as mean±standard deviation.

	90th percentile controls	baseline	change after year-1	SRM	*P*
ejection fraction, EF (%)	67	55.6±11.9	+2.7±3.1	**0.9**	0.56
water T_2 (ms)	49.9	48.0±3.9	-1.6±2.7	0.6	0.38
water T_1 (ms)	1330	1342±55	-66±39	**-1.7**	0.23
extracellular volume, ECV	0.30	0.30±0.04	-0.02±0.01	**-2.0**	0.07

✓ Baseline cardiac MRI outcome measures were not different as compared to normal values.

✓ Values did not change significantly over the course of one year.

✓ Cardiac MRI outcomes are, however, very sensitive to change (see high SRM values).

✓ Four out 18 patients received medication for heart disorders.

Conclusion

✓ This new LGMD 2I natural history study has confirmed the heterogeneity in disease severity[3], with strong variations in FF between patients and patient populations/sites.

✓ The current natural history study also included the assessment of disease activity indices (water T_2, water T_1) and demonstrated that some muscles showed elevated values as compared to controls.

✓ The cardiac MRI data did not reveal abnormalities.

✓ The preliminary results showed little changes after one year, (skeletal and cardiac MRI) except for posterior thigh muscle FF values.

✓ These natural history data, however, will establish a strong data base for comparison with data from the LGMD 2I clinical trial (ATA-001-FKRP, NCT05224505, initiated in August 2022).

References

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