Muscular Dystrophies: What the radiologist should know

J. Carmen Timberlake, MD;
Kristina Siddall, MD; Christopher Bang, DO;
Marat Bakman, MD; Gwy Suk Seo, MD;
Johnny UV Monu, MD

Department of Imaging Sciences
University of Rochester Medical Center, Rochester, NY

UNIVERSITY OF ROCHESTER MEDICAL CENTER

Muscular Dystrophies: Introduction

- The muscular dystrophies are
  - a group of inherited, progressive muscle disorders
  - caused by mutations in genes encoding proteins required for normal muscle function.
- Biopsy reveals fiber degeneration
  - this manifests clinically as weakness.

Muscular Dystrophies: Introduction

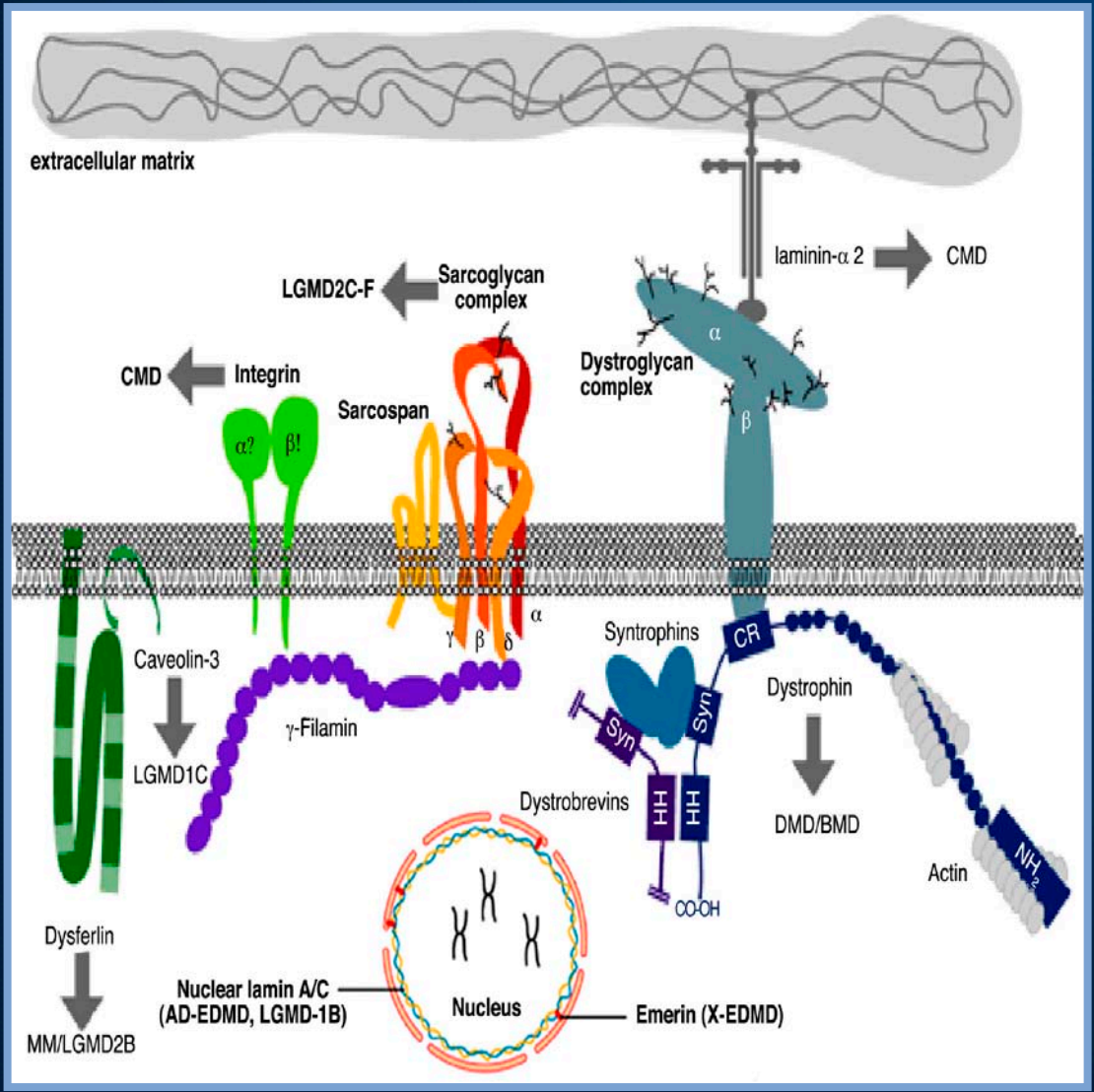
- Role of imaging in diagnosis and management
  - Historically, diagnosis and evaluation of disease progression depend on clinical, pathologic, and biochemical parameters.
  - Imaging has not been used for primary diagnosis or for routine follow-up evaluation.
  - MRI, however, has a potential role in the work up, management, and study of muscular dystrophies

Muscular Dystrophies: Introduction

Teaching points:

1. Review of spectrum of muscular dystrophies.
2. Review patterns of inheritance, pathophysiology of disease, clinical manifestations, and clinical management.
3. Review radiologic findings in muscular dystrophies, with emphasis on MRI.
4. Explore potential role of MRI in evaluation, management, and scientific investigation of muscular dystrophies.

Muscular Dystrophies: Classification by physiology



- Disruption of the dystrophin-glycoprotein complex
  - DMD/BMD
  - CMDs (most)
  - LGMDs (some)
- Disruption of gene expression or chromosomal organization
  - FSHD
  - EDMD
  - Oculopharyngeal dystrophy
  - Myotonic dystrophy

Modified from O'Brien and Kunkel, Children's Hospital, Boston, MA and Expert Reviews in Molecular Medicine 2002, Cambridge University Press.

Muscular Dystrophies: Classification

- The classification of muscular dystrophies continues to evolve with advances in understanding of their molecular genetics.
- Subdivisions of the major clinical categories are defined by their molecular features.
- Imaging features are not a component of established classification schema.

Muscular Dystrophies: Classification

- On the next slide is an overview of the major subtypes of muscular dystrophies. Click on highlighted links for more detailed information, including what is known about their patterns of specific muscle involvement and sparing.
- Description of major categories
  - Limb Girdle Muscular Dystrophies: Heterogeneous group of diseases characterized by proximal muscle weakness
  - Congenital Muscular Dystrophies: Diseases characterized by muscular weakness in early infancy (typically obvious at birth) and elevated CK in neonatal period (normalizes by 6-10 wks)
  - Other Muscular Dystrophies: Heterogeneous group of diseases, which do not fit into the above two major categories

Muscular Dystrophies: Major Subtypes

LIMB GIRDLE MDs (LGMDs)

- Dystrophinopathies – prototypes of LGMDs
  - Duchenne MD
  - Becker MD
- Autosomal dominant LGMD
  - LGMD1A through 1C
- Autosomal recessive LGMD
  - LGMD2A through 2J

CONGENITAL MDs (CMDs)

- CMD without major brain malformation
  - Merosin-absent CMD
  - CMD
  - CMD with rigid spine disease
  - Ullrich myopathy
- CMD with major brain malformation
  - Fukuyama CMD
  - Muscle-eye-brain disease
  - Walker Warburg syndrome

OTHER MDs

- Table 1:
  - Facioscapulohumeral MD
  - Emery Dreifuss syndrome
- Table 2:
  - Oculopharyngeal MD
  - Myotonic Dystrophies

Muscular Dystrophies: Diagnosis

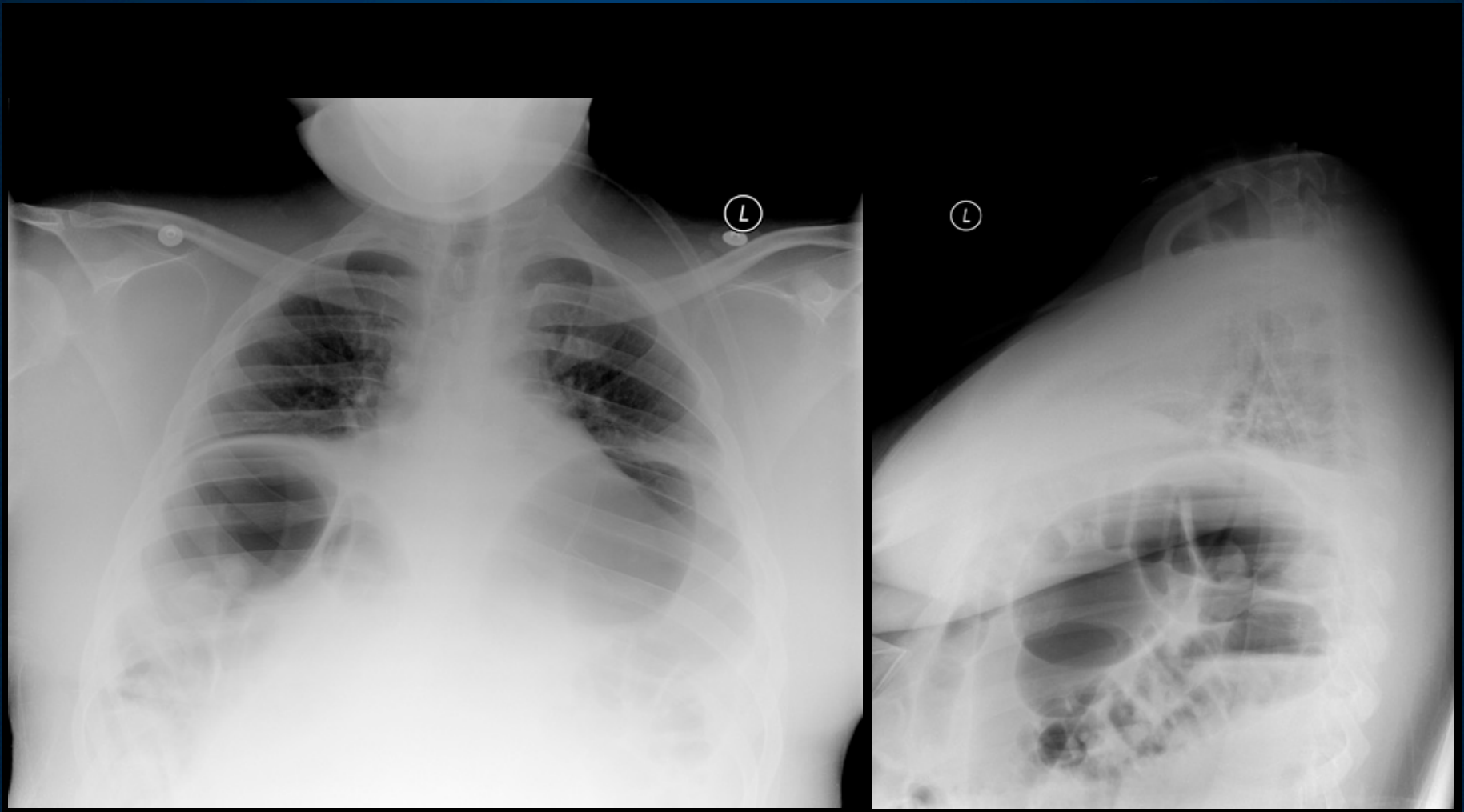
Mainstays of diagnosis:

