MUSCLE IMAGING OF POMPE DISEASE

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OUTLINE

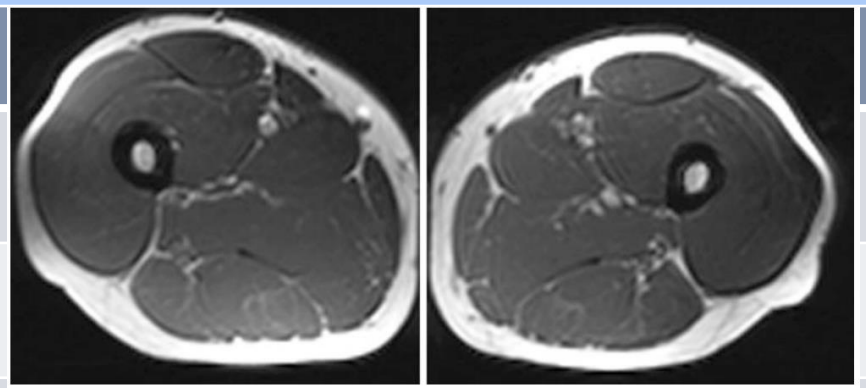
- Basic principles of muscle MRI for neuromuscular disease
- Update in literature of muscle MRI in Pompe disease
- Imaging guided muscle biopsy

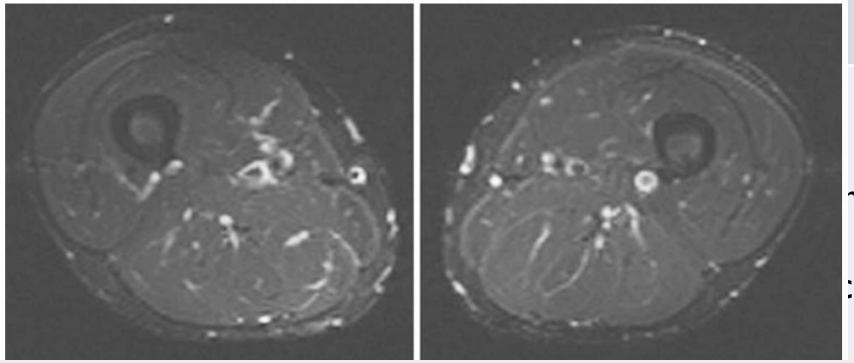
VARIOUS MRI TECHNIQUES IN EVALUATING MUSCLE DISEASE

	Qualitative MRI	Quantitative MRI
Muscle bulk	**Visual evaluation** - Hypertrophy, atrophy	**Cross sectional area** **Muscle volume**
Fat infiltration	**T1 weighted image** - Fat signals	**Dixon method** - Fat fraction (i.e. % Fat)
Inflammation/edema	**T2 weighted image with fat suppression** - Water signals	**T2 mapping** - T2 value
Metabolites	-	**MR spectroscopy (research setting)** - 1H and 13C spectroscopy: **glycogen accumulation** in muscles. - 31P spectroscopy: assesses **muscle metabolites involved in energy processes,** e.g. phosphocreatine (PCr), inorganic phosphate (Pi).

TYPICAL PROTOCOL OF MUSCLE MRI

	Qualitative MRI
Muscle bulk	**Visual evaluation** - Hypertrophy, atrophy
Fat infiltration	**T1 weighted image** - Fat signals
Inflammation/edema	**T2 weighted image with fat suppression** - Water signals
Metabolites	-





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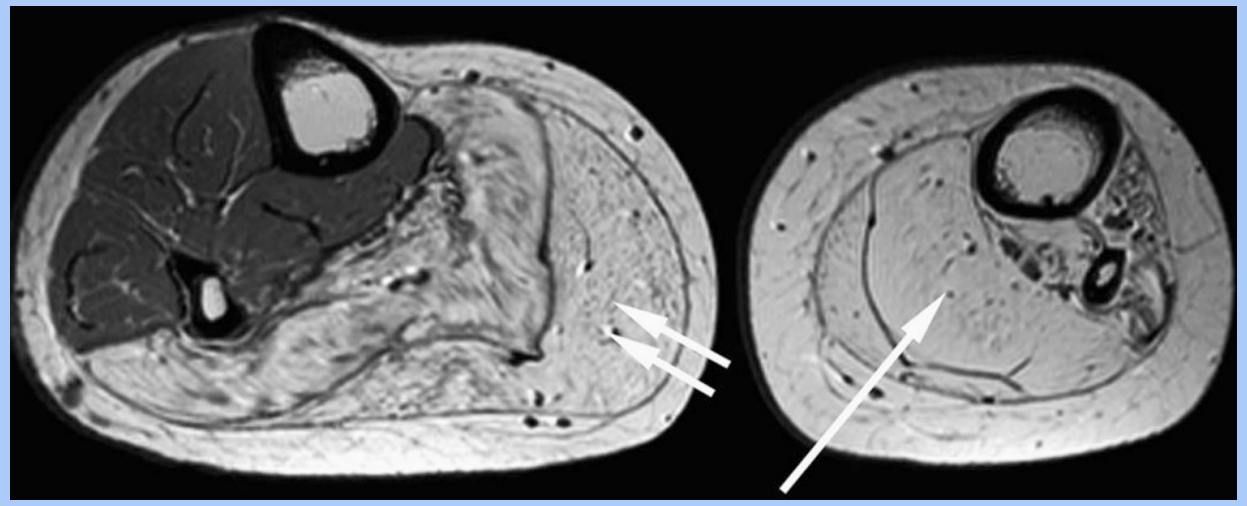
FATTY MUSCLE REPLACEMENT IN T1 WEIGHTED IMAGE

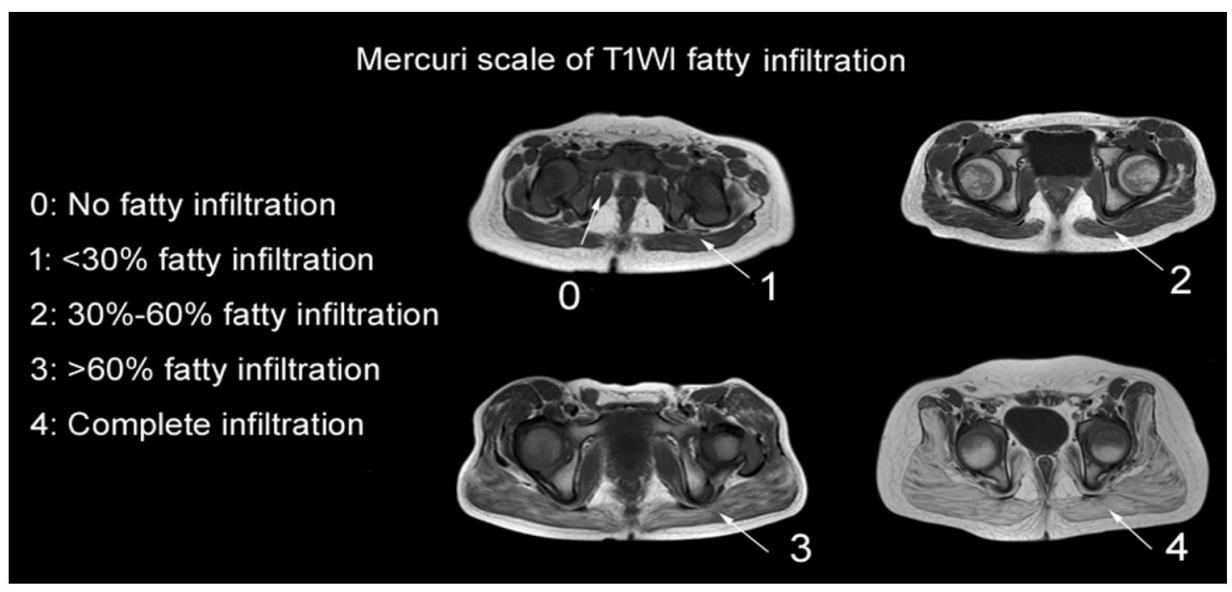
- Fatty replacement occurs in **chronic** neuromuscular disease
  - Muscular dystrophy
  - Metabolic myopathy (including Pompe disease)
  - Chronic phase of inflammatory myopathy
  - Chronic phase of denervation injury



