MYO-MRI

MRI & MRS IN NEUROMUSCULAR DISEASE

Imaging in Neuromuscular Disease 2019

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New imaging applications in NMD

1

Kevin Keene

Feasibility of quantitative MRI in eye muscles

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Background: Quantitative MRI of individual extraocular muscles (EOM) might have diagnostic and prognostic value in myasthenia gravis (MG) and Graves' orbitopathy (GO), as conventional neuro/ophthalmic evaluations fail to quantify muscle pathology in EOMs directly. Since the EOMs are small and prone to eye-motion artefacts, they are challenging to image with MRI.

Aims: Our aim was to study the feasibility of determining fatty infiltration, volume and water T2 relaxation in EOMs in healthy controls (HC), GO and MG.

Methods: 12 HC (41±9yrs, 42% male), 11 MG (52±10yrs, 64% male) and 6 GO patients (47±11yrs, 50% male) were scanned at 7T (Philips), using a cued-blinking paradigm. A 3-point-Dixon was acquired (TE/TR/FA/ΔTE:2.4ms/10ms/3°/0.33ms) to determine fat fractions (FF). In a subgroup of 6 MG, 1 GO and 5 HCs a multi-echo spin-echo (ME-SE) of four recti EOMs (ΔTE/TR:12/4000ms) was obtained. Dixon scans of EOMs were semi-automatically 3D-segmented, using a seed-growing-algorithm in ITK-SNAP, to determine muscle volume and FF using the manufacturers reconstruction. The ME-SE data were fitted using Extended Phase Graphs (EPG) in which the FF, fat-T2, water-T2, B1 and pulse-profile were incorporated, and a manual delineation of an ROI. Measurements were compared using T-tests (significance at $p<0.05$).

Results: Mean FF of the EOMs in MG (14,1±0.5%) was higher than in HC (10,4±0.8%) and similar in GO. Mean muscle volume was higher in GO (1.2±0.17 cm^3) and MG patients (0.8±0.05 cm^3) compared to the HC (0.6±0.05 cm^3). The average T2 of all EOMs of the GO patient (33±3ms) was increased compared to HCs (28±1ms). Although the average T2 was not increased in MG patients, four individual EOMs of the MG patients had a T2 higher than two standard deviations from the mean of HCs.

Conclusion: It is feasible to perform quantitative MRI of the EOMs in HC and patients with neuromuscular disease and eye muscle involvement. We were able to 3D-segment the EOMs and measure the FFs and volumes of individual EOMs. Contrary to current pathophysiological knowledge, our results show increased FF and volumes of the EOM's in MG. Using ME-SE and EPG analysis we measured T2 values of EOM comparable to skeletal muscle and an elevated T2 in a GO patient.

2

Thom Veeger

Using a linear mixed-effects model and longitudinal fat infiltration data to study the effect of muscle characteristics on muscle fatty infiltration in DMD

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Background: Progressive fatty infiltration in skeletal muscle of Duchenne muscular dystrophy (DMD) patients starts in specific muscles. The

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underlying paradigm for this specific order is unknown. The structural role of dystrophin, the reduced force propagation along the muscle in absence of dystrophin and the start of muscle weakness in proximal muscles all indicate that architectural characteristics, such as pennation angle, fibre length and muscle volume, could play a role in muscle fat infiltration. Availability of longitudinal MRI data enables determination of the order of muscle fat infiltration in DMD, while accounting for the effects of age on disease progression.

Aims: To test the effect of specific muscle architectural parameters on muscle fatty infiltration, while controlling for age.

Methods: 3-Point Dixon MRI data of 19 DMD patients were acquired at yearly intervals over two years. Fat fractions (FF) of 11 upper leg muscles were averaged over 6 middle slices. Three pre-specified muscle characteristics (muscle mass, pennation angle and relative fibre-over-muscle length (Lf/Lm, %)), were tested and obtained from literature. The relationships between the muscle characteristics and log odds transformed FF data were analysed in the software-package R using a linear mixed-effects analysis. Age and muscle characteristics were included as fixed effects. To account for varying disease progression between patients, a by-patient random slope for the effect of age was included. Because onset and progression of FF can vary between muscles, a by-muscle random intercept and slope for the effect of age were included.

Results: As expected, age significantly predicted FF (b=0.35, t=7.93, p.05.

Conclusion: Our results suggest an association between muscle mass and relative muscle fibre length with fat fractions in upper leg muscles in DMD, while pennation angle did not. The quantitative association between mass and relative muscle fibre length and the fat fractions is yet hard to interpret due to the log odds transformation of the FF data. For future studies we plan to add lower leg muscles to the model and include more FF data.

3

Klaus Dieterich

Muscle involvement in pediatric and adult patients with Amyoplasia: an MRI study

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Background: Amyoplasia is the most common form of Arthrogryposis multiplex congenita (AMC). However, information about the pattern of muscle involvement in amyoplasia is limited.

Aims: The aim of this study was to determine if there are specific patterns of muscle involvement in Amyoplasia and to find out if there is a fibro-adipose infiltration of the muscles with age.

Methods: Between 2008 and 2017, we examined 65 patients affected by Amyoplasia (33 children and 32 adults), at the Centre Hospitalo-Universitaire Grenoble Alpes. 14 patients had atypical clinical findings. MRI was performed with T1-weighted turbo spin echo (T1W-TSE) sequences. We analyzed the fibro-adipose infiltration and "grelot" sign of the muscles of the neck, the shoulder and pelvic girdle, trunk, upper and lower limbs.

Results: Compared with atypical patients, the absence of the biceps brachii, brachialis, tibialis anterior, gracilis, and sartorius was significantly more frequent in typical patients. Mercuri scores were higher in adult patients in tensor fasciae latae, semimembranosus and vastus lateralis muscles. The adductor longus and brevis were selectively preserved.

Conclusion: Our data provide evidence that muscle MRI can identify a specific pattern of muscle involvement in Amyoplasia patients and constitutes a diagnostic biomarker with a high positive predictive value. Increasing fibro-adipose infiltration with age was observed in some muscles in a subset of patients. However further evidence is needed to

determine if this reflects disease progression. The "grelot" sign gives further arguments for the congenital neurogenic origin of Amyoplasia.

4

Benjamin Marty

MR fingerprinting with water and fat separation (MRF T1-FF): validation and evaluation of water T1 as a biomarker of disease activity in inclusion body myositis

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Background: Quantitative T1 mapping might be an appealing alternative for monitoring disease activity in neuromuscular disorders (NMDs), knowing it has been validated to quantitatively evaluate inflammation, necrosis or fibrosis in the myocardium. However, T1 values are confounded by the presence of fat in diseased muscles. We recently proposed an MRF sequence (MRF T1-FF) which separates water and fat signals, allowing simultaneous estimation of water T1 (T1-H_2O), fat fraction (FF), apparent B1 and off-resonance (Df) values in skeletal muscles.

Aims: Here, we evaluated the accuracy of the different MRF T1-FF variables in patients suffering from inclusion body myositis (IBM) and investigated the potential of T1-H_2O for monitoring disease activity in this myopathy characterized by a combination of inflammatory and myodegenerative features.

Methods: NMR experiments were performed in the lower limbs of 48 patients (64±8 years old) with IBM. The MRF T1-FF sequence was acquired with a radial-golden angle echo train following non-selective inversion (acquisition time = 10 sec/slice). The echo time, repetition time and flip angle were varied throughout the acquisition. For each slice, 175 images were reconstructed by non-uniform fast Fourier transform and a bi-component fitting was applied to generate the quantitative maps. For comparison, reference FF and Df values were obtained with standard 3pt-Dixon and T2-H_2O were determined from a multi-spin echo sequence and 2-component EPG fitting.

Results: In these patients, FF, B1 and Df values derived from MRF T1-FF were highly correlated with the reference values (R = 0.97, 0.87 and 0.98, respectively, $p<0.001$). We also observed a significant relationship between T1-H_2O and T2-H_2O values over the whole group of patients (Spearman correlation, rho = 0.56, $p<0.001$). However, in several subjects, elevated T1-H_2O values were detected in muscles with normal T2-H_2O, and vice-versa.

Conclusion: In conclusion, the MRF T1-FF sequence allowed to derive accurate FF, Df and apparent B1 values in patients with fatty infiltrated muscles. For the first time, a significant relationship between T1-H_2O and T2-H_2O was demonstrated in patients with muscle lesions such as in IBM. The discrepancies between T1-H_2O and T2-H_2O contrasts observed in some patients encourages a more systematic evaluation of T1-H_2O with MRF T1-FF as an additional biomarker of disease activity in NMDs.

5

Matthew Birkbeck

Motor Unit Magnetic Resonance Imaging (MU-MRI) to Determine the Morphology and Distribution of Human Motor Units

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Background: Linear dimensions of the human motor unit (MU) have been investigated using invasive needle electromyography whilst glycogen depletion experiments in animals infer shape and size of MUs. MRI can detect signal changes consistent with motor unit activity and provides a non-invasive method to study the human MU in more detail than conventional techniques.

Aims: To use MUMRI to study size, shape, distribution and recruitment order of human MUs in healthy volunteers using a protocol of ramped electrical stimulation.

Methods: Leg muscles of 6 healthy volunteers (mean age: 44 years, range: 29-80 years), were scanned using a 3T Philips MR scanner and a pair of 10cm elliptical surface coils during incremental electrical stimulation of the left peroneal or tibial nerve. To define the first MUs which were activated, DWI images were acquired time-locked to the electrical stimulation with sensitization along the muscle fibre axis (Single Shot SE-EPI, b = 20 s/mm^2, voxel size=1.5x1.5x7.5 mm, TR/TE = 1000/36 ms, Δ/δ = 18.5/4.5 ms). The electrical stimulation started at a current showing clear signal change and was decreased in steps of 0.01 mA until signal changes were not present (5 repetitions per stimulus strength, 1080 stimuli). MU activity maps were created by taking the difference between the images with signal change and those without. These images were used to determine the Feret diameter of resultant signal hyper-intensities, which reflect the MU activity. Images were also used to record recruitment order and morphology.

Results: During graded reduction in electrical stimulation, the signal voids representing MU activity disappeared sequentially in defined regions comprising multiple pixels. As the MU approached the firing threshold we observed alternation of signal changes in consecutive images until no activity was observed. Detected MUs were ovate in shape. Minimum and maximum Feret diameters of the first active MU were 6.4 mm (range: 4.3-11.7) and 12.7 mm (range: 8-18.8 mm) respectively.

Conclusion: MUMRI was able to detect the first activated MUs using an incremental electrical stimulation protocol. Observed alternation is a further support of the signal changes being indeed MUs. The detected MUs had Feret diameters in agreement with literature.

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Karoline Lolk Revsbech

Quantitative magnetic resonance imaging of paraspinal muscles in patients with limb-girdle muscular dystrophy type 2I

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Background: The autosomal recessive limb-girdle muscular dystrophy type 2I (LGMD2I) is characterized by progressive weakness of shoulder- and hip-girdles. Affection of the proximal extremity muscles is well-described whereas description of paraspinal muscle involvement is lacking.

Aims: In this study, we investigate the involvement of paraspinal muscles in patients with LGMD2I.

Methods: We used quantitative MRI (Dixon technique) to investigate fat replacement in leg and paraspinal muscles: erector spinae at C6, Th12 and L4/L5 and multifidus at Th12 and L4/L5. Back strength was measured by Biodex stationary dynamometry. The study plans to include 20 LGMD2I patients and 24 matched healthy controls (HC). Currently, 10 LGMD2I patients (mean age 37.6 (range 19–60), M:F=6:4) and 24 HC (mean age 41 (25–62), M:F=12:8) have been studied. MRI has been performed in all LGMD2I patients and 20 HC. Stationary dynamometry was done in all LGMD2I patients and 11 HC.

Results: LGMD2I patients have a significantly increased mean fat fraction (mFF) in paraspinal muscles. At cervical level: mFF is 29.3% vs 14.0% in HC (p=0.001), thoracic level: 34.2% vs 14.5% (p=0.001), and lumbar level: 59.3% vs 21.1% (p=0.0001). The psoas major muscle was also severely affected with a mFF of 57.7% vs 10.0% in HC (p=0.00009). In the legs, especially the hamstrings have increased mFF (53.5% vs 9.3% (p=0.00002)). Patients have reduced strength of the back muscles as well as the abdominal muscles. Mean trunk extension peak torque is 99.8 Nm vs 296.9 Nm in HC (p=0.0001) and mean trunk flexion

peak torque is 68.3 Nm vs 133.4 Nm in HC (p=0.001). Data shows no correlation between mean fat fraction and muscle strength.

Conclusion: In conclusion, the results suggest that patients with LGMD2I have affection of the paraspinal muscles in addition to the well-described involvement of the shoulder- and hip-girdle. Stabilization and mobility of the spine is dependent on the paraspinal muscles. Affection of these muscles might compromise balance, posture and the ability to walk, which should be taken into account in the clinical evaluation and management of LGMD2I patients.

7

Alfredo Lopez Kolkovsky

Mapping blood tissue perfusion and myoglobin oxygen saturation in the calf during ischemia-reperfusion at 3T

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Background: Myoglobin is an intramyocytic oxygen carrier which in its deoxygenated form(dMb) has a 1H NMR resonance at ~79 ppm with 100% visibility. Its short T1 allows for fast signal averaging and dMb dynamics has been measured using non-localized pulse-acquire (FID) sequences. Location dependence of dMb content, resaturation time, energy metabolism and blood flow has been reported and combining spatial information of tissue perfusion and reoxygenation rates is a potentially powerful tool to investigate their interrelation and the spatial heterogeneity of skeletal muscle oxidative metabolism non-invasively.

Aims: To develop a NMR pulse sequence to simultaneously track blood tissue perfusion and myoglobin resaturation in multiple muscles dynamically. Methods: Experiments were performed at 3T in 2 healthy subjects during an 8-min ischemia paradigm. A modified 2D CSI acquisition (TR=2s,256 points,40kHz bandwidth,30 elliptically-weighted averages,7x7 encoding matrix,9cm slab thickness) was interleaved with an FID acquisition (256 points,40kHz bandwidth,8 averages). A pulsed ASL sequence was then added (TR=4 s,radial FLASH,192 points, 64 spokes,TR/TE=5.86/2.4 ms). This sequence was also evaluated with a 9x9 encoding-matrix CSI (22 elliptically-weighted averages, 160x160 mm² FOV).

Results: Deoxygenated myoglobin(dMb) was detected in CSI and FID spectra during ischemia, reaching a plateau at about 4 min and dropping to noise levels within ~10 seconds upon release. dMb relative concentration time courses measured with the 7x7 encoding-matrix CSI showed no discrepancies between the 2 and 4 s temporal resolutions and no artefact was observed due to the ASL module.

The CSI acquisitions using a 9x9 encoding matrix allowed tracking dMb dynamics in 22 voxels out of the 28 covering the leg. The other 6 voxels were covering the tibia or only partially contained muscle of the internal face of the calf. The Mb resaturation time constants averaged from multiple voxels for the anterior/lateral leg compartment (nvoxel=3), soleus (nvoxel=6) and soleus/gastrocnemius (nvoxel=2) were 7.45±0.99s, 9.16±3.47s and 9.71±1.26s, respectively."

Conclusion: The spatially-resolved dynamics of dMb was tracked using CSI interleaved with ASL measurements in the calf. As such, the proposed interleaved sequence may be useful for the investigation of peripheral arterial disease. When it will be combined with 31P NMRS, it will offer the possibility to deepen the relations between the regulatory elements of the mitochondrial oxidative phosphorylation.

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L.E. Habets

Handbike platform for in vivo 31P MRS study of arm muscle ATP metabolism in Spinal Muscular Atrophy

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Background: Spinal Muscular Atrophy (SMA) is a congenital debilitating neuromuscular disease. SMA is characterized by progressive skeletal muscle weakness with heterogeneously affected agonist and antagonist muscles. Muscle biopsies taken from patients with SMA and SMA animal models indicate abnormal mitochondrial biogenesis. If confirmed in vivo, this may provide a therapeutic target to partly restore muscular function.

Aims: To determine metabolic function during exercise in relatively affected (m. triceps) and unaffected (m. biceps) muscles of the upper arm in SMA type 3/4 patients using a novel MR handbike platform.

Methods: Patients visited our clinic twice. On visit #1, they performed a bout of supine arm-cycling exercise (90 rpm; static resistance 7 W) outside the MR scanner to determine exercise tolerance. On visit #2, patients performed two consecutive bouts of arm-cycling exercise in the MRI scanner with concomitant recording of in vivo 31P MR spectra during exercise and recovery from the biceps and triceps muscles respectively. We included twenty minutes of rest between bouts.

Results: Twelve patients (mean age(y): 37.5, range 12 - 63; m/f: 5/7) with SMA and ten age and gender matched controls enrolled thus far. Arm-cycling endurance during the two in-magnet exercise bouts in patients was the same (bout 1: 192 ± 114s vs bout 2: 183 ± 127 s, mean ± SD). Intramuscular phosphocreatine (PCr) depletion during exercise was >95% in all subjects. Triceps acidification during exercise was profound in some, but not all SMA patients (e.g. end-exercise pH=6.3 vs pH=6.9; controls end-exercise pH=6.9; resting muscle pH=7.0). Post-exercise metabolic recovery was abnormally slow in some, but not all SMA patients.

Conclusion: This is the first study that provides in vivo data on metabolic function of upper arm muscles in SMA by using a novel handbike platform for in vivo 31P MRS study of arm muscle ATP metabolism. Preliminary results suggest metabolic capacity for homeostasis of muscle energy and pH balance in SMA is heterogeneously affected.

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Karin Naarding

Last but not least: preserved thenar muscles in non-ambulant Duchenne muscular dystrophy

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Background: Duchenne muscular dystrophy (DMD) is characterized primarily by limb-weakness. Hand function is preserved until late in the disease, and is crucial for daily-life activities of non-ambulant patients such as using a phone and operating a wheelchair. It is unclear to what extent intrinsic hand muscles are preserved.

Aims: We used quantitative MRI (qMRI) to study the relation between thenar muscle fat fraction (FF), total volume (TV), contractile volume (CV), and pinch strength.

Methods: Sixteen non-ambulant DMD patients (range 10.2-24.1 years) without scoliosis surgery or daytime ventilation, and eleven healthy controls (range 9.5-25.4 years) participated. 4-point Dixon scans of the right hand (25 slices, voxel size 0.89x0.89x4mm) were acquired at 3T at Leiden University Medical Center (LUMC) using two microcoils. Patients were positioned on their right side on a custom-built arm rest to ensure consistent positioning. Thenar mean FF, TV and CV (TV corrected for FF) were determined using regions of interest on the ventral thenar. Pinch strength (kg) was measured using MyoPinch. Differences in FF, TV, CV and specific strength (pinch strength/CV) were assessed using Mann-Whitney U tests. Spearman correlation was used to correlate qMRI values to pinch strength. Significance was set at $p<0.05$.

Results: Median Brooke upper extremity rating scale in DMD patients was 3 (range 2-4). Due to artefacts four MRI datasets from DMD patients were excluded. TV, CV and specific strength were lower

in DMD: 6.8cm^3 (3.0-12.9cm^3) versus 14.3cm^3 (4.6-20.7cm^3); 6.2cm^3 (2.5-12.0cm^3) versus 13.2cm^3 (4.2-18.9cm^3); 0.38 kg/cm^3 (0.19-0.86kg/cm^3) versus 0.85 kg/cm^3 (0.62-1.33kg/cm^3). By contrast, FF was only slightly elevated in DMD (10.2% (6.9-14.2%) versus 7.9% (6.1-10.0%)), even in patients with higher Brooke scales. Pinch strength correlated with TV and CV in DMD patients (ρ=0.75; ρ=0.71) and controls (ρ=0.84; ρ=0.84), but not with FF.