- Clinical features
- Genetic testing
  - Myopathies with commercially available genetic testing include:
    - DMD/BMD
    - LGMD2B
    - Oculopharyngeal MD
    - DM1 and DM2
  - Additional genetic testing may be available through research laboratories
- Muscle biopsy with immunohistochemical staining

Muscular Dystrophies: Imaging

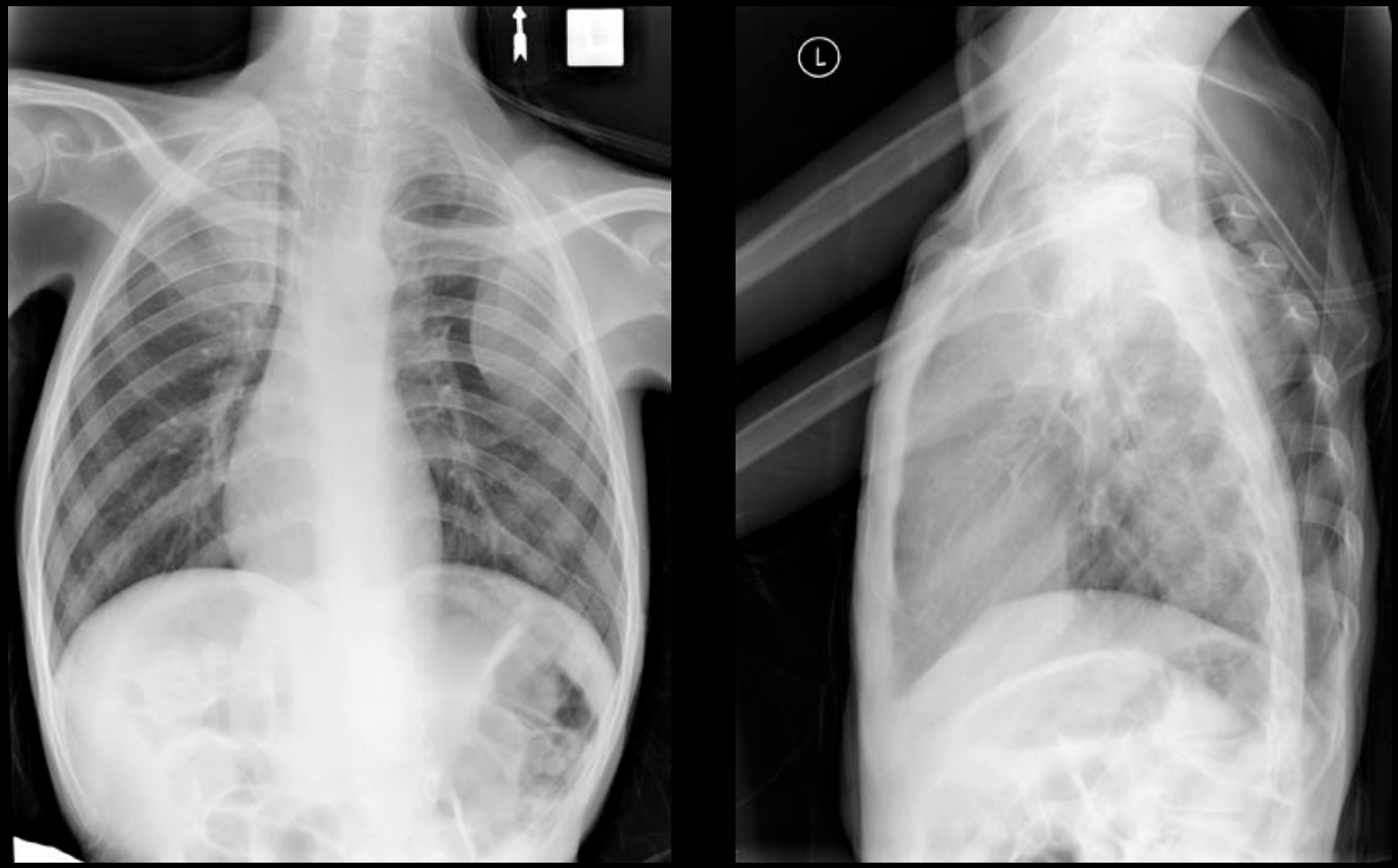
- Plain film
  - secondary features demonstrated

Muscular Dystrophies: Plain Film



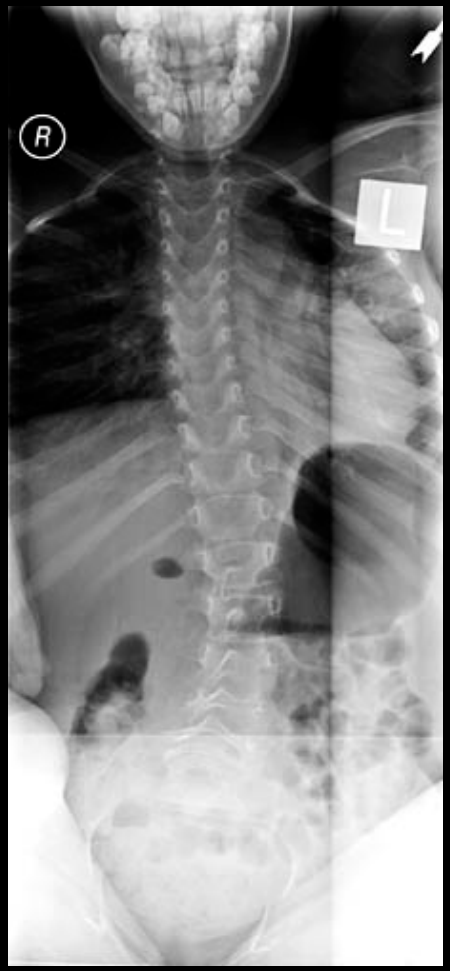
Duchenne MD: Severely hypoventilatory lungs. Respiratory failure is a common cause of death in Duchenne MD.

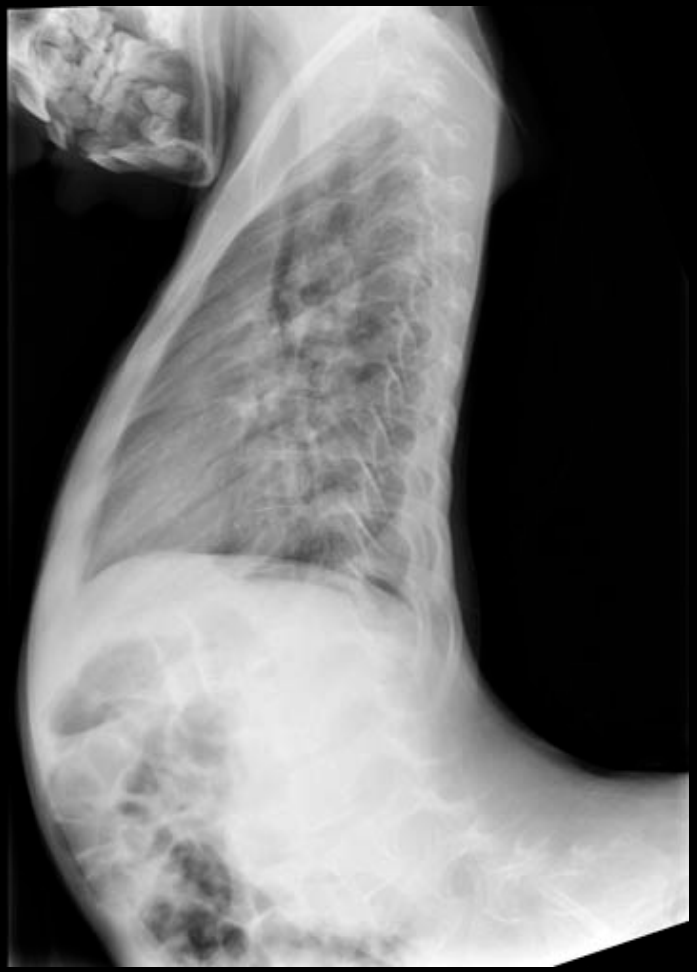
Muscular Dystrophies: Plain Film



Duchenne MD: Gracile bones. Near translucent soft tissues (see arms) due to fatty replacement of muscles.