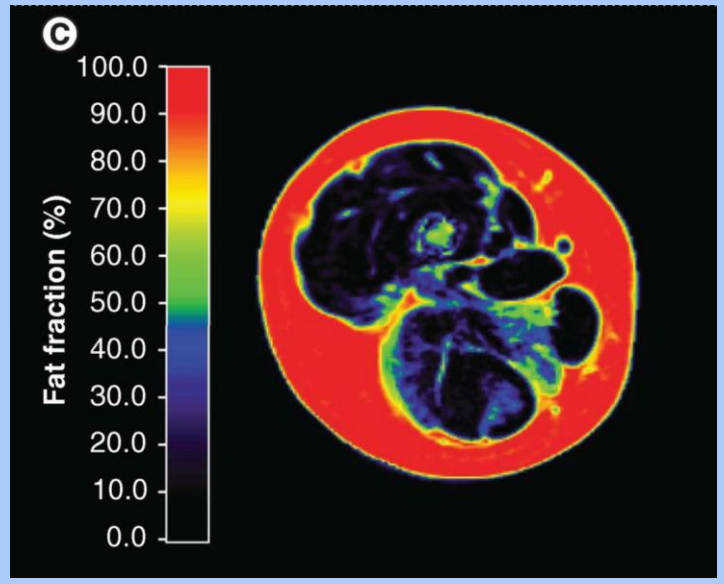
Poliomyelitis

QUANTIFICATION OF FATTY INFILTRATION

Semiquantitative - Mercuri scale



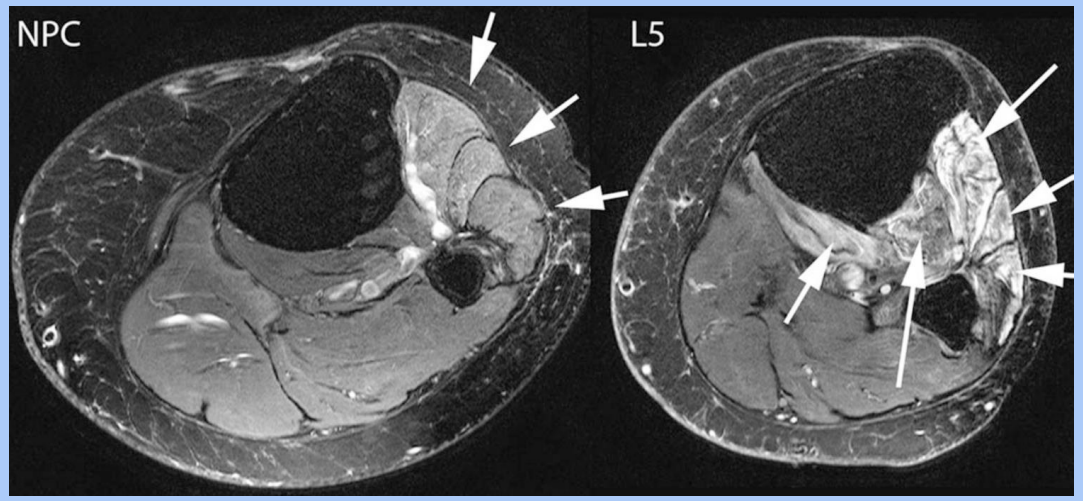
Quantitative – Fat Fraction



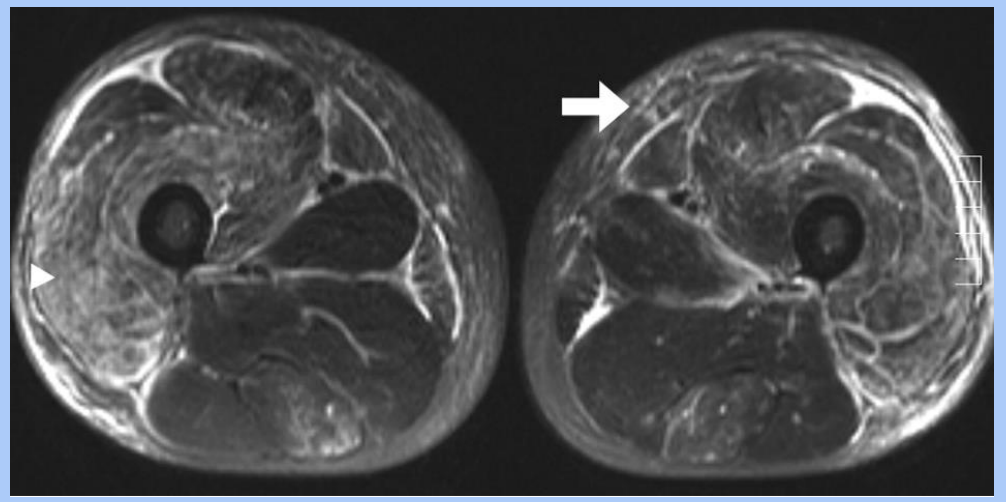
Liang et al. J Musculoskelet Disord Treat 2019, 5:069

Sherlock SP et al . Biomark Med. 2021 Jun;15(10):761-773.

INCREASED T2 MUSCLE SIGNALS - INFLAMMATION AND DENERVATION



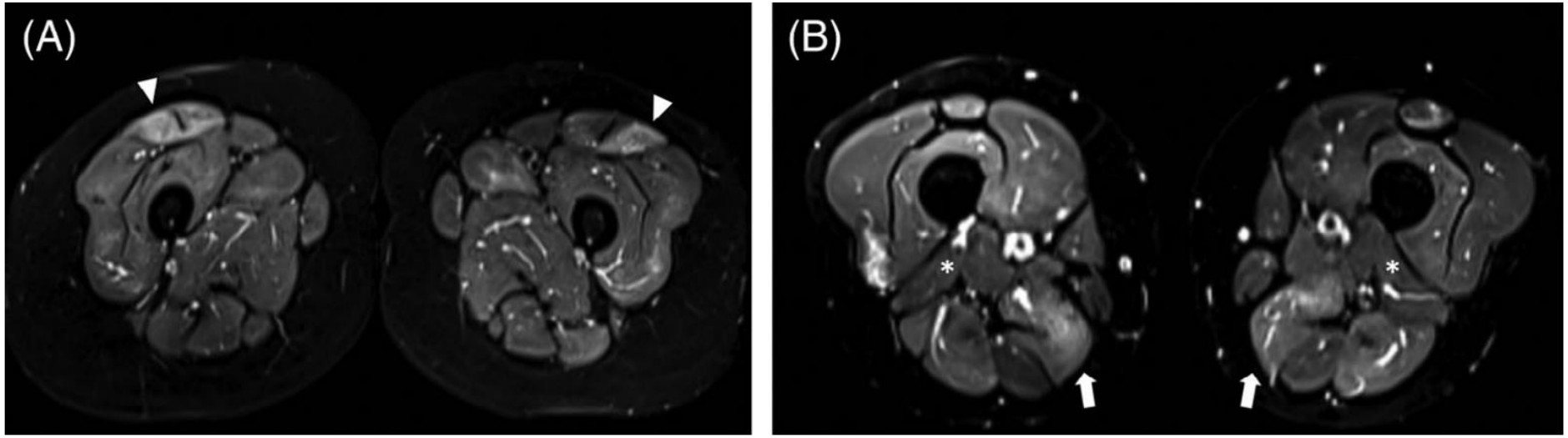
Denervation edema in peroneal neuropathy



Fascial edema in dermatomyositis

Schulze M, Kötter I, Ernemann U et al. *American Journal of Roentgenology, 192(6), 1708–1716.*
Magnetic Resonance Imaging of the Skeletal Musculature. 1st Ed.

