DSS-1

No financial disclosures

Clinical History

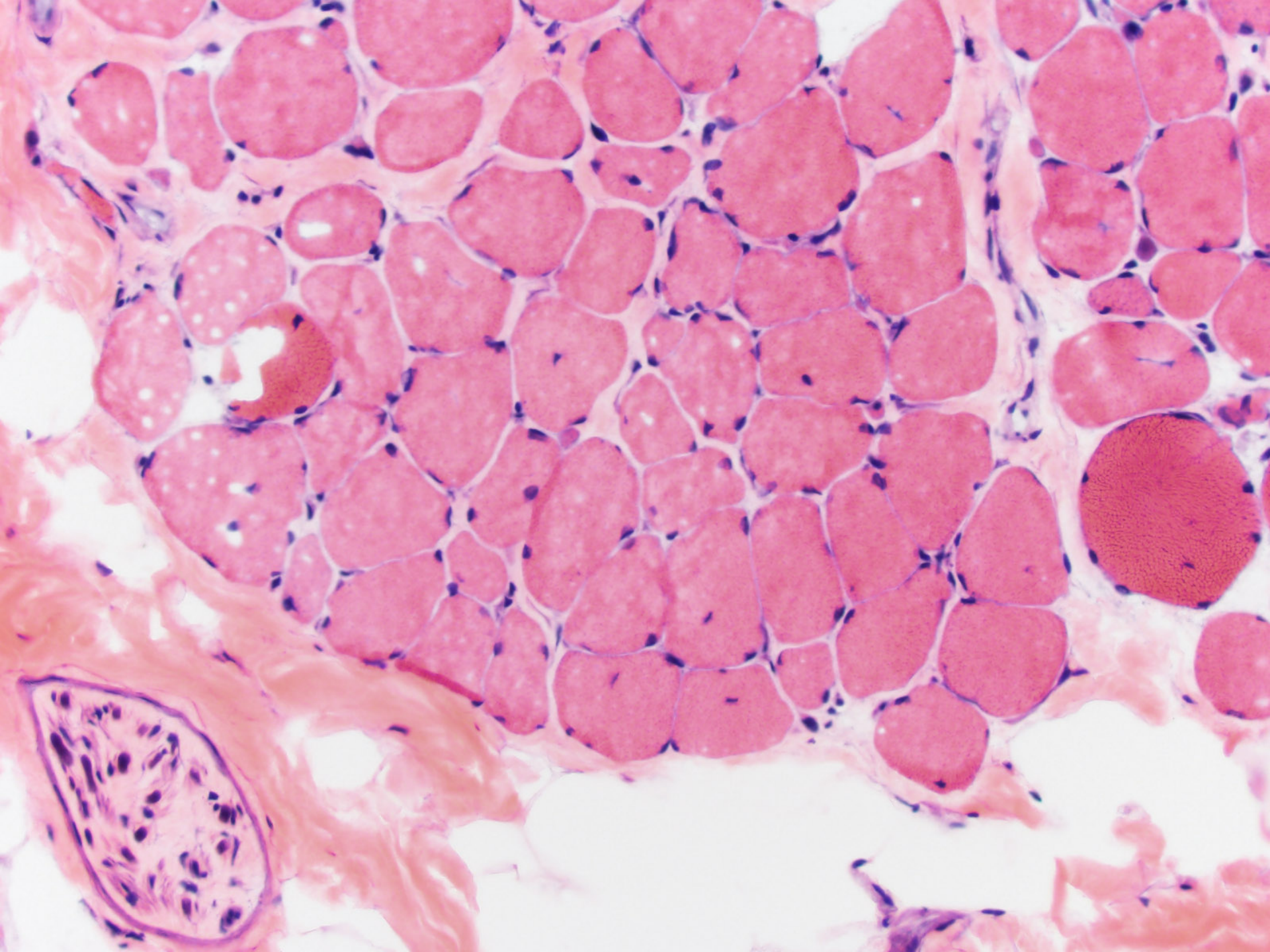
- 9 year old boy with past medical history significant for cerebral palsy, in-turning right foot, left clubfoot that was surgically corrected at 3 years of age
- Able to crawl before surgery, able to walk afterwards, and ultimately walk independently
- His parents report a 6-month history of increasing weakness that is both proximal and distal on examination
- No family history of neuromuscular problems