Muscular Dystrophies: Plain Film





Congenital MD: Scoliosis. Contractures. Hyperlordotic lumbar spine due to loss of muscle tone. Gracile bones.

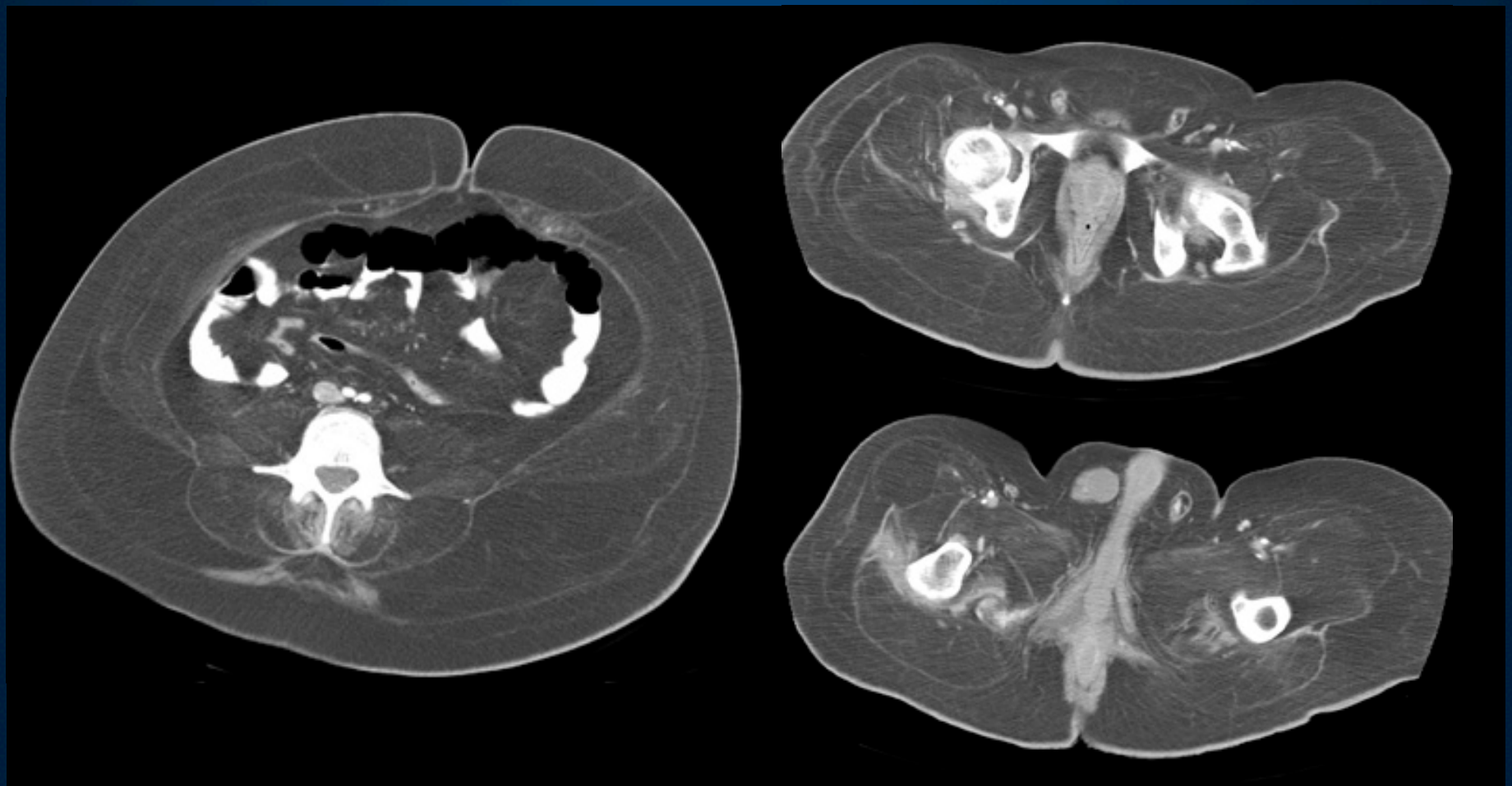
Muscular Dystrophies: Imaging

- **U/S**
  - proposed as a noninvasive screening technique in children with neuromuscular disease
  - evaluation of muscle echogenicity (fatty infiltration), muscle thickness
  - limited anatomic detail

Muscular Dystrophies: Imaging

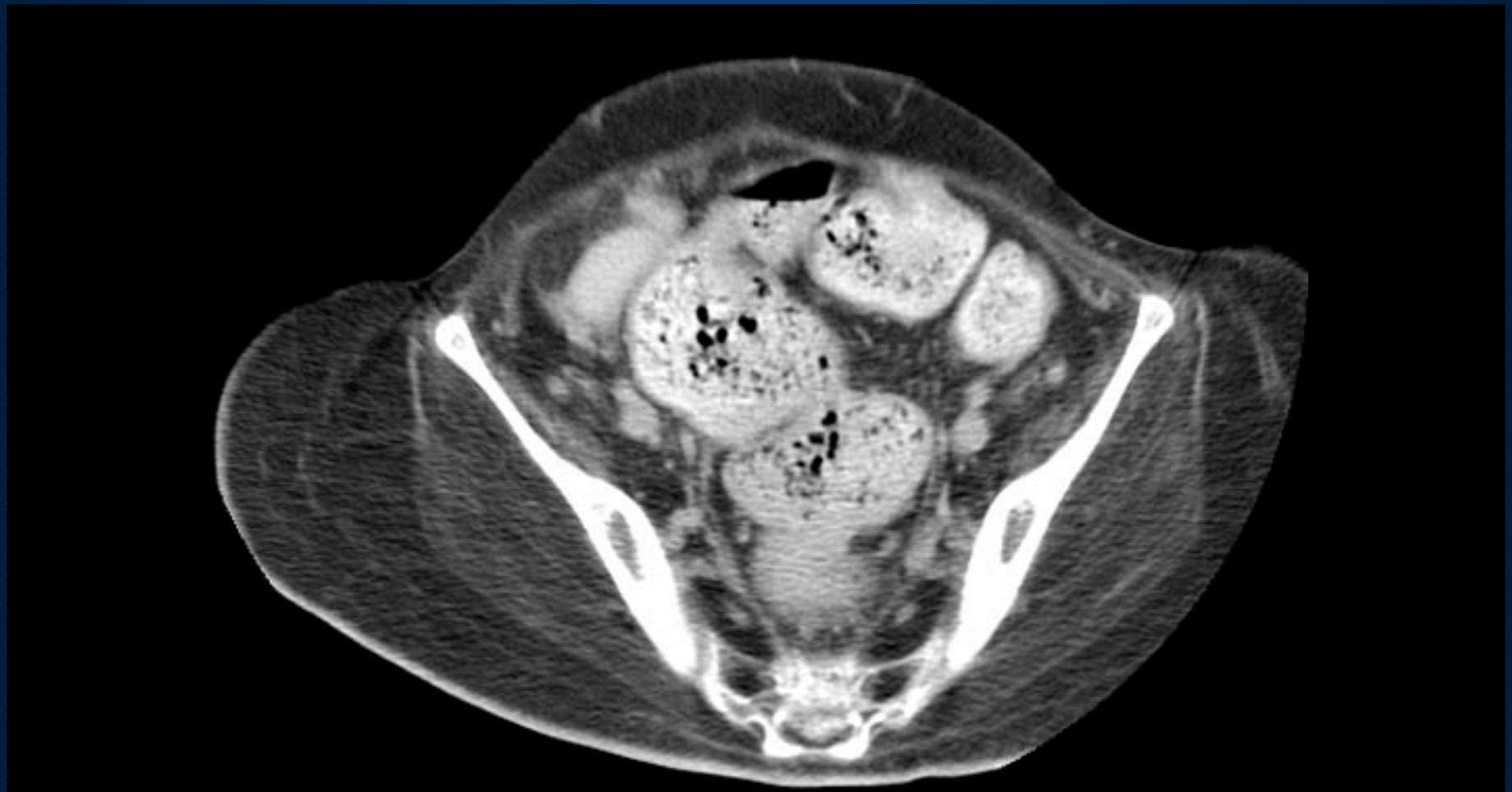
- **CT**
  - evaluation of relative fatty infiltration of muscle and muscle thickness
  - good anatomic detail
  - use of ionizing radiation may be a disadvantage, particularly in children

Muscular Dystrophies: CT



Duchenne MD: (Advanced stage, same patient as slide showing severely hypoventilatory lungs). Diffuse fatty infiltration of muscles of the abdomen and pelvis.

Muscular Dystrophies: CT



Duchenne MD: Fatty infiltration of gluteal muscles.