INCREASED T2 MUSCLE SIGNALS - NECROTIZING MYOPATHY



Anti-HMGCR necrotizing myopathy

- Anterior thigh compartment: Anterolateral predominant (rectus femoris and vastus lateralis)
- Posterior thigh compartment: Predominantly involving long head of biceps femoris

Lee KH, Gao Y, Lau V. Muscle Nerve. 2021 Oct;64(4):500-504

TABLE. PATTERNS OF LOWER LIMB MUSCLE INVOLVEMENT IN SELECTED INHERITED MYOPATHIES

Type of muscular dystrophy or myopathy	Duchenne	Myotonic type 1	Myotonic type 2	Facioscapulohumeral	Oculopharyngeal	Limb-girdle					Congenital				Myofibrillar			
Gene	*DMD*	*DMPK*	*CNBP*	*DUX4*	*PABPN1*	*CAPN3*	*DYSF*	*SGCA-SGCD*	*FKRP*	*ANO5*	*SELENON*	*RYR1*	*DNM2*	*COL6 A1-3*	*DES*	*CRYAB*	*MYOT*	*FLNC*
Gluteus maximus	I	V	V	V	V	V	V	V	I	V	I	V	I	V	I	I	V	V
Gluteus medius	I	V	V	V	V	I	V	I	V	V	V	V	V	V	V	V	I	V
Gluteus minimus	I	V	V	V	V	I	I	I	V	V	S	V	V	V	V	V	I	V
Vastus lateralis	I	V	V	V	S	V	V	V	V	V	I	V	V	I	V	I	V	S
Vastus intermedius	I	V	V	V	V	V	V	V	V	V	V	V	V	I	V	I	I	I
Vastus medialis	I	V	V	V	V	V	V	V	V	V	V	I	V	I	V	I	I	I
Rectus femoris	V	S	V	V	S	V	S	V	S	S	V	S	V	V	S	I	S	S
Adductor magnus	I	V	V	I	I	I	I	I	I	I	I	I	I	V	V	V	I	I
Adductor longus	S	S	V	V	V	I	I	V	I	I	S	S	I	S	V	V	I	I
Gracilis	S	S	V	V	S	V	S	S	S	S	S	S	S	S	I	I	S	S
Sartorius	S	V	V	V	V	S	S	S	V	S	I	I	S	S	I	I	S	S
Biceps femoris	V	V	V	I	I	I	I	V	I	I	V	V	I	V	V	V	I	I
Semitendinosus	S	V	V	I	V	I	I	V	I	I	S	V	I	V	I	I	S	S
Semimembranosus	S	V	V	I	I	I	I	V	I	I	I	V	I	V	S	S	I	I
Gastrocnemius	I	I	V	I	V	I	I	S	V	I	V	V	V	I	I	I	I	I
Soleus	I	I	V	I	I	I	I	S	V	I	I	I	I	I	I	V	I	I
Tibialis posterior	S	S	V	S	V	S	V	S	S	S	S	S	S	V	V	V	I	V
Tibialis anterior	S	V	V	I	S	S	V	S	S	S	S	S	I	S	V	I	I	I
Peroneus longus	V	V	V	S	V	S	V	S	V	S	V	V	V	V	I	I	I	V

Abbreviations: I, preferentially involved; S, preferentially spared; V, variably involved or without sufficient data.

Accuracy of a machine learning muscle MRI-based tool for the diagnosis of muscular dystrophies

José Verdú-Díaz, Jorge Alonso-Pérez, MD,* Claudia Nuñez-Peralta, MD,* Giorgio Tasca, MD, PhD, John Vissing, MD, PhD, Volker Straub, MD, PhD, Roberto Fernández-Torrón, MD, Jaume Llauger, MD, Isabel Illa, MD, PhD, and Jordi Díaz-Manera, MD, PhD

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Neurology® 2020;94:1-9. doi:10.1212/WNL.0000000000009068

Abstract

Objective

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. 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 supervised machine learning was applied to develop a model useful to identify the correct diagnosis. Two thousand different models were generated and the one with highest 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 95.7% accuracy, with 92.1% sensitivity and 99.4% specificity. When compared with experts on the field, the diagnostic accuracy of the model generated was significantly higher in a new set of 20 MRIs.

Conclusion

Machine learning can help doctors in the diagnosis of muscle dystrophies by analyzing patterns of muscle fatty replacement in muscle MRI. This tool can be helpful in daily clinics and in the interpretation of the results of next-generation sequencing tests.

Classification of evidence

This study provides Class II evidence that a muscle MRI-based artificial intelligence tool accurately diagnoses muscular dystrophies.

Figure 4 Suggested diagnosis for every case analyzed of 20 sets of testing MRIs

Case	Real diagnosis	Suggested diagnosis				
		Software	Expert 1	Expert 2	Expert 3	Expert 4
1	OPMD	OPMD	OPMD	OPMD	FKRP/dysferlin/calpain	OPMD
2	Sarco.	Sarco.	Sarco.	Sarco.	Pompe/sarco.	Sarco.
3	Calpain	Calpain	Calpain	Calpain	Calpain	Calpain
4	FSHD	FSHD	FSHD	FSHD	Dysferlin/FSHD	FSHD
5	Dystrophin	Dystrophin	LMNA/sarco./Pompe	Sarco./calpain/FKRP	Sarco./Pompe	Sarco.
6	Dystrophin	Dystrophin	FKRP/calpain/sarco.	Calpain/dysferlin/FKRP	Dystrophin	Pompe/calpain/ano5
7	ANO5	ANO5	ANO5	ANO5	Dysferlin/ANO5	FSHD/ANO5
8	Dysferlin	FSHD/dysferlin	Dysferlin	Dysferlin	ANO5	Dysferlin
9	Dysferlin	Dysferlin	Dysferlin	LMNA/FSHD/calpain	OPMD	OPMD/dysferlin
10	Pompe	Pompe	Pompe	Pompe	Sarcoglycan/Pompe	Calpain/FKRP/ANO5
11	Sarco.	Sarco.	Sarco.	Sarco.	Pompe/sarco.	Sarco.
12	LMNA	LMNA	FSHD/ANO5	LMNA	LMNA	LMNA
13	Pompe	Pompe	Pompe	Pompe	Pompe	Calpain/ANO5
14	Calpain	ANO5/calpain	FKRP/sarco./calpain	Dystrophin/dysferlin/FKRP	FKRP/calpain	OPMD/LMNA
15	OPMD	OPMD	FKRP	Dystrophin/dysferlin/LMNA	Dystrophin/OPMD	OPMD
16	FSHD	FSHD	FSHD	FSHD	FSHD	FSHD
17	Dystrophin	Dysferlin/LMNA/calpain	FKRP	Dystrophin	Dysferlin/calpain/dystrophin	Dysferlin/ANO5
18	Dysferlin	Dysferlin	Dysferlin	ANO5/dysferlin	ANO5/dysferlin	FSHD/ANO5
19	LMNA	LMNA	Dysferlin/LMNA	LMNA	LMNA	Dysferlin/FKRP
20	Calpain	Calpain	Calpain	Dystrophin/dysferlin/FKRP	Calpain	LMNA/OPMD
Score		**55**	**42**	**41**	**38**	**31**

POMPE DISEASE (ACID MALTASE DEFICIENCY)

Autosomal recessive metabolic myopathy due to deficiency of alpha-glucosidase

GGA deficiency leads to accumulation of glycogen within lysosomes in skeletal, smooth and cardiac muscles

Two main clinical phenotypes

Infantile onset Pompe disease (IOPD)

- Onset before within first year of life
- Severe cardiomyopathy, respiratory insufficiency and hypotonia

Late onset Pompe disease (LOPD)

- Onset after age of one
- Fatigue, myalgia and progressive limb-girdle weakness

FAT REPLACEMENT IN LATE ONSET POMPE DISEASE

- Early and prominent involvement of the **tongue**.

- Involvement of **proximal muscles**
  - **Shoulder girdle** muscles (the subscapularis and latissimus dorsi)
  - **Gluteal muscles** (gluteus minimus and medius > maximus)
  - **Paraspinal, psoas and abdominal wall muscles**
  - In the thighs, the **adductor magnus** and long head of the biceps femoris show fat replacement earlier than other muscles.

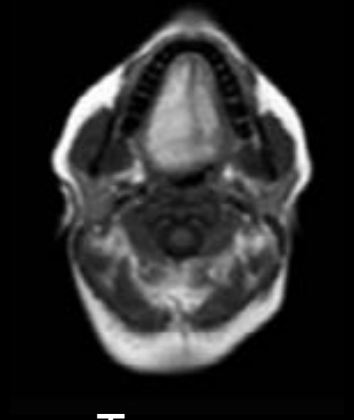
Díaz-Manera J et al. Muscle Nerve. 2021 May;63(5):640-650.