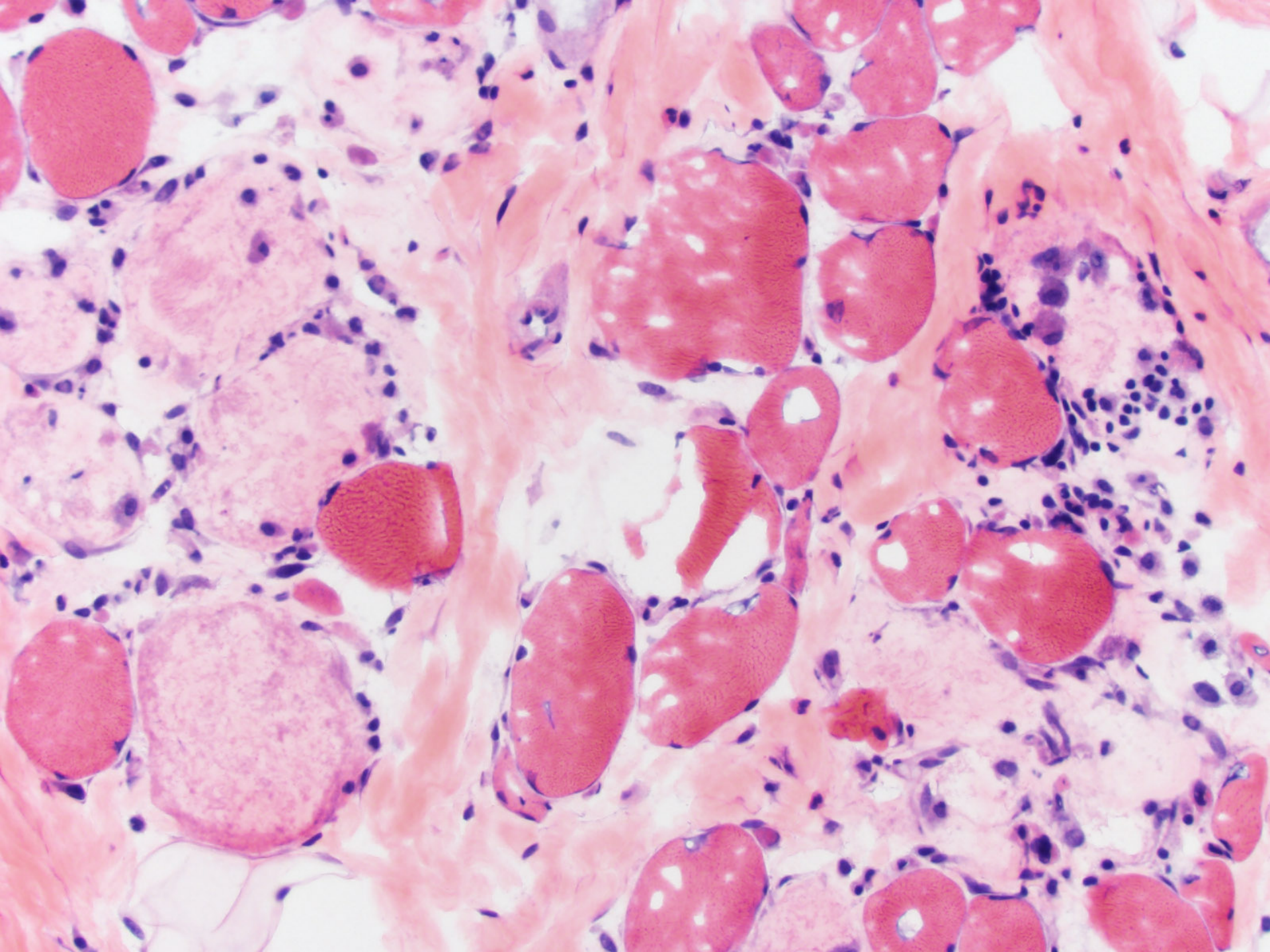
Physical Examination

- Has difficulty rising from the floor and uses a Gowers-type maneuver by pulling up on a chair
- Shows a steppage gait that is slightly wide based
- Stretch reflexes absent
- Serum creatine kinase: 2800 IU/L
- Electromyography: Complex repetitive discharges