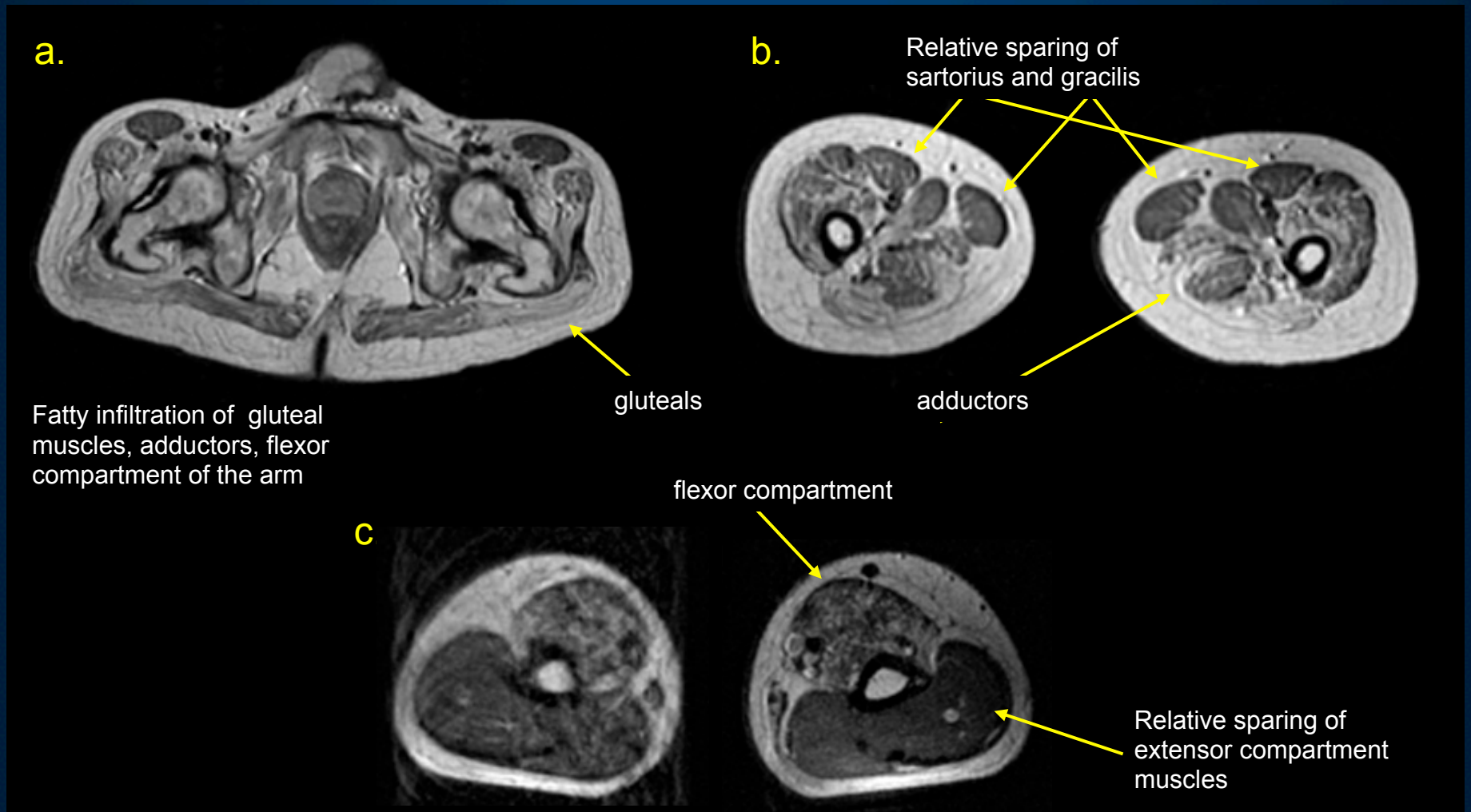
Muscular Dystrophies: Imaging

- **MRI**
  - modality of choice due to its superior soft tissue contrast
  - typically T1W, axial images only
  - to improve efficiency, a limited number of selected slices through pelvis, thigh, calf, arm may be obtained
  - evaluation of atrophy, hypertrophy, pseudohypertrophy

Muscular Dystrophies: Imaging

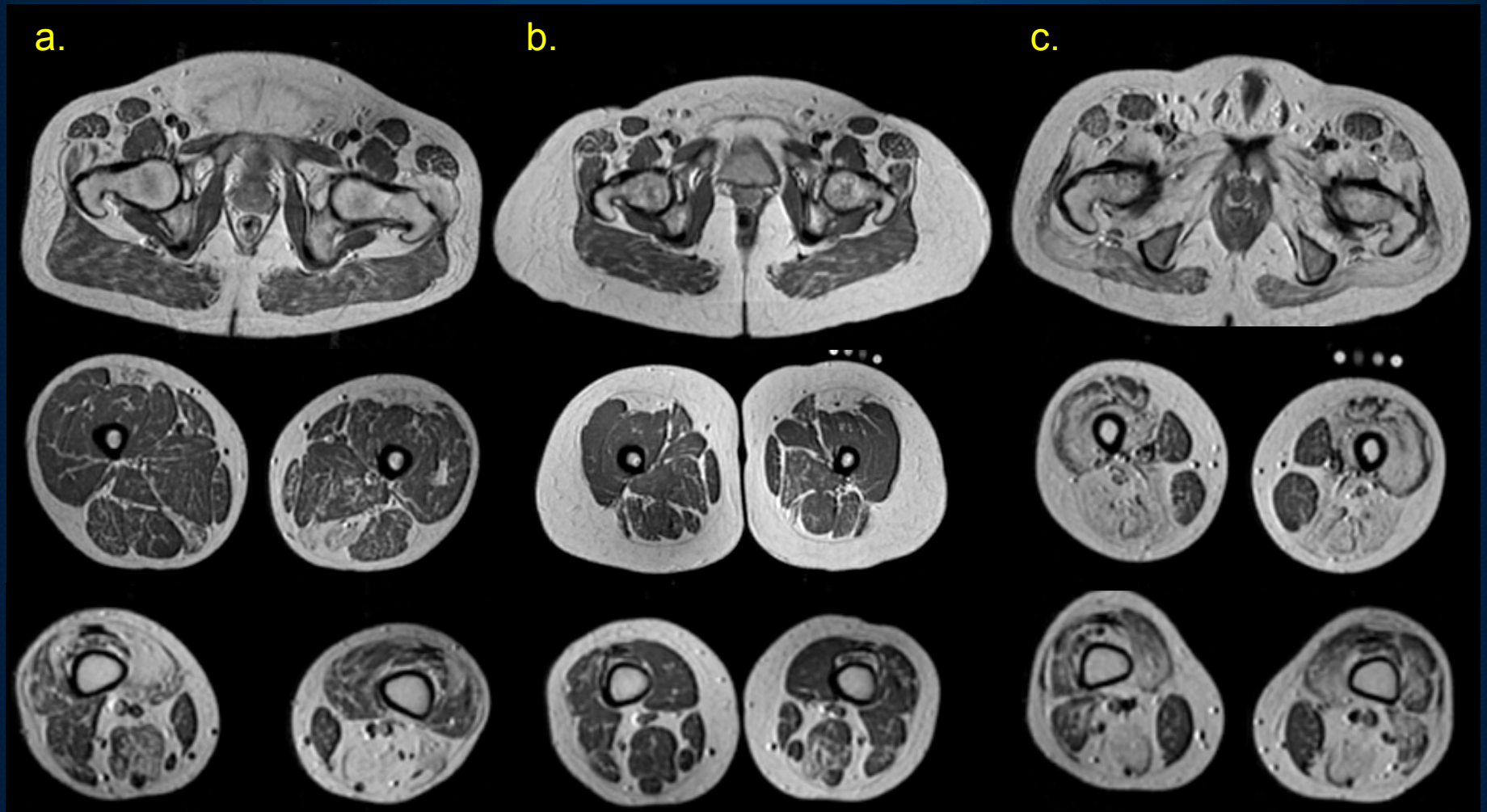
- **MRI**
  - T1W for evaluation of relative fatty infiltration
  - T2W for evaluation of edema-like changes (has not been widely used)
  - contrast enhanced studies are not required
  - limited use of other features, such as MR spectroscopy and diffusion weighted imaging

Muscular Dystrophies: MRI



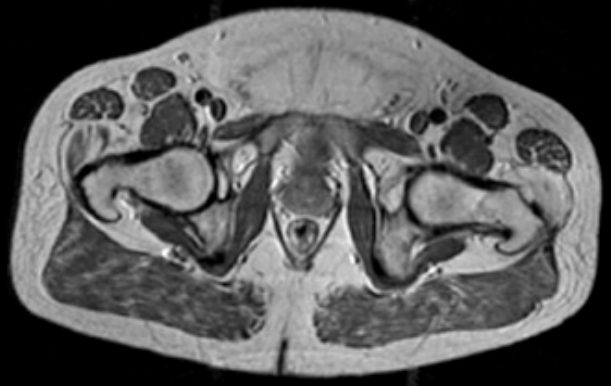
Becker MD: T1W axial MR images of (a) pelvic girdle, (b) upper thigh, and (c) upper arms. Note pattern of fatty infiltration of proximal muscles with relative sparing of gracilis and sartiorius of the upper thigh and extensor compartment of the upper arms.