FAT REPLACEMENT IN LATE ONSET POMPE DISEASE

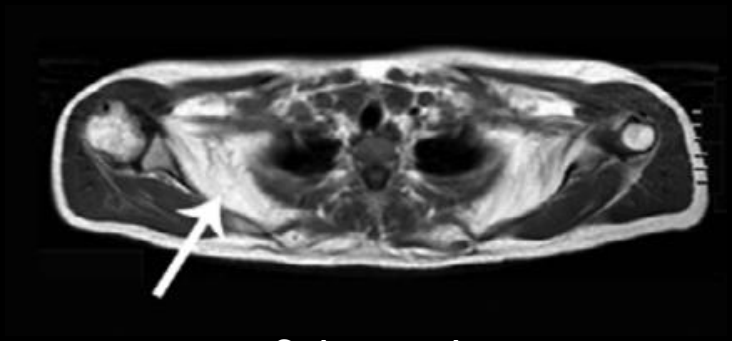
Proximal-distal gradients:

- 1st gradient: Greater involvement in proximal thigh muscles (such as vasti) compared to distal.
- 2nd gradient: Greater involvement in thigh compared to leg.

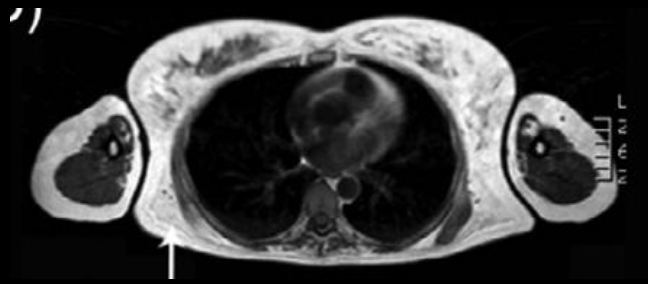
Díaz-Manera J et al. Muscle Nerve. 2021 May;63(5):640-650.



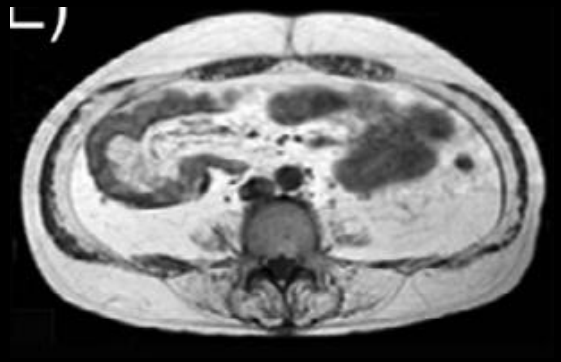
Tongue



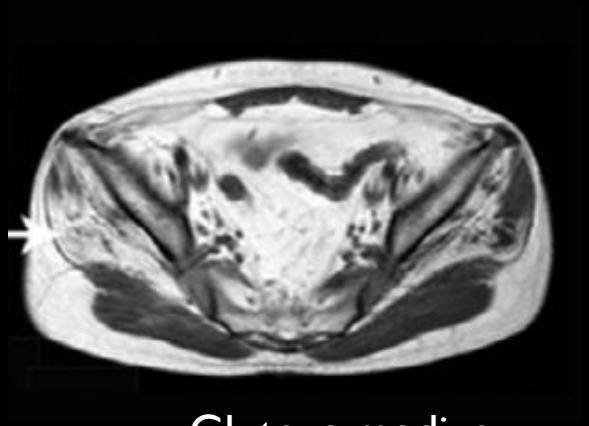
Subscapularis



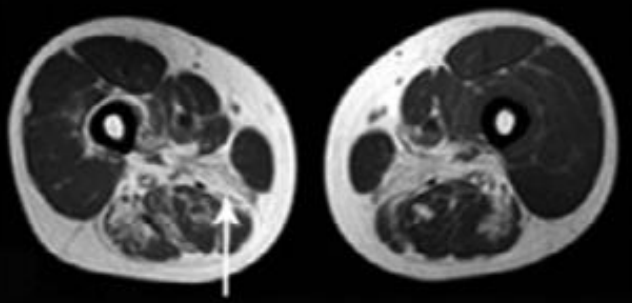
Latissimus dorsi



Abdominal wall &
paraspinal muscles



Gluteus medius
and minimus



Adductor magnus

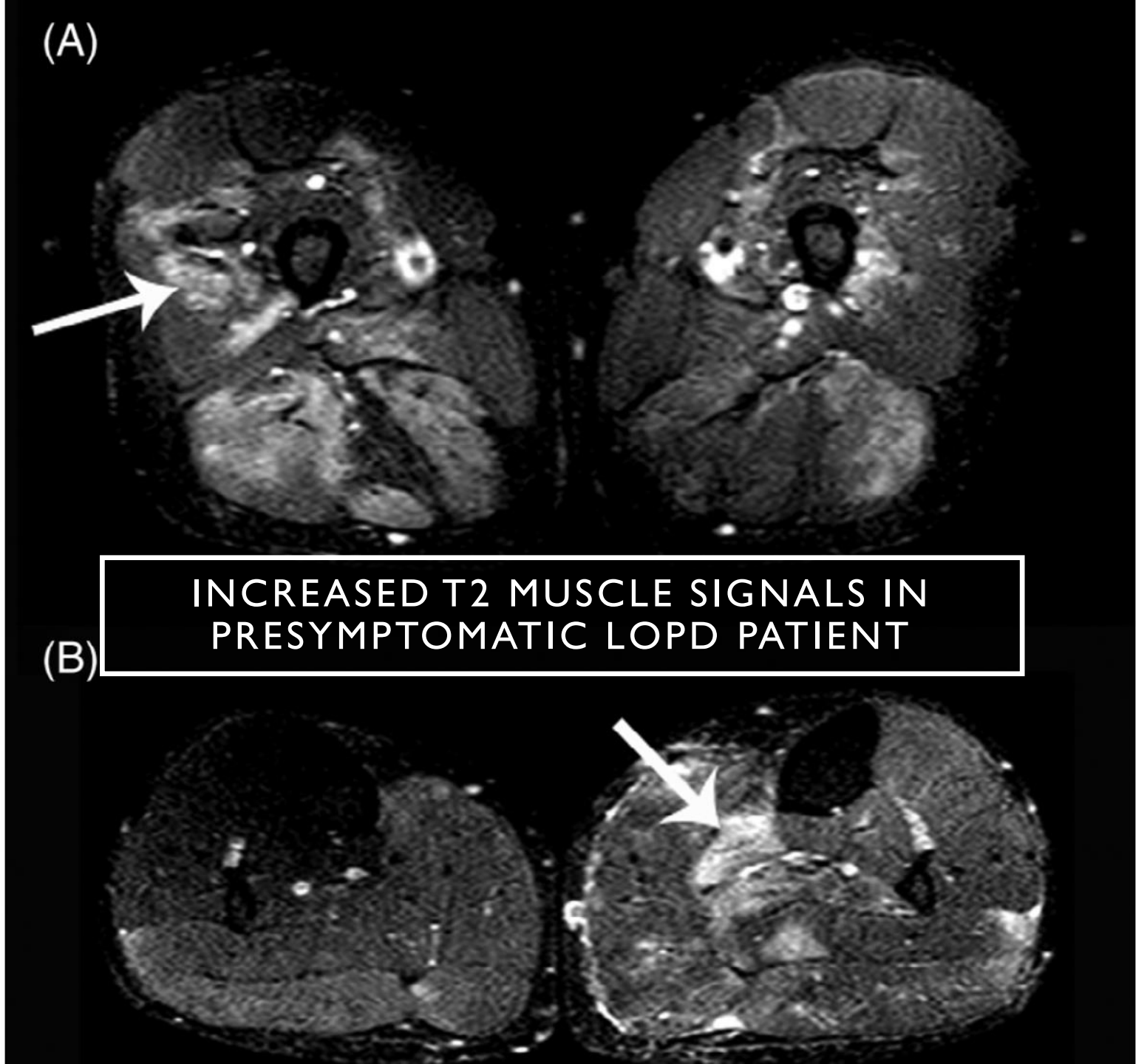
Díaz-Manera J et al. *Muscle Nerve*. 2021;63(5):640-650.

MUSCLE EDEMA IN POMPE DISEASE

- Around **one-third of muscles** analyzed in LOPD patients showed increased T2 time at baseline.
- The **adductor magnus, semi-membranous and biceps femoris** are most severely involved.
- The origin of STIR/T2 changes is unclear
  - No inflammatory infiltrates in muscle biopsy of LOPD patients.
  - ?Active muscle necrosis
  - ?Increased water retention from glycogen accumulation.
- Associated with **greater fat increase** on follow-up MRI

Carlier PG, Azzabou N, de Sousa PL et al. J Inherit Metab Dis. 2015 May;38(3):565-72.

Díaz-Manera J et al. Muscle Nerve. 2021 May;63(5):640-650.