Conclusion: In our cohort of non-ambulant patients, FF was only marginally increased, while thenar volume, contractile volume and specific strength were significantly lower in DMD patients compared to controls. Because the thenar muscle is important in daily life, has low fat fraction in non-ambulant patients and shows a correlation between strength and size, it seems a valuable target for therapies, even in advanced stages of the disease.

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Linda Heskamp

Functional Magnetic Imaging of Human Motor Unit Fasciculation in Amyotrophic Lateral sclerosis

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Background: The diagnostic delay in amyotrophic lateral sclerosis (ALS) prevents instigation of life-prolonging therapies. The first abnormality in muscles of ALS patients are pathological spontaneous motor unit (MU) contractions (fasciculation). Therefore, we developed a diffusion-weighted imaging (DWI) sequence to detect this fasciculation, called MUMRI.

Aims: We first tested if MUMRI is sensitive to MU contraction. Thereafter, we optimized the sequence sensitivity to fasciculation and applied MUMRI in ALS patients to study fasciculation.

Methods: The sensitivity to MU contraction was tested in 6 healthy volunteers (24-47y). Leg muscles were scanned using a 3T Philips MR scanner and a pair of 10cm elliptical surface coils during incremental electrical stimulation of the left peroneal or tibial nerve (50 stimuli, step:+0.05mA/acquisition). DWI images were acquired time-locked to electrical stimulation with sensitization along the muscle fibre axis (SE-EPI, b=0,10,20s/mm^2 voxel-size=1.5x1.5x10mm, TR/TE=1000/36ms, Δ/δ=18.5/4.5ms). MU activity maps were created by selecting pixels with signal<5SD compared to baseline to determine the signal voids' maximum Feret diameter. Fasciculation detection was performed in 5 controls (31-47y) and 4 ALS patients (Awaji-defined probably or definite, 33-69y). DWI images were acquired for 3min per b-value (b=1,10,20,50,100,150,200,250,300, and 400s/mm^2) and we determined the number of spontaneous signal voids and percentage area of fasciculating muscle.

Results: During electrical stimulation signal voids appeared in a defined sequence of discrete regions comprising multiple pixels in an "all or nothing" manner, with a diameter ranging between 3.2-19.7mm. Shifting the nerve stimulation in relation to the imaging window (-80 to +400, step=8ms) revealed that voids appeared 20-25ms after nerve stimulation and returned to baseline within 125-250ms. The number of detected spontaneous signal voids in healthy volunteers increased with b-value and plateaued between b=200s/mm^2 to b=300s/mm^2, wherefore we continued with b=250s/mm^2. ALS patients had higher fasciculation frequencies compared to controls (mean (range), 99.1min-1 (25.7-161min-1), vs. 7.7min-1 (4.3-9.min-1), $p<0.05$). Furthermore, the percentage area of fasciculating muscle was higher in patients vs. controls (15.9%±2.8 vs. 2.9%±1.6, $p<0.05$).

Conclusion: The properties of signal voids on MUMRI images are consistent with the contraction of individual MUs. Furthermore, we demonstrated the clinical potential of MUMRI as a non-invasive mean of fasciculation detection in ALS.

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Martin Schwartz

MR imaging and analysis of spontaneous muscular activities in several body regions of healthy subjects and patients with neuromuscular disease: preliminary results

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Background: Quantification and subclinical detection of spontaneous mechanical activities in musculature (SMAM) (Steidle,2015) is of high interest for diagnostic assessment in patients with neuromuscular disorders (Whittaker,2019).

Aims: Previous studies on SMAM were restricted to lower leg musculature; however, patients with neuromuscular disorders might show fasciculations or other unintended muscular activities in several further muscular regions. In the present study, feasibility of detection of SMAMs in different areas of the entire body by MRI is investigated. Moreover, preliminary results from two patients with diagnosed amyotrophic lateral sclerosis (ALS) were evaluated.

Methods: Whole-body measurements were performed in 4 healthy subjects (age: 32±14 years). In two ALS patients (P1: 75 years, P2: 61 years), measurements were restricted to the lower leg and shoulder region with additional recordings from the tongue in patient 2 (P2). A prototype diffusion-weighted stimulated-echo EPI sequence (Siemens Healthcare GmbH) with matrix-size: 160x90/80x80, FoV: 480x270/240x240mm², slice-thickness: 8mm, b-value: 100s/mm², TE: 30ms, TR: 1000ms, and diffusion-sensitizing time: 28ms was applied on a 3T scanner (Prismafit, Siemens Healthcare GmbH). Time-series of motion sensitive single-shot DWI measurements were co-registered and spontaneous activities were detected by an encoder-decoder neural network with subsequent long short-term memory to include temporal information into the detection process for distinguishing between vessel pulsation and muscular activities.

Results: High inter-individual differences over the entire body were detected ranging in an overall percentage of SMAM-affected DWI from 14-86/16.5-36.5/0-27.5% (min.-max. lower leg/thigh/shoulder) for the healthy subgroup. An increase up to 80.8% was observed for ALS patients in the shoulder region. Measurements of the tongue of P2 showed an overall high activity of 63.4% (P2) which contrasted a SMAM rate of up to 7% from two healthy subjects.

Conclusion: Quantification of SMAMs in various body areas might present a novel imaging biomarker candidate for neuromuscular/neurodegenerative diseases. These pilot findings pave the way for future studies on the distribution and overall activity in healthy subjects and patients with neuromuscular/neurodegenerative disease. Spontaneous activity was detected in several muscle regions, verifying that these activities are not restricted to the human lower leg. Furthermore, an increase of spontaneous activity in some (probably involved) muscular regions was observed in two patients with ALS.

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Magdalena Mroczek

Application of MRI as a diagnostic decision support tool in a large cohort of exome sequenced limb-girdle muscular dystrophy patients

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Background: Muscular dystrophies are a heterogeneous group of rare genetic disorders that are characterised by progressive skeletal muscle wasting and weakness. Over 38 genes are associated with LGMD, highlighting the clinical and genetic heterogeneity of muscle disorders. Additionally, the large number of genetic variants obtained through exome sequencing makes interpreting their pathogenicity challenging.

Aims: To study the utility of lower limb MRI in interpreting pathogenicity of genetic variants in a large cohort of patients with LGMD.

Methods: Whole exome sequencing (WES) was applied to >1700 patients with unexplained limb-girdle weakness as part of the MYO-SEQ project. Muscle MRI was requested to help interpreting pathogenicity of genetic variants and also in cases with a particularly challenging diagnosis. The MRIs were performed at the centres participating in the MYO-SEQ project (usually as lower limb axial T1 weighted images and fat saturation images).

Results: As part of the MYO-SEQ project, we gathered 87 muscle MRIs and whole body MRIs and one muscle CT (in this case muscle MRI was not possible due to severe dyspnoea). Among the aforementioned 88 patients, 27 had no gene reported as pathogenic/likely pathogenic. The most frequent genes with pathogenic/likely pathogenic variants in this cohort of 88 patients were: COL6 (5 patients, 3 COL6A3, 2 COL6A2), TTN (5 patients), TRIM32 (4 patients), RYR1 (3 patients), CAPN3 (3 patients) and POMT2 (3 patients). In addition, we gathered muscle MRI for extremely rare likely pathogenic variants and genes recently associated with myopathy (ADSSL1, FXR1, BVES, ACTN2).

Conclusion: Muscle MRI can help to narrow down the number of likely pathogenic variants and to identify a causative variant if there is a specific pattern of muscle involvement and in cases where likely pathogenic variants are commonly encountered during exome data analysis (e.g. COL6, RYR1, TTN). Muscle MRI can have a higher diagnostic value than segregation analysis and is an important tool for diagnostic evaluation of molecular diagnosis in patients with LGMD.

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Chiara Marini-Bettolo

Resting-state functional MRI shows altered default-mode network functional connectivity in Duchenne muscular dystrophy patients

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Background: Difficulties with attention/inhibition, working memory and information processing are well described in patients with Duchenne muscular dystrophy (DMD). Reduced functional connectivity in the motor cortex, assessed with resting state fMRI (RS-fMRI), has been reported in DMD. However, other cortical networks remain unexplored. The default mode network (DMN) is of particular interest as it is involved in cognitive functions known to be at risk in DMD, such as attention/inhibition and information processing.

Aims: The aim of this study was to assess the DMN connectivity in DMD patients compared to controls, as this could help to better understand the cognitive profile in DMD.

Methods: T1-weighted and RS-fMRI scans were acquired from 33 DMD and 24 male age-matched controls at two clinical sites (LUMC and Newcastle; 3T Philips Achieva). Scans were analysed using FSL v.5.0.8 including ICA-AROMA motion correction. Differences in the DMN and the visual network were assessed using FSL RANDOMISE, with age as covariate and threshold-free cluster enhancement multiple comparison correction. Post-hoc analyses were performed on the visual network, executive control network and fronto-parietal network with the same methods.

Results: Twelve clusters were found with stronger connectivity in DMD compared to controls in relation to the DMN. Several clusters fell within the control DMN, indicating hyper-connectivity within the DMN, which was similar to that reported for patients with attention deficit disorders. In addition, several clusters fell outside the control DMN, indicating connectivity to brain regions outside of those that were included in the control DMN, which was similar to reports in patients with autism spectrum disorders. No differences were found between DMD

and controls in the visual network, the executive control network or the fronto-parietal network.

Conclusion: The hyper-connectivity within the DMN in DMD patients may result in greater deactivation when a task is performed due to the inverse relationship with task-related activity. The additional regions with the same activity patterns as the DMN may be indicative of alterations in maturation. Overall, our findings can provide a better understanding of the attention/inhibition, working memory and information processing difficulties in DMD if explored further in a longitudinal format including task-based MRI.

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Erin Englund

Changes in lumbar extensor muscle blood flow following exercise assessed with intravoxel incoherent motion

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Background: Intravoxel Incoherent Motion (IVIM) MRI can evaluate muscle blood flow changes, which may allow for spatial analysis of muscle activation following exercise. Patterns of activation differ in patients with low back pain (LBP) compared to individuals without pain. IVIM uses diffusion-weighted images over a range of b-values, sensitizing the images not only to diffusion (D) but also microvascular blood flow (so-called pseudo-diffusion, D*), which can be represented as:

$$S/S0=(1-f)e-bD+fe-bD* \quad [1]$$

Where S/S0 is the measured data and f is the perfusion fraction.

Aims: To compare IVIM signal changes in the lumbar extensor muscles in response to resisted lumbar extension exercise and to compare those changes between subjects with and without LBP.

Methods: IVIM data were collected at 3T in five healthy subjects, and thirteen patients with LBP before and after a bout of high-intensity lumbar extensor exercise (3 min duration), performed outside of the scanner. IVIM data were obtained with 2D DW-SE-EPI with: resolution=1.5×1.5×5mm^3, 22 slices, TR/TE=2000/50.2ms, averages=4, b-value range=0-700s/mm^2, total acquisition time 300s. Standard fitting methods were used to solve [Eq. 1] for D, f, and D*. Parameters were averaged in an ROI comprising the lumbar extensor muscles. Responses pre-post exercise and between groups were compared via repeated measures ANOVA.

Results: Preliminary analyses for this ongoing study show that all subjects had a significant increase in D (pre-to-post exercise=1.34±0.13 to 1.44±0.09 ×10-3mm^2/s, $p<0.005$) and D* (31.9±11.9 to 45.4±10.9 ×10-3mm^2/s, $p<0.01$), but the change in f was not significant (10.9±0.3 to 11.3±0.2 %, $p=0.3$). Trends towards differences between patients and controls were observed for D ($p=0.06$) and D* ($p=0.08$).

Conclusion: These preliminary results suggest that blood velocity changes in response to lumbar extensor exercise, but this is not necessarily true of blood volume changes. Additional recruitment of healthy controls will help to evaluate whether back pain significantly changes the magnitude of the response of D and D*. Future analyses will compare the temporal dynamics of the responses, as well as patterns of muscle activity between groups.

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Aisha Sheikh

Assessment of Paraspinal Muscle Affection in Becker Muscular Dystrophy using MRI and Muscle Strength Measure

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Background: Trunk muscles are imperative in providing trunk stability and mobility, and it is equally important to explore the nature of these muscles in patients with neuromuscular disorders. Previous studies have shown that trunk muscles are affected in a number of myopathies, such as fascioscapulohumeral muscular dystrophy. However, in patients with Becker muscular dystrophy (BMD), the affection has not yet been investigated.

Aims: The purpose of this study was to investigate the paraspinal muscle affection in BMD.

Methods: In this observational, cross-sectional study we aim to include 20 male subjects with genetically verified BMD and 20 age matched male healthy controls (HC). Currently we have included 18 subjects (age range 19 to 64) with BMD and 12 HC. All subjects underwent an MRI scan and muscle fat fraction percent was used to quantify paraspinal muscles involvement at level C6, Th12, and L4/L5. Maximum isometric trunk muscle force was measured with a stationary dynamometer (Biodex System 4 Pro)."

Results: This abstract presents the preliminary results of 6 subjects with BMD (age range 30 to 50) and 6 healthy controls (age range 30 to 50). A complete reporting of the results will be presented at the conference. Compared with healthy controls, mean fat fraction percent was higher in subjects with BMD in right m. erector spinae (Th12, 42.738 % BMD and 11.653 % HC), left m. multifidus (Th12, 23.869 % BMD and 17.069 % HC), left erector spinae (Th12, 42.457 % BMD and 14.175 % HC), right m. multifidus (L4/L5, 44.827 % BMD and 14.542 % HC), right m. erector spinae (38.569 % BMD and 15.498 % HC), left m. multifidus (L4/L5, 46.480 % BMD and 13.220 % HC), and left. m. erector spinae (L4/L5, 41.681 % BMD and 15.156 % HC). Strength measurement showed a significantly lower peak torque in back extension ($p = 0.04$) in subjects with BMD (mean 131.26 Newton meter) compared with healthy controls (mean 292.46 Newton meter)."

Conclusion: Individuals with BMD are affected in paraspinal muscles, and this correlates to reduced muscle force in back extension.

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Jannette Nassar

Sub-voxel estimation of fat infiltration in degenerative muscle disorders using multi-T2 analysis – a quantitative disease biomarker

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Background: T2 relaxation is an effective biomarker for muscle pathologies. One of the hallmarks of muscle disorders is infiltration of subcutaneous fat and a loss of muscle volume, causing a mixture of two T2-components in each image voxel. Quantification of T2 values is hampered due to the bias of fast multi-echo-spin-echo (MESE) protocols by stimulated echoes. The echo-modulation-curve (EMC)algorithm overcomes this problem and provides accurate T2's, stable across scanners,scan-settings. Here, we present an extension of the EMC-algorithm alongside two quantitative biomarkers of disease-state, estimating fat-water fractions within a single voxel, and the T2 and proton-density values of each component. This is demonstrated on a calf muscle of a patient with Dysferlinopathy and compared to conventional Dixon analysis.

Aims: In this work, we present two new quantitative biomarkers for muscle health, based on two T2 component EMC fitting, simultaneously estimating fat and water fractions within a single voxel, along with the T2 and PD(proton density) values of each component.

Methods: The patient was scanned on a 3T scanner using a standard MESE protocol. Bloch simulations were performed using the exact pulse-sequence scheme. Maps of the patient's calf were segmented to exclude subcutaneous fat, tibia and fibula bones. Biomarker1: voxels whose fat-fraction was >50% were labeled as 'fat' (diseased muscle), and the rest were labeled as 'muscle'(healthy muscle).The %fraction of healthy-to-whole muscle was then calculated. Biomarker2: the average fat fraction across all voxels in the healthy muscle area, yielding a "fat infiltration index".

Results: In addition to conventional fat/water fraction, the EMC also produced the tissue's global T2 value and the T2 value of the water component only.

Quantitative fat-water fraction maps of healthy and diseased muscle segments based on the EMC-algorithm and conventional-Dixon showed good agreement. Similar fat-infiltration indices were produced (15.7±10.8% and 11.4±11% respectively). Moreover, the EMC-algorithm produces the tissue's global and component-only T2's– information not given by Dixon.

Conclusion: The ability to quantify sub-voxel tissue components is highly valuable in clinical applications. Using an extension of the EMC-algorithm, we can quantify water-fat fraction maps, and water and fat T2's, indicative of underlying inflammatory processes, leading to improved diagnosis and treatment in muscle pathologies. This framework is a novel post-processing quantitative approach aiming to overcome the penalties associated with different MRI scan settings, scan parameters and biased interpretations by physicians and radiologists. This will allow the assessment of the state, severity, and progression of musculoskeletal diseases.

Abstracts 17-27

Diffusion Imaging

17

Laura Secondulfo

A novel DTI method for quantification of skeletal muscle pennation angles

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Background: Muscle volume, fibers length and pennation angles (PA) are important characteristics influencing muscle function. PA has shown to change due to training, in muscle injury and in muscle diseases (Kellis, 2016). However, assessment of PA over the full volume of an individual muscle is challenging.

Aims: In this study we propose a diffusion-tensor imaging (DTI) based method to measure the PA and to create PA color maps of the whole muscle volume.

Methods: Lower leg MRI datasets of 5 healthy volunteers were acquired twice, using a 16-channel coil and the 12 table top coils. The foot was immobilized in 3 positions: 15˚dorsiflexion (D15), 0˚neutral position (N0) and 30˚plantar flexion (P30). The MRI protocol included a 3-point mDixon scan for anatomical reference and a SE-EPI DTI. Once the DT-MRI data were de-noised and registered to the anatomical scans with DTI-Tools, the tensor was fitted and the eigenvectors were calculated. In our method the PA maps are calculated in the entire volume using the eigenvector in each voxel and the vector parallel to a reference line running through 2 points, manually selected on the anatomical scan. After that, the segmentations, manually drawn on the water images, were used to select the regions of interest. Repeatability of the PA measurements was assessed by Bland–Altman analysis for the Tibialis Anterior (TA) and the Soleus (SOL) muscles.

Results: Our method facilitated visualization and quantification of PA and minor changes therein with foot position in the whole muscle body of the lower leg: the results show an increased PA in dorsiflexion for the TA and in plantar flexion for the SOL muscle. Bland–Altman analysis of average PA showed better agreement between repeated measurements for the SOL muscle. The coefficients of variation in three positions N0/D15/P30 for the TA and for the SOL were 14.57/18.27/6.47 and 3.81/4.38/7.01, respectively.

Conclusion: Our approach facilitates the generation of reproducible PA color maps of leg muscles and allows to quantify small changes in PA with passive foot stretch. This method can be applied to study changes in PA with training, injury or disease; the preliminary results are in agreement with literature (Hodgson, 2006).

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Lara Schlaffke

Advantages of tractography for the interrater independency of diffusion parameters in human thigh muscles

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Background: Muscle diffusion tensor imaging can indirectly provide information about muscular microstructure and architecture, which plays an increasing role in the evaluation of neuromuscular disease progression and treatment monitoring. The

separation of different muscles is essential to evaluate intermuscular differences and variances.

Aims: To compare three methods to assess diffusion metrics of thigh muscles and evaluated their rater dependency.

