Some lower back pain, here and there

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History of Present Illness

History of Present Illness:

- 76 year-old woman → 6 years of constant lower back pain,
  - present at rest and worse with standing/walking.
- Unable to stand straight.
- Cannot climb stairs secondary to the pain.
- Few falls.
- Has had a few years of breathing difficulty.
- Denies ptosis, diplopia, speech or swallowing impairment, weakness in upper extremities or sensory loss.

Further History

Past medical History:

- Strokes, two in past 7 years
  - Alexia and agraphia
  - Hand clumsiness.
- COPD.
- Hypertension.
- Hyperlipidemia.

Surgical History:

- Left hip fracture repair (had fall).
- Hysterectomy.

Family History:

- Father: died at age 86, dementia.
- Multiple siblings who were smokers.

Social History:

- Has never smoked, but reports second hand smoke exposure.
- Competitive Ballroom dncer.

We now invite Dr. Jeffrey Rosenfeld to elicit further history and examine the patient

Physical Exam

PFTs:
FVCs in the 50-70% in prior PFTs. In 5/29/2019: FVC = 35% predicted.

Neurological exam:

- CN: normal.
- Motor: Reduced bulk of paraspinal muscles in the lumbar region. Normal bulk in limbs.
  - Strength:
    - BUE: 5/5
    - BLE, symmetric:
      - 4/4 in hip flexors,
      - 2/2 in hip extensors
      - 5-/5 in knee flexion
      - 5-/5 in dorsiflexion
- Sensory: mildly reduced vibratory sense distally in lower extremities.
- Coordination: mild action tremor in the left hand.
- Gait/Posture: Forward stooped posture. Marked difficulty standing from a seated position with arms crossed. Narrow-based with adequate stride. There is pelvic dipping with casual gait. Lumbar curve is reduced/ straightened. She is able to tiptoe and stand on her heels.

Studies

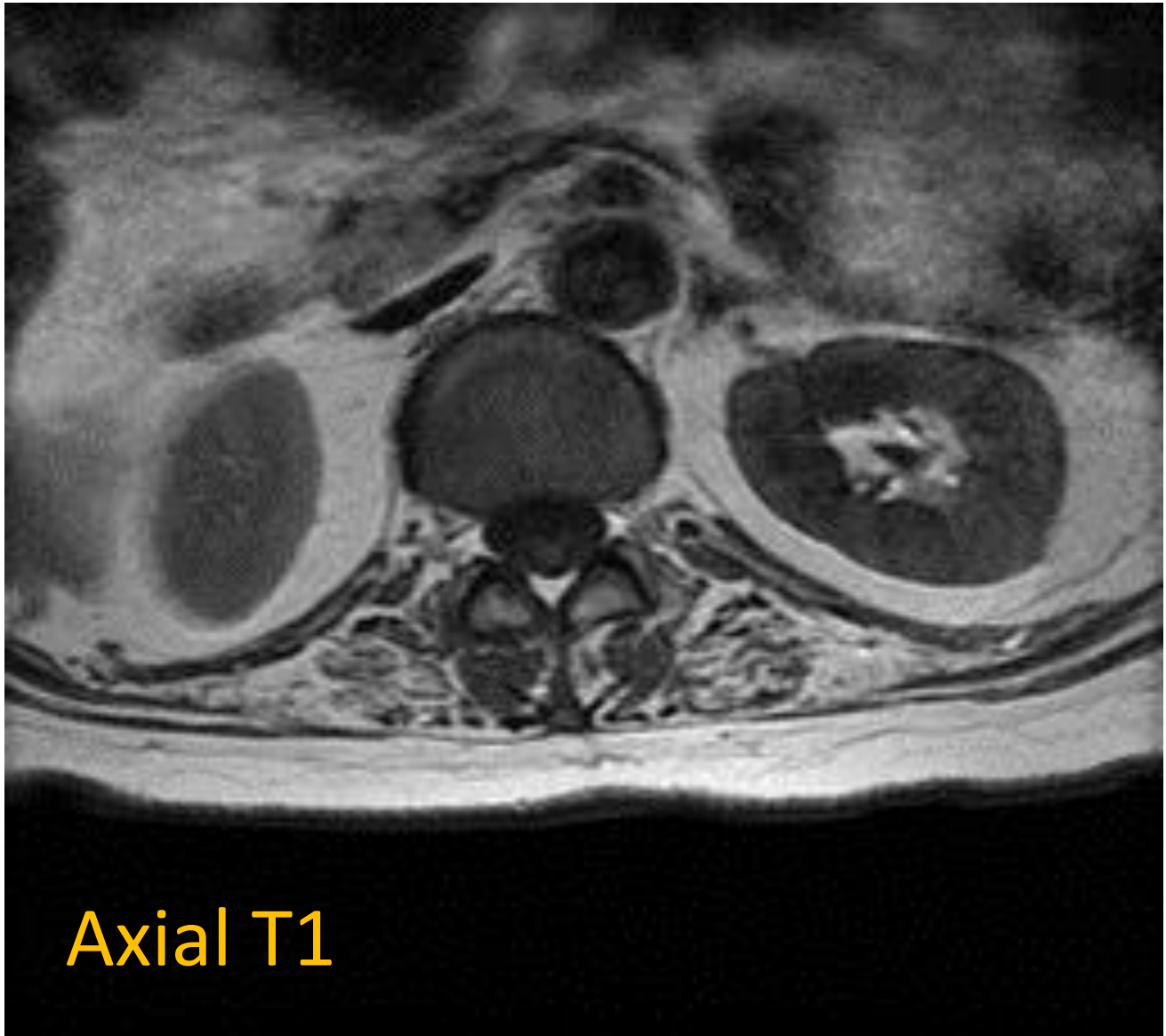
- Labs:
  - CK 196 U/L
  - AChR Antibody:
    - Binding: <0.30 (<0.30 nmol/L)
    - Blocking: <15 (<15%)
  - Normal ESR, vitamin B12.