INCREASED T2 MUSCLE SIGNALS IN PRESYMPTOMATIC LOPD PATIENT

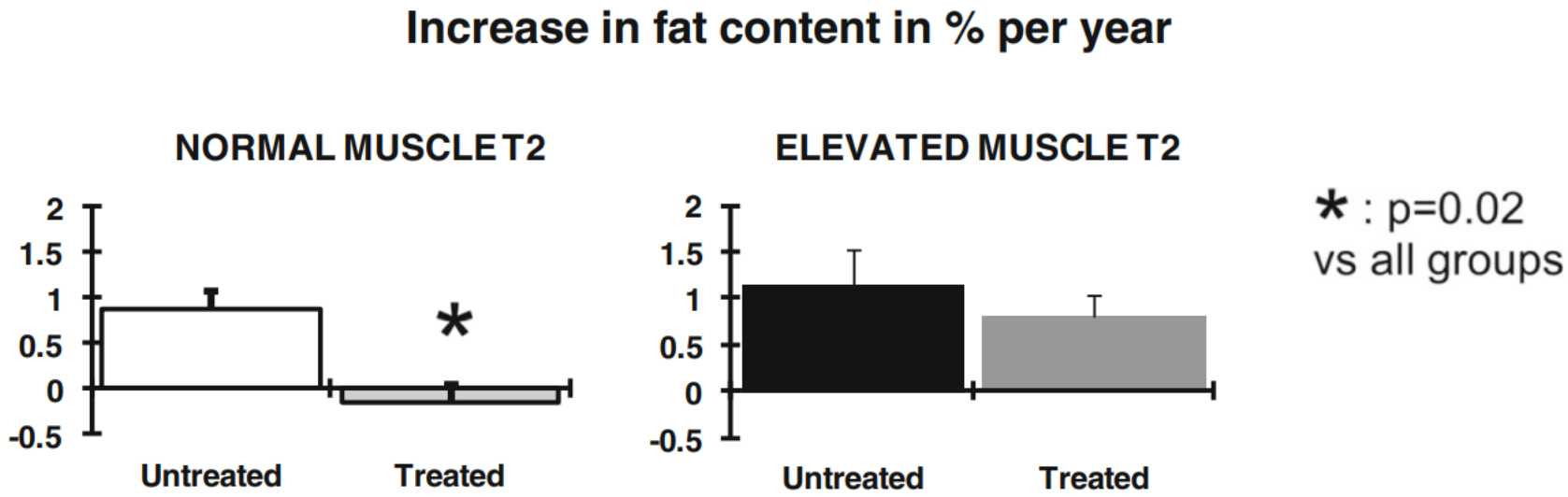


Fig. 4 Effect on enzyme replacement therapy on the progression of the fatty degenerative changes. Treatment was effective both in muscle with normal T2 (*left panel*) and with elevated T2 (*right panel*). In muscles with normal T2s, the progression of the degenerative changes was completely blocked

Carlier PG, Azzabou N, de Sousa PL et al. J Inherit Metab Dis. 2015 May;38(3):565-72.

USE OF MRI IN MONITORING ERT EFFECT

- MRI change of fat replacement is slow.
  - EMBASSY trial (multicenter study evaluating glycogen clearance in muscle tissue samples collected pre- and post- ERT in LOPD patient)
  - Percent tissue area occupied by glycogen in quadriceps and deltoid muscles decreased at 6 month
  - **No changes were detected on MRI.**

- Fat replacement continues despite ERT
  - In LOPD received ERT , the **average yearly progression rate** of fatty infiltration rate was **0.9 – 1.9 %.**

- Fat replacement rate lowered by 0.68 %/year as compared to the untreated patients.
  - In muscles with normal water T2, muscle degenerative changes were completely stopped.

van der Ploeg A, Carlier PG, Carlier RY et al. Mol Genet Metab. 2016 Sep;119(1-2):115-23.
Carlier PG, Azzabou N, de Sousa PL et al. J Inherit Metab Dis. 2015 May;38(3):565-72.

DIFFERENTIAL DIAGNOSIS OF LATE ONSET POMPE DISEASE

- Sarcoglycanopathies
  - **Similarity** to Pompe disease: **paraspinal and abdominal** involvement; prominent **gluteal** muscle involvement; a **proximal-to-distal gradient** of fat replacement in the vasti; **relative sparing** of the distal leg muscles
  - **Difference:**
    - **Do not** have involvement of the **tongue**
    - **Severe involvement of the scapular, biceps, and triceps brachii muscles**
    - Early complete fat replacement of the gluteus maximus
- Dystrophinopathies, dysferlinopathies, or calpainopathies
  - Involvement of the distal leg muscles, mainly the gastrocnemius medialis and soleus
- Inflammatory myopathies
  - Can present with increased STIR/T2 signal. Muscle biopsy will show inflammatory infiltrates unlike LOPD.

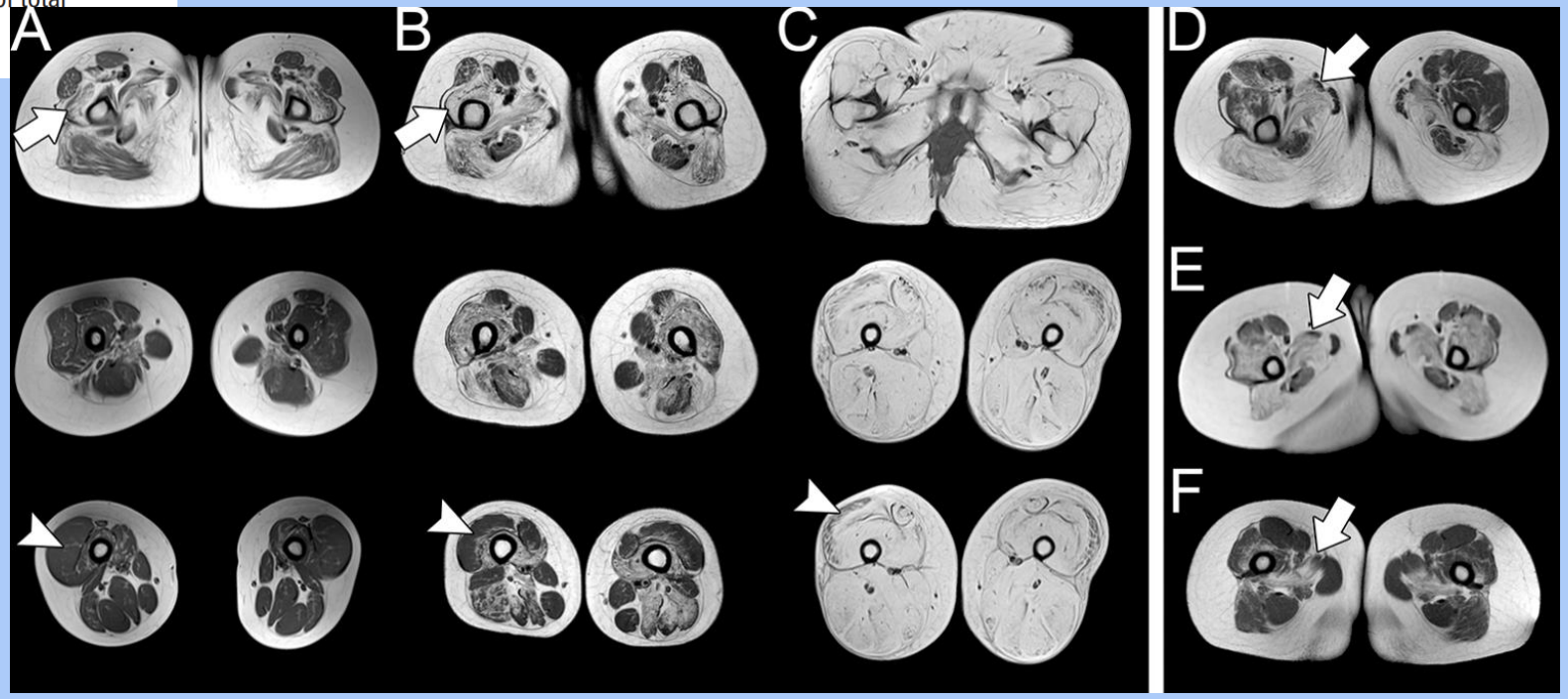
MRI PATTERN FOR SARCOGLYANOPATHIES

Table 1 'Gestaltic' criteria

Criteria	
Quadriceps gradient	58/58* (100%)
Relative sparing of tibialis posterior and flexor digitorum longus	66/69 (96%)
Adductor longus medial sparing	41/56* (73%)
Normal or almost normal leg	45/69 (65%)
Relative sparing of tensor fasciae latae	41/69 (59%)
Hypertrophy of either sartorius or gracilis	24/69 (35%)

*In the remaining patients the feature could not be assessed because of total muscle sparing or incomplete scans.