Methods: Data from thigh muscles of 30 healthy volunteers were acquired on a Philips 3T system. The protocol included a T1w scan for anatomical reference and a spin-echo EPI to acquire DWIs with 17 gradient orientations. The three methods to assess diffusion parameters for each muscle were:

Standard Tractography (STT): Seed- and Not Gates (ROIs) were drawn to segment the tracts of the upper leg muscles. This yielded sets of fiber tracts for each muscle, from which the diffusion parameters could be calculated.

Volume based Tractography (VBT): slice-by-slice manual segmentations on T1w images were registered to the diffusion space. The preprocessed diffusion data were split according to the segmentations and tractography was performed within the resulting segments of diffusion data.

Manual segmentation based (MSB): The manual segmentations were smoothed and eroded by one voxel and registered to the diffusion space to extract the diffusion metric for each muscle

Manual segmentation and ROI definition was performed by 2 independent raters. ANOVA analysis were performed to investigate the main effect of muscle and Partial Eta² to measure the effect size. Rater dependency was analyzed by using correlation analysis including the ICC.

Results: All methods show significant main effects of muscle ($p<0.001$). Partial Eta² was highest for VBT (FA: .656, MD: .277, L1: .452, RD: .350). ICC for absolute agreement were highest for VBT (FA: .974, MD: .982, L1: .969, RD: .986).

Conclusion: Using tractography, we have less variance in diffusion parameters for each muscle, which is most likely due to a weighting of the tissue by the number of tracts. Higher effect sizes of different muscles, making it more likely to distinguish between muscles based on the diffusion metrics. Furthermore, the VBT method is less dependent on interrater variability and therefore allows to pool data from different raters.

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Nadia Smith

Simulation-based investigation of the spatial distribution of barrier permeability and interstitial diffusivity in muscle tissue for diffusion MRI

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Background: Recent simulation-based investigation of Duchenne muscular dystrophy (DMD) pathology revealed that changes in permeability have a large effect on the diffusion signal. DMD is known to cause increased permeability of muscle fibres. Sub-voxel patterning of permeability in muscle tissue has been shown to have an effect on the diffusion MR signal. We investigate the effect of the density of disordered patterns of permeability in a model of muscle tissue.

Aims: We investigate the diffusion signal as a function of diffusion time and b-value in models of permeable muscle tissue. We then identify the most relevant scan parameter ranges for differentiating changes in permeability in muscle tissue.

Methods: We generate synthetic pulsed gradient spin-echo (PGSE) diffusion-weighted signal curves over a wide range of scan parameters using a Finite Element Method (FEM) to numerically solve the Bloch-Torrey equations for spins in muscle tissue excited via a synthetic PGSE sequence and integrate over the sample volume to compute the diffusion-weighted signal. A hexagonal lattice with a fixed unit cell size was used as a tissue model. Hexagonal cells are separated by a narrow interstitial space with a given diffusivity. Exchange between the cells and interstitial space was via boundaries with a controlled permeability. We calculate diffusion signal as a function of scan parameters in two scenarios: one where permeability is changed uniformly across the tissue, and another in which barriers are permeable or impermeable randomly across the tissue, over a range of barrier permeability probabilities and interstitial diffusivities.

Results: Differences between the signal curves for the uniform and the mean non-uniform boundaries

patterns became significant at long diffusion times and high gradient strengths. The effect is more pronounced for higher permeabilities and interstitial diffusivities.

Conclusion: Sub-voxel distribution of permeability does lead to observable differences in the diffusion signal. The range of scan parameters for which this effect is observable is dependent on the value of the interstitial diffusivity. For diffusivities at the upper end of the range considered we observe differences in scenario at clinically accessible diffusion times and b-values.

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Robert Rehmann

Muscle Diffusion tensor imaging reveals changes in non-fat infiltrated muscles in late-onset Pompe disease

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Background: Patients with late-onset glycogen storage disease type II (LOPD) show symptoms from elevated serum creatine-kinase to slowly progressive limb girdle weakness. To monitor therapeutic approaches and the disease course, non-invasive quantitative imaging markers are essential.

Aims: The purpose of this study was to evaluate differences in diffusion parameters in thigh and calf muscles in LOPD patients using muscle diffusion tensor imaging (mDTI) and mDixon compared to healthy controls (HC).

Methods: We evaluated thigh and calf-muscles of 18 LOPD patients and 29 HC. MRI scans were performed at 3T and comprised muscle diffusion tensor imaging, T1-weighted and mDixonquant imaging.

Mean values of the eigenvalues (λ1-λ3), mean diffusivity (MD), radial diffusivity (RD) and fractional anisotropy (FA) were obtained from tractography for six thigh and seven calf muscles in both legs.

Furthermore, 6-minute-walking-test (6-MWT) data was obtained in 15/18 LOPD patients and correlated with mDTI metrics.

Results: mDTI metrics displayed significant differences between LOPD and HC in FA, MD, λ1-3 in thigh and MD and λ1-3 in calf muscles with all muscles analysed. Healthy appearing thigh muscles of LOPD patients <10% fat-fraction also showed significant differences in MD, RD, λ1-3. Furthermore, MD was positively correlated with 6-MWT data ($p=0.014$).

Conclusion: mDTI metrics could reveal significant diffusion restrictions in muscles of LOPD patients without apparent fat infiltration and thus reflect structural abnormalities in muscles of LOPD patients prior to fatty degeneration. We hypothesize that mDTI might be a quantitative method for the evaluation of disease progression in LOPD.

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David Berry

Varying diffusion time to discriminate between simulated skeletal muscle injury models using stimulated echo DTI

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Background: Diffusion tensor imaging (DTI) has been used to assess restricted diffusion in skeletal muscle, which is thought to track microstructural, and thereby functional changes. While the sensitivity of DTI to muscle microstructure is dependent upon diffusion time, diffusion time has not been systematically optimized or rigorously tested. Here, the relationship between muscle fiber size and the diffusion tensor is precisely tested.

Aims: To compare the relationship between the DT and muscle fiber size at relevant diffusion times in simulated models of skeletal muscle with histology informed geometry in order to determine the diffusion time that maximizes signal contrast between different injury models.

Methods: The MRI simulation tool DifSim was used to model DTI experiments. Models with muscle geometry were derived from histology of uninjured control muscle and injury models including botox-injected, cardiotoxin-injected, and surgically denervated or tenotomized rat tibialis anterior muscles at 1, 3, 7, 14, and 30 days after injury. Mean fiber area was calculated for each model. A stimulated echo DTI pulse sequence was simulated at 12 diffusion times ranging from 20ms–750ms, with fixed TR/TE. The differences in DT metrics (e.g. fractional anisotropy, mean and radial diffusivities) between injured and normal muscle data were calculated to determine the diffusion time that maximized contrast between normal and injured muscle.

Results: Across all models, fractional anisotropy provided greater contrast between injured and control models than diffusivity measurements. Compared to healthy muscle, atrophic injury models (botox, denervation) had the greatest difference in FA at diffusion times between 90ms–250ms. In models with acute edema (cardiotoxin), the contrast between injured and control muscle increased with more prolonged diffusion time, even though these models had smaller mean fiber areas.

Conclusion: These findings may better inform pulse sequence parameter selection for in vivo DTI experiments and may aid in interpretation of how the DT is related to microstructure. If only a single diffusion experiment can be performed, the diffusion time should be ~170ms to maximize sensitivity to muscle pathology. However, ideally data sampled at several diffusion times between 90–500ms would provide optimal contrast to a variety of underlying muscle microstructural changes.

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David Berry

Multiparametric MRI characterization of level dependent differences in lumbar muscle size, quality, and microstructure.

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Background: The posterior muscles of the lumbar spine provide mechanical stability to vertebral segments, as well as support the upper trunk. Normative values of MRI-based biomarkers of muscle health and function can serve as baseline values against which pathology, injury, and low back pain related changes can be compared.

Aims: To perform a systematic, level-by-level evaluation of the size, fat signal fraction, and the restricted diffusion profile of the lumbar muscles in a highly-active, healthy population.

Methods: Forty-two active-duty Marines volunteered for this study. Marines were scanned supine in a 3T MRI scanner. The imaging protocol consisted of; 1) a high resolution anatomical scan (FSPGR), 2) a fat-water separation scan (IDEAL), and 3) a spin-echo DTI scan with echo planar acquisition from the superior endplate of L1 to the inferior endplate of S1.

Results: The erector spinae and multifidus muscles were manually defined at each level. Muscle physiology measurements were compared using two-way repeated-measures analysis of variance with post hoc Sidak tests (factors: lumbar level, muscle). 3D reconstructions were generated to qualitatively assess muscle size, fatty infiltration, and tractography. The erector spinae was larger than the multifidus above L5, had higher fat signal fraction above L3, and a less restricted diffusion profile than the multifidus above L4 ($p<0.0001$). This pattern was reversed in the lower lumbar spine, where the erector spinae was smaller than the multifidus, had a higher fat signal fraction, and demonstrated a more restricted diffusion profile ($p<0.0032$). 3D reconstructions visually depicted muscle composition and fiber orientation, as well as demonstrated normal variation between subjects.

Conclusion: This is the first study to demonstrate level dependent, MRI-based microstructural differences between the erector spinae and multifidus muscles. The macro- and microstructural properties of the lumbar muscles suggest the erector spinae provides little to no support below L4, making the multifidus the predominant muscle stabilizing the lower lumbar spine. 3D reconstruction can be used to observe key features of muscle health such as intra- vs epimuscular fat or fiber orientation. Future studies comparing these data to patients with low back pain may elucidate muscle microstructural changes associated with disease or pathology, which may affect spine stability.

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Judith Lionarons

Brain microstructure detected with DTI in relation to reading performance in Duchenne muscular dystrophy

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Background: Loss of dystrophin expression in brain due to mutations in the DMD gene has been associated with learning disabilities in Duchenne muscular dystrophy (DMD). Reading disabilities are common in DMD, but little is known about their origin. Structural architecture of certain white matter tracts has been related to reading performance in both dyslectic and typically developing children.

Aims: We aimed to investigate microstructural integrity of reading-related white matter tracts in relation to reading performance of DMD patients and healthy controls (HC) to gain insights into the origin of reading disabilities in DMD.

Methods: 3D T1-weighted and diffusion tensor images (DTI; TE/TR=56ms/9.440ms, spatial resolution=1.96x2x2mm, 32 dir, b=0 and 1000s/mm^2, 6:40 min) were obtained in two sites (NL and UK: 3T Philips Achieva, 8-channel head coil; DMD n=40, HC n=29, age=8-21 years). After performing whole brain tractography (seed point resolution 2x2x2 mm, fibre length 20-500mm, step size 1), five reading-related tracts were delineated, and semi-automatically reconstructed using ExploreDTI. Multiple linear regression was used to assess the relation between reading scores, mean diffusivity (MD) and fractional anisotropy (FA) in each tract, per group, with age as a covariate and Bonferroni multiple comparison correction.

Results: Unexpectedly, no correlations with reading scores were found in the reading-related tracts in the HC. Yet a correlation was found between reading scores and FA, and MD and age in the splenium of DMD patients, but not in the other four investigated tracts. This age effect was also found in the HC.

Conclusion: A decrease in FA was correlated to worse reading performance in the splenium of DMD patients, and not of HC. Within our age range splenium development is prominent, which might explain the effect found in solely this tract. Because we did not find any correlations in the HC, our findings should be interpreted with caution. Linking brain connectivity to function in DMD is challenging, as the brain is diffusely affected which does not always lead to cognitive impairment. Based on our findings, the origin of reading disabilities in DMD remains unclear. This might suggest that DTI is insufficient to provide insights into brain function in DMD.

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Marieke Helena Johanna van Rosmalen

Diffusion tensor imaging of the brachial plexus in inflammatory neuropathies

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Background: Magnetic resonance imaging (MRI) is increasingly used as a technique for the diagnostic work up and as a biomarker for disease progression or treatment effects in neuromuscular diseases. MRI of the brachial plexus is used to differentiate between treatable inflammatory neuropathies and clinically relevant mimics as motor neuron disease, bus has limited sensitivity. Quantitative techniques, such as diffusion tensor imaging (DTI) derived parameters have been used on central nervous system

studies, but occasionally in the peripheral nervous system, including the brachial plexus.

Aims: The aim of this study is to explore the feasibility of DTI of the brachial plexus and to assess whether it can differentiate between patients with chronic inflammatory polyneuropathies and disease controls.

Methods: We performed a cross-sectional cohort study in patients with chronic inflammatory

demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), amyotrophic lateral sclerosis (ALS) and progressive muscular atrophy (PMA). We performed DTI and fat-suppressed T2-weighted scans of the brachial plexus on a 3.0 T MRI scanner. DTI data was automatically processed using a custom-build pipeline. Processing comprised data denoising, affine registration to correct for subject motion and eddy currents, bspline registration to correct for EPI distortions, tensor estimation using an iWLLS algorithm, whole volume fiber tractography and nerve root segmentation. Fibre tractography was used to visualize the brachial plexus and for tract based analysis of the diffusion parameters. Independent samples T-test and one-way ANOVA test were used to compare quantitative DTI parameters between groups.

Results: Interim analysis of 62 patients (CIDP=18, MMN=23, disease controls=21) shows significantly lower mean FA in CIDP patients (FA=0.25, SD=0.03, p=0.004), especially in treatment naive patients (FA=0.24, SD=0.02, p=0.001), and a trend towards higher FA in treatment naive MMN patients (FA=0.31, SD=0.04, p=0.106) compared to disease controls (FA=0.29, SD=0.03). Mean FA in MMN compared to CIDP patients differed significantly (p=0.001). MD, RD and AD did not show any differences between groups.

Conclusion: These findings suggest that DTI parameters of the brachial plexus differ between patients with MMN, CIDP and disease controls. However, our results still need to be confirmed after completion of the inclusions.

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Donnie Cameron

Long-diffusion-time diffusion tensor imaging for the assessment of skeletal muscle microstructure in Becker Muscular Dystrophy

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Background: In Becker muscular dystrophy (BMD), only partially functional dystrophin is present at reduced levels. This leads to progressive muscle weakness, fat infiltration, muscle fibre size changes, increased membrane permeability, and fibrosis in skeletal muscle. Diffusion tensor imaging (DTI) is sensitive to altered skeletal muscle architecture if applied with a sufficiently long diffusion time and thus represents a promising method for studying BMD pathology non-invasively.

Aims: Our goal was to compare the diffusion properties of five leg muscles between BMD patients and healthy controls using long-diffusion-time DTI data.

Methods: Seven BMD patients, age 21-58yrs, and seven healthy subjects, age 23-65yrs, were scanned on a 3T Ingenia MR system, where a STEAM-DTI sequence was applied with a mixing time of 300ms and fat suppression comprising a combined SPAIR and echo-shift method. Regions of interest (ROIs) were drawn in five muscles—soleus (SOL), medial gastrocnemius (GM), lateral gastrocnemius (GL), tibialis anterior (TA), and tibialis posterior (TP)—and histogram-based statistics of DTI data were calculated. The signal-to-noise ratio (SNR) for each ROI was determined, with ROIs being excluded if SNR<10. One-way and two-way ANOVA tests were used to assess intra- and intergroup differences in median ROI measures, respectively.

Results: After excluding four GM and three GL ROIs in BMD patients due to low SNR, mean ROI SNRs were 24.4 in BMD, and 23.2 in controls. Two-way ANOVA showed that overall fractional anisotropy (FA) was significantly higher in BMD patients: mean (SD)=0.268 (0.041) vs 0.246 (0.042); p=0.009). For between-muscle differences, in both BMD patients and controls, one-way ANOVA showed differences in FA (p=0.004 and pGL, TA&TP>SOL).

Conclusion: Our long-diffusion-time DTI data show higher FA in BMD patients, indicating that FA is sensitive to changes in muscle microstructure associated with BMD. Inter-muscular differences in

the principal eigenvalue may also indicate differences in intracellular furniture between muscles.

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Baris Kanber

Segmentation of lower limb MR images using contemporary machine learning methods

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Background: Quantitative MRI may provide outcome measures for treatment trials in neuromuscular diseases. Conventionally this has required labour- and time-intensive manual delineation of muscle boundaries.

Aims: To employ contemporary machine learning approaches to anatomically segment lower limb MR images from patients with a broad range of disease severity.

Methods: We used calf-level, 3 point Dixon MR data (Siemens 3T Skyra, TR = 125.0 ms, TE = 3.45/ 4.60/ 5.75 ms, NSA = 4, 11 slices, FOV= 180 mm, voxel size = 0.6 × 0.6 × 10.0 mm3) from a longitudinal study including patients with amyotrophic lateral sclerosis (n=21) and spinal bulbar muscular atrophy (n=21), and healthy controls (n=16). In total 114 MR images were available for analysis. For each dataset, a single observer manually delineated, on a single, mid-level slice, regions enclosing the muscle compartments. Fat and water images were obtained with the conventional algorithm due to Glover (1991). We employed two machine learning methods for segmenting lower limb MR images: first a LightGBM classifier trained on the normalised fat, water, TE=3.45, and 5.75 ms Dixon MR image intensities of each voxel and its 100-neighbourhood (404 features per voxel), and second a 4-channel, U-net also trained on the same images. For the latter, we augmented the data by randomly downscaling (in the range 90-99%) the available images. Performance was measured as the spatial overlap between the manually and computationally segmented regions employing the Dice score coefficient in a nested cross-validation setting.

Results: The LightGBM classifier achieved a mean spatial agreement with the manually drawn muscle region masks, over the whole dataset of 0.944, while the 4-channel, U-net achieved a slightly higher spatial agreement of 0.955. Visual inspection highlighted the greater resolving power of the U-net approach of the subtle boundaries between the muscle- and non-muscle compartments.

Conclusion: Contemporary machine learning methods appear to show promise for segmenting muscle- and non-muscle regions from lower limb MR images. These approaches might alleviate the need for labour- and time-intensive manual delineation that is required for quantifying and monitoring lower-limb muscle/fat fraction in neuromuscular diseases.

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Johannes Forsting

Diffusion Tensor Imaging of the Human Thigh: Consideration of DTI-based fiber tracking stop criteria

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Background: Muscle diffusion tensor imaging (mDTI)-based fiber tracking is a quantitative magnet resonance image (MRI) technique. There are different approaches to analyze DTI data: manual segmentation-based and tract-based analysis. Tract-based analysis has the advantage to weight diffusion information and to reveal 3D information about tissue architecture. This method has been used for DTI analysis in different pathological conditions,

e.g. denervation, inflammation, injuries and muscular dystrophies. Tract-based analysis has limitations and is still not standardized and variation between studies results in missing comparability.

Aims: To consider the tract-based analysis of DTI parameters in muscle by assessing different fiber tracking stop criteria settings on diffusion parameters.

Methods: All volunteers underwent a magnetic resonance (MR) examination in a 3T scanner and 16-channel Torso XL coil. Diffusion-weighted images were acquired to perform DTI and fiber tracking analysis for six upper leg muscles. Whole thigh muscles of 30 healthy volunteers were evaluated by fiber tractography using different fiber tracking stop parameters [FA (0.01-0.15) - (0.4-0.99); angle 10-30 degrees, step size 0.75mm, 1.5mm, 3mm]. Diffusion and tractography-derived parameters per stop criterion were compared by using a repeated measure ANOVA including Bonferroni-corrected post-hoc tests.