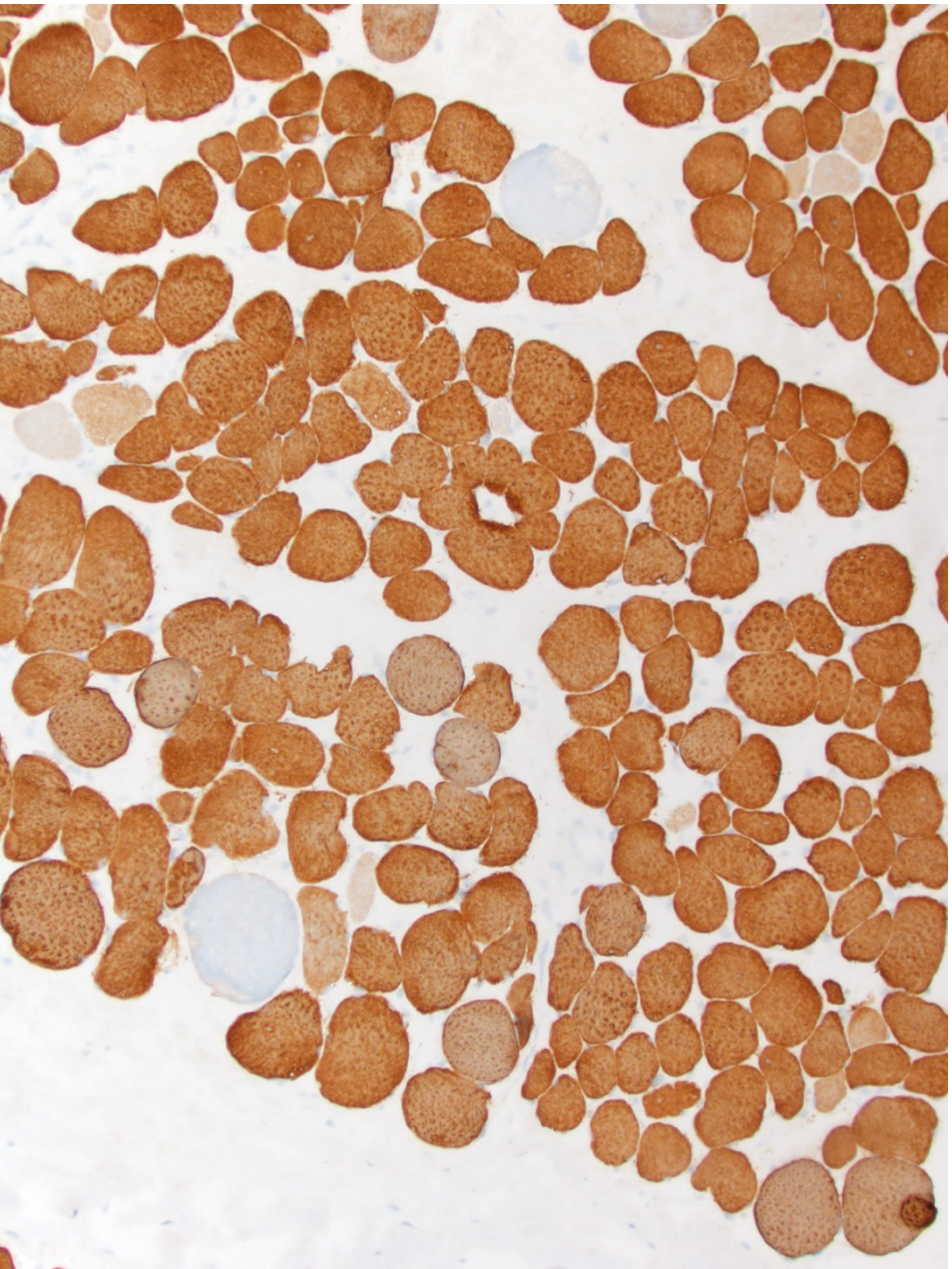
Work-up

- A left quadriceps muscle biopsy is performed