Muscular Dystrophies: MRI

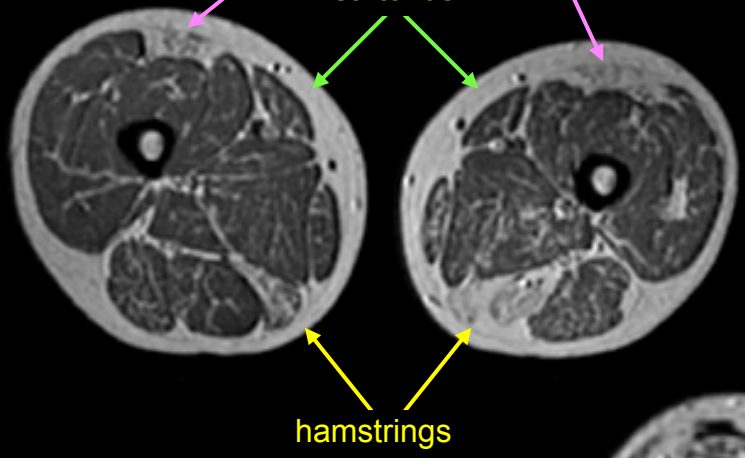


Fascioscapulohumeral MD: Axial T1W MR images of pelvic girdle, upper thigh, and lower thigh from 3 different patients (a-c). Note differences in severity of fatty infiltration and asymmetry of involvement between right and left limbs.

Muscular Dystrophies: MRI

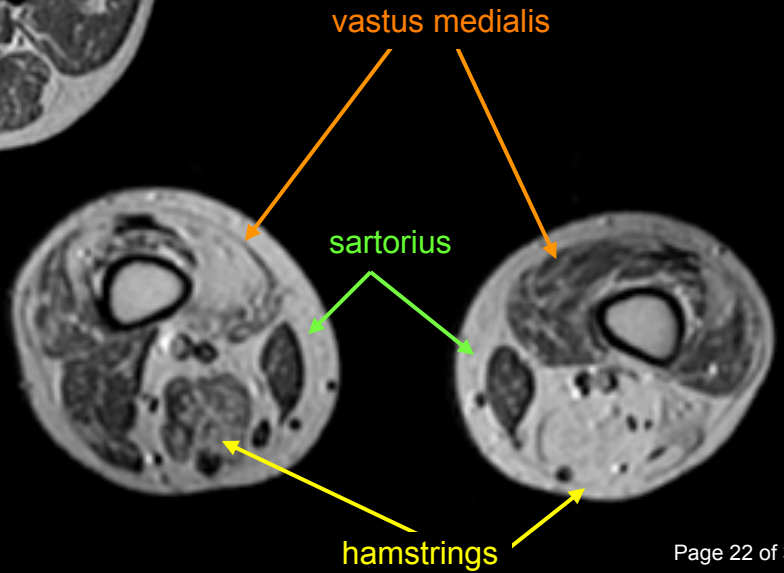


Fascioscapulohumeral MD: Patient A



Severe involvement of

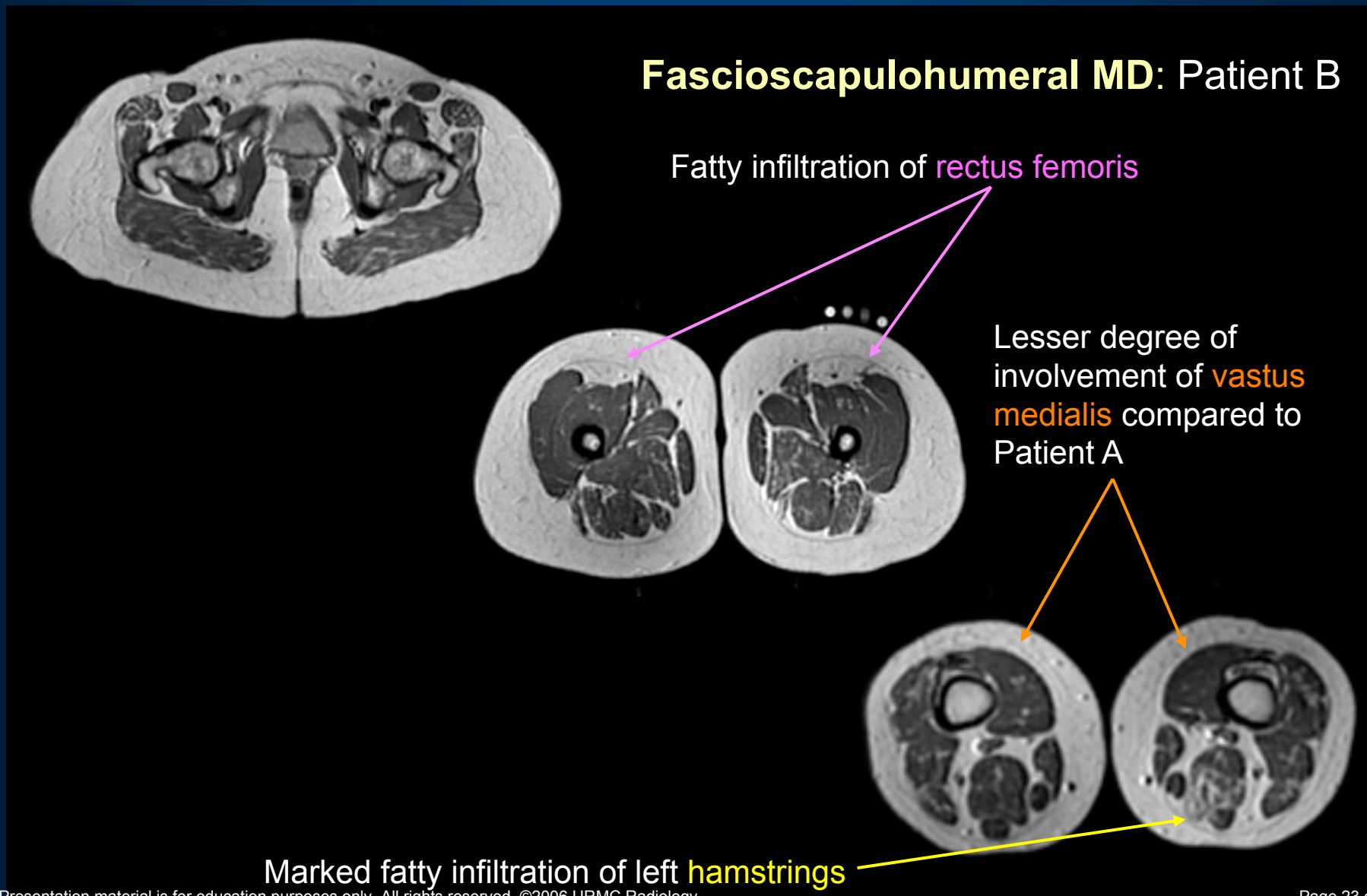
- hamstrings (left > right)
- vastus medialis (right > left)
- rectus femoris