Results: We found significant differences in all examined diffusion parameters between different stop criteria (Main effect: $p < 0.001$). We showed different influence of tracking parameters on diffusion parameters in examined muscles (Main Effect: $p \leq 0.001$).

Conclusions: Statistically significant differences in fiber tracking results using different stop criteria were shown. Fiber tracking stop criteria do have an important influence on study results and should be considered in the development of study protocols and comparison of studies. We recommend a FA minimum of 0.10 and a step size lower than voxel size, e.g. a half with a constant ratio between step size and angle of 10°/mm.

Abstracts 28-32

Deep Learning

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Jordi Díaz-Manera

MYO-GUIDE: artificial intelligence muscle MRI-based tool for diagnosis of muscular dystrophies

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Background: Genetic diagnosis of muscular dystrophies (MDs) has classically been guided by clinical presentation, muscle biopsy and muscle MRI data. Muscle MRI suggests diagnosis based on the pattern of muscle fatty replacement. However, patterns overlap between different disorders and knowledge about disease-specific patterns is limited.

Aims: Our aim was to develop a software-based tool that can recognize muscle MRI patterns and thus aid diagnosis of MDs.

Methods: We collected 976 pelvic and lower limbs T1 weighted muscle MRIs from 10 different MDs. Fatty replacement was quantified using Mercuri score and files containing the numeric data were generated. Random forest unsupervised machine learning was applied to develop a model useful to identify the correct diagnosis. 2000 different models were generated and the one with higher accuracy was selected. A new set of 20 MRIs was used to test the accuracy of the model, and the results were compared with diagnoses proposed by 4 specialists in the field.

Results: A total of 976 lower limbs MRIs from 10 different MDs were used. The best model obtained had a 95.7% accuracy, with 92.1% sensitivity and 99.4% specificity. We tested the model with a new of MRIs, and it proposed a diagnosis that was correct in a 18/20 new patients

Conclusion: Machine learning can help medical doctors in the diagnosis of muscle dystrophies by analyzing patterns of muscle fatty replacement in muscle MRI. This tool can be helpful for daily clinics but also in the interpretation of the results of next generation sequencing tests.

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Fabian Balsiger

Learning Shape for Peripheral Nerve Segmentation in Magnetic Resonance Neurography

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Background: Magnetic resonance neurography (MRN) provides complementary but qualitative insights to electrodiagnostic studies when assessing peripheral neuropathy. Recently, automatic segmentation of peripheral nerves from MRN has been explored for obtaining cross-sectional and volume biomarkers. However, even for modern convolutional neural networks (CNNs), peripheral nerve segmentation is difficult due to large volumes of interest, high class imbalances, and difficulties in learning shape representations.

Aims: We aim to improve over traditional CNN-based segmentation by leveraging the sparsity and

shape of peripheral nerves by using a point cloud representation.

Methods: We propose a three-step approach: First, an MRN image is processed by a CNN to obtain a probability map. Second, the probability map is transformed into a point cloud representation. Third, the point cloud is processed by a second CNN that classifies point-wise into peripheral nerve or background yielding a segmented peripheral nerve. For evaluation, we used 52 turbo spin-echo T2-weighted MRN images of the thigh of healthy volunteers (n=10) and patients diagnosed with peripheral neuropathy (n=42). Sequence parameters were TR of 4690ms, TE of 82ms, FOV of 384×330mm^2, FA of 134°, voxel size of 0.52×0.52×4.0mm^3, and 60 axial-oriented slices with gap of 0.4mm. The sciatic nerve was manually segmented by three raters for inter-rater variability quantification and four-fold cross-validation was applied for evaluation.

Results: The segmentation yields Dice coefficients of 0.866±0.044, volumetric similarities of 0.946±0.041, and 95th percentile Hausdorff distances of 4.5±9.7mm, which is a statistically significant improvement over CNN-only segmentation of Balsiger et al. with 0.746±0.130, 0.903±0.101, and 12.6±15.6mm. Inter-rater variabilities are 0.802±0.091, 0.905±0.082, and 9.2±17.6mm. Therefore, the approach achieved statistically significant better results for the Dice coefficient and the volumetric similarity and on-par results for the Hausdorff distance compared to the inter-rater variability. Qualitatively, 3-D renderings show a high agreement between the automatic and manual segmentations. By synthetic experiments, we showed that the point cloud processing allows to explicitly learn a sciatic nerve-like shape.

Conclusion: The results suggest that peripheral nerve segmentation from MRN is feasible and achieves human inter-rater performance. Such automatic segmentation might allow quantifying peripheral neuropathies for disease progression and outcome or serve as volume of interest for further quantitative MRN techniques.

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Fabian Balsiger

Quantification of fat fraction and water T1 in neuromuscular diseases using deep learning-based magnetic resonance fingerprinting with water and fat separation

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Background: Magnetic resonance imaging provides outcome measures such as fat fraction (FF) and water T2 for neuromuscular diseases (NMDs). Lately, water T1 (T1-H_2O), quantified with magnetic resonance fingerprinting (MRF), is also being considered as a possible biomarker of disease activity. While MRF comes with fast acquisitions, the reconstruction relying on dictionary matching lacks scalability, is discrete, and time-consuming.

Aims: We aim to perform MRF reconstruction for NMDs using deep learning as accurate and fast alternative to the dictionary matching.

Methods: We used MRF T1-FF, an MRF sequence for quantification of FF and T1-H_2O in NMDs. MRF T1-FF relies on a 1400 radial spokes FLASH echo train with variable TE, TR, and FA after an inversion pulse. Eight spokes were used to reconstruct a temporal frame using non-uniform fast Fourier transform, and a subsequent dictionary matching was used to reconstruct FF, T1-H_2O, off-resonance frequency (B0), and flip angle efficacy (B1) maps. To replace the dictionary matching, we propose a convolutional neural network (CNN), which operates patch-wise to reconstruct the four parametric maps. Input are patches of the temporal frames, and output are the parametric maps. The CNN relies on an interleaved temporal and spatial feature learning, leveraging both the temporal and spatial correlation of fingerprints. Patients with various NMDs imaged at

thigh and leg were used to evaluate our approach (training/validation/testing=94/20/50).

Results: Qualitatively, the four parametric maps show good agreement to the dictionary matching reconstructed maps. Region of interest analysis of the major muscles showed excellent agreement between CNN and dictionary matching reconstructions with coefficient of determinations of 0.99, 0.89, 0.99, 0.99 for FF, T1-H_2O, B0, and B1. Bland-Altman analysis showed little to no bias and 95% limits of agreement below the dictionary sampling step size for FF, B0, and B1. For T1-H_2O, the 95% limits of agreement were ±60ms. The CNN required one minute for reconstruction, whereas the dictionary matching required eight hours.

Conclusion: The results suggest that deep learning-based reconstruction of MRF is feasible with good accuracy and excellent robustness to a highly heterogeneous dataset. MRF with deep learning-based reconstruction could be clinically relevant for quantifying FF and T1-H_2O in NMDs.

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Francesco Santini

Deep neural network with regional regularization for fat/water reconstruction of multi-echo gradient-echo images

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Background: The quantification of the fat present inside the muscle tissue is an important biomarker of muscle health, and the current gold standard for the imaging of fat infiltration is the use of multi-echo gradient-echo acquisitions. Accurate reconstruction of fat and water images is performed by algorithms that take into account multiple fat spectral peaks and spatial regularization. However, these algorithms are usually slow, requiring hours per dataset.

Aims: Our aim was to use a deep neural network (DNN) to quickly generate fat fraction maps of musculoskeletal datasets. As a tradeoff between generality and spatial homogeneity, a local regularization was introduced by the inclusion of neighboring voxels as input values.

Methods: A DNN with two hidden layers was implemented with the Tensorflow/Keras framework in Python and trained on five three-dimensional datasets (4 patients suffering from neuromuscular diseases, 1 healthy volunteer) acquired with a 6-echo gradient-echo sequence (matrix size: 432x396x52, TR 35ms, TEs 1.7…9.2ms, resolution 1.0x1.0x5mm^3). The input data were 2D patches of 5x5 complex voxel values at each echo, and the ground truth was provided by the FattyRiot [1] algorithm. The training set was extracted from the acquired datasets for a total of 1e5 datapoints. The test of the network was performed on an additional patient dataset not included in the training set.

Results: The network was able to produce images qualitatively consistent with the ground truth. On the test data, the median absolute error in the estimation of fat fraction estimation was 1.9%. In some parts of strong B0 inhomogeneities, the local regularization was not sufficient to avoid misassignment of fat and water.

Conclusion: The usage of DNN is a promising approach to increase the reconstruction speed of fat/water algorithms, and local regularization is an attractive alternative to the usage of whole images for training, as it may provide more general results. However, the patch size needs to be optimized to avoid artifacts and the network architecture improved to increase accuracy. The framework for data preparation, fitting and optimal trained network will be made available as open-source to promote collaborative optimization efforts.

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David Bendahan

Segmentation of individual muscles in MR images using Convolutional Neural Networks can be improved using Muscles and Borders parcellations

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Background: Segmentation of muscles in MR images has been well-recognized as challenging given, among other things, the variability of muscle shapes within and between subjects, the variable positions of subjects within a scanner, the variable positions of RF coils on the imaged part of the body, the histological changes which can erase the borders between individual muscles etc .

Aims: The segmentation performance of two convolutional neural networks i.e. Bayesian SegNet and UNet was assessed for the four individual muscles of the quadriceps in a group of healthy volunteers. More particularly, the effect of muscles and borders parcellations was assessed. The networks performance taking into account each muscle individually or the whole set of muscles was also considered. The corresponding results were compared with those obtained using a conventional multi-atlas method.

Methods: A dataset of 500 images was used as a training set while 180 additional images were used for the validation process. The testing phase was performed for two other datasets with 140 images each. Four different variants were assayed considering simultaneous segmentation of individual muscles (On5), separate segmentation of individual muscles (Fn2) and the use of additional classes related to muscle borders in both cases (On9 and Fn3) and so for both Bayesian SegNet and UNet.

Results: Both CNN largely outperformed the multi-atlas segmentation strategy. The higher DSI values i.e. 0.96 ± 0.01 for the rectus femoris muscle, 0.93 ± 0.01 for the vastus intermedius muscle, 0.94 ± 0.03 for the vastus lateralis muscle and 0.96 ± 0.01 for the vastus medialis muscle were obtained with the On9 and Fn3 variants i.e. taking into account the muscle borders labels in addition to the muscle labels.

Conclusion: Deep-learning based methods are optimal for the segmentation of thigh muscles. The results obtained with both CNN disclosed that the corresponding efficiency can be improved when considering labels for both muscles and borders.

Abstracts 33-72

MR Outcome Measures

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Harmen Reyngoudt

Can global muscle segmentation detect changes in neuromuscular disorders using quantitative nuclear magnetic resonance imaging?

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Background: The degree of fatty infiltration, as measured using water-fat NMR imaging separation techniques (such as Dixon) is now a widely accepted muscle imaging biomarker and an often proposed outcome measure in many neuromuscular disease longitudinal studies. The question remains which is the specific muscle (group) to evaluate during the study period.

Aims: We aimed to compare different segmentation approaches in a variety of neuromuscular disorders: immune-mediated necrotizing myopathy (IMNM), sporadic inclusion body myositis (sIBM), GNE myopathy (GNEM), Duchenne muscular dystrophy (DMD), limb-girdle muscular dystrophy types 2B and 2I, Pompe disease (GSD2) and spinal muscular atrophy (SMA).

Methods: In 109 patients (21 IMNM, 21 IBM, 10 GNEM, 20 DMD, 12 LGMD2B, 7 LGMD2I, 13 GSD2, 5 SMA) two NMR scans were obtained at one year interval; on a clinical 3T Prisma Fit Siemens system. A fat-water separation 3-point Dixon NMR sequence was performed in 5 slices at the level of the thigh as well as at the level of the leg. Regions of interest (ROIs) were drawn in individual muscles, muscle groups and in the whole segment. From these ROIs, values for fat fraction (FF) and contractile cross-sectional area (cCSA) were derived. Changes in FF and cCSA using all methods (individual muscles, muscle groups, combinations of individual muscles or muscle groups or the whole segment were evaluated. SRM, defined as the mean change in FF or cCSA (ΔFF or ΔcCSA) divided by the mean standard deviation of ΔFF or ΔcCSA, were calculated and SRMs ≥0.8 were evaluated as being highly responsive change.

Results: Global segmentation gave a satisfactory SRM (≥0.8) in thigh for IMNM, IBM, GNEM, LGMD2B and DMD. In leg, this was the case for IMNM, GNEM, LGMD2B and DMD. In some diseases, higher SRMs were found in individual muscles or muscle groups (including for LGMD2I and SMA).

Conclusion: Global segmentation is in some cases at least as sensitive as individual muscle or muscle group segmentation, implying that individual muscle segmentation is not always mandatory. A significant increase in FF does not imply automatically a high SRM, which means that the best muscle candidates to detect a treatment effect are not systematically the ones experiencing the most severe and fastest disease progression.

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Harmen Reyngoudt

Prediction of disease progression in forearm muscle in Duchenne muscular dystrophy using quantitative fat-water NMRI: possible or not?

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Background: Several studies in Duchenne muscular dystrophy (DMD) have shown longitudinal trajectories of both functional and qNMRI outcome measures. Here, we present longitudinal qNMRI data in forearm for up to seven years in the AFM Genethon-sponsored DMD natural history study.

Aims: We investigated how well disease progression could be predicted using a sigmoidal model of the muscle fat fraction (FF).

Methods: A fat-water separation 3-point Dixon NMR sequence was performed on a clinical 3T Prisma Fit Siemens scanner at 1-year intervals in anterior forearm muscles. Thirty-five DMD boys (12.6±3.3 years) were included. A 2-parameter sigmoidal model was fitted on each individual FF trajectory (constraints: FF at age=0 years is smaller than 1%; slopes > 0; asymptote at 90% FF). First, we investigated the whole data set when using only the 1st time point (TP) for fitting. Then, in 8 of 35 subjects who all had 5 consecutive yearly NMR exams, trajectories were fitted in four different ways: using 1/2/3/4 TPs. The difference between the actual measured and the predicted FF value on subsequent TPs was calculated.

Results: Using only the first time point in the overall data set, mean FF prediction errors of 3.7% (n=26), 5.4% (n=22), 5.0% (n=16), 7.5% (n=9), 8.4% (n=7) and 10.1% (n=5) were measured for the 2nd/3rd/4th/5th/6th/7th TP, respectively. In 8 patients with 5 consecutive TPs, using only the first TP led to errors of 4.0%/5.7%/5.9%/8.4% for the 2nd/3rd/4th/5th TP, respectively. Using the first two TPs, errors of 4.3%/8.4%/11.0% were measured for the 3rd/4th/5th TP, respectively. Using the three TPs, errors of 4.9%/7.0% were measured for the 4th/5th TP, respectively. Finally, using the four first TP, an error of 3.8% was obtained for the 5th TP.

Conclusion: These data indicate that, when using at least 3 and 4 TPs in the sigmoidal fitting, the prediction error on the FF values for subsequent TPs decreases. In this subset, adding a 2nd TP did not decrease the difference with the actual measured FF values, due to some trajectories deviating strongly from the imposed sigmoid. Further investigations on the choice of prediction model are necessary to assess whether FF trajectories can actually be used to predict disease progression, including a confrontation with functional and clinical data.

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Harmen Reyngoudt

Title: About the origin of decreased 1H NMRS-based water T2 in highly fatty infiltrated skeletal muscles of subjects with neuromuscular disorders

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Background: Skeletal muscle water T2 (T2w) is a sensitive, yet non-specific qNMRI marker of 'disease activity' in neuromuscular diseases. Although quantitative water T2 mapping is usually performed, disentangling of water and lipid contributions is non-trivial, leading to possibly biased values in highly fatty infiltrated muscles. For this reason, 1H NMRS is still perceived as the 'gold standard' for determining the T2w value in skeletal muscle due to the frequency-based separation between water and lipids.

Aims: We investigated the behavior of 1H NMRS-based T2w in patients with muscle fat fraction (FF) between 0%-80%.

Methods: A series of 14 unsaturated single voxel STEAM acquisitions with TEs from 20ms-288ms (TR=6500 ms, 4 averages) were obtained in one specific muscle (vastus lateralis, gastrocnemius

medialis or tibialis anterior) of 214 patients with various neuromuscular disorders (sporadic inclusion body myositis, Duchenne muscular dystrophy, …). T2w and FF (based on the different lipid peaks corrected for their respective T2 value) were determined. Peak areas were fitted to a mono-exponential model.

Results: T2w was weakly correlated with FF (ρ=0.41, P<0.001). From the data, it was evident that this correlation was mainly determined by those subjects with FF≥60%. When looking more closely to these heavily affected patients, we found that in the subjects with lower T2w values (T2w = 27.2±2.1 ms) spectra presented larger water resonance linewidths (LW = 25.6±3.6 Hz) than in subjects with higher T2w values (T2w = 34.5±2.5 ms, LW = 18.3±3.3 Hz, P<0.001). Furthermore, T2w negatively correlated with the water resonance linewidth (ρ=0.67, P<0.001).

Conclusion: Lower T2w values at high FF values is not a new finding (either with NMRI or NMRS). We merely want to stress that we should be careful with the interpretation of 1H NMRS-based T2w values that seem to decrease in patients with a very high degree of fatty infiltrations. The larger linewidths observed in the spectra characterized by shorter T2w may be explained by the local B0 gradients induced by susceptibility differences between muscle and fat. These susceptibility-induced field gradients might cause the water diffusion to negatively bias the apparent T2w in those regions with specific fatty infiltration patterns. Confronting 1H NMRS with CPMG measurements using short inter-echo spacing should allow us to verify this hypothesis.

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Lara Schlaffke

Multicenter evaluation of stability and reproducibility of quantitative MRI measures in healthy calf muscles

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Background: Quantitative MR-Imaging techniques play an increasingly important role as biomarkers for the diagnosis of different neuromuscular diseases (NMD) as well as for disease and treatment monitoring.

To monitor and quantify non-invasively disease progression or the effect of new therapies in individual subjects, reproducible quantitative measurements for unbiased comparisons are required.

Aims: The purpose of this study was to evaluate temporal stability, multicenter reproducibility and influence of covariates on a multimodal MR-protocol for quantitative muscle imaging and to facilitate its use as a standardized protocol for evaluation of pathology in skeletal muscle.

Methods: Quantitative T2, quantitative diffusion and 4-point Dixon acquisitions of the calf muscles of both legs were repeated within one hour. Sixty-five healthy volunteers (31 females) were included in one of eight 3T MR-systems. Five travelling subjects were examined in six MR-scanners. Average values over all slices of water-T2 relaxation time, proton-density fat-fraction (PDFF), and diffusion metrics were determined for seven muscles. Temporal stability was tested with repeated measured ANOVA and 2-way random Intraclass-Correlation coefficient (ICC). Multicenter reproducibility of travelling volunteers was assessed by a 2-way mixed ICC. The factors age, BMI, gender and muscle were tested for covariance.

Results: ICC's of temporal stability were between 0.963 and 0.999 for all parameters. Water-T2 relaxation decreased significantly (p<10-3) within one hour by ~1ms. Multicenter reproducibility showed

ICCs within 0.879–0.917 with the lowest ICC for mean diffusivity. Different muscles showed the highest covariance, explaining 20-40% of variance for observed parameters.

Standardized acquisition and processing of quantitative muscle MRI data resulted in high comparability between centers. The imaging protocol exhibited high temporal stability over one hour except for water T2 relaxation times.