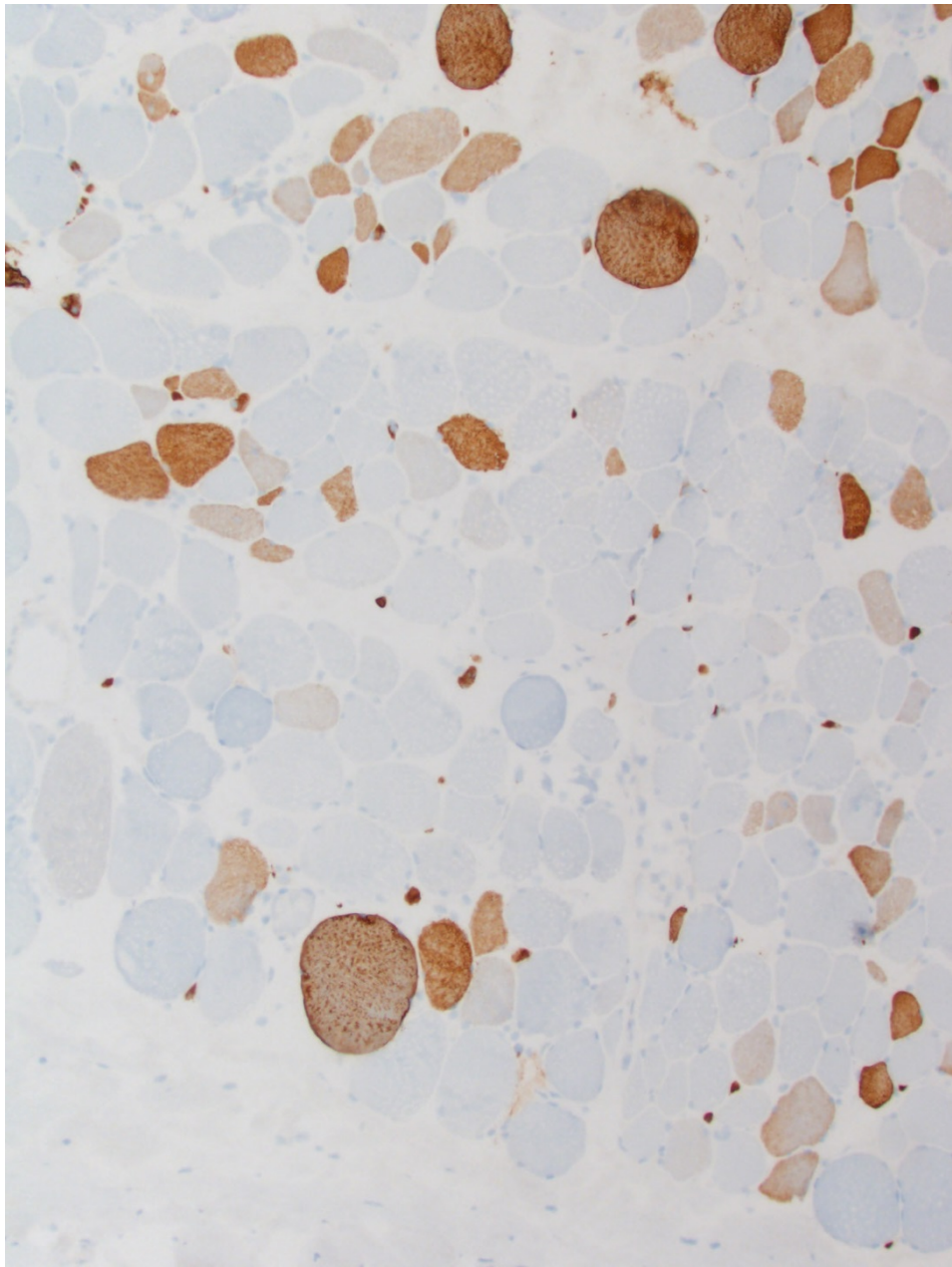




Slow myosin (type I fibers)