- MRI of the brain (from previous stroke): small acute left periventricular white matter infarct.

Studies

- MR imaging of the lumbar spine without contrast, 8/24/2016:

  Severe atrophy and fatty replacement of lumbar paraspinous muscles and bilateral iliopsoas.



Differential?

What would you do?

Studies – EMG/NCS

SNC

Nerve / Sites	Rec. Site	Onset Lat ms	Peak Lat ms	Amp µV	Distance mm	Velocity m/s	Temp. °C
R Median - Digit II (Antidromic)							
Wrist	Dig II	2.55	3.39	39.5	130	51	31.5
R Ulnar - Digit V (Antidromic)							
Wrist	Dig V	1.93	2.66	36.9	110	57	31.6
R Sural - Ankle (Calf)							
Calf	Ankle	2.92	3.80	8.3	140	48	28.9
L Sural - Ankle (Calf)							
Calf	Ankle	3.18	4.01	8.1	140	44	32.9

Studies – EMG/NCS

MNC

Nerve / Sites	Muscle	Latency ms	Amplitude mV	Duration ms	Area mVms	Segments	Distance mm	Lat Diff ms	Velocity m/s	Temp. °C
R Median - APB										
Wrist	APB	3.59	6.4	4.06	15.5	Wrist - APB	70			31.6
Elbow	APB	6.41	6.3	4.58	15.0	Elbow - Wrist	185	2.81	66	31.9
R Ulnar - ADM										
Wrist	ADM	3.02	9.5	4.53	25.1	Wrist - ADM	70			32.2
B.Elbow	ADM	6.20	8.9	4.53	23.0	B.Elbow - Wrist	195	3.18	61	32.4
A.Elbow	ADM	7.76	9.0	4.74	24.0	A.Elbow - B.Elbow	105	1.56	67	32.4
R Peroneal - EDB										
Ankle	EDB	3.65	6.6	4.74	17.0	Ankle - EDB	80			28.5
Fib head	EDB	9.01	6.2	5.16	16.6	Fib head - Ankle	275	5.36	51	28.7
Pop fossa	EDB	10.83	6.2	5.10	16.4	Pop fossa - Fib head	95	1.82	52	28.8
R Tibial - AH										
Ankle	AH	5.63	6.9	4.64	11.8	Ankle - AH	80			28.9
Pop fossa	AH	11.20	5.1	6.20	12.2	Pop fossa - Ankle	370	5.57	66	29

Studies – EMG/NCS

Needle EMG										
	Spontaneous				Volitional MUAPs					
Muscle	IA	Fibs/PSW	Fasc	Other	Dur.	Amp	Poly	Recruit	Rate	Comment
R. Tibialis anterior	Normal	None	None	.	Normal	Normal	None	Normal	Normal	.
R. Gastrocnemius (Medial head)	Normal	None	None	.	Normal	Normal	None	Normal	Normal	.
R. Vastus lateralis	Normal	None	None	.	Normal	Normal	None	Normal	Normal	.
R. Lumbar paraspinals (mid)	Normal	2+	None	.	Normal					.
R. Lumbar paraspinals (low)	Normal	None	None	CRD; ?Myotonic Discharges	Normal					.
R. Lumbar paraspinals (up)	Normal	2+	None		Normal					.