Conclusion: These results show that data pooling is feasible and allows assembling data from patients with neuromuscular diseases, paving the way towards larger studies of rare muscle disorders.

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Xeni Deligianni

Dynamic muscle MRI comparison to water T2 on facioscapulohumeral muscular dystrophy patients with phase contrast imaging of electrically stimulated quadriceps muscles

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Background: The most challenging characteristic of facioscapulohumeral muscular dystrophy (FSHD) is the non-linear muscle-by-muscle involvement. Quantitative MRI is used for FSHD follow-up, but progression of the disease is still very hard to predict.

Aims: The purpose of this study was to use dynamic phase contrast MR imaging of electrically stimulated quadriceps muscles to explain muscle changes that are not reflected in other types of quantitative MRI images such as water T2 and therefore contribute to the understanding of this challenging disease.

Methods: 18 FSHD patients were scanned on a clinical 3T MRI at two different time points approximately 6 months apart. The protocol included dynamic MRI of the quadriceps on both legs, clinical severity scores (CSS) and dynamometry measurements (force peak measured in kilos), as well as 6-Minute Walk Test (6MWT). For the dynamic MRI acquisition, an electrical muscle stimulation device was synchronized with a 3D high-temporal-resolution cine phase contrast velocity encoding acquisition[1]. The current was set to a sufficient level to evoke muscle twitching without knee extension. During periodic contraction of the quadriceps muscle group, a parasagittal slice was acquired with voxels of 2.3x2.3x5mm^3 and a temporal resolution of 42ms. Strain rate and strain vectors were calculated from the velocity fields and normalized by the value of stimulation current for comparison. Texture analysis (to extract contrast properties) was performed in addition. A multi-echo TSE sequence was used for calculation of the water T2 maps through EPG-fitting[2]. As a control, fat-water maps were also analyzed.

Results: From the analysis at 0-time point there was a good correlation(>0.4) of the dynamic data (contrast of strain & strain rate) and the results of dynamometry and 6MWT. The comparison of water T2 and dynamic data did not show any correlation or dependence. Similar results were given by the comparison of fat fractions and dynamic data. In addition, differences of dynamic data for different time points were not reflected by water T2.

Conclusion: Dynamic MRI data show differences that are not correlated to water T2 changes, which indicates that it could potentially be a useful additional biomarker.

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Ericky Caldas de Almeida Araujo

Assessing the short-T2-signal fraction in patients with congenital myopathies using an Ultrashort-TE sequence

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Background: Non-invasive quantification of skeletal muscle (SkM) fibrosis would provide a most important biomarker in NMDs. There is no validated imaging alternative to biopsy, an invasive procedure which is not representative of the whole muscle. It has been stated that the short-T2 signal observed in UTE could reflect extra cellular matrix (ECM) content, suggesting UTE as a potential candidate.

Aims: To assess the short-T2 signal fraction in the skeletal muscle of patients with congenital myopathies (CM).

Methods: Fat-fraction (FF), T2*, and short-T2-fraction (sT2f) maps were extracted from UTE data acquired in the calf of 16 controls (age: 30±8 years) and 10 CM patients (age: 45±21 years) using the method described in (Araujo et al. MRM. 78:997-1008 (2017)). Regions of interest (ROIs) were draw in the Soleus, Gastrocnemius Lat. and Med. ROIs' FF, T2* and sT2f statistics were compared between the two groups using one-way ANOVA. Parameters' heterogeneity in each ROI was assessed by means of their respective standard deviations. A global sT2f (gsT2f) was calculated per subject, as the mean sT2f weighted by the ROIs' sizes.

Results: Fasciae and aponeurosis were systematically highlighted in the sT2f maps. No differences in sT2f were observed between the groups. The sT2f was negatively correlated to FF ($r=-0.50$, $p<0.001$). In patients, a negative correlation was observed between gsT2f and age ($r=-0.54$, $p<0.05$). Mean FF, FF heterogeneity and T2* heterogeneity were increased in CM patients ($p<0.001$). T2* presented negative correlations with FF ($r=-0.24$, $p<0.001$) and T2* heterogeneity correlated with FF ($r=0.70$, $p<0.001$).

Conclusion: Alterations observed in T2* reflect the tissue heterogeneity in fatty infiltrated muscles (different T2* characterizing muscle and fat; and reduced T2* in fat-muscle interfaces). Although fibrosis is one of the pathologic features of CM, especially in elder patients, no alteration of sT2f was observed in these patients. Although a high sT2f was systematically observed in fasciae for all subjects, in SkM, the short-T2 signal may as well arise from macromolecular pools in the contractile apparatus. So, while fatty replacement seems to lead to a decrease of sT2f, increased ECM fraction might not be systematically reflected by an increase of sT2f.

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Linda Heskamp

Intramuscular Pattern of Fat Infiltration Measured by MRI to Identify Disease Initiation in FSHD

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Background: Facioscapulohumeral muscular dystrophy (FSHD) is an inherent muscular dystrophy. Its key genetic defect is a loss of DUX4 suppression leading expression of the DUX4 protein. To develop new treatments it is important to know which factors are involved DUX4 initiation and disease progression. Discovering the location of DUX4 initiation and the subsequent muscular fat infiltration could therefore guide therapy development in FSHD.

Aims: To study the intramuscular fat infiltration pattern in the lower extremity muscles of FSHD patients from tendon to tendon using quantitative MRI and semi-automatic muscle segmentation.

Methods: The lower extremity muscles (left and right) of 9 FSHD patients were scanned on a 3T Siemens MR scanner. We acquired 2pt-Dixon images from which we reconstructed fat fraction (FF) maps.

For every leg, 12 upper and 10 lower leg muscles were manually segmented on every fifth slice and used to automatically segment the remaining slices. In this way, on average 44 slices were semi-automatically segmented per muscle. Subsequently, FF was calculated per slice for every muscle. Each muscle was then divided in five equally spaced proximo-distal segments to test if FF depended on its position along the proximo-distal axis using a linear mixed model.

Results:The linear mixed model revealed that FF depended on the segment position along the muscle ($p < 0.001$), being highest distally. Post-hoc analysis showed that all five segments differed significantly from each other. The muscles exhibited a fat infiltration front, being most evident in intermediately fat infiltrated muscles (10%<FF<50%) compared to normally appearing muscle (FF50%). Visual inspection of the fat infiltration front in the intermediately fat infiltration muscles showed that the position of the fat infiltration front was more proximally when the muscle's average FF was higher.

Conclusion: Muscles in FSHD patients exhibit a fat infiltration front that appears to start distally and to move from distal to proximal over time. This indicates that DUX4 expression is likely to start in the distal part of the muscle as well. To confirm our findings, longitudinal assessment of this fat infiltration front is essential.

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Jorge Alonso Perez

A prospective 4 years longitudinal study of quantitative muscle MRI in a large cohort of patients with Late Onset Pompe disease

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Background: Late onset Pompe disease (LOPD) is a genetic disorder characterized by progressive degeneration of skeletal muscles produced by a deficiency of acid alpha-glucosidase. Enzymatic replacement therapy (ERT) with alfa-glucosidase seems to reduce the progression of the disease, although at this moment is not completely clear to what extent and how long.

Aims: The aim of this study was to describe the radiological progression of a long cohort of late onset Pompe disease (LOPD) patients over 4 years using quantitative muscle magnetic resonance imaging (qMRI) and correlate these results with clinical data.

Methods: A total of 36 LOPD patients were visited once every year for four years. In every visit, several muscle function tests, spirometry, activities of daily living scales, quality of life scales and quantitative muscle MRI were performed. Muscle MRI consisted in 3-point Dixon studies of the trunk and thigh muscles. Longitudinal analysis of the measures were performed using linear mixed models applying Greenhouse-Geisser test.

Results: Fat fraction significantly increased in most of the muscles of the thighs and the trunk both in treated and in presymptomatic patients (Greenhouse-Geisser $p<0.05$). As an average, fat fraction increased a 1.9% per year in treated patients, while it increased a 0.8% in presymptomatic patients. In parallel, we identified a significant worsening of lower limbs muscle strength (decrease of 4.7 points on lower limbs manual muscle score) and in spirometry values (decrease of 6.9% in Forced Vital Capacity seated) over the 4 years follow-up. We identified as independent modifiers of fat fraction progression over the 4 years the baseline results of muscle function tests and the baseline mean thigh fat fraction (ANCOVA analysis, $p<0.05$). We identified the paraspinal and the adductor major muscles as the most useful for the follow-up presymptomatic patients, while biceps femoris and vastus lateralis were the most useful in treated patients.

Conclusion: Muscle qMRI is able to detect subclinical disease progression in LOPD patients, even in presymptomatic patients. The information provided in this study may be critically important for the design of upcoming clinical trials, allowing identification of better outcome measures to detect the effect of new drugs.

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Nienke van de Velde

Size matters: Contractile properties of fat free muscle tissue are more preserved in upper leg than lower leg muscle in BMD

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Background: Becker muscular dystrophy (BMD) is characterized by progressive muscle fat replacement. Quantitative MRI (qMRI) previously showed no relation between strength and contractile cross sectional area (cCSA) in lower leg (LL) muscles of BMD patients, suggesting reduced muscle quality.

Aims: In this study, we aimed to investigate if muscle quality is also reduced in upper leg (UL) muscles of BMD and whether fat fraction (FF) distribution over the proximo-distal axis of the muscle contributes to this.

Methods: FFs per slice were determined using 3-point Dixon 3T MRI scans from 23 BMD patients (median age 42.3 years, IQR 31.0-54.6, 23 slices of 1 cm). In the UL, vastus lateralis (VL) and semitendinosus (SET) mean whole muscle weighted (wFF) and three middle slices (wFF3) FF were calculated at the insertion of the biceps femoris short head. In the LL, tibialis anterior (TA) muscle wFF and wFF3 were calculated centered at its maximal CSA (CSAmax). cCSAmax was calculated by correcting total CSA by FF of that slice. To assess the proximo-distal distribution, ranges of FF were compared on a slice-by-slice basis. The three parameters (wFF, wFF3, cCSAmax) were correlated to strength measured by quantitative muscle assessment using Spearman's correlation (significance $p<0.05$).

Results: The median difference between the slice with the lowest and highest FF of the VL was 25% (range 6-59%), of the SET 28% (1-70%) and of TA 18% (3-76%). Upon visual inspection, FF of both VL and TA appeared highest approaching the origo and insertion (U shaped curve), while in SET, the FF was low near the origo and higher near the insertion. In VL and SET, the three parameters correlated well to knee extension and knee flexion (ρ=-0.759 and ρ=-0.709 for wFF, ρ=-0.688 and ρ=-0.728 for wFF3, ρ=0.819 and ρ=0.730 for cCSAmax), while in TA the correlation to dorsiflexion was moderate (ρ=-0.532, ρ=-0.479 and ρ=0.497).

Conclusion: Contractile properties seem to be more preserved in UL than LL muscles in BMD. This is an important consideration when testing new therapies, as strength cCSA relations may respond differently between UL and LL. The different distribution of fat replacement along the proximo-distal axis did not influence this correlation.

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Linda Heskamp

Do carnosine and acetylcarnitine tissue concentrations vary along the human tibialis anterior muscle?

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Background: Recently, we reported that the phosphocreatine recovery rate after exercise (kPCr), reflecting oxidative capacity, varies along the tibialis anterior (TA). The underlying physiological mechanism for this intramuscular variation could be related to differences in fibre type and mitochondrial metabolism. Carnosine is a potential biomarker for muscle fibre type and acetylcarnitine is a compound buffering acetyl groups involved in mitochondrial metabolism and has been shown to correlate with kPCr. Both compounds can be assessed with 1H-MR spectroscopy (MRS).

Aims: To determine carnosine and acetylcarnitine levels along the TA as surrogate measures of intramuscular variation in fiber type c.q. mitochondrial metabolism.

Methods: Nine volunteers participated in this study. Carnosine was assessed in six of these volunteers and acetylcarnitine in all nine. 1H MRS measurements were performed on a 3T Siemens MR system using a 15-channel Tx-Rx knee coil and sLASER sequence (TR=3000ms, water suppression, bandwidth=1200Hz). Carnosine was measured with at two positions along the TA (TE=33ms, voxel-size: 17x17x60mm, number of averages (NA)=144). The

amplitude of the 8 ppm carnosine peak was fitted with a jMRUI and normalized to water. Acetylcarnitine was assessed with a long TE at 2 or 3 positions along the TA (TE=350ms, voxel-size=17x17x40mm to 17x17x60mm, TR=6000ms, NA=128-192). The signals of creatine (3.03ppm) and acetylcarnitine (2.13ppm) were integrated and corrected for T2 relaxation. Tissue concentrations of acetylcarnitine were then determined assuming creatine at 30mM/kgww.

Results: The carnosine/water ratio did not differ between the distal and proximal voxel (1.8±0.4 vs. 1.7±0.5, p=0.884). Acetylcarnitine levels varied between volunteers and was visible in both the distal and proximal voxel in 4 out 9 volunteers. In those 4 volunteers, acetylcarnitine levels did not differ between distal and proximal (1.7±1.5 vs. 1.5±1.2, p=0.308). In the other 5 volunteers, acetylcarnitine was only visible in the proximal voxel for 2 volunteers, middle voxel for 2 volunteers or distal voxel for 1 volunteer.

Conclusion: Carnosine did not vary along the TA, while acetylcarnitine showed large individual variations, but no systematic proximodistal difference. This suggests that variations in fiber type and mitochondrial metabolism do not explain the intramuscular gradient in PCr recovery rate in the TA.

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Meredith James

The Clinical Outcome Study For Dysferlinopathy: Relationship between quantitative MRI and Physiotherapy outcomes of strength and disease progression over three years

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Background: The Jain Clinical Outcome Study for Dysferlinopathy (LGMDR2), an international natural history study of 197 patients, aims to identify outcome measures for this heterogeneous degenerative disease to facilitate trial readiness.

Aims: Here we examined the relationship between muscle MRI findings, strength and functional motor performance in 54 patients, year by year, over three years.

Methods: We report on 54 subjects from Newcastle and Paris. NMRI was performed on two clinical MR platforms (Siemens and Philips) at 3T. Three-point Dixon scans were acquired with optimised echo times, repetition times and flip angles. Thigh and leg muscles were manually delineated to obtain mean Fat Fraction (FF) values, per muscle, per year. Using Spearman correlations, we examined the relationship between FF of individual muscles, thigh and leg segments to muscle strength as measured by manual muscle testing (MMT) and hand-held dynamometry (HHD) at each time point. We examined those patients with rapid disease progression as measured by a functional scale, the North Star Assessment for Limb Girdle Type Muscular Dystrophies (NSAD) to look for potential FF predictors of disease progression. Change in FF was measured by paired t-test and NSAD using Wilcoxon test for non-parametric data.

Results: MMT and HHD showed significant change in most muscle groups each year and were highly and significantly correlated with each other. Strength measurements were highly correlated with NSAD. Some muscle groups were more responsive to change at different stages of disease. FF increased by an average of 2% across all muscles in all subjects each year. In some subjects, greater change was seen indicating rapid progression. A rapid clinical decline in motor ability measured by NSAD was observed in 13 subjects compared to whole COS cohort average change. At above 60% FF, most patients were noted to have severe disease. Below 10% FF, most were defined as clinically mild. Considerable overlap between severity groupings existed when using a mean FF for weighted segments.

Conclusion: Progression in dysferlinopathy can be demonstrated using strength (MMT and HHD), NSAD and muscle wasting as measured by FF.

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Fiona E Smith

Fat fraction determination by quantitative MRI in a global, natural history study of dysferlinopathy over four years

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Background: Dysferlinopathy or limb-girdle muscular dystrophy type R2 (LGMD R2) is caused by mutations in the dysferlin gene (*DSYF*) and is characterised by progressive muscle wasting with variable rates of progression. The Jain Clinical Outcome Study (COS) is an international study of 203 adults with dysferlinopathy from eight countries. Muscle MRI and clinical assessments were performed annually over four years to determine outcome measures for future clinical trials.

Aims: Here we report a subset of the fat fraction (FF) MRI data collected from two centres over the entire course of the study.

Methods: FF data were evaluated in 54 patients (30 Female, 24 Male, mean (SD) age = (37.3 ± 12.4) years from baseline to year 3. MRI was performed on two clinical MR platforms (Siemens and Philips) at 3T. Three-point Dixon scans were acquired with optimised echo times, repetition times and flip angles. Bilateral thigh and leg muscles were manually delineated to obtain the mean fat fraction value per muscle. The change in FF over each year was compared for each muscle using a paired t test (significance = $p < 0.05$). Pearson r analysis was used for correlations.

Results: In all muscles, FF increased by an average of 2% each year, over all subjects. In the leg, the gastrocnemius lateralis muscle showed the greatest absolute increase in FF of 6% ($p<0.009$) from baseline to year 1. In the thigh, almost every muscle showed significant increases in FF over each year, with the greatest increase of 5% occurring between years 1 and 2 in the biceps femoris ($p = 0.001$), vastus lateralis ($p = 0.0001$) and vastus medialis muscles ($p = 0.001$). In some subjects, the mean increase in FF over each year, over all muscles exceeded 10%, indicating faster progression for these subjects. There was a significant correlation (Pearson's $r = 0.5$ ($p< 0.0001$)) between fat fraction in all muscles at baseline and the number of years since symptom onset of the disease.

Conclusion: Progression of muscle wasting in dysferlinopathy can be demonstrated using FF analysis. FF can discriminate between faster and slower progression of the disease in some subjects.

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Francesco Santini

A fast open-source implementation of water T2 with integrated fat fraction measurements from multi-echo spin-echo acquisitions

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Background: T2 is an important parameter for the assessment of muscle health, as it is elevated in case of inflammation, which itself is a precursor of permanent muscle damage. However, in case of neuromuscular diseases, fat infiltration in the muscle tissue might prevent the correct quantification of T2. However, using conventional multi-echo spin-echo acquisitions, it is possible to estimate the water T2 values and fat fractions [1].

Aims: While the acquisition sequence is standard on clinical MR scanners, for reproducibility and

comparability of results, it is important to have a publicly-available, standardized version of the fitting procedure. To this end, we hereby present a fast open-source implementation of an extended phase graph (EPG)-based fitting algorithm for water T2. The full code will be released on the Github website for public use.

Methods: An EPG simulation for a multi-echo spin-echo sequence, including slice profile, was implemented in Python/NumPy. The simulation is run over a range of water-T2, fat fraction (FF) and B1 values to generate a dictionary to which the acquired signals are then compared using cross-correlation. The algorithm was implemented on a GPU (Nvidia 1660Ti) using the CUDA framework for optimal performance. The method was tested on the thigh of two healthy volunteers and six patients suffering from neuromuscular diseases (facioscapulohumeral muscular dystrophy (n=5) and amyotrophic lateral sclerosis (n=1)), scanned at 3T with the following sequence parameters: TE/TR 10.9/4100.0 ms, resolution 1.2x1.2x10.0 mm³, number of echoes 8 or 17, number of slices 4 or 6. T2 and FF were evaluated in a region of interest in the vastus lateralis.

Results: The software required 1.9±0.15 seconds per slice. In patients, the considered muscle did not present any visually discernible sign of disease. Measured T2 values were 40.6±3.8ms (patients) and 38±1.2ms (volunteers). The FF was 1.8%±3.9% in patients and 0.1%±0.5% in volunteers.