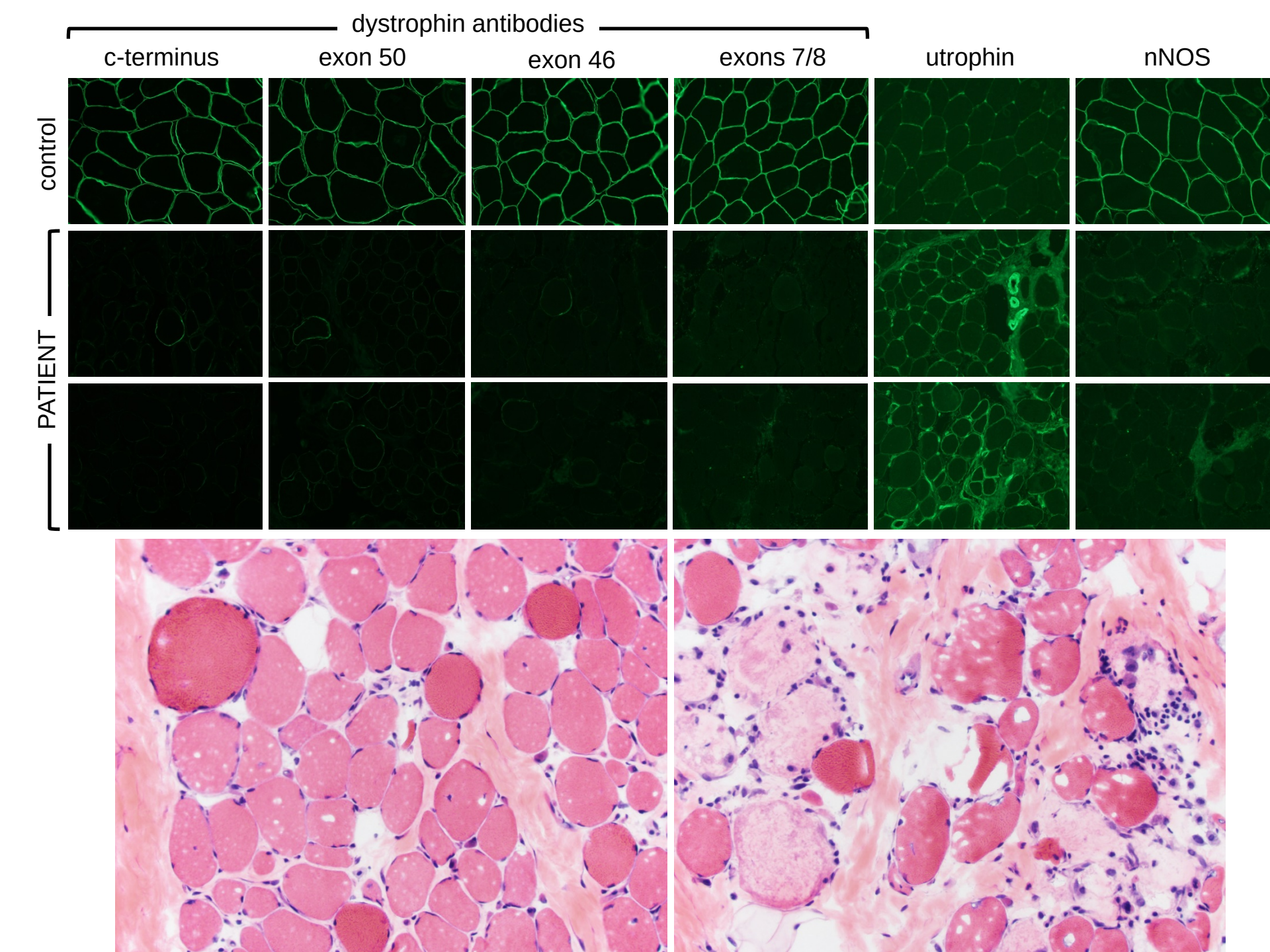


Fast myosin (type II fibers)