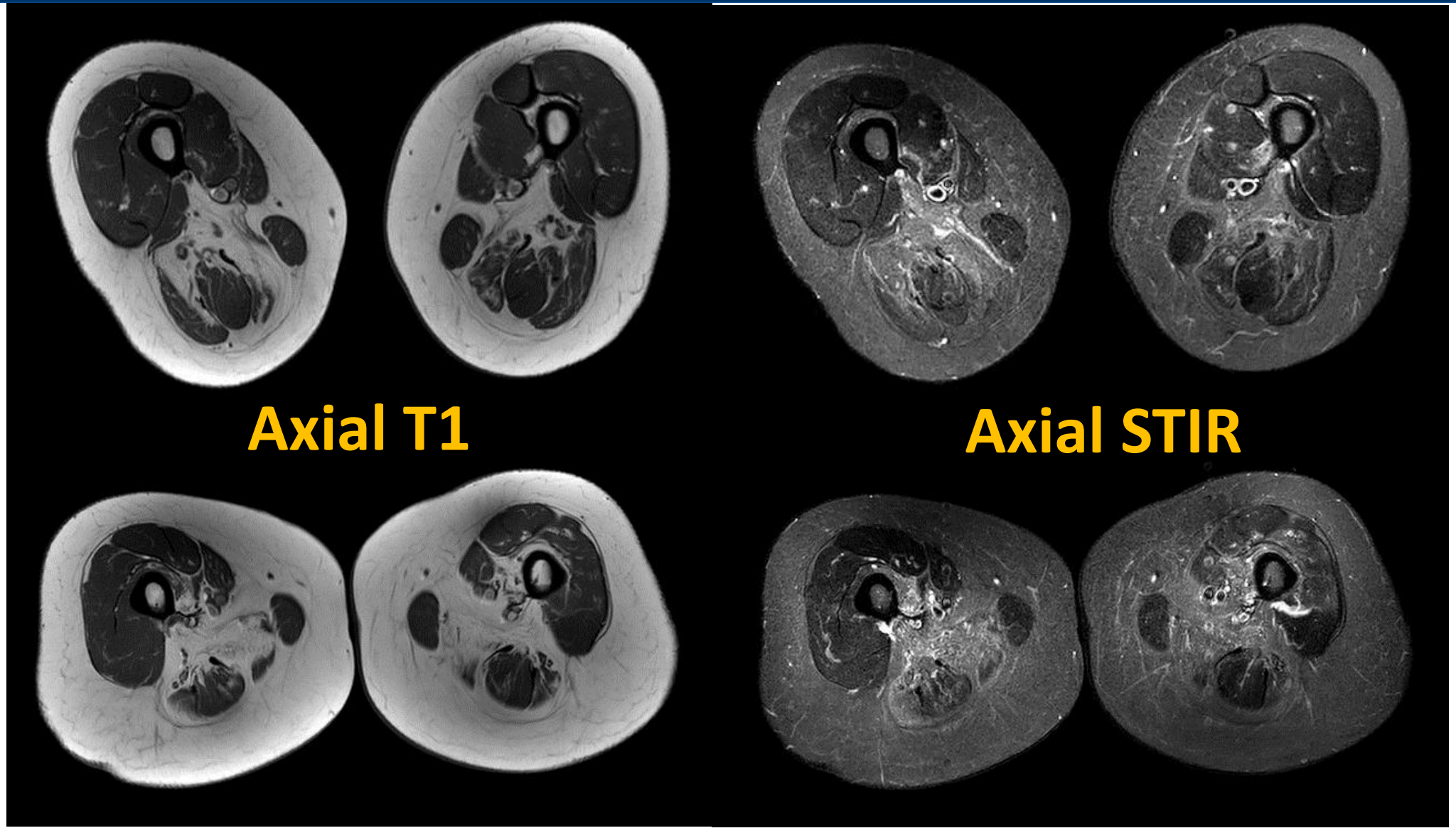
Diagnostic tests were performed

- Alpha glucosidase enzyme activity: **2.40** (>3.88 pmol/punch/hr)

- Genetic testing:
  - **heterozygous c-32-13T>G**: single nucleotide change within the first intron of GAA gene, commonly observed in adult-onset Pompe disease, affects splicing of exon 2
  - **heterozygous duplication c.840_842dup** in exon 4: results in duplication of Arg281. Does not alter reading frame. Not previously reported as mutation causing Pompe OR as known polymorphism in the population.