Conclusion: The proposed software delivers good performance and quantitative results that are in line with the known underlying pathological substrates in neuromuscular diseases. Because of its open-source nature, it has the potential to be used for standardized and comparable acquisitions.

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Nick Zafeiropoulos

Tissue-water CPMG T2 and fat fraction mapping of upper and lower limb skeletal muscle in amyotrophic lateral sclerosis, Kennedy’s disease and Duchenne muscular dystrophy

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Background: Skeletal muscle-water spin-spin relaxation time (T2m), and fat fraction estimated from multi-echo MRI

Aims: We aimed to optimise the estimation of skeletal muscle-water spin-spin relaxation time (T2m), and fat fraction estimated from multi-echo MRI, as potential biomarkers, by accounting for instrumental factors such as B1 errors, non-Gaussian noise and non-ideal echo train evolution.

Methods: A multi-component slice-profile-compensated extended phase graph (sEPG) model for multi-echo Carr-Purcell-Meiboom-Gill (CPMG) spin-echo sequence signals was implemented, with the fat signal modelled as two empirically calibrated sEPG components with fixed parameters, and the remaining unknown parameters (B1 field factor, T2m, fat fraction (ffa), global amplitude and Rician noise SD) determined by maximum likelihood estimation. After validation using a calibrated test object the algorithm was used to analyse clinical muscle study data from patient groups with amyotrophic lateral sclerosis (ALS), Kennedy’s disease (KD) and Duchenne muscular dystrophy

(DMD) – and their longitudinal follow up scans – and matched healthy controls. Parameter maps were generated with a pipeline including quality control steps rejecting pixels failing fit quality or physical meaningfulness criteria. Muscle fat-fraction was also determined independently by 3-point Dixon MRI (ffd), allowing quantitative comparison of ffa and ffd.

Results: In ALS and KD median T2m were significantly elevated compared with healthy controls ($p = 0.001$ & 0.003 respectively; 1-way ANOVA) in varied patterns and time courses, whereas it was decreased in DMD ($p = 0.026$; 1-way ANOVA); other T2m distribution histogram metrics such as the skewness and full width at quarter maximum also differed significantly between patients and healthy volunteers. Quantitative comparison of ffa and ffd in the same muscles revealed a monotonic relationship deviating from linearity due to differing deviations from the assumed ideal signal behaviour in each method.

Conclusion: Clinically practical conventional CPMG sequences, combined with an appropriate signal model and parameter estimation method can provide robust T2m and ffa measures which change in disease and may sensitively reflect different aspects of neuromuscular pathology.

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Jasper Morrow

Long term follow up of quantitative lower limb MRI outcome measures in inclusion body myositis

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Background: Quantitative MRI has been shown to be a responsive outcome measure in muscle diseases including inclusion body myositis (IBM), but the majority of longitudinal studies have been over a short duration and demonstration of longitudinal validity is often lacking.

Aims: 1) Define long term progression of intramuscular fat accumulation in patients with IBM compared with healthy controls. 2) Assess longitudinal correlation of MRI biomarkers and clinical parameters

Methods: This work is an extension of the Quantitative MRI study in IBM undertaken at the MRC Centre for Neuromuscular Diseases with published 12 month follow-up data. Study participants were invited to return for further assessments with the same clinical assessments and MRI protocol including 3-point Dixon fat quantification, pseudo-T2 mapping and magnetisation transfer imaging.

Results: An additional 21 visits occurred in 10 patients with IBM, providing 41 MRI scans in total for analysis. The mean follow up interval was 4.9 years, range 2.6-8.9 years. Eleven controls also undertook further assessments and showed no significant change in quantitative MRI measurements. In IBM patients, at both thigh and calf levels, muscle fat fraction (FF) and pseudo-T2 continued to increase whilst MTR continued to reduce over the duration of follow up.Considering individual muscles greatest FF increase was seen in adductor magnus (22.4%) whilst the increase in tibialis posterior was negligible (0.8%). Although progression in individual muscles varied, the progression of the overall FF at both thigh and calf level appeared linear for each patient. The rate of FF progression varied significantly ranging from +1.3% to +8.9% FF/year at thigh level and +0.3 to +5.9% FF/year at calf level. Thigh muscle FF progression correlated significantly with calf FF progression ($R=0.88$), and overall muscle FF progression correlated significantly with rate of decline in functional measures including IBM-FRS ($R=0.66$).

Conclusion: Intramuscular fat accumulation continues to progress over long term follow up (up to 9 years) in patients with IBM and shows longitudinal correlation with functional outcome measures. Rate of progression varies between patients, with both slow and fast progressors evident, which has potential relevance to studies of disease pathogenesis and clinical trial design.

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Blair Johnston

Comparison of fat fraction calculation approaches in healthy adults and adults with secondary muscle wasting

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Background: In MRI, the Dixon method is the accepted method of quantifying muscle fat fraction (FF). However, automated processing approaches can produce inaccurate results due to segmentation errors or fat/water inverting. An alternative approach, proposed by Azzabou et al (2015), using a T2 fitting method reported a strong correlation with the Dixon FF in healthy adults and subjects with a variety of neuromuscular diseases.

Aims: The sequence required to perform the T2 method is routinely acquired to measure muscle inflammation via muscle water content. Therefore the aim of the study was to investigate whether the T2 method could also maintain or increase the precision in quantifying muscle FF, to reduce scan time by removing the need for the Dixon sequence in the protocol.

Methods: VIBE Dixon and multi-slice multi-echo (MSME) sequences were acquired at distal femur on a 3T MRI scanner. A 6-point VIBE Dixon sequence was used with an automated algorithm to calculate muscle FF. A tri-exponential fit was applied to the MSME images to quantify the muscle water T2 and FF. FF was quantified in 9 healthy adults and 17 adults with Crohn's disease (CD), a patient group with secondary cause of muscle wasting. Three subjects were excluded from the study as the automated Dixon calculation failed. FF values obtained from both sequences were compared using Bland-Altman analysis.

Results: FF differed by an average of 1.2% (SD: 2.1%) between the methods, with the CD group showing a larger average difference, 1.7% (SD: 1.6%), compared with the control group, 0.2% (SD: 2.6%). The difference (bias) between FF values obtained varied across the measurement range, showing a linear positive trend.

Conclusion: Further work is required to ensure the methods are robust across the full clinical range, given the systematic bias between the Dixon and T2 fitting method. If the T2 fitting method can be shown to maintain or increase the precision in quantifying muscle FF, in addition to the muscle inflammation measure, then the Dixon sequence would not be required. This would lead to a reduction in scan time which may have the additional benefit of reducing movement artefact.

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Title: Matteo Paoletti matteo.paoletti87@gmail.com Muscular involvement in amyotrophic lateral sclerosis (ALS) assessed by quantitative MRI

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Background: ALS is a neurodegenerative disease that targets motor neurons, even if other cells (including muscle cells) may be affected. Muscle involvement in ALS is traditionally considered as secondary to neuronal damage, and has recently been demonstrated on qualitative T1-SE sequences.

Aims: Our aims are to apply quantitative muscle MRI (qMRI) to the evaluation of disease involvement in ALS and to explore any correlation with clinical scores.

Methods: In a longitudinal prospective study of 12 months, 20 subjects with ALS are evaluated with quantitative 3T MRI including a 6-echo water fat separation sequence (1) and a T2 TSE multi-echo sequence (17 echo times)(2). Seven healthy age-matched subjects are enrolled as controls (15 planned). Sequences are centered on the thigh and lower leg muscles. Twelve regions of interest (ROI) are manually drawn on the thigh muscles and six on the lower leg muscles. Fat Fraction (FF) and water T2 (wT2) are extracted for each ROI. The clinical scale ALSFRS-R is collected ± 1 month from the MRI date.

Results: So far, we enrolled 13 ALS subjects in a precocious clinical phase (8 spinal form, 5 with bulbar onset) at baseline, [average age 63.9 years, range 32-80], and 11 at 6-months follow-up. The preliminary transversal analysis did not show an increased FF in the thigh and leg muscles of ALS subjects compared to controls ($p>0.05$). In ALS subjects FF nonetheless showed a negative correlation with motor items of the ALSFRS-r ($rho < -0.55$, $p < 0.05$). wT2 differed significantly compared to controls both in thigh and leg muscles ($p<0.05$). By contrast, wT2 measures did not correlate with the motor items of ALSFRS-r. Longitudinally FF increased significantly only in vastus lateralis and intermedius and adductor magnus, bilaterally; wT2 decreased only in the peroneal muscles ($p<0.05$).

Conclusion: Current preliminary data show a diffuse increase of wT2 in thigh and leg muscles of ALS subjects; a mild FF increase was shown only in the longitudinal analysis and for selected muscles. wT2 increase may suggest structural modifications in muscular micro-setting, possibly correlated to the effects of denervation rather than to true muscular edema. The scheduled follow-up will further elucidate such findings.

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Matteo Paoletti

Assessment of muscular involvement in facio-scapulo-humeral dystrophy (FSHD) by quantitative muscle MRI

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Background: Quantitative MRI (qMRI) is a promising tool in the assessment of disease involvement in muscular dystrophies. In particular fat fraction and quantitative measures of intramuscular edema are of particular interest as they are able to quantify fat replacement and muscle free water (so far mainly evaluated qualitatively) and have a role as outcome measures for clinical trials.

Aims: To evaluate qMRI as an outcome marker of disease progression in FSHD, both transversally and longitudinally.

Methods: A cohort of 20 subjects with diagnosis of FSHD is going to be evaluated through a 3 Tesla MRI protocol including a 6-echo fat-water separation sequence (1) and a TSE T2 multi-echo sequence with EPG fitting (17 echo times) (2). Sequences are centered on the thigh and lower leg muscles.

A total number of 12 regions of interest (ROI) are manually drawn on the thigh and 6 on the lower leg muscles. Fat Fraction (FF) and water T2 (wT2) times are extracted for each ROI. In all subjects multiple clinical scores are collected (Clinical Severity

Scale [CSS] the 6 minute walking test score [6MWS]) as well as dynamometric measures for the quadriceps and for hamstring muscles.

Results: Up to now 14 subjects have been scanned at baseline, and 11 at 6 months follow-up. Recruitment is scheduled to be completed by 2020. Fat fraction of tibialis anterior, hamstring muscles and also adductor magnus showed positive correlation with CSS and negative correlation with 6MWT and dynamometric measures. wT2 for the same muscle groups also showed a positive correlation with CSS and a negative correlation with 6MWT and dynamometric measures. Longitudinally wT2 showed a significant reduction at 6mo follow-up, mainly in the hamstring muscles, adductor magnus, soleus and extensor digitorum longus. No significant change in FF at 6 months was showed.

Conclusion: FF and waterT2 shows a good correlation with clinical measures in FSHD in more extensively involved muscles (hamstring and anterior muscles of the leg). Longitudinally waterT2 decreases mainly in the same muscles. As quantitative data may represent clinico-metric properties and track the severity of involvement, they stand out as a promising biomarker of disease in FSHD.

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Paolo Felisaz

Texture analysis and machine learning to predict fat fraction and water T2 in muscles affected with FSHD

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Background: Quantitative MRI (qMRI) provides estimations of clinically relevant parameters in facio-scapular-humeral disease (FSHD) such as at fraction (FF) and edema (waterT2) of muscles, but is not routinely used in most clinical departments. Instead conventional non-quantitative MRI is typically applied. However, texture analysis and machine learning classifiers can allow to extract quantitative data from qualitative measures.

Aims: To predict qMRI parameters using non-quantitative MRI derived texture parameters and machine learning regression models.

Methods: 16 FSHD patients were imaged on a 3T clinical MRI at both thighs. The protocol included quantitative sequences for calculations of waterT2 and FF maps (a multi-echo TSE sequence with EPG-fitting1 and a multi-echo gradient echo 6pt fat separation technique2) and a conventional axial TSE PD weighted sequence (matrix 384x192, TR/TE 4100/10.9 ms, slice thickness 10mm, gap 30 mm, 5 slices). We analyzed regions-of-interest (ROIs) for each muscle of the thigh (12 ROIs per side) on the PDw sequence. 48 features including first and second order statistics were extracted from each ROI with the software LifeX3. We investigated the performance of different Machine Learning models on the extracted features to predict corresponding ROIs mean values of FF and Water T2 (Python4). The algorithms were trained on a training set (350 ROIs) with and without PCA and tested on an independent validation set (38 ROIs). Performance was evaluated in terms of Mean Absolute Error (MAE) and Root Mean Squared Error (RMSE) (ranges 0-1).

Results: 5 regressive machine learning methods were tested (trees, linear regression (Ridge), k Nearest Neighbour, Support Vector Machine, Random Forest). Random forest without PCA obtained the best performance in predicting FF (MAE 0.115, RMSE 0.161). Comparable results were obtained with Ridge regression and Support Vector Machines without PCA (RR: MAE 0.125, RMSE 0.169; SVM:

MAE 0.137, RMSE 0.183). For the prediction of Water T2, Random Forest with PCA obtained the best result (MAE 0.102, RMSE 0.158), closely followed by Support Vector Machines (MAE 0.124, RMSE 0.159). PCA yielded a variable impact on all ML methods.

Conclusion: Texture analysis and machine learning regression models provide promising results for predicting FF and Water T2 from non quantitative-MRI.

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Claudia Weidensteiner

Assessment of T2, diffusion, and fat content in paretic calf muscles of children with cerebral palsy after botulinum toxin treatment

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Background: Cerebral palsy (CP) is a sensorimotor dysfunction caused by damage to the not yet developed brain. This leads to weakness and spasticity of the affected muscles. Functional muscle contractures in the leg are treated with botulinum toxin (BTX) injections to improve gait.

Aims: Our aim is to assess the effect of BTX with MRI. Here, we focus on potential changes in T2, diffusion, and fat content in the treated muscles of CP patients. Results from this pilot study may help to explain failures of the current treatment procedures.

Methods: To date, 4 CP patients (3 male, age 11-13 years, 3 hemiparetic, 1 diparetic) were scanned at 3T pre injection, 6 weeks and 12 weeks post BTX injections in the gastrocnemius und soleus calf muscles. T2 maps were measured with a multi SE sequence (voxel size 1.0x1.0x3.0 mm, TR/TE= 4.3 s/11ms…115 ms, fat-suppressed) (1). A Dixon protocol (voxel size 1.1x1.1x3.0 mm, TR/TE=20 ms/1.41 ms…8.71 ms) was used to measure fat fraction (2). ADC maps were acquired with an EPI sequence (2.5 mm isotropic resolution, b=700 s/m2, 30 directions). Gait analysis was performed at each time point.

Results: Hyperintensity on T2w scans and increased T2 (by approx. 10 ms) were observed in the gastrocnemius and – more pronounced – in a region of the soleus at the injection site at 6w and 12w compared to baseline. ADC and fat fraction did not change significantly in these hyperintense regions.

Conclusion: This study showed elevated T2 at BTX injection sites up to 12w post injection. This is in line with studies after BTX injections in the gastrocnemius of healthy adults (3) and stroke patients (4). The increase in T2 is presumably caused by an increase in the extracellular space around the atrophic muscle fibers after treatment (3). We could not detect a significant increase in ADC, as one would expect with an increase in extracellular space. BTX showed an effect in parts of the soleus and not in the complete cross section of this muscle. The extent of BTX induced effect on the T2 maps may help to explain the limited treatment effect on the gait of these CP patients.

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Uros Klickovic

Skeletal muscle MRI differentiates SBMA and ALS and correlates with disease severity

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Background: Amyotrophic lateral sclerosis (ALS) and spinal bulbar muscular atrophy (SBMA) are two progressive neuromuscular disorders in differential diagnosis, both characterized by the degeneration of lower motor neurons and progressive muscle weakness, for which there is no effective treatment. One crucial obstacle to the development of disease-modifying therapies is the lack of reproducible biomarkers to monitor disease progression.

Aims: To investigate the use of muscle MRI for the differential diagnosis and as a disease progression biomarker for the two major forms of motor neuron disorders SBMA and ALS.

Methods: We applied quantitative 3-point Dixon and semi-quantitative T1-weighted and STIR imaging to bulbar and lower limb muscles, and performed clinical and functional assessments in ALS (n=21) and SBMA (n=21) patients, alongside healthy controls (n=16). Acquired images were analyzed for the presence of fat infiltration or edema as well as specific patterns of muscle involvement. Quantitative MRI measurements were correlated with clinical parameters of disease severity in ALS and SBMA.

Results: Quantitative imaging revealed significant fat infiltration in bulbar ($p<0.001$) and limb muscles in SBMA compared to controls (thigh: $p<0.001$; calf: $p=0.001$), identifying a characteristic pattern of muscle involvement. In ALS, semi-quantitative STIR imaging detected marked hyperintensities in lower limb muscles, distinguishing ALS from SBMA and controls. Lastly, MRI measurements correlated significantly with clinical scales of disease severity in both ALS and SBMA.

Conclusion: Our findings show that muscle MRI differentiates between SBMA and ALS and correlates with disease severity, supporting its use as a diagnostic tool and biomarker for disease progression. This highlights the clinical utility of muscle MRI in motor neuron disorders and contributes to establishing objective outcome measures crucial for trialing new therapies.

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Claudia Alejandra Nuñez Peralta

Lower limbs magnetic transfer contrast (MTC) correlates with muscle function in patients with Pompe disease

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Background: Magnetic transfer contrast (MTC) is an MRI technique that serves to observe the interaction between bulk water protons and the protons contained in the macromolecular pool. This MT effect can be quantified obtaining the magnetization transfer ratio (MTR). MTR has demonstrated to be useful in the analysis of muscle damage in patients with muscle dystrophies.

Aims: The aim of this study was to study a long cohort of patients with late onset Pompe disease

(LOPD) using the magnetic transfer technique combined with a Dixon sequence.

Methods: A total of 25 LOPD patients and 35 healthy controls were included in the study. Our MRI protocol included MT-Dixon sequence and a standard three-point Dixon of the thigh muscles in a Philips scanner, Ingenia1.5 T.

We analyzed both sequences in 4 different muscles of the thighs: vastus lateralis, biceps long head, adductor major and sartorius. All patients were also studied with muscle function tests including MRC, dynamometry, 6MWT, timed up&go test, time to climb up 4 steps and MFM-20. Conventional spirometry was performed to all patients obtaining FVC seated and in supine. Daily live activities were analyzed using the Activlim scale and the rPACT scale.

Results: We observed that MTR was lower in patients with Pompe disease compared to healthy controls (Mann whitney U test, $p<0.005$). There was a negative correlation between MTR values and the amount of fat measured using three-point Dixon (Spearman test, RR: -0,71, $p=0.0001$). We compared MTR values in muscles with less than 20% of fat measured by Dixon, but we did not observe significant differences. There was a significant correlation between MTR values and the results of the muscle function tests.

Conclusions: MTR is a good tool to identify muscle loss in patients with Pompe disease, that can be useful in the follow-up of muscle degeneration in this disease in clinical trials or natural history studies.

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Felix Kurz

Low serum cholesterol is associated with peripheral nerve damage in type 2 diabetes

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Background: Distal symmetric polyneuropathy is a increasingly prevalent severe complication in patients with type 2 diabetes. While lowering serum cholesterol levels is considered a common treatment to control cholesterol metabolism in type 2 diabetes, recent studies found that a decrease in high-density lipoprotein cholesterol levels was associated with an increase in severity of clinical symptoms, and also with an increase in a specific lesion form in magnetic resonance neurography imaging of the sciatic nerve in patients with distal symmetric polyneuropathy.