Once again, relative sparing of

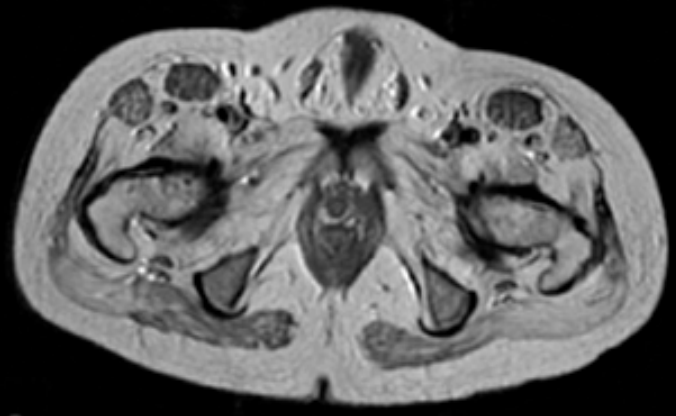
- sartorius

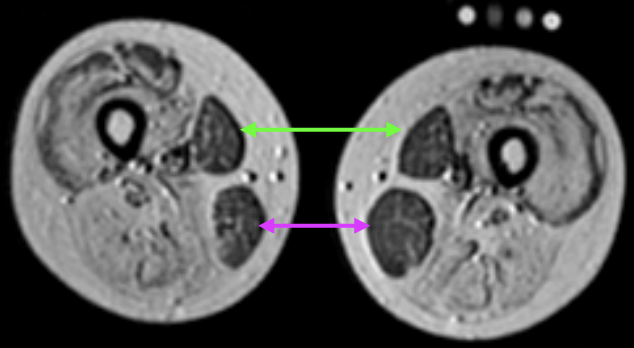
Muscular Dystrophies: MRI



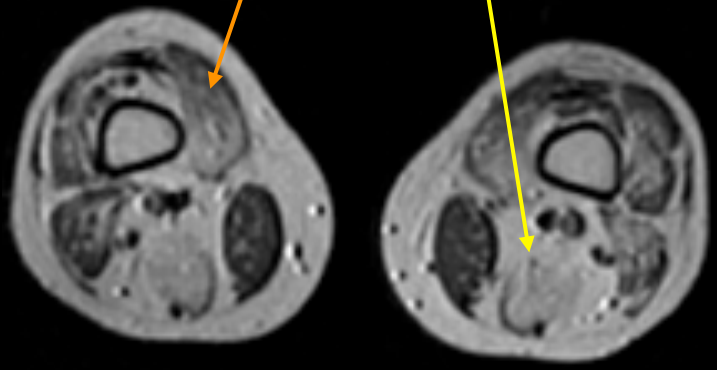
Muscular Dystrophies: MRI

Fascioscapulohumeral MD: Patient C





Fatty infiltration of hamstrings and vastus medialis

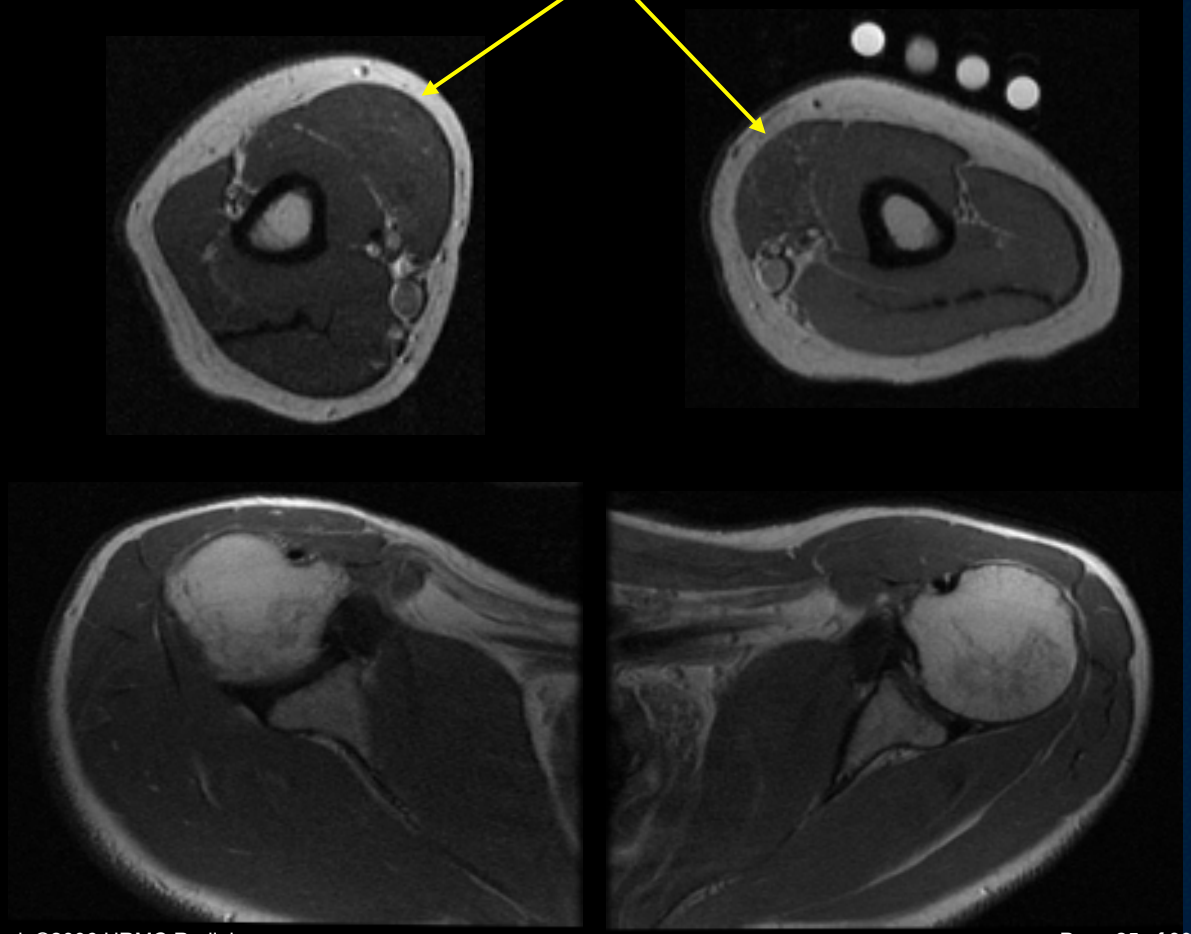


Severe fatty infiltration of most muscles of the limb girdle and upper thigh with relative sparing of the sartorius and gracilis muscles

Muscular Dystrophies: MRI

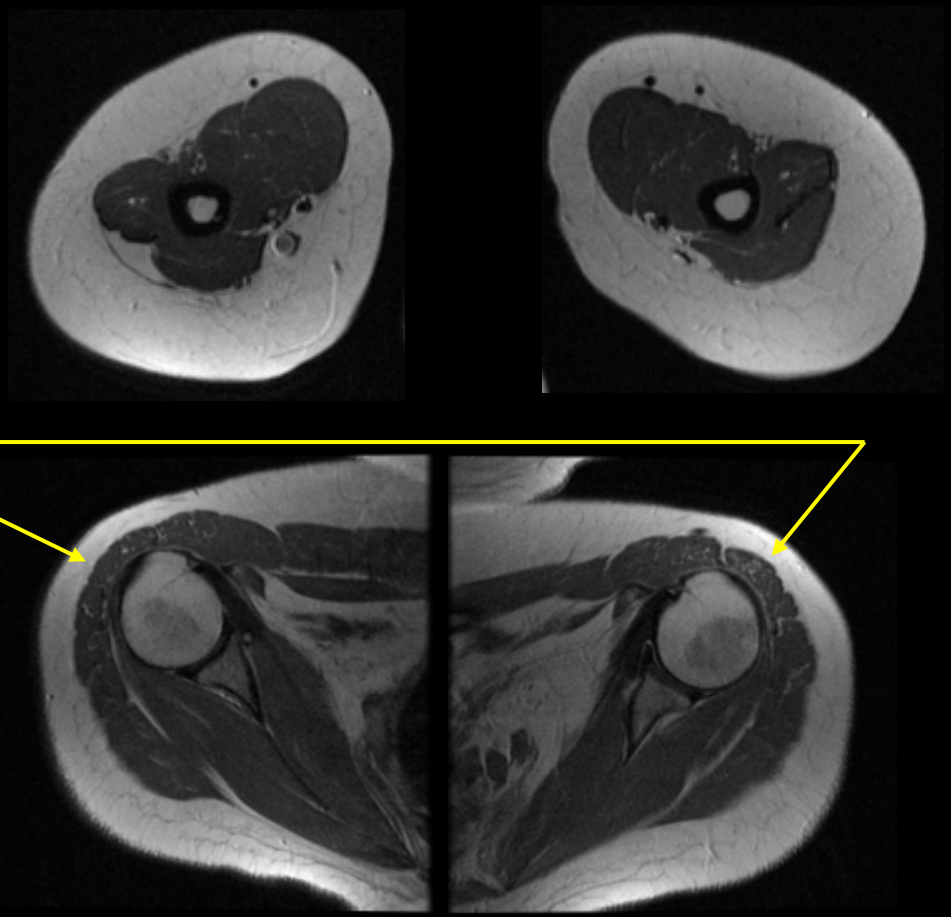
Fascioscapulohumeral MD:
Patient A

Mild disease with mild fatty infiltration of biceps brachii



Muscular Dystrophies: MRI

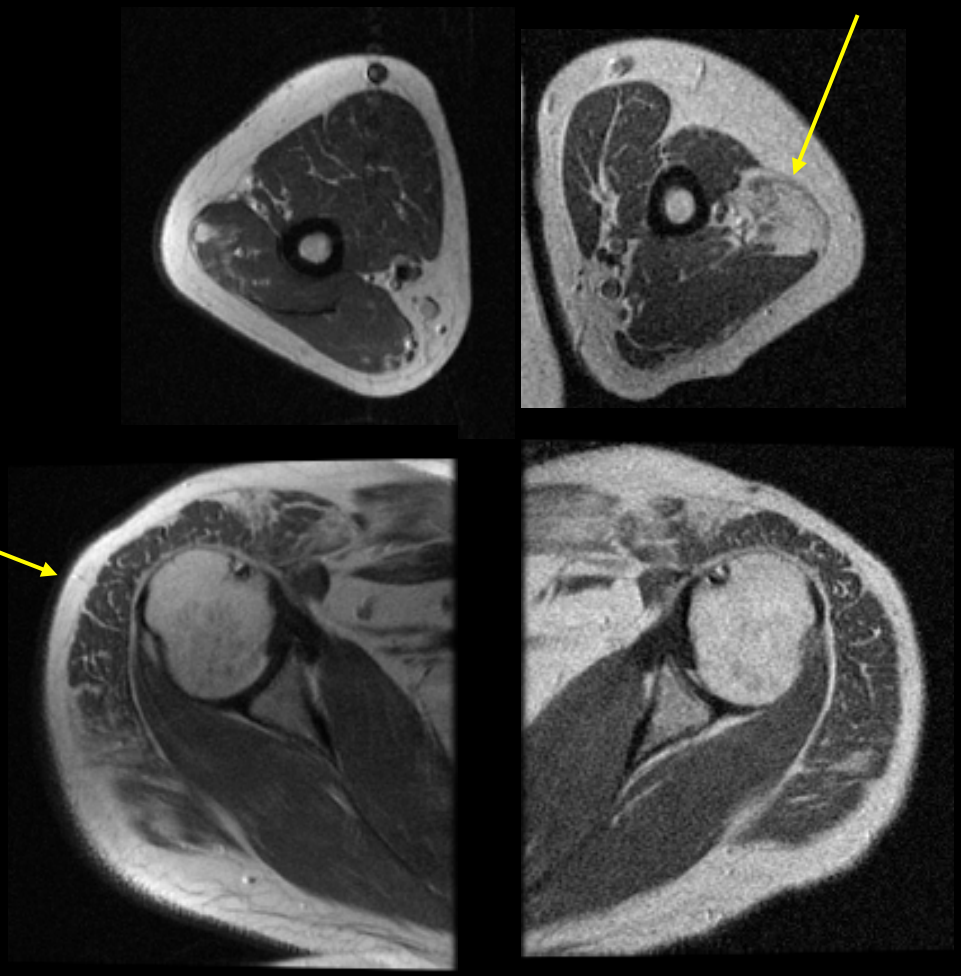
Fascioscapulohumeral MD:
Patient B



Mild upper extremity disease with mild fatty infiltration of deltoids

Muscular Dystrophies: MRI

Fascioscapulohumeral MD:
Patient C



Muscular Dystrophies: Imaging Trends Past and Present

- Grading system
  - MR grading system for Duchenne MD proposed by Liu et al, Radiology 1993
- Muscle compositional analysis
  - Study of age-related changes in composition in diseased muscle in boys with Duchenne MD by Marden et al, Skeletal Radiology 2005
- Differentiation among MD subtypes
  - Numerous papers by Mercuri et al describing comparative muscle involvement in EDMD, CMD (rigid spine phenotype and Ullrich phenotype), LGMD2A, published 2002-2005
  - Differentiating LGMD2I from other LGMDs by Fischer et al, J Neurol 2005