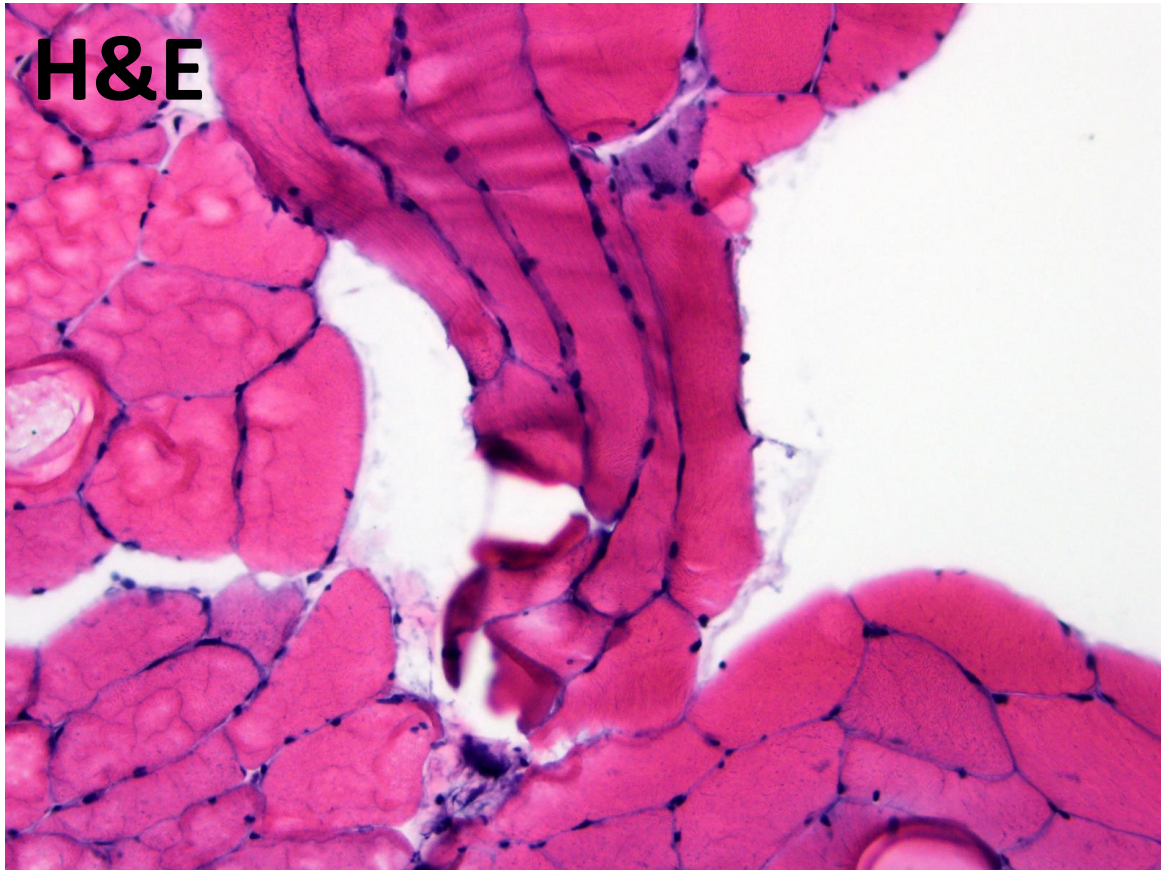
- MRI of the femur, bilateral 3/26/2018: Fatty atrophy and mild muscle edema of multiple muscle groups.