Aims: Our objective was to investigate the association between peripheral nerve lesions in patients with diabetic distal symmetric polyneuropathy and serum cholesterol levels.

Methods: In this cross-sectional, prospective cohort study, we obtained clinical, serologic, and electrophysiologic data of 100 patients (distal symmetric polyneuropathy: 64, no polyneuropathy: 36) with type 2 diabetes, and performed magnetic resonance neurography of the right leg at a Siemens Trio 3T scanner. We applied an axial turbo spin-echo T2-weighted sequence with relaxation time: 5.97 seconds, echo time: 55 milliseconds, field of view: 160 x 160 square millimeter, matrix size: 512 x 512, slice thickness: 0.05 mm, intersection gap: 0.35 mm, in-plane-resolution: 0.5 x 0.3 mm, number of slices: 24. Lipid-equivalent nerve lesions were segmented and quantified with a semi-automatic approach.

Results: We found that the tibial nerve conduction velocity was positively correlated with total serum cholesterol ($p=0.02$) and with serum low-density lipoprotein levels ($p=0.04$), while no such correlation was found for either serum high-density lipoprotein levels. Lipid-equivalent nerve lesions were positively correlated with the nerve's mean cross-sectional area ($p<0.001$), and negatively with total serum cholesterol levels ($p<0.001$) and low-density lipoprotein levels ($p=0.003$), as well as nerve conduction velocities of tibial and peroneal nerves ($p=0.01$, $p<0.001$, respectively).

Conclusion: The findings indicate that low serum cholesterol levels in patients with type 2 diabetes and distal symmetric polyneuropathy are associated

with the amount of lipid-equivalent nerve lesions in magnetic resonance neurography. This agrees with recent studies that found low serum cholesterol levels to be associated with impaired nerve regeneration after axonal damage, presumably due to an insufficient supply of cholesterol to Schwann cells and neurite tips of the regenerating axon.

With emerging therapies in type 2 diabetes such as PCSK9 inhibitors, that promote an aggressive lowering of cholesterol levels, our findings suggest that close attention should be paid to clinical signs of polyneuropathy.

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David Bendahan

Areas of muscle tissue alteration can differ from activated regions during electrically-induced isometric contractions

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Background: Skeletal muscle isometric contractions resulting from neuromuscular electrostimulation (NMES) can generate damage within activated muscles.

Aims: This study aimed at comparing the localization of activated and damaged muscle areas using magnetic resonance imaging.

Methods: Thirteen subjects performed a single bout of NMES-induced isometric contractions known to induce a decrease in maximal voluntary isometric contraction (MVC) and an increase in muscle volume and transverse relaxation time (T2). This whole set of parameters was measured before, immediately after (POST), seven days (D7), fourteen days (D14) and twenty-one days (D21) after the NMES session. Spatial normalization of T2 maps were performed in order to compare the localization of activated and damaged muscle areas from statistical mapping analyses.

Results: A significant decrease in MVC was measured at POST (-26 ± 9%), D7 (-20 ± 6%) and D14 (-12 ± 5%). Based on immediate T2 changes, activated muscle areas were detected in superficial parts of the two muscles located beneath the stimulation electrodes (i.e., vastus lateralis and medialis) at POST. Unexpectedly, altered areas, determined on the basis of persisting T2 changes, were mainly located in the deep region of the vastus lateralis (+57 ± 24%) and superficial area of the vastus medialis (+24 ± 16%) at D7 and were still present at at D21.

Conclusion: Based on immediate and persisting T2 changes, we determined that activated and damaged muscle areas are different. Alteration of tissues other than active skeletal muscle fibers could account for changes measured during unaccustomed NMES-induced isometric contractions.

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David Bendahan

Fat fraction distribution in lower limb muscles of CMT1A patients: a quantitative MRI study

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Background: Charcot-Marie-Tooth disease (CMT) is a heterogeneous group of hereditary and sensory neuropathies. The CMT 1A type (CMT1A) is the most frequent form representing more than half of the cases with a prevalence of about 1 in 5000. Clinical features combine length-dependent motor deficits and sensory symptoms. CMT neuropathy ONLS scores have been validated for CMT patients. Electrophysiological measurements such as MUNIX

could represent a potential biomarker of interest. Skeletal muscle quantitative MRI has been scarcely used in CMT and the corresponding metrics have been only quantified in a single central slice.

Aims: In the present study, we intended to combine an MRI quantitative approach to a dedicated segmentation method in order to quantify fat fraction in 14 individual muscle compartments of leg and thigh. The corresponding metrics were quantified in the whole set of MRI slices such as a potential proximal-to-distal gradient could be assayed. Correlations with clinical scores were also analyzed.

Methods: MRI fat fraction was assessed in lower-limb musculature of CMT1A patients and healthy controls. Muscle compartments (14) were selected at leg and thigh levels and for proximal, distal and medial slices. Muscle fat infiltration profile was determined quantitatively in each muscle compartment and along the entire volume of acquisition to determine a length-dependent gradient of fat infiltration. Clinical impairment was evaluated using muscle strength measurements and CMT examination scores (CMTES).

Results: A total of 16 CMT1A patients were enrolled and compared to 11 healthy subjects. CMT1A patients showed a larger muscle fat fraction at leg and thigh levels with a proximal to distal gradient. At the leg level, the largest fat infiltration was quantified in the anterior and lateral compartments. CMTES score was correlated with fat fraction, especially in the anterior compartment of leg muscles. Strength of plantar flexion was also correlated with fat fraction of the posterior compartments of leg muscles.

Conclusion: Based on quantitative MRI measurements combined to a dedicated segmentation method, muscle fat infiltration quantified in CMT1A patients disclosed a length-dependent peroneal-type pattern of fat infiltration and was correlated to main clinical variables. Quantification of fat fraction at different levels of the leg anterior compartment might be of interest in future clinical trials.

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Alina Sprenger

Monitoring axonal injury and neurogenic muscle atrophy by use of a multimodal MRI protocol

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Background: Clinical examination and electrophysiology are currently standard for diagnostics and monitoring in chronic inflammatory demyelinating polyneuropathy (CIDP), non-systemic vasculitic neuropathy (NSVN) and amyotrophic lateral sclerosis (ALS). However, these measures are restricted to accessible nerves or insensitive to detect subtle changes regarding axonal injury and regeneration.

Aims: To investigate the utility of a multimodal MRI protocol to detect and differentiate subtle peripheral nerve lesions and neurogenic muscle damage in patients with different neuropathic conditions.

Methods: 10 NSVN patients and 10 age-matched controls, 11 CIDP patients and 11 age-matched controls as well as 14 ALS patients and 13 age-matched controls underwent MRI, electrophysiological and clinical assessments. Patients and controls were assessed by diffusion tensor imaging (DTI) of sciatic or tibial nerve and multiecho Dixon MRI of quadriceps and biceps femoris muscle (CIDP, ALS) or soleus and gastrocnemius muscles (NSVN). MRI parameters were correlated with clinical and electrophysiological data.

Results: DTI scans of sciatic and tibial nerve showed significant lower mean fractional anisotropy (FA) values compared to healthy controls. Intramuscular fat fractions in the measured muscles were significantly higher in patients compared to healthy controls. In NSVN patients FA values correlated negatively with clinical measure of pain.

Conclusion: Our data provide proof-of-concept that DTI and multiecho Dixon are useful to assess axonal integrity and neurogenic muscle changes in different neuropathic conditions. Further studies are needed to establisch DTI and multiecho Dixon as diagnostic and surrogate marker in neuromuscular diseases.

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Tokunbor Lawal

Ryanodine receptor 1-related myopathies: Semi-automated quantification of intramuscular fatty infiltration from T1-weighted MRI.

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Background: Variations in the ryanodinee receptor 1 (RYR1) gene remain the most frequent cause of congenital myopathies. The main subtypes of RYR1-related myopathies (RYR1-RM) include central core disease, multi-minicore disease, core-rod myopathy, centronuclear myopathy, and congenital fiber type disproportion. RYR1-RM are dominantly and recessively inherited, and present with a wide spectrum of clinical severity. RYR1-RM can present with a selective pattern and gradient of muscle involvement on magnetic resonance imaging (MRI). In dominant cases, this is often characterized by relative sparing of the rectus femoris, adductor longus, gracilis and tibialis anterior muscles in the lower extremity however recessive cases can exhibit more widespread fatty infiltration. This makes muscle MRI a useful ancillary tool for differential diagnosis, interpretation of novel genetic findings, and scoring disease severity.

Aims: To quantify intramuscular fatty infiltration in an RYR1-RM cohort using T1-weighted MRI.

Methods: Muscle imaging was performed using a single 3-T whole-body MRI system (Verio, Siemens Medical Systems, Erlangen, Germany) using flexible phased array body-matrix coils. Axial images of the lower extremity muscles were acquired by T1-weighted fast spin-echo and short tau inversion recovery (STIR) sequences. A modified ImageJ-based program with a MidGrey threshold was used to quantify intramuscular non-contractile tissue.

Results: Grey-scale quantification of muscle fat from T1-weighted images of the upper and lower leg from 39 genetically confirmed RYR1-RM affected individuals (32 dominant and 7 recessive) with varying degrees of disease severity were evaluated.

Conclusion: A modified ImageJ-based program was able to select and quantify areas of fatty infiltration in a cohort of heterogeneously-affected individuals with RYR1-RM. Standardized MRI acquisition protocols and validated quantification programs can be used to rate disease severity, quantify disease progression, and identify optimal muscle biopsy locations, in individuals affected with neuromuscular disorders such as RYR1-RM.

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Natasha Hornby

T2 map Magnetic Resonance Imaging and histopathology of skeletal muscle in the deltaE50-MD dog model of Duchenne Muscular Dystrophy

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Background: Duchenne Muscular Dystrophy (DMD) is a fatal, X-linked, muscle wasting disease that affects approximately 1 in 5000 boys with no cure. Clinically-applicable translational trials rely heavily on use of animal models, such as the unique deltaE50-MD dystrophin-deficient dog model maintained at the Royal Veterinary College. Non-invasive Magnetic Resonance Imaging (MRI) biomarkers in patients with DMD enable overall assessment of skeletal muscle disease progression, that can be compared with histopathological evaluation of muscle biopsy samples.

Aims: The aim of this study was to validate and assess variability of selected MRI and histopathological biomarkers in the deltaE50-MD dog model, to demonstrate disease progression.

Methods: MRI was conducted in 15 deltaE50-MD and 10 age-matched littermate wildtype (WT) male dogs under general anaesthesia, every 12 weeks from 3 to 18 months of age. Up to 7 pelvic limb and 4 lumbar muscles were assessed bilaterally in each dog and T2 map signal intensities (SI) were measured. Mixed model analyses (SPSS) were used to

examine differences between groups at different ages. Minimum Feret diameter of muscle fibres and picrosirius red fraction were compared in the cranial sartorius (CS) and vastus lateralis (VL) muscles between groups.

Results: T2 map SI were significantly higher in affected deltaE50-MD dogs ($p<0.001$) when compared to WT dogs in all pelvic limb and lumbar muscles. Median muscle fibre minimum Feret diameter in 18-month-old WT dogs was significantly smaller in the CS muscle when compared to the VL muscle ($p<0.001$). However, in 18-month-old deltaE50-MD dogs there was no significant difference found between the two muscles. Picrosirius red fraction was significantly higher in both the CS ($p<0.001$) and VL muscles ($p<0.01$) in 18-month-old deltaE50-MD dogs when compared to WT dogs. Variability within DMD animals for most MRI biomarkers was low.

Conclusion: Quantitative T2 mapping, minimum Feret diameter and picrosirius red fraction are useful MRI and histopathology biomarkers when monitoring skeletal muscle disease progression in the deltaE50-MD dog model. Low variabilities between animals means that these biomarkers will be useful to determine efficacy of clinical therapeutic agents in the colony with high statistical power and relatively low sample sizes.

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Karin Naarding

Reasons for non-participation in Duchenne muscular dystrophy MRI studies

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Background: In 2019, 33 interventional clinical trials are recruiting patients with Duchenne muscular dystrophy (DMD). Previous trials have underscored the importance of knowledge of the natural history, and for this, another 14 studies are including simultaneously. In natural history studies, direct benefit to patients is lacking and the burden, especially in MRI studies can be perceived as high. At the same time, recruitment efficiency is essential and selection bias unwanted.

Aims: To understand reasons for not participating we studied decision making and patient characteristics of DMD patients in several natural history MRI studies conducted at Leiden University Medical Center. Results from the first study on upper extremity outcome measures are presented.

Methods: Patients were recruited from the Dutch Dystrophinopathy Database. Inclusion criteria were male non-ambulant DMD patients ≥8 years. The protocol consists of three half-day visits at 0-12-18 months. Reasons for non-participation, current age, travel-time, mutation, and age at loss of ambulation were recorded. Differences between participants and non-participants were analyzed using Mann-Whitney U and chi-square tests.

Results: After pre-screening for age using the database, 132 of these patients were reached by phone. 102 patients met all inclusion criteria, of whom 22 patients (21.6%) consented. 80 patients who declined could give several reasons. The most common were: 'too much time required' (32.5%), 'travel-distance' (26.3%), 'energy cost/burden' (25%), 'already many tests required for regular care' (23.8%), 'difficulty lying on the side for the MRI' (13.8%), and 'not wanting the MRI' (8.8%). Participants were significantly younger (median 13.2 versus 16.1y), lost ambulation at a later age (median 11.5 versus 10.0y) and less often had a distal mutation (13.6% versus 32.3%) than non-participants. By contrast, travel-time was similar in both groups (median 1:21 versus 1:15 hours).

Conclusion: Younger participants with prolonged ambulation may affect results of natural history studies that target muscle performance. Distal mutations in the DMD gene are associated to a higher incidence of learning and behavioral disabilities which is essential when assessing neurocognition. Recruitment efficiency may be increased by decreasing the impact on the family's daily life, since time-consumption (i.e. not travel-time) and burden of the study were important reasons to decline participation.

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Kenneth Kagoiya

A Total Variational Wavelet Based Structural MRI Denoising Method with Bilateral Feature Enhancement

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Background: MRI is one of the most advanced techniques in medical diagnosis however MRI images are affected by Rician noise. Rician noise causes random fluctuations in the data and also introduces bias that reduces image contrast. Rician noise also degrades images in both qualitative and quantitative senses and hinder image analysis, interpretation and feature detection.

Aims: Various de-noising methods are used to improve signal to Noise ratio and also visual quality. In this paper a total variational minimization based denoising algorithm is developed .The objective is therefore to minimize intensity and phase difference between pixels in the noisy image and a test noise free.

Methods: This algorithm ensures that the de-noising process is carried out while preserving the image features and also enhance them by used of bilateral filter. An automatically stopping criterion for the wavelet TV minimization methods is applied to wavelet bases. A bilateral filter is also used for enhancement of feature boundaries. To tests the effectiveness of the algorithm the method is implemented in Matlab. MRI images with different level of artificial noise are de-noised using the algorithm, the process is carried with different weighting parameters of the filters to establish the combination of parameters that give optimum results.

Results: Measures of performance including PSNR, MSE, UQI, SSIM, CoC, EPI and also visual inspection are used. It is realized that there is significant improvement from results obtained using stand alone methods such as Gaussian smoothing, wiener filter, NLM filter ,bilateral filter and wavelet thresholding. For example, the combination of filter improves the PSNR of a cranium MRI from 29.5 to 35.86 dB. This improvement is also replicated in other test images such torso and hip.

Conclusion; It is evident that the total variational denoising combination method outperforms other state of image denoising method. This is due to the fact that it takes into consideration Rician noise distribution and each filter in the combination ensures specific aspects of de-noising such edge preservation and smoothing are optimized.

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Claudia Maria Cinnante

Muscle MRI in Becker Muscular Dystrophy: 6-point DIXON and functional tests

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Becker Muscular Dystrophy (BMD) is a neuromuscular disorder due to mutations in the DMD gene, leading to altered dystrophin expression in muscle fibers. Phenotype is generally characterized by juvenile onset of proximal muscle weakness, mainly in lower limbs. The high clinical heterogeneity and slower progression of BMD make challenging using standard outcome measures, such as the Six Minute Walking Test (6MWT) and the Motor Function Measure (MFM) scale, in clinical trials, since they may not be sensitive enough to detect variations in a small amount of time. Muscle magnetic resonance imaging (MRI) is proven to be helpful in detecting fibro-fatty substitution and inflammation.

Aims: To describe muscle MRI features in a cohort of BMD patients and to identify altered parameters in this population, correlate them with functional tests and evaluate their role as outcome measure.

Methods: We selected 24 BMD patients able to perform 6MWT with a distance of between 200 and 450 meters and with a left ventricular ejection fraction over 50%. All of them underwent clinical evaluation, functional assessments (6MWT, MFM scale, timed function tests, muscle strength measurement) and 1.5 Tesla muscle MRI. We evaluate fibro-fatty

degeneration calculating the mean fat fraction (MFF) of eight selected muscles of pelvic girdle and thigh (gluteus maximus, adductor magnus, vastus lateralis, long head of biceps femoris, gluteus medius, gracilis, rectus femoris, semitendinosus) on axial sections and with a 6-point DIXON approach.

Results: Clinical presentation of patients ranged from milder to more severe cases with a mean age of 38 ± 12 years and a mean disease duration of 21 ± 9 years. MRI study confirmed a specific pattern of muscle involvement. Mean MFF of all examined muscles was 43.9 ± 7.5 (%) and showed a significant negative correlation with the D1 score of the MFM scale and the 6MWT and a positive one with the timed function tests.

Conclusion: This study confirms the broad spectrum of BMD clinical manifestations and suggests the usefulness of muscle MRI in detecting fibro-fatty substitution, especially using quantitative measurements. Moreover, it demonstrates a correlation between MFF and functional measures.

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Claudia Brogna

Patterns of muscle involvement in SMA patients

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Background: So far, only few studies have explored muscle involvement in spinal muscular atrophy (SMA) using muscle Magnetic Resonance Imaging (MRI) but this has not been systematically explored in a large cohort of both paediatric and adult patients with type 2 and 3 SMA.

Aims: The aim of the present study was to define specific pattern of muscle involvement on MRI, assessing both fatty replacement and muscle atrophy, in a cohort of type 2 and 3 SMA children and adults (age range: 2-45 years), including both ambulant and non-ambulant patients.

Methods: Muscle MRI consisted of TSE/FSE T1-weighted sequences acquired on axial plane covering the pelvis, the thigh and the leg with contiguous slices. Each muscle was examined through its whole extension using a grading system that allows a semi-quantitative evaluation of fatty infiltration. Thigh muscles were also grouped in anterior, posterior and medial compartment for global atrophy classification purpose.

Results: The results showed a large variability in both type 2 and type 3 SMA, with a various degree of proximal to distal gradient. In all patients, the involvement was a combination of muscle atrophy and muscle infiltration. The variability observed ranging from minimal to diffuse involvement.

Conclusion: These findings may help to better understand both natural history of this disease and response to new treatments.

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Simonetta Gerevini

Effect of two years of treatment with Givinostat on muscle atrophy and fat infiltration assessed by MRI in Patient with Duchenne muscular dystrophy (DMD).

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Background: Progressive atrophy and fat infiltration is observed in DMD muscles. In a phase II study Givinostat was shown to increase muscle area and reduce muscle necrosis, fibrosis, and fat replacement in muscle biopsies taken after 12 months of treatment.