Muscular Dystrophies: Imaging Future

- Potential for MRI in diagnosis of muscular dystrophies:
  - Biopsy planning, limitation of false negative biopsies
  - Distinguishing conditions with similar clinical phenotypes
  - Using pattern of muscle involvement to inform genetic/biochemical work up
  - To assess if muscle grossly normal or abnormal in cases of confusing clinical presentation in patient with suspected neuromuscular disease
- Potential for MRI in management of muscular dystrophies:
  - Marker for disease progression
  - Marker for response to therapy
- Potential for MRI in research/clinical trials:
  - Marker for disease response to therapy
  - Tool for better understanding pathophysiology of disease – expanded use of T2W, MR spectroscopy and diffusion weighted imaging

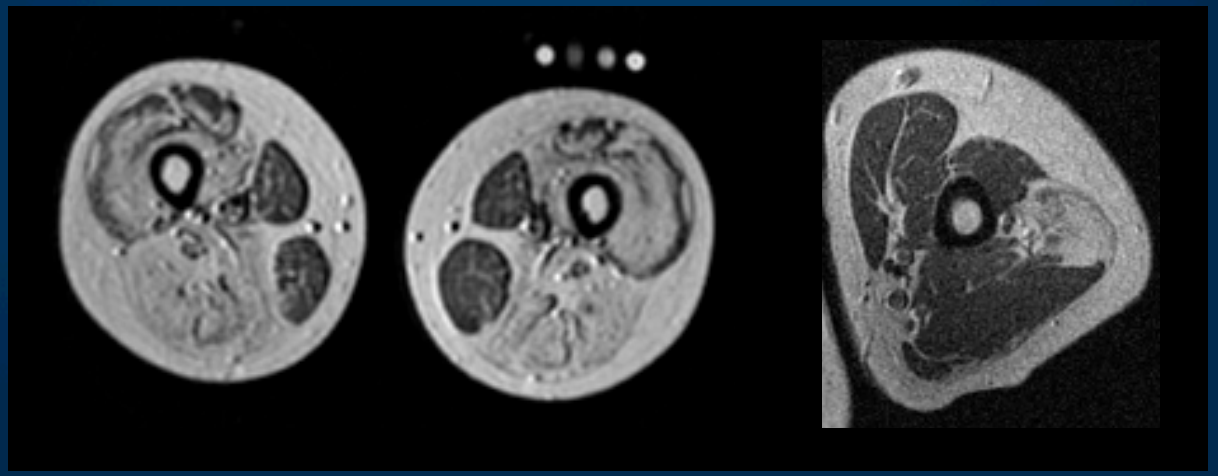
Muscular Dystrophies: Conclusions

- MR imaging reveals a fascinating variation in pattern of muscle involvement and relative sparing among and within the subtypes of muscular dystrophies.
- While overlap and variations in these patterns preclude widespread use of MR in diagnosis of muscular dystrophies, investigators are finding gaps in traditional diagnostic methods into which MRI may fall and become useful.
- Furthermore, MRI may become useful as a marker for disease progression, response to therapy, and as a tool for better understanding the pathophysiology of disease.

Muscular Dystrophies: Closing Thoughts

The most intriguing question remains:

- Why is one muscle affected and its neighbor spared?



- Perhaps information gained through MR imaging of the muscular dystrophies will help guide investigators to the answer(s) to that question.

References

- Fischer D, et al. Diagnostic value of muscle MRI in differentiating LGMD2I from other LGMDs. J Neurol 2005; 252:538-547.
- Fleckenstein JL. MRI of neuromuscular disease: the basics. Seminars in Musculoskeletal Radiology 2000; 4(4):393-419.
- Heckmatt JZ, Pier N, Dubowitz V. Real-time ultrasound imaging of muscles. Muscle & Nerve 1988;11:56-65.
- Lamminen AE, et al. Magnetic resonance of diseased skeletal muscle: combined T1 measurement and chemical shift imaging. The British Journal of Radiology 1990; 63(752):591-596.
- Liu G-C, et al. Duchenne muscular dystrophy: MR grading system with functional correlation. Radiology 1993; 186:475-480.
- Lovitt S, et al. MRI in myopathy. Neurol Clin 2004; 22:509-538.
- Maravilla KR, Tsuruda JS. MR neurography and muscle MR imaging for image diagnosis of disorders affecting the peripheral nerves and musculature. Neurol Clin 2004; 22:643-682.
- Marden FA, et al. Compositional analysis of muscle in boys with Duchenne muscular dystrophy using MR imaging. Skeletal Radiology 2005; 34(3): 140-148.
- Matthews KD. Muscular dystrophy overview: genetics and diagnosis. Neurol Clin N Am 2003; 21:795-816.
- Mercuri E, et al. Clinical and imaging findings in six cases of congenital muscular dystrophy with rigid spine syndrome linked to chromosome 1p (RSMD1). Neuromuscular Disorders 2002; 12:631-638.
- Mercuri E, et al. Muscle magnetic resonance imaging in patients with congenital muscular dystrophy and Ullrich phenotype. Neuromuscular Disorders 2004; 13:554-558.
- Mercuri E, et al. Muscle MRI findings in patients with limb girdle muscular dystrophy with calpain 3 deficiency (LGMD2A) and early contractures. Neuromuscular Disorders 2005; 15:164-171.
- Mercuri E, et al. Muscle MRI in Ullrich congenital muscular dystrophy and Bethlem myopathy. Neuromuscular Disorders 2005; 15:303-310.
- Mercuri E, et al. Selective muscle involvement on magnetic resonance imaging in autosomal dominant Emery-Dreifuss Muscular Dystrophy. Neuropediatrics 2002; 33:10-14.
- Mercuri E, Jungbluth H, Muntoni F. Muscle imaging in clinical practice: diagnostic value of muscle magnetic resonance imaging in inherited neuromuscular disorders. Curr Opin Neurol 2005; 18:526-537.
- Murphy WA, Totty WG, Carroll JE. MRI of normal and pathologic skeletal muscle. AJR 1986; 146:565-574.
- Ozsarlak O, et al. Hereditary neuromuscular diseases. European Journal of Radiology 2001; 40:184-197.
- Schwartz MS, et al. Patterns of selective involvement of thigh muscles in neuromuscular disease. Muscle & Nerve 1988; 11:1240-1245.
- Swash M, Brown MM, Thakkar C. CT muscle imaging and the clinical assessment of neuromuscular disease. Muscle & Nerve 1995; 18:708-714.

Dystrophinopathies

Name	Genetics	Genetic Location	Protein	Clinical Features	Muscles Affected	Muscles Relatively Spared	Other Imaging Features	Genetic overlap with
Duchenne MD	XLR	Xp21	Dystrophin Complete or near complete absence of dystrophin protein	• 1:3500 live male • onset @ 2-3 yrs • ower then upper extremities • wheelchair by 12 yrs • death late teens/ 20s – respiratory failure – arrhythmia • primary cardiomyopathy • progressive scoliosis • mental retardation	**Earlier:** • Gluteus maximus • Adductor magnus • Gastrocnemii **Later:** • Quadriceps • Rectus femoris • Biceps femoris	• Sartorius • Gracilis • Semitendinosus • Semimembranosus	Edema-like signal on T2W tends to precede fibrofatty infiltration seen on T1W	Isolated cardio-myopathy
Becker MD	Same	Same	Same Decreased quantity of abnormal or normal MW dystrophin	• 1:30K live male • later onset than DMD • ambulatory 15+ yrs • survive > 30 yrs • less severe mental retardation, contractures • preserved neck flexor strength • +/- more severe cardiac disease	Similar to DMD	Similar to DMD	Similar to DMD	

Key: MD (muscular dystrophy); MW (molecular weight)