Tasca, G., Monforte, M., Díaz-Manera, J et al(2017). *MRI in sarcoglycanopathies: a large international cohort study. Journal of Neurology, Neurosurgery & Psychiatry, 89(1), 72–77.*



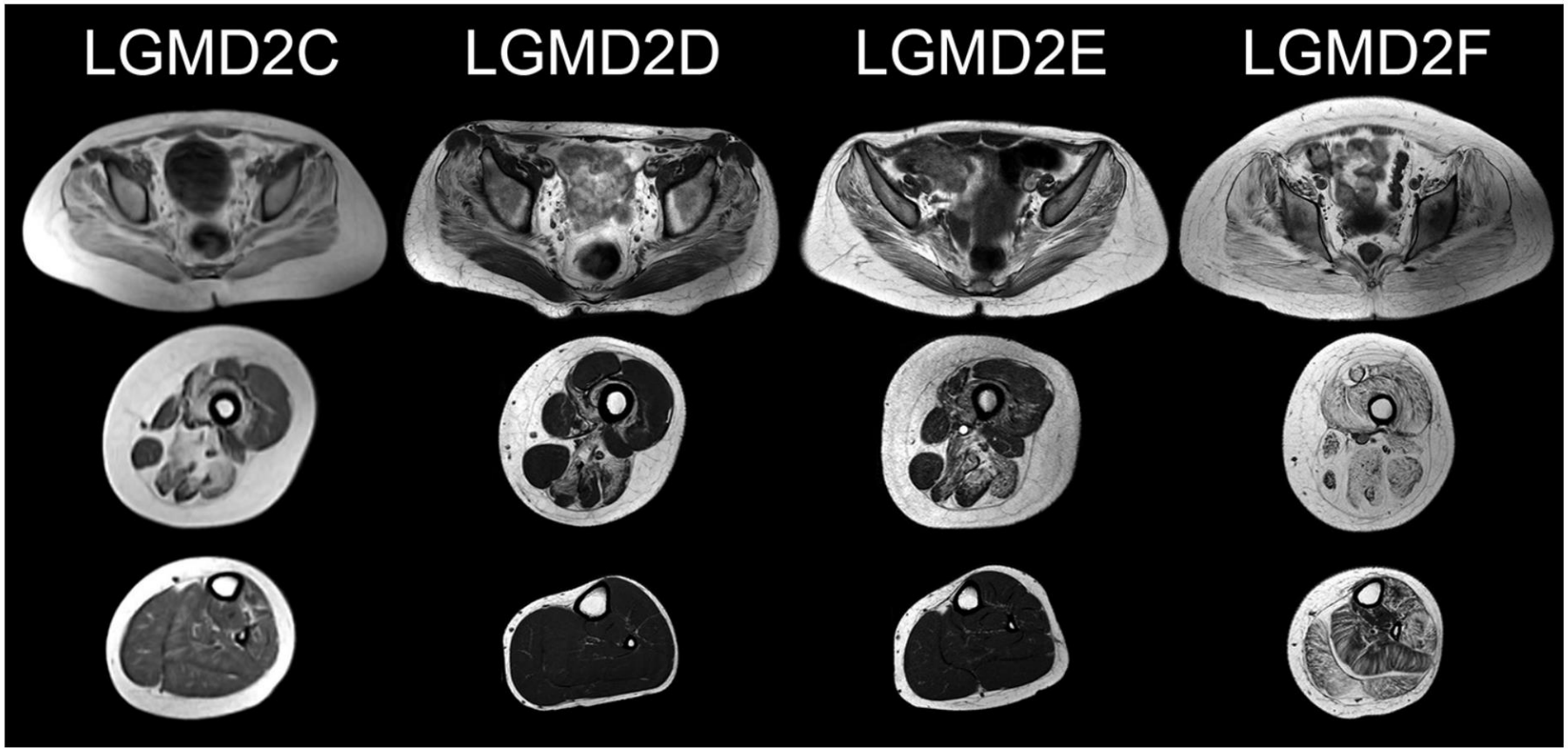


Figure 4 Examples of involvement at pelvis, thigh and lower leg level in the different sarcoglycanopathies. A similar pattern is shared by the different sarcoglycanopathies. IT1_2, LGMD2C; IT3_3, LGMD2D; IT3_4, LGMD2E; IT3_8, LGMD2F. LGMD, limb-girdle muscular dystrophies.

MUSCLE MRI IN INFANTILE ONSET POMPE DISEASE

- Very limited data

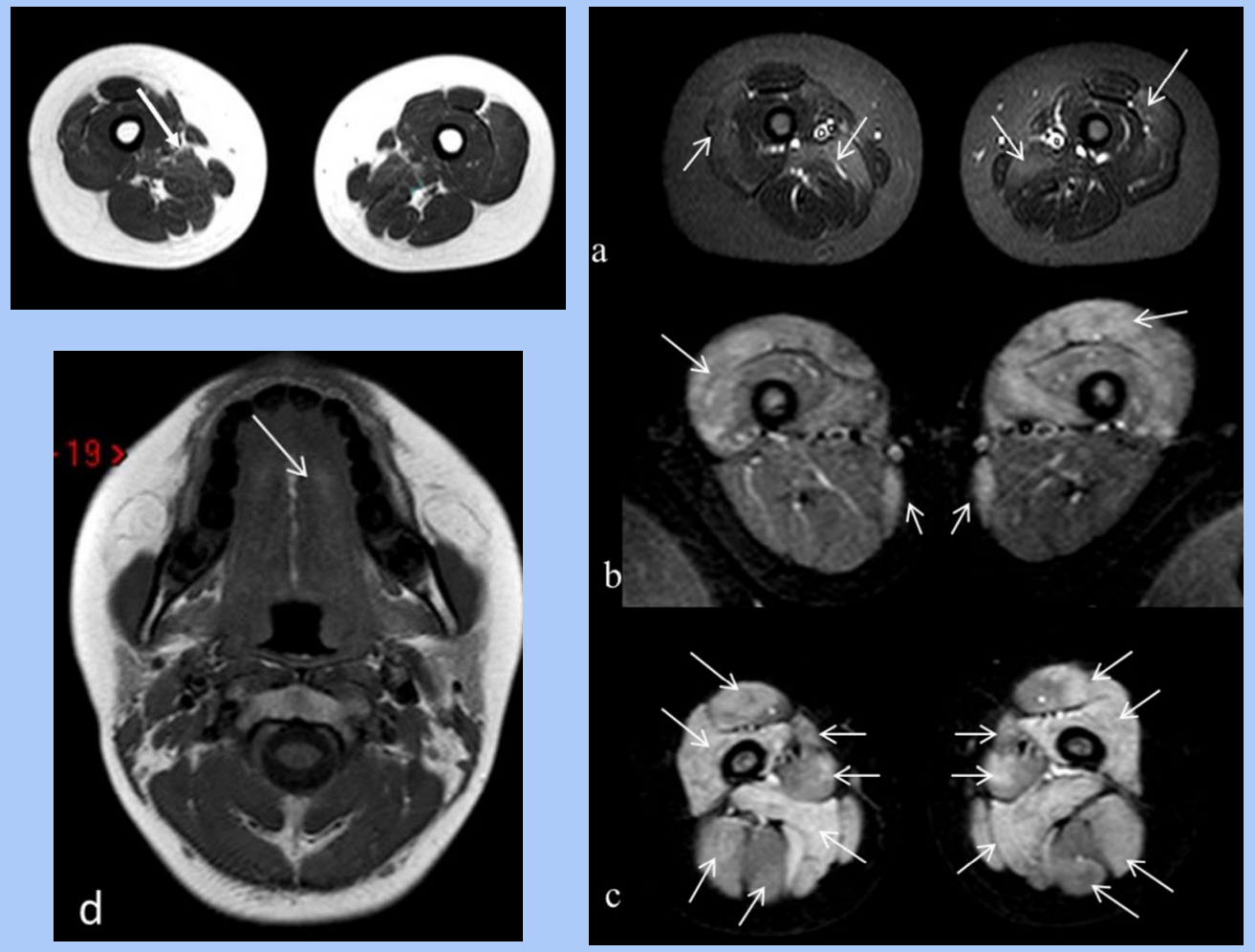
- Early MRI study before introduction of ERT
  - No significant fatty replacement (T1W) or edema (T2W)
  - May have muscle hypertrophy (due to accumulation of glycogen)

Wens SC, van Doeveren TE, Lequin MH, et al. J Rare Disord Diagn Ther. 2015;1:10-13.