Aims: To evaluate the effects of Givinostat on atrophy and fat infiltration (FI) measured by MRI.

Methods: 17 patients enrolled in the aforementioned phase II study underwent MRI at baseline and after 2 years of treatment with Givinostat. The effects of Givinostat on atrophy and FI were compared to a natural history cohort of 13 patients matched by age, steroid treatment and 6 Minute Walk Distance at baseline. Muscles were analyzed at baseline and and after 24 months singularly and by compartments. A total of 60 MRI studies were analyzed. Atrophy and FI were evaluated with a semiquantitative scale (0-1-2-3) and (1-2-3-4) by 2 independent readers blinded to treatment and sequence.

Results: At baseline the highest atrophy scores were in the Glutei, and in the Thighs (medial, anterior and posterior compartments). The FI scores followed the same pattern with the Glutei nd the thigh being more affected than the leg. After two years atrophy increased in the Glutei and Thighs with little changes in the Legs. FI worsened in all compartments. When the changes in atrophy and FI were compared between Givinostat and control patients using Bayesian statistics, atrophy was increasing less in givinostat in the Glutei and Anterior Thigh compartment, whil FI was increasing less with Givinostat in the Anterior Thigh and Posterior Leg compartments (Probability >80%). "Atrophy scores increase even if the impact is smaller than pseudohypertrophic evolution. Fat infiltration increases in all copartments with age. Our results suggest that Givinostat reduces atrophy and fat infiltration progression.

Conclusion: Atrophy and FI at baseline and after 2 years in the Givinostat and Natural history groups and difference between groups with probablity that the change in atrophy and FI is smaller in the Givinostat group.

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Joanne Donovan

A Composite of MRI T2 of Five Lower Leg Muscles Is Highly Correlated with Timed Function Tests and Functional Status in ImagingDMD Natural History Database, and Supports Positive Effects of Edasalonexent in 4 to 7-Year Old Patients with Duchenne Muscular Dystrophy

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Background: Edasalonexent, an oral NF-κB inhibitor, is being investigated as a potential foundational therapy in DMD regardless of mutation. Based on natural history data of muscle MRI-T2 and fat fraction (FF) in DMD from the ImagingDMD Consortium, MoveDMD was designed as a proof-of-concept trial with MRI in 4-7 year old boys with DMD not on steroids.

Aims: We hypothesized that a composite of MRI-T2 of five lower leg muscles (LLC5-T2; soleus, medial gastrocnemius, tibialis anterior, tibialis posterior and peroneals) comprising muscles at different stages of the disease process, could be highly predictive of function and provide greater sensitivity than data from individual muscles.

Methods: Correlations of LLC5-T2 with functional measures were assessed in the natural history database collected by the ImagingDMD Consortium with up to 5 years of observation. In the MoveDMD

study with open-label extension, MRI and functional measures were assessed before treatment, at baseline and after up to 72 weeks of edasalonexent. The off-treatment control period in most boys enabled off- and on-treatment comparisons. LLC5-T2 was planned to be the primary MRI assessment.

Results: In the ImagingDMD database, LLC5-T2 was highly correlated with velocity of timed function tests (TFTs) and 6-minute-walk distance, with the degree of correlation similar to previously reported values for the vastus lateralis fat fraction, and greater than that for individual lower leg muscle MRI-T2. LLC5-T2 progressively increased as ability to complete TFTs declined, with a 2 ms difference demonstrating clinically relevant differences in loss of functional milestones. LLC5-T2 also predicted loss of ambulation over the subsequent 2-year period. In the MoveDMD study, the off-treatment annualized rate of increase in LLC5 T2 was 3.8 msec/year, and after up to 72 weeks of daily treatment with edasalonexent 100 mg/kg/day, the annualized rate was 0.4 msec/year. These results were consistent with slowing of disease progression that was observed with functional measures.

Conclusion: A composite measure of five lower leg muscles, LLC5-T2, was more highly correlated than individual muscles with TFT velocity. LLC5-T2 also correlated well with current ability to perform TFTs, and provided predictive ability of future clinical loss of ambulation in the ImagingDMD natural history database,. In the MoveDMD study, annualized changes in LLC5-T2 were significantly improved with edasalonexent compared to an off-treatment period, supporting disease-modifying potential in DMD. A Phase 3 study is underway.

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Joanne Donovan

MoveDMD, a Phase 2 with Open-Label Extension Study of Treatment of Young Boys with Duchenne Muscular Dystrophy with the NF-κB Inhibitor Edasalonexent Showed a Slowing of Disease Progression as Assessed by MRI and Functional Measures

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Background: The ImagingDMD Consortium has demonstrated that MRI assessments of skeletal muscle are sensitive markers of disease progression in Duchenne muscular dystrophy (DMD) and can be performed in young boys reproducibly and consistently across multiple centers. Edasalonexent (edasa, CAT-1004) is an oral inhibitor of NF-κB, which is a central mediator of disease progression in skeletal and cardiac muscle in DMD.

Aims: A proof-of-concept study, MoveDMD, was designed using MRI as the primary endpoint to investigate the effects of edasalonexent in young boys with DMD.

Methods: Prior to an initial Phase 1 one-week dose-ranging assessment of edasalonexent, baseline MRI T2 and MRS fat fraction of the lower leg and muscle function were assessed in steroid-naïve 4 to 7 year-old (up to 8th birthday) boys with DMD. Selected doses were then studied in a 12-week Phase 2 study with open-label extension. The design enabled comparison of an off-treatment period with changes on treatment. An MRI T2 composite of the five lower leg muscles was identified as the primary MRI outcome measure.

Results: Baseline MRI assessments correlated with assessments of function including timed function tests (TFTs: 10-meter walk/run, time-to-stand and 4-stair climb) and the North Star Ambulatory Assessment (NSAA). Disease progression in the off-treatment control period was consistent with natural history changes in boys not on steroids in this age range. At 12 weeks, comparison of the composite MRI T2 endpoint of the treated group to the placebo group showed trends for the 100 mg/kg/day dose, while comparison to the off-treatment period demonstrated significant slowing of disease progression ($p<0.05$), which persisted through 72 weeks of treatment. Assessments of function by NSAA and TFTs

also showed slowing of disease progression compared to the off-treatment control period. Muscle enzymes decreased at 12 weeks and beyond, as did CRP. Edasalonexent was well tolerated, and growth continued age-appropriately.

Conclusion: In the MoveDMD trial, treatment with edasalonexent was associated with slowing of disease progression compared to an off-treatment control period. Use of a composite MRI T2 endpoint in a study design comparing off-and on-treatment periods enabled a proof-of-concept study that supported design of a Phase 3 study. Edasalonexent has potential to be disease-modifying in DMD patients regardless of mutation, and the Phase 3 PolarisDMD study is ongoing.

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Sean Forbes

Relationship between 31P-MRS markers of pathology and inflammation in young mdx mice

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Background: Previous studies have reported altered energetic and acid-base status in dystrophic muscle using 31phosphorus magnetic resonance spectroscopy (31P-MRS). However, the relationship between these alterations and inflammation is unclear. Young mdx mice undergo a well characterized phase of enhanced inflammation early in life. Furthermore, whether resting ATP turnover is elevated during this phase due to enhanced degeneration/regeneration has not been examined.

Aims: The purposes of this study were to: 1) examine energetic status (Pi/PCr and ATP flux) at a young age in dystrophic mice and relate it to $1H_2O$ T2, a marker of inflammation/muscle damage and 2) determine the effects of enhancing inflammation/muscle damage on energetic status and 31P markers of sarcolemma integrity by performing downhill running.

Methods: In vivo 31P-MRS spectra were acquired from the gastrocnemius and soleus muscles in C57BL/10ScSn-DMDmdx (mdx, n=44) and wild-type mice (C57BL/10, n=21) between 4-10 weeks of age at 11.1T. ATP flux was measured by saturation transfer experiments. Downhill running was performed in a subset of wild-type and mdx (n=10/group). Relative concentrations of high-energy phosphates were measured and intracellular pH and magnesium (Mg2+) were calculated. $1H_2O$ T2 was measured using single voxel 1H-MRS from the gastrocnemius and soleus at 4.7T.

Results: At rest, T2 was elevated ($p<0.05$) in mdx in the gastrocnemius (mdx: 30.8±3.1ms; wild-type 28.2±1.2ms) and soleus (mdx: 31.6±3.9ms; wild-type 27.5±1.8ms). Intracellular pH was also elevated in the gastrocnemius in mdx (7.21±0.07) vs. wild-type (7.14±0.05). No differences were observed in Pi/PCr, and ATP flux was, on average, slightly lower ($p=0.10$) in mdx (10.5±1.1mM/s) vs. wild-type (11.1±0.8mM/s). Downhill running further amplified the differences in T2 between wild-type and mdx. No changes were observed in wild-type pre to post running, while mdx decreased ($p<0.05$) Mg2+ and increased ($p<0.05$) intracellular pH, with no changes in Pi/PCr and ATP flux.

Conclusion: Despite clear differences in T2 between mdx and wild-type, Pi/PCr and ATP flux were not significantly different, suggesting there is no direct relationship between inflammation and energetic status in young mdx mice at rest. However, downhill running resulted in a reduced Mg2+ and increased pH in mdx mice, consistent with impaired sarcolemma integrity.

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Louise Otto

Muscle MRI in a cross-sectional cohort of patients with Spinal Muscular Atrophy types 2-3

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Background: Spinal Muscular Atrophy (SMA) is a severe neuromuscular disease presenting with muscle weakness following the characteristic pattern of predominantly proximal and axial muscles. Using quantitative MRI the pattern of fat infiltration has been investigated. However, studies using multimodal qMRI parameters in a relatively large cohort encompassing a broad range of SMA severity and disease duration are lacking.

Aims: The aim of this study is to provide a cross-sectional description of quantitative MRI (qMRI) measurements in a cohort representing a wide spectrum of SMA type 2-3, of various ages and disease duration.

Methods: Thirty SMA patients were included, 15 were classified as type 2 and 15 as type 3, all with genetically confirmed diagnosis, mean age 28.7 +/- 17.6 yrs (range 7.6-73.9 yrs). Twenty matched control subjects participated, mean age 34.4 +/- 11.2 yrs (range 17.7-71.6yrs). All SMA patients underwent muscle strength assessment, and motor function assessment. Muscle MRI of the upper legs was performed on a 3T MR scanner. The protocol included a 4-point DIXON (ΔTE 0.76ms; voxel size: 1.5x1.5x6mm; time: 1min20s), multi-echo spin-echo T2 mapping (ΔTE 7.6ms; voxel size: 3x3x6mm with 6mm slice gap; time: 3min5s) and spin-echo EPI DTI (42 diffusion-weighted volumes; b-values from 1-600 mm/s²; voxel size: 3x3x6mm; time: 3min30s).

Results: Data from two patients were excluded because image quality was not sufficient. Muscles over 10 voxels of size were included in the analysis. SMA patients show significant alterations on all qMRI parameters compared to healthy controls (fat fraction 45.6+/-16.9 vs 7.5 +/-1.4%, p=.000; T2 27.4 +/-1.5 vs 28.9 +/- 0.4ms, p =.000; FA .41+/- .09 vs .24+/- .02, p=.000; MD 1.14+/-.28 vs 1.46+/-.10 mm 2/s,p=.000). SMA patients showed an increase of FA and a decrease of MD and T2 which could only partially be explained by fat partial volume effects. In patients, good correspondence between fat fraction and FA and clinical measures (HFMSE, disease duration; MRC sum score) was found, whereas T2 showed poor correlation.

Conclusion: Quantitative MRI measurements disclose distinct properties of skeletal muscle in SMA and its subtypes, that have not been described before. Longitudinal data will prove the biomarker potential of qMRI in monitoring disease progression.

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Alicia Alonso-Jiménez

Comparing three methods to measure fat fraction of the thigh

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Background: Quantitative skeletal muscle MR imaging such as 3-point Dixon has repeatedly proved to be useful to measure the amount of fat within the muscle. Furthermore, it is able to detect small changes in muscle composition with superior sensitivity over standard functional evaluation. Therefore, it is a useful outcome measure for clinical trials. ¬¬However, there is no standardized method to assess the analysis. This analysis requires drawing areas of interest (ROIs) on the obtained images. Whether evaluating individual muscles is better than assessing compartments or even the whole thigh or not has not been studied.

Aims: To show whether there are differences or not with three different methods of analysis.

Methods: We are carrying out a study where we compare these three approaches (analysis of individual muscles, of anterior and posterior compartment and of the whole thigh) in 3-point Dixon skeletal muscle MRI in Pompe patients at basal visit and at one-year visit. We are also calculating the time needed to perform this analysis in every group. We have performed the study in a Philips Achieva XR 1.5 Tesla located at HSCSP. We have analyzed fat fraction using the PRIDE (Philips Research Image development Environment) platform provided by Philips. We will compare the results using ANOVA test at baseline. To see if the three analysis are able to detect differences after one year, we will perform a Wilcoxon study. P will be considered significant if it is lower than 0.05.

Results: This is an ongoing project. Our results will show if there are significant differences in the

mean thighs fat fraction calculated using the different approaches. We will also show if the measured fat fraction increment after one year is influenced by the method used.

Conclusion: If there are not significant differences, the amount of time required to analyze 3-point Dixon muscle MRIs of the highs can be clearly reduced, making the analysis of fat fraction with quantitative muscle MRI an easier study

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Sophelia Hoi Shan Chan

Unravelling Pattern of Muscle Changes in hereditary muscle diseases using muscle MRI

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Background: The term "hereditary muscle diseases" encompasses a wide spectrum of childhood and adulthood onset inherited diseases affecting skeletal muscle that causes muscle weakness. Other clinical features that may be variably associated are muscle pain, contractures, exercise intolerance, myoglobinuria, and multi system involvement including the heart, liver, central and peripheral nervous system.

The diagnosis of hereditary muscle diseases requires the clinical, electromyographic, muscle pathological and genetic studies. The availability of Next Generation Sequencing (NGS) including genetic panel, Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS), have revolutionizing the diagnostic process, allowing us to detect several molecular changes early whose role and pathogenicity often need to be evaluated in the relevant specific context. In the past years, magnetic resonance imaging (MRI) has become a very powerful tool in the diagnosis of muscle diseases because it can show the specific pattern of muscle involvement and its severity of tissue damage in different muscles of the body.

Aims: We studied in our University Hospital our experience in using muscle MRI in guiding the muscle biopsy sites in adult patients, and in the diagnosis of childhood and adulthood onset hereditary myopathies and muscular dystrophies using pattern recognition of muscles damage distribution in complementing clinical evaluation, genetic workup and variants interpretation.

Methods: Patients: Adulthood and Childhood onset inherited myopathy or muscular dystrophies.

Results: Specific pattern recognition are illustrated with the findings in our patients with collagen VI-related muscular dystrophy, LMNA related muscular dystrophy, CHKB related megaconial congenital muscular dystrophy, RYR1 related myopathy, and SMALED, myofibrillar myopathies 5 and hereditary myopathy with early respiratory failure. The future role of the advances and the perspectives of the application of advanced quantitative MRI (qMRI) techniques in this field is discussed.

Conclusion: Muscle MRI is a valuable tool for the diagnosis of patients with rare hereditary myopathies or muscular dystrophies. We need more data on larger cohorts of patients for these rare conditions so international collaboration is important. A high degree of experience is needed for pattern recognition. Machine learning to assist the quantification of MRI findings will assist the automation of imaging evaluation and the diagnostic algorithms.

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Jorge Alberto Diaz Manera

Exercise influences muscle degeneration in patients with dysferlinopathy: an MRI based study

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Background: Dysferlinopathies are a group of muscle disorders characterized by continued degeneration of skeletal muscles that leads to a progressive muscle weakness and disability. Dysferlin is a protein associated with muscle membrane repair. It has been recently shown that

practice of sports during childhood or adolescence correlates with a more severe and quickly progressive phenotype.

Aims: Our aim was to identify the impact of exercise on the degree of muscle fatty replacement measured using muscle MRI.

Methods: This work has been done with the data collected in the Clinical Outcome Study (COS) for dysferlinopathy, which is a prospective natural history study performed in more than 200 patients with a genetically confirmed dysferlinopathy. For this study, we selected patients with less than 10 years of disease progression since the first symptoms of muscle weakness. We retrospectively collected data about the practice of exercise and sports before the onset of symptoms. All patients had a muscle MRI of the pelvic and lower limb muscles done at baseline using T1 weighted sequences. We quantified the degree of fatty degeneration in every muscle using the Mercuri score. We used the Student T test and the Pearson test to identify differences between patients, and a lineal general model to know if exercise influenced the progression of the disease.

Results: We included a total of 39 patients with less than 10 years of progression of symptoms: 28 patients performed sports or exercise often before the onset of symptoms, while 11 patients did not perform any sport. In patients that exercised, we identified a significant higher degree of muscle fatty degeneration at baseline MRI in the following muscles: glutei minor, glutei medius, pectineus and quadratus femoris (Student T test, $p<0.05$). The combination of time from onset with exercise was an independent predictor of the result of muscle MRI in the lineal general model.

Conclusion: Our results suggest that exercise increases the progression of muscle degeneration, particularly of the pelvic muscles, in patients with dysferlinopathy.

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Julia Sargent

MRI and echocardiographic assessment of the cardiac phenotype of the DE50-MD dog; a novel preclinical model of Duchenne Muscular Dystrophy

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Background: Cardiomyopathy has become the leading cause of death in patients with Duchenne muscular dystrophy, (DMD). Effective management strategies targeting DMD's cardiac manifestations are urgently needed. Overt systolic dysfunction occurs late in the disease but cardiac magnetic resonance imaging (CMR) can identify preclinical myocardial involvement. The novel canine model of DMD at the Royal Veterinary College harbours a dystrophin gene mutation in the principal human DMD ""hot-spot"" (deletion of exon50; DE50-MD dogs). The model is consequently highly relevant for studying promising molecular treatments. While affected DE50-MD dogs are known to lack cardiac dystrophin, their cardiac phenotype is unknown.

Aims: To provide detailed cardiac phenotypic evaluation of the DE50-MD model, with direct comparison to age-matched littermate wild type (WT) dogs.

Methods: 14 DE50-MD dogs and 13 WT dogs were studied every 12 weeks from 3 to 18 months of age. Left ventricular (LV) mass and volumes were quantified using CMR (1.5T) and late gadolinium enhancement (LGE) studies were performed in a subset of 5 DE50-MD dogs and 4 WT dogs. Contemporaneous evaluation of left chamber dimensions, global systolic function, global longitudinal (GLS) and circumferential strain (GCS) was performed consciously using echocardiography. Differences in repeated measures across groups with age were analysed using linear mixed models.

Results: Across all ages, DE50-MD dogs had smaller weight-normalised LV volumes ($p<0.001$) and mass ($p<0.001$) compared to WT dogs. While global systolic function and GLS were preserved, DE50-MD GCS markedly deteriorated between 15-18 months. At 18 months, LGE was detected exclusively in (2/5) DE50-MD dogs. The mean GCS of the 2 dogs with LGE was -15.6% versus -21.9% in age-matched LGE-negative DE50-MD dogs.

Conclusion: Young DE50-MD dogs share the cardiac phenotype of young boys with DMD: reduced LV size, LGE and progressive decline in GCS despite preservation of global LV function. We suspect these defects represent key early features that are useful biomarkers of cardiac involvement in therapeutic trials using the DE50-MD model.

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