Limb-girdle Muscular Dystrophies (LGMDs) – Autosomal Dominant Subtypes

Name	Genetics	Genetic Location	Protein	Clinical Features	Muscles Affected	Muscles Relatively Spared	Other Imaging Features	Genetic overlap with
LGMDs in general				• Variable age onset • AR – typically childhood onset • AD – typically adult onset • Slowly progressive • Weakness predominantly affecting hip girdle • +/- neck flexor and extensor involvement • +/- mild facial weakness • Extraocular muscles spared • Preferential weakness biceps • Distal muscles preserved • Low back pain • Intellect normal • Cardiac – rarely • Can be confused with DMD/BMD – but intellect normal in LGMDs				
LGMD1A	AD	5q31	Myotilin					
LGMD1B	AD	1q11-21	Lamin A/C	• Cardiac involvement				AD-EDMD Dunnigan-type familial partial lipodystrophy Dilated cardiomyopathy and cardiac conduction system defect
LGMD1C	AD	3p25	Caveolin-3	• +/- Cardiac involvement				Rippling muscle syndrome Hyper-CK-emia

Key: AD (autosomal dominant), AR (autosomal recessive), CMD (congenital muscular dystrophy), MD (muscular dystrophy)

Limb-girdle Muscular Dystrophies (LGMDs) – Autosomal Recessive Subtypes

Name	Genetics	Genetic Location	Protein	Clinical Features	Muscles Affected	Muscles Relatively Spared	Other Imaging Features	Genetic overlap with
LGMDs in general				• Variable age onset • AR – typically childhood onset • AD – typically adult onset • Slowly progressive • Weakness predominantly affecting hip girdle • +/- neck flexor and extensor involvement • +/- mild facial weakness • Extraocular muscles spared • Preferential weakness biceps • Distal muscles preserved • Low back pain • Intellect normal • Cardiac – rarely • Can be confused with DMD/BMD – but intellect normal in LGMDs				
LGMD2A	AR	15q15-21	Calpain 3		**Thigh:** • Early involvement of posterior thigh muscles • In young ambulatory patients: – Adductors – Semimembranosus • In patients with restricted ambulation: More diffuse involvement of posterolateral muscles of the thigh and vastus intermedius	**Thigh:** • Vastus intermedius • Vastus lateralis • Sartorius • Gracilis	Pattern at thigh level different and more extensive than AD EDMD General pattern of muscle atrophy	
					Calf: • Soleus • Medial head gastrocnemius	**Calf:** • Lateral head of gastrocnemius	Pattern at calf level similar to AD EDMD	
LGMD2B	AR	2p13	Dysferlin					Myoshi myopathy Distal myopathy
LGMD2C	AR	13Q12	Gamma-Sarcoglycan	• Cardiac involvement				
LGMD2D	AR	17q12-21	Alpha-Sarcoglycan	• +/- Cardiac involvement				
LGMD2E	AR	4q12	Beta-Sarcoglycan	• Cardiac involvement				
LGMD2F	AR	5q33-34	Delta-Sarcoglycan	• Cardiac involvement				
LGMD2G	AR	17q11-12	Telethonin	• Cardiac involvement				
LGMD2H	AR	9q31-34	TRIM32					
LGMD2I	AR	19q13.4	Fukuyama-related protein		**Thigh:** • Predominant involvement of adductor magnus and posterior thigh muscles • More involvement of anterior compartment than LGMD2A • Hypertrophy of sartorius and graciilis		Muscle hypertrophy common (compared to atrophy in LGMD2A	CMD 1C
					Calf: • Variable with predominantly posterior compartment involvement. • No significant differential involvement between medial and lateral head of gastrocnemius (in comparison to LGMD2A)			
LGMD2J	AR	2q31	Titin					Tibial MD

Key: AD (autosomal dominant), AR (autosomal recessive), CMD (congenital muscular dystrophy), MD (muscular dystrophy)

Congenital Muscular Dystrophies (CMDs) – Subtypes without Major Brain Malformation

Name	Genetic Location	Protein	Clinical Features	Muscles Affected	Muscles Relatively Spared	Other Imaging Features	Allelic Disorders
CMDs in general			• Hypotonic and weak at birth or early infancy • Elevated CK at birth, which falls to normal range by 6-10 wks • Muscle bx c/w MD • Non- or slowly progressive				
Merosin-absent CMD	6q2	Merosin Alpha chain of laminin	• Normal IQ • +/- cardiac involvement			**Brain MRI:** White matter abnormal	
CMD	19q13.3	Fukutin-related protein	• Normal IQ • Spine rigidity • Early restrictive lung disease			**Brain MRI:** Normal	LGMD2I
Rigid Spine Disease (RSMD1)	1p35-36	Selenoprotein N	• Normal IQ • Spine rigidity • Early restrictive lung disease	**Thigh:** • Variable • Sartorius, always and often severely affected (spared in Ullrich CMD) • Postero-lateral muscles less affected compared to Ullrich CMD	**Thigh:** • Rectus femoris • Gracilis	**Brain MRI:** Normal	
Ullrich myopathy	21q22.3 (COL6A1, A2) 2q37 (COL6A3)	Collagen VI	• Normal IQ • Very early contractures • Artrhogryposis (contracture of of ≥ 2 joints at birth) • Distal hyperlaxity • Flat feet	**Thigh:** • Diffuse involvement of all posterior and lateral muscles	**Thigh:** • Sartorius • Gracilis • Adductor longus • +- Rectus femoris	Signal increased at periphery of the muscle with relative preservation of the muscle belly on T1WI (not typically seen in Ulrich-like phenotype without collagen VI mutation) **Brain MRI:** Normal	Bethem myopathy – similar imaging features as Ullrich, but milder

Congenital Muscular Dystrophies (CMDs) – Subtypes with Major Brain Malformation

Name	Genetic Location	Protein	Clinical Features	Muscles Affected	Muscles Relatively Spared	Other Imaging Features	Allelic Disorders
CMDs in general			• Hypotonic and weak at birth or early infancy • Elevated CK at birth, which falls to normal range by 6-10 wks • Muscle bx c/w MD • Non- or slowly progressive				
Fukuyama CMD	9q31-33	Fukutin	• Mild to moderate MR • +/- eye involvement • Almost exclusively Japanese population			**Brain MRI:** Cobblestone cortex, cerebellar and brainstem hypoplasia	
Muscle-eye-brain disease	1p32	POMGnT1	• Severe MR • Myopia • Cataracts • Ganglion cell and optic nerve atrophy • Common in Finland			**Brain MRI:** Cobblestone cortex, pachygyria/agyria, cerebellar and brainstem hypoplasia, mild hydrocephalus	
Walker-Warburg syndrome	9q34	POMT1, others	• Severe MR • Retinal abnormality • Myopia • Cataracts • Ganglion cell and optic nerve atrophy			**Brain MRI:** Cobblestone lissencephaly, severe hydrocephalus, abnormal white matter, polymicrogyria, cerebellar and brainstem hypoplasia, misline fusion, abnormal corpus collosum	

Other Muscular Dystrophies

Name	Genetics	Genetic Location	Protein	Clinical Features	Muscles Affected	Muscles Relatively Spared	Other Imaging Features	Allelic Disorders
Fascioscapulohumeral MD	AD	4q35	Transcription repressor proteins	**General:** • Early weakness of the face, shoulder girdle, proximal arms • Increased incidence of hearing loss • Rarely, MR and seizures				
				Infant form: • Sporadic • Onset 1st few yrs • Rapid progression • Wheelchair by age 9-10 • Lumbar lordosis • Wrist drop • +/- seizures, MR, SN hearing loss	• Facial muscles • Later muscles of shoulder and hip girdle			
				Classical form: • Onset 2nd-3rd decade • Slow progression • Normal lifespan	• Facial muscles • Muscles of shoulders and upper arms • Hypertrophic extensor digitorum brevis	• Deltoid • Distal muscles		
EDMD	XL (more common than AD)	Xq28	Emerin	• Indistinguishable from AD form • Childhood-onset weakness starting in the shoulder girdle and lower legs • Early contractures (especially elbows, Achilles tendons, neck) • Restrictive cardiomyopathy AV block • Isolated atrial paralysis is strongly suggestive of EDMD • Sudden death in 50% • +/- mild facial weakness • Female carriers may develop heart block, but do not typically have skeletal muscle weakness	**Thigh:** • Variable severity • XL with minimal involvement **Calf:** • soleus			
	AD	1q11-q23	Lamin A/C	• Indistinguishable from XL form in affected male	**Thigh:** • AD form with moderate to severe involvement of – Vastus lateralis – Vastus intermedius – +- adductor magnus		Abnormal distribution of body fat – accumulation of fat in the neck and abdomen and little fat in subcutaneous tissue of the limbs	Dunningan lipo-dystrophy
					Calf: • Medial head gastrocnemius	**Calf:** • Lateral head gastrocnemius		

Key: XL (X-linked), AD (autosomal dominant), MR (mental retardation)

Other Muscular Dystrophies

Name	Genetics	Genetic Location	Protein	Clinical Features	Muscles Affected	Muscles Relatively Spared	Other Imaging Features	Allelic Disorders
Oculopharyngeal MD	AD with complete penetrance		Poly (A) binding protein (gene transcription)	• Progressive ptosis, dysphagia • +/- proximal and distal muscle weakness • Onset mid-adulthood • Onset asymmetric • Usually slowly progressive				
Myotonic Dystrophies in general				• Multisystem disorders • Clinically indistinguishable, except that most severely affected patients with DM1 have cognitive impairment • Myotonia • Cardiac conduction defects • Premature cataracts • Diabetes/insulin resistance • Slowly progressive muscle weakness				
DM1 (type 1)	AD	19q13.3						
DM2 (type 2)	AD	3q13.3-q24						

Key: XL (X-linked), AD (autosomal dominant), MR (mental retardation)