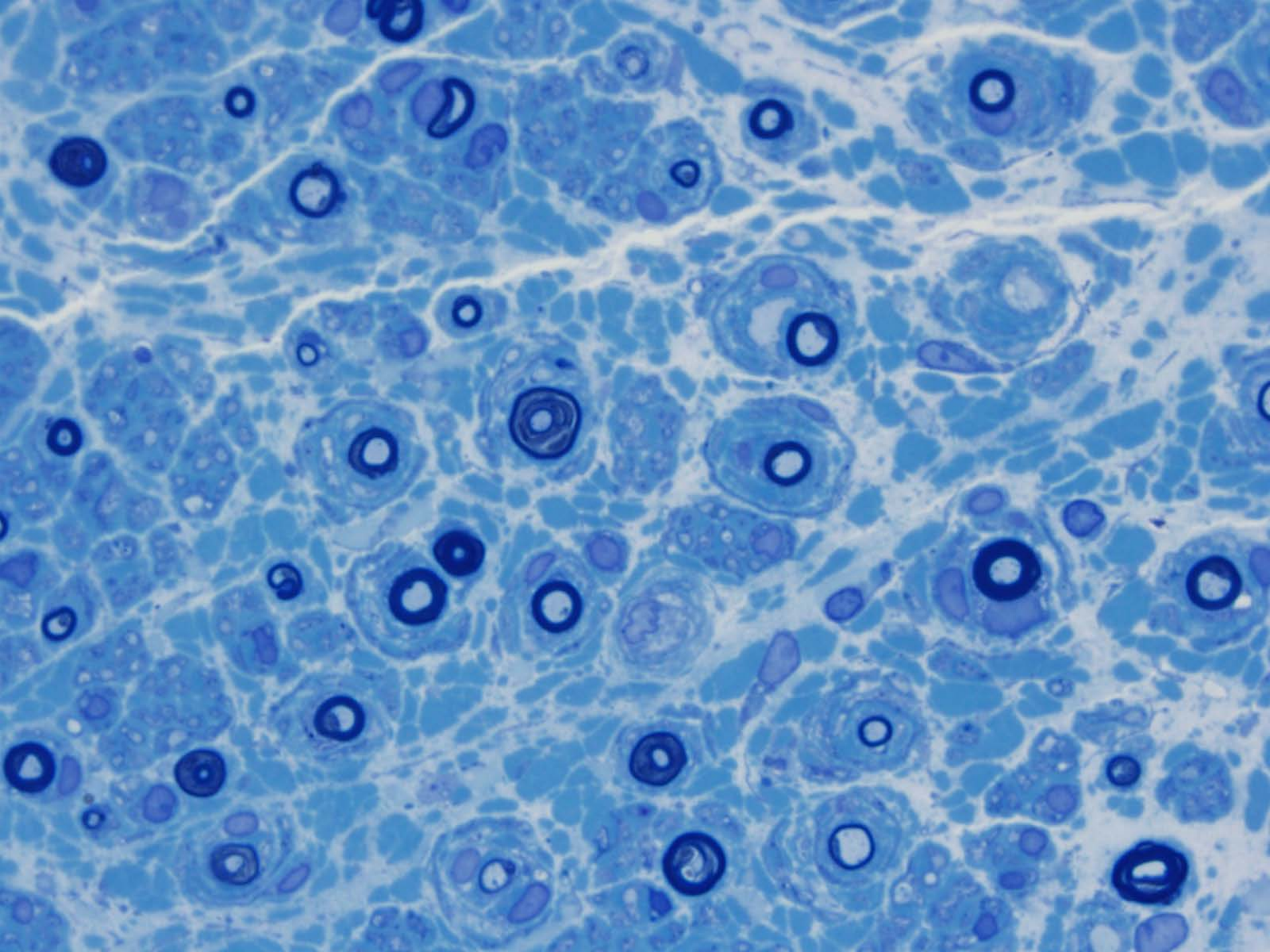
Points for Discussion

1. Approach to diagnostic testing
2. Differential diagnosis


dystrophin antibodies
c-terminus
exon 50
exon 46
exons 7/8
utrophin
nNOS
control
PATIENT