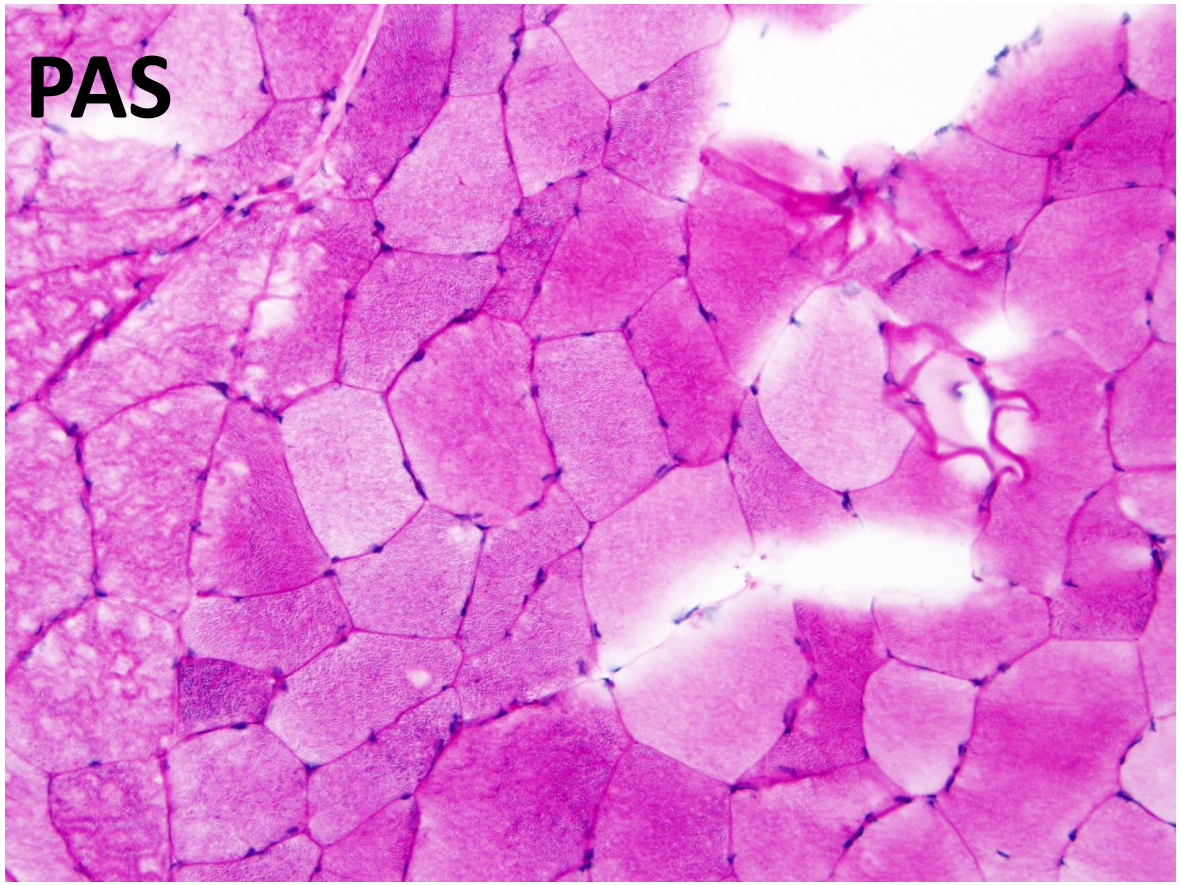
Diagnostic tests were performed



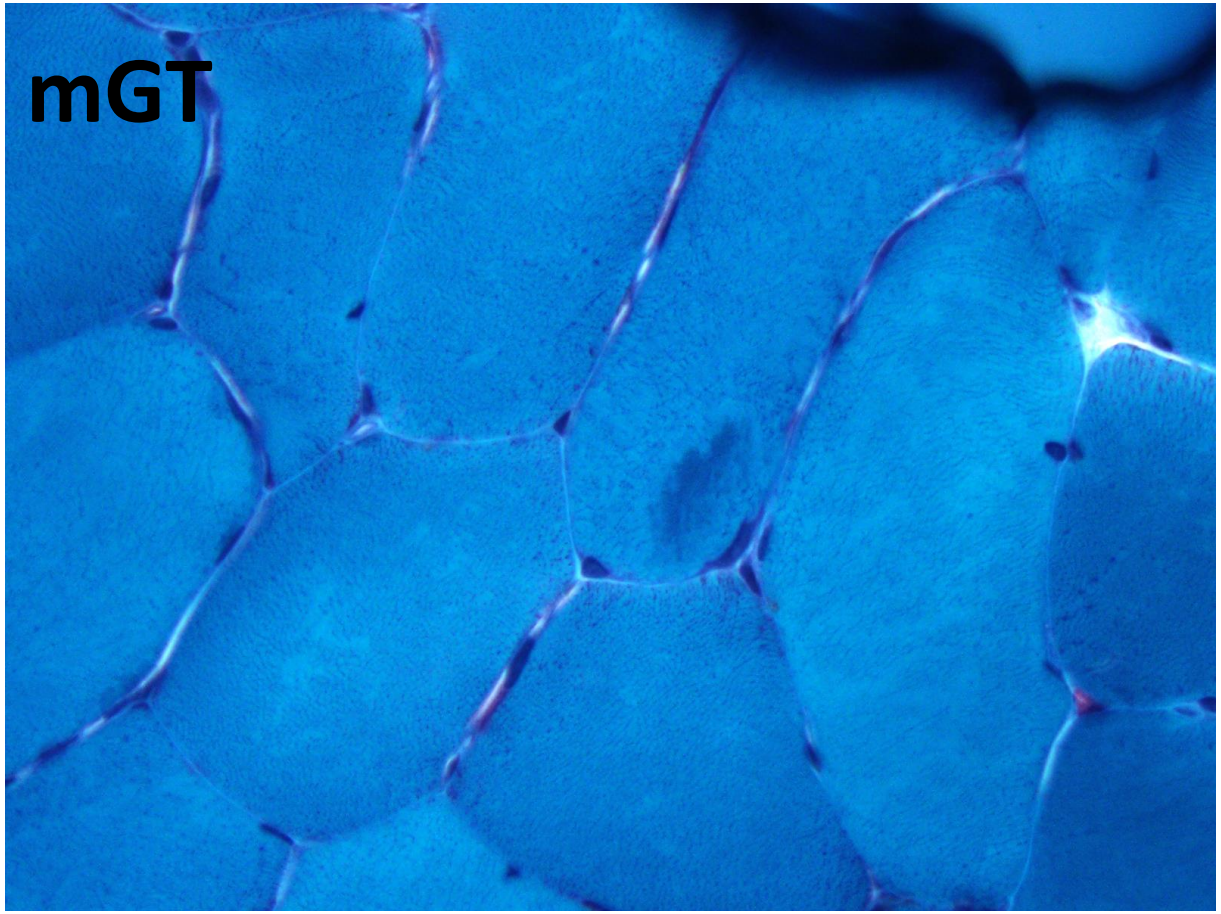