- MRI of ERT-treated children with IOPD
  - Mild fatty replacement in adductor magnus and tongue muscles
  - Muscle edema of thigh and calf muscles

Pichiecchio A, Rossi M, Cinnante C et al. Muscle Nerve. 2017 Jun;55(6):841-848.

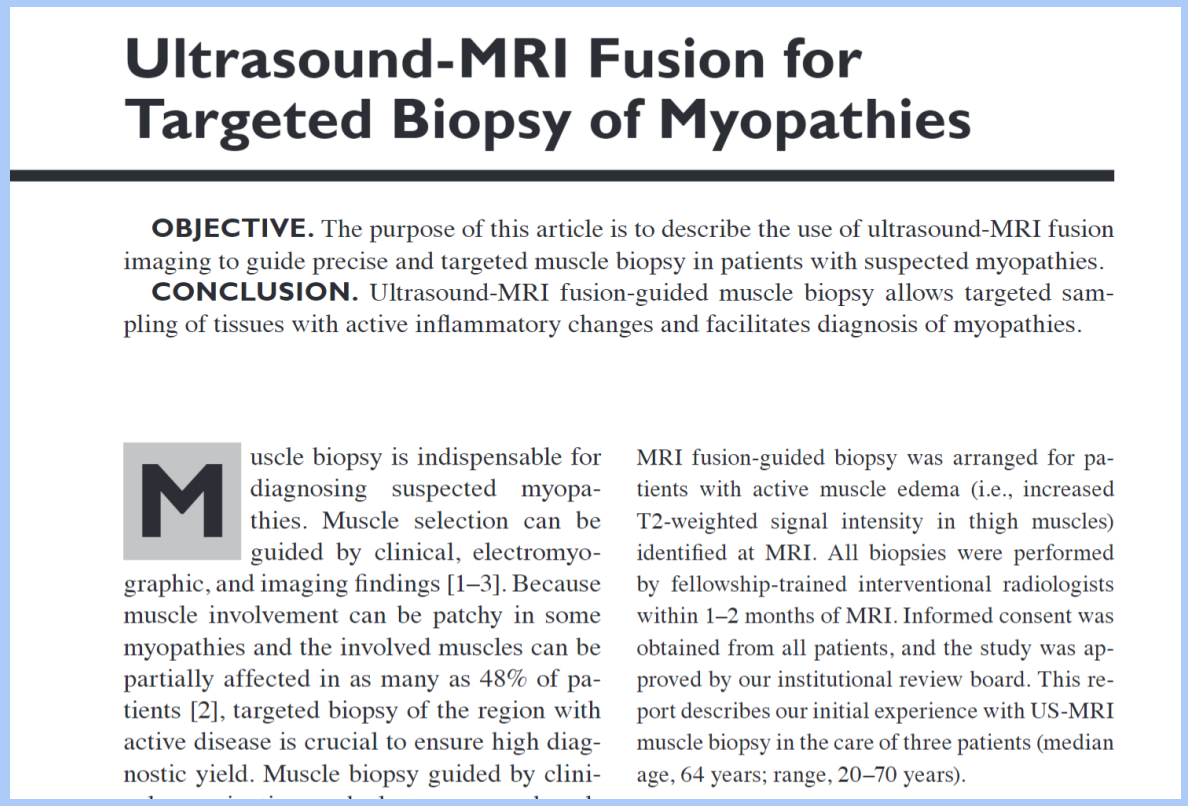
MRI OF ERT-TREATED CHILDREN WITH IOPD



Pichiecchio A, Rossi M, Cinnante C et al. Muscle Nerve. 2017 Jun;55(6):841-848.

UTILITY OF MRI IN GUIDING MUSCLE BIOPSY

- Muscle selection
  - Clinical, EMG and/or imaging findings
- In patients with suspected idiopathic inflammatory myopathy
  - Use of MRI to select target of muscle biopsy decreased the false-negative sampling rate from 23% to 19%



Ultrasound-MRI Fusion for Targeted Biopsy of Myopathies

OBJECTIVE. The purpose of this article is to describe the use of ultrasound-MRI fusion imaging to guide precise and targeted muscle biopsy in patients with suspected myopathies.

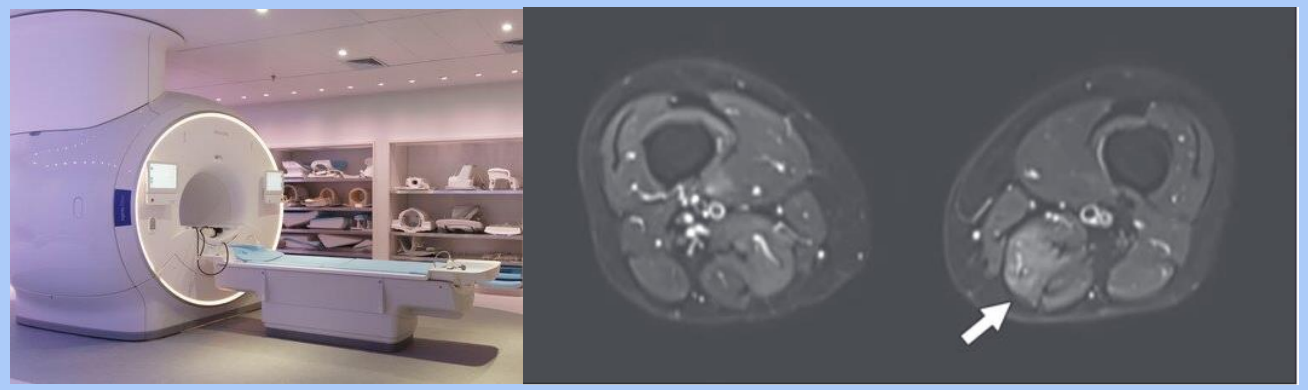
CONCLUSION. Ultrasound-MRI fusion-guided muscle biopsy allows targeted sampling of tissues with active inflammatory changes and facilitates diagnosis of myopathies.

Muscle biopsy is indispensable for diagnosing suspected myopathies. Muscle selection can be guided by clinical, electromyographic, and imaging findings [1–3]. Because muscle involvement can be patchy in some myopathies and the involved muscles can be partially affected in as many as 48% of patients [2], targeted biopsy of the region with active disease is crucial to ensure high diagnostic yield. Muscle biopsy guided by clini-

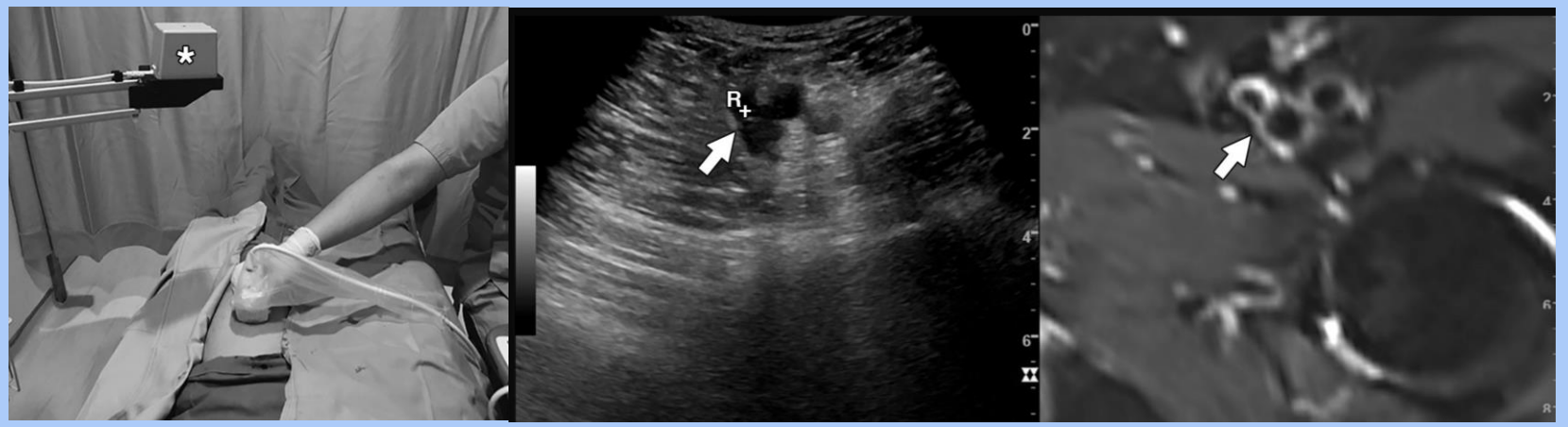
MRI fusion-guided biopsy was arranged for patients with active muscle edema (i.e., increased T2-weighted signal intensity in thigh muscles) identified at MRI. All biopsies were performed by fellowship-trained interventional radiologists within 1–2 months of MRI. Informed consent was obtained from all patients, and the study was approved by our institutional review board. This report describes our initial experience with US-MRI muscle biopsy in the care of three patients (median age, 64 years; range, 20–70 years).