Diagnostic tests were performed

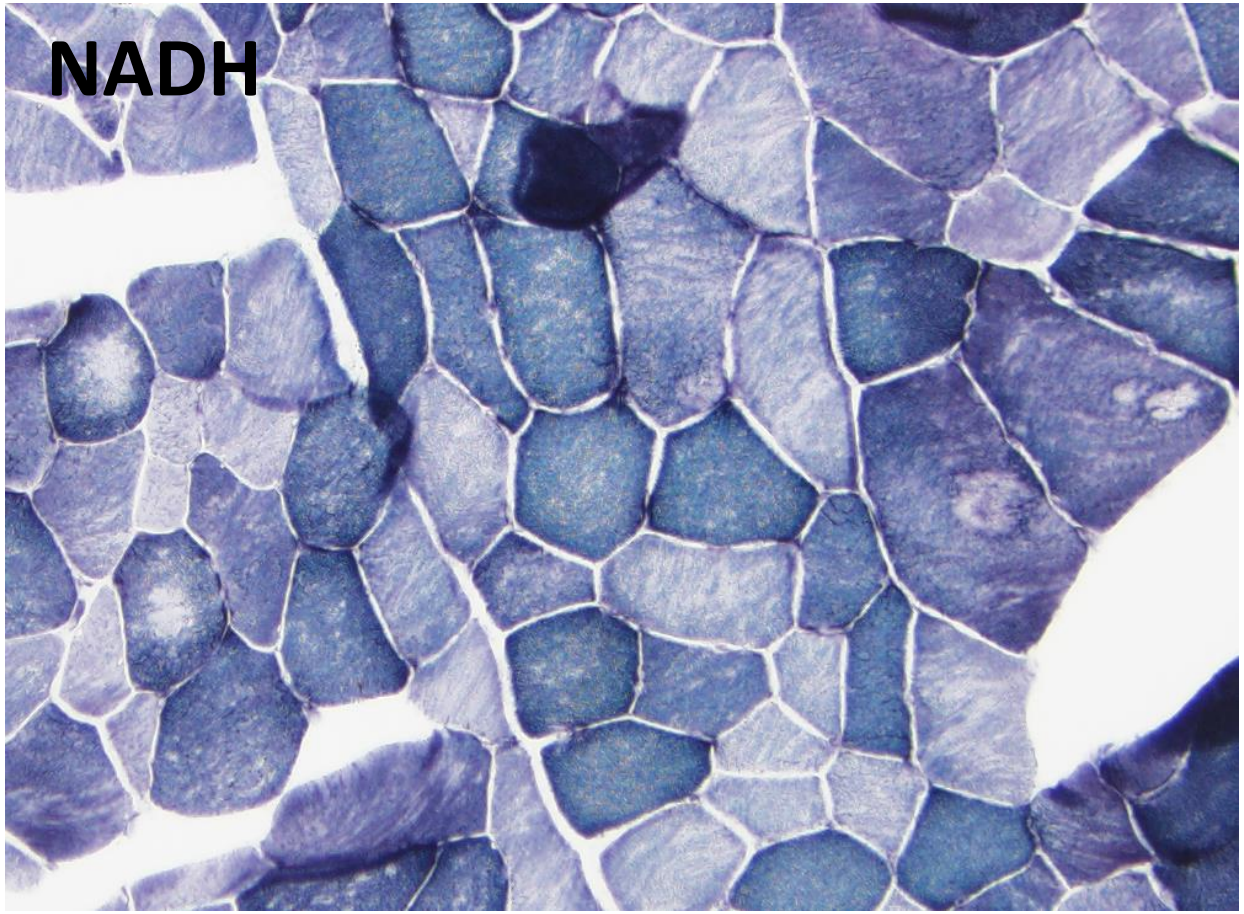
- Biopsy of right vastus lateralis 5/11/2019:



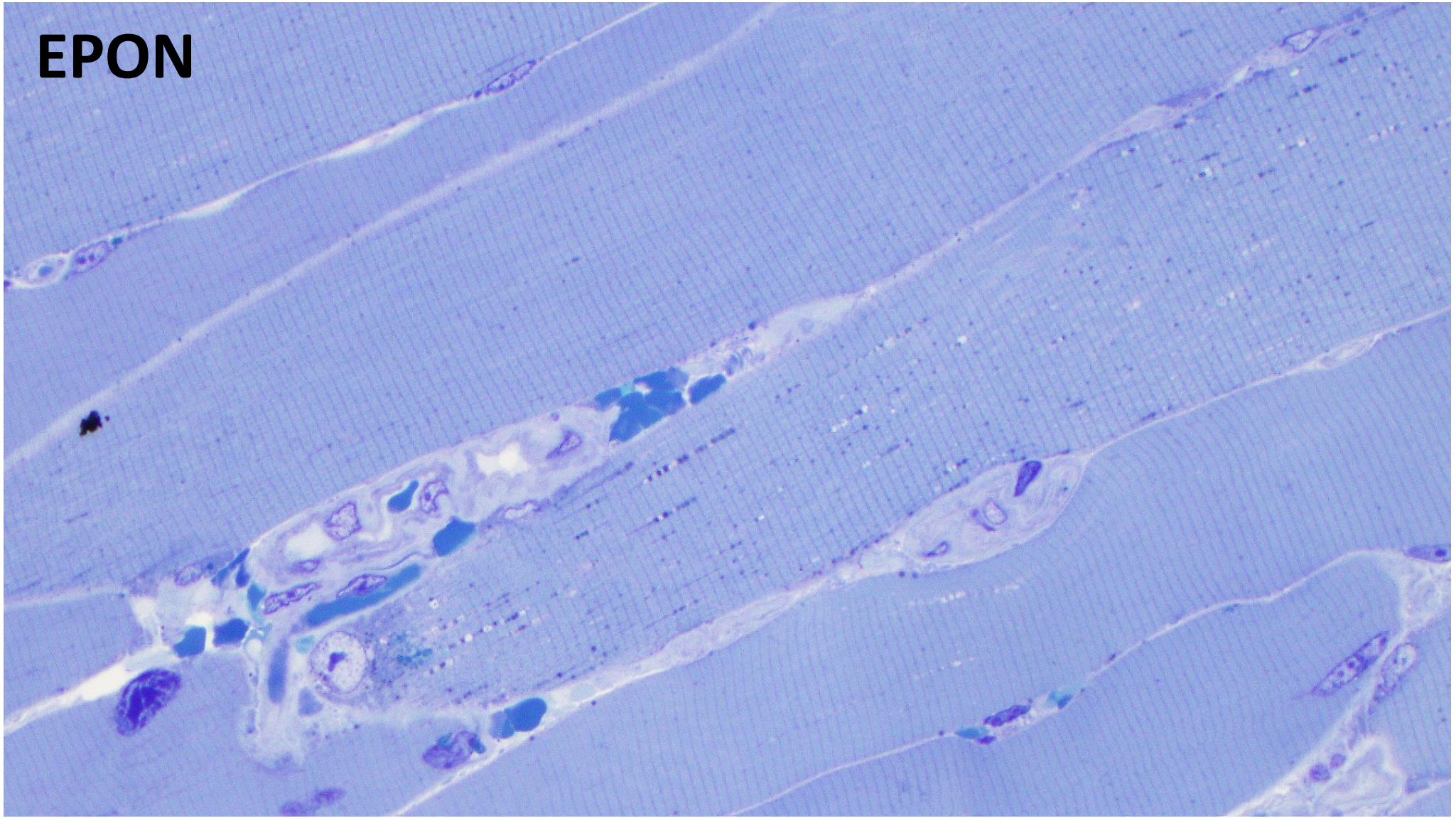


Muscle biopsy of the right vastus lateralis muscle





Muscle biopsy of the right vastus lateralis muscle



Late Onset Pompe Disease

- Pompe disease → single disease continuum with variable rates of disease progression and different ages of onset.
- Lysosomal acid alpha-glucosidase (GAA) deficiency.
  - glycogen storage disease type II
  - acid maltase deficiency (AMD)
- Autosomal recessive disorder → considerable allelic heterogeneity.
  - Mutations in the gene encoding lysosomal acid alpha-1,4-glucosidase (GAA), located at 17q25.2-q25.3
- Estimated incidence of GAA deficiency is 1 in 40,000.