Lee KH, Lau V, Gao Y, et al. *AJR Am J Roentgenol*. 2019;212(5):1126-1128.

ULTRASOUND-MRI FUSION MUSCLE BIOPSY

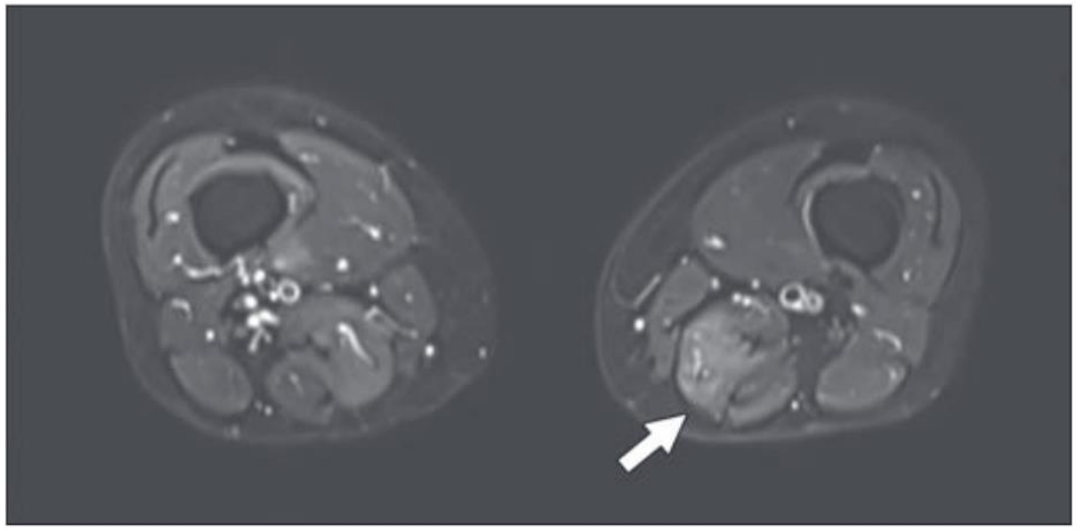


MRI thigh

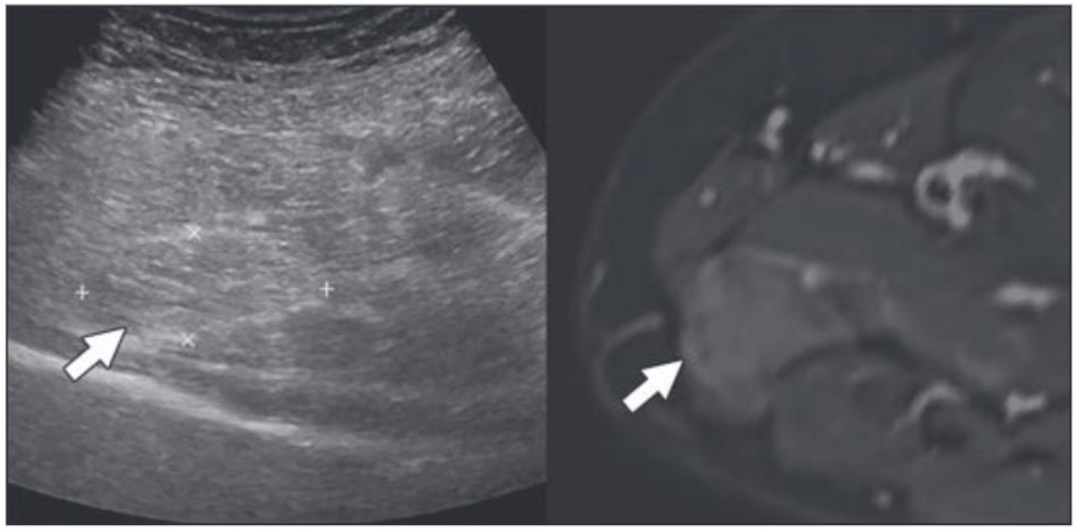


Plane and point registration

Real time US-MRI guidance



A



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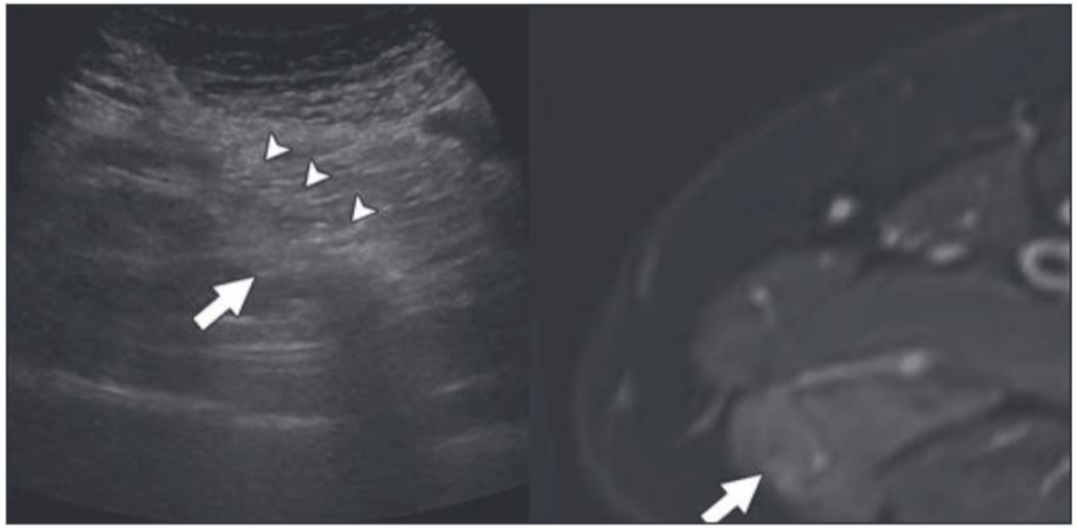

C

Fig. 2—64-year-old woman with necrotizing myopathy.
A, Axial T2-weighted water-only MR image shows focal high signal intensity in distal portion of left semimembranosus muscle (*arrow*), indicating active inflammatory changes.
B, Coregistered ultrasound (*left*) and T2-weighted MR (*right*) images of left thigh muscle show high MRI signal intensity in left semimembranosus muscle (*arrows*) but normal ultrasound appearance.
C, Coregistered ultrasound (*left*) and MR (*right*) images of left thigh muscle show left semimembranosus (*arrows*) sampled with 14-gauge semiautomatic spring-loaded biopsy system (*arrowheads*) in slightly oblique plane.

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POTENTIAL BENEFITS OF US-MRI GUIDANCE MUSCLE BIOPSY IN POMPE DISEASE

1. Target muscle with active edema
   - Muscle edema in Pompe disease can be patchy
   - Involved muscle can be only partially affected
2. Avoid muscle with fatty atrophy
3. Increase diagnostic yield and better radio-pathological correlation

TAKE HOME MESSAGE

- Muscle MRI is helpful in assessing various neuromuscular disease, both morphologically and quantitatively.
- Late onset Pompe disease has characteristic pattern of fatty replacement in T1 weighted MRI, mainly involving tongue, paraspinal, shoulder girdle and gluteal muscles.
- USG-MRI fusion guided muscle biopsy can be a helpful adjunct in diagnosis of neuromuscular disease.

THE END

Thank you very much!

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