Late Onset Pompe Disease

Clinical presentation:

- Proximal muscle weakness and atrophy → proximal limbs, axial muscles, respiratory function.

Classification:

- *Infantile-onset Pompe disease* (IOPD)→ < age 12 months + cardiomyopathy. → Median onset: 4 months
  - hypotonia, generalized muscle weakness, feeding difficulties, failure to thrive, **respiratory distress**, and **hypertrophic cardiomyopathy**.
  - Death by age 2 without treatment → progressive left ventricular outflow obstruction and respiratory insufficiency.
- *Late-onset Pompe disease* (LOPD)
  - A) Onset < age 12 months WITHOUT cardiomyopathy.
  - B) Onset > 12 months.
    - Proximal muscle weakness & respiratory insufficiency.

Late Onset Pompe Disease

- Diagnosis:
  - Deficiency of acid alpha-glucosidase enzyme activity.
    - Rapid and sensitive → dried blood spots, muscle, peripheral leukocytes or skin fibroblast cultures.
  - Biallelic pathogenic variants in *GAA* on molecular genetic testing.
    - Single gene testing, targeted analysis for pathogenic variants, multigene panel.
  - Newborn screen:
    - Positive screen + supportive physical exam/Echo/CK.
    - Confirm with molecular genetic testing or GAA enzyme activity.

Late Onset Pompe Disease

- Supportive tests:
  - **Electrophysiologic** studies → myopathy on EMG.
    - Needle EMG of the paraspinal muscles.
  - **CK levels:** elevated in IOPD and some with LOPD.
  - **Urinary oligosaccharides:** tetrasaccharide → highly sensitive in IOPD.
  - **Muscle biopsy**:
    - Increased acid phosphatase activity and vacuoles are the primary findings.
    - Most vacuoles are filled with glycogen, almond shape.
    - Adult form of the disease has fewer fibers with vacuoles (10-50%) than the infantile or childhood forms (near 100% and 75%, respectively).
    - Vacuoles can be absent or present in a very reduced amount of fibers.

Late Onset Pompe Disease

- Management:
  - Enzyme replacement therapy – Clinical trials.
  - Multidisciplinary approach
    - Cardiology: cardiomyopathy and conduction abnormalities
    - Pulmonology: respiratory insufficiency, assistive devices, tracheostomy
    - Audiologic evaluation,
    - Nutrition
    - Disability inventory
    - Genetic counseling

Axial Myopathies

Axial myopathies divided according to age of onset		
Congenital to 0 years	**>10-25**	**>25**
DNM2 myopathy Dystrophinopathy FHL1 myopathy Lamin A/C myopathy (MFM) RYR1 myopathies SEPN1 myopathy TPM2/3 myopathies Titinopathy	Calpainopathy DM2 Dysferlinopathy (FHL1 myopathy) Lamin A/C myopathy MFM Mitochondrial myopathy MYH7 myopathy	SLONM Calpainopathy (DM2) IBM /PM INEM Matrin-3 myopathy RYR1 myopathies VCP myopathy

Witting, N., et al. (2016). "Axial myopathy: an overlooked feature of muscle diseases." Brain **139**(Pt 1): 13-22.

Axial Myopathies

Axial myopathies divided according to accompanying features				
Respiratory affection	**Cardiac involvement**	**Dropped head**	**Pain**	**Asymmetry**
SEPN1 myopathy (DM1) FHL1 myopathy GSDII Matrin 3 myopathy MFM Titinopathy	FHL1 myopathy DM1 Dystrophinopathy Lamin A/C myopathy MFM NLSDM Titinopathy	DM1 FSHD1 IBM/PM/DM Lamin A/C myopathy Matrin-3 myopathy Radiation VCP myopathy Calpainopathy DM1 FSHD1 MFM PM/DM RYR1 SLONM	Adult onset RYR1 myopathies DM2 DM/PM FSHD1	Dysferlinopathy FHL1 myopathy FSHD1 NLSDM

Witting, N., et al. (2016). "Axial myopathy: an overlooked feature of muscle diseases." Brain **139**(Pt 1): 13-22.

Take-Away Points

- Paraspinal weakness and respiratory affection should raise suspicion for Pompe Disease and prompt testing.
- Muscle MRI should be considered as a diagnostic tool → paraspinal and limb muscles.
  - Quantify fat infiltration and muscle edema.
  - Pattern of muscle involvement.
- Characteristic features on muscle biopsy may be absent or be subtle.

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Thank You!