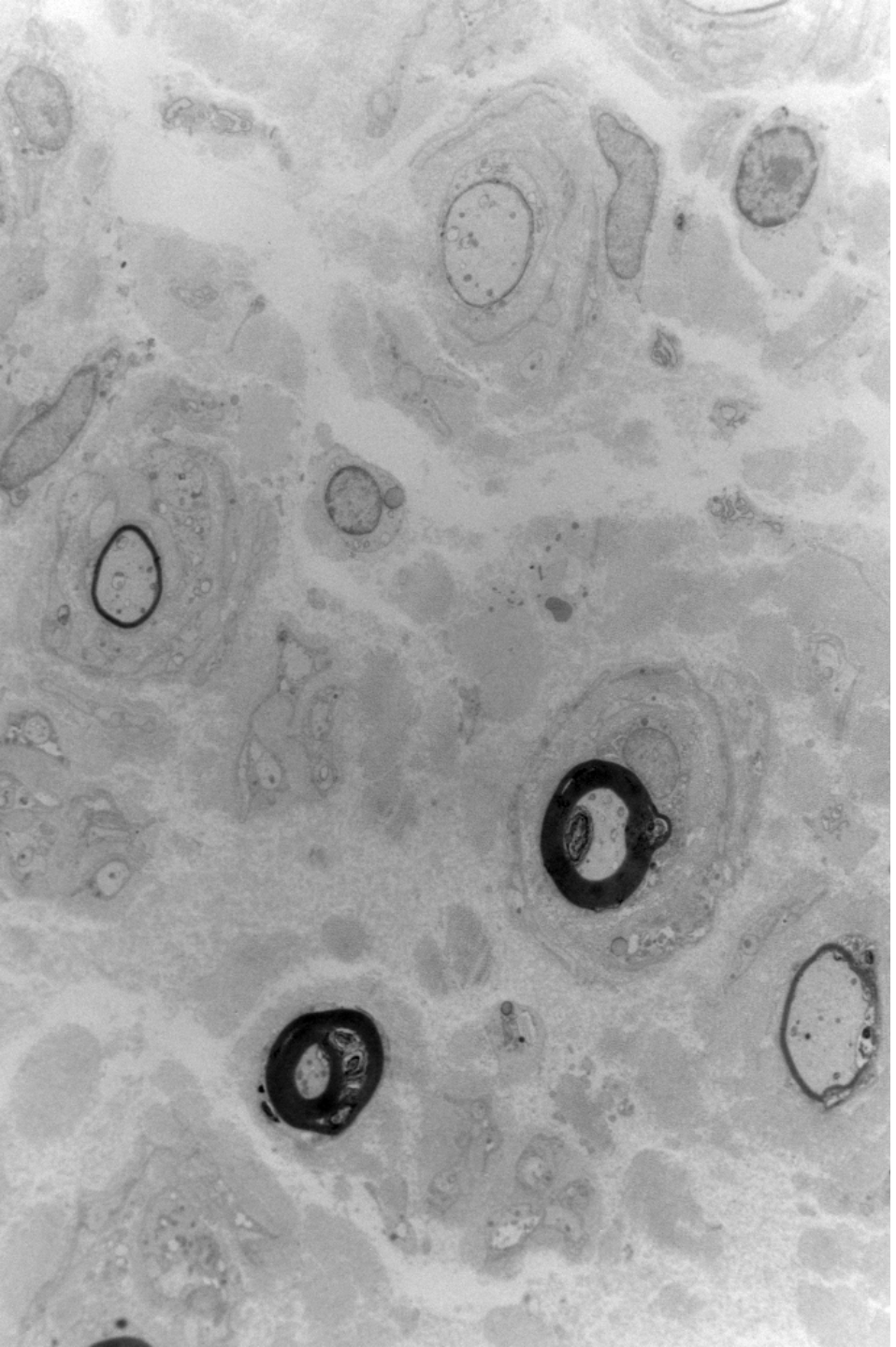
Further Clinical History

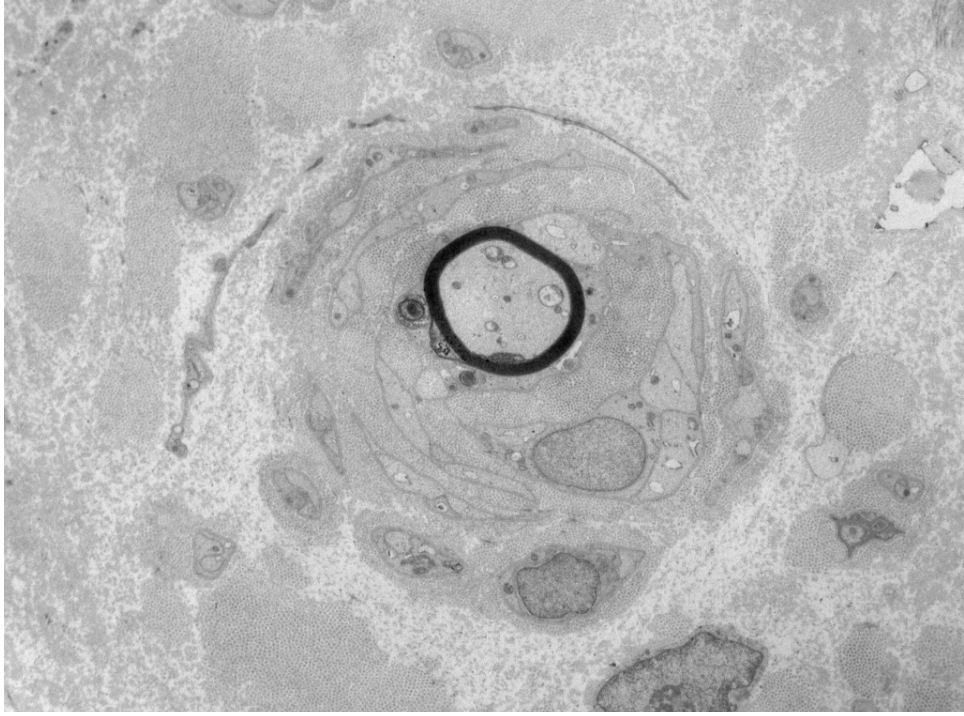
- Nerve conduction studies are performed and show markedly prolonged distal motor latency and a conduction velocity of 7 m/sec (ref: 45-70 m/sec) in the right median nerve
  - Right median sensory, right tibial motor, and right sural sensory responses are unrecordable
- Sural nerve biopsy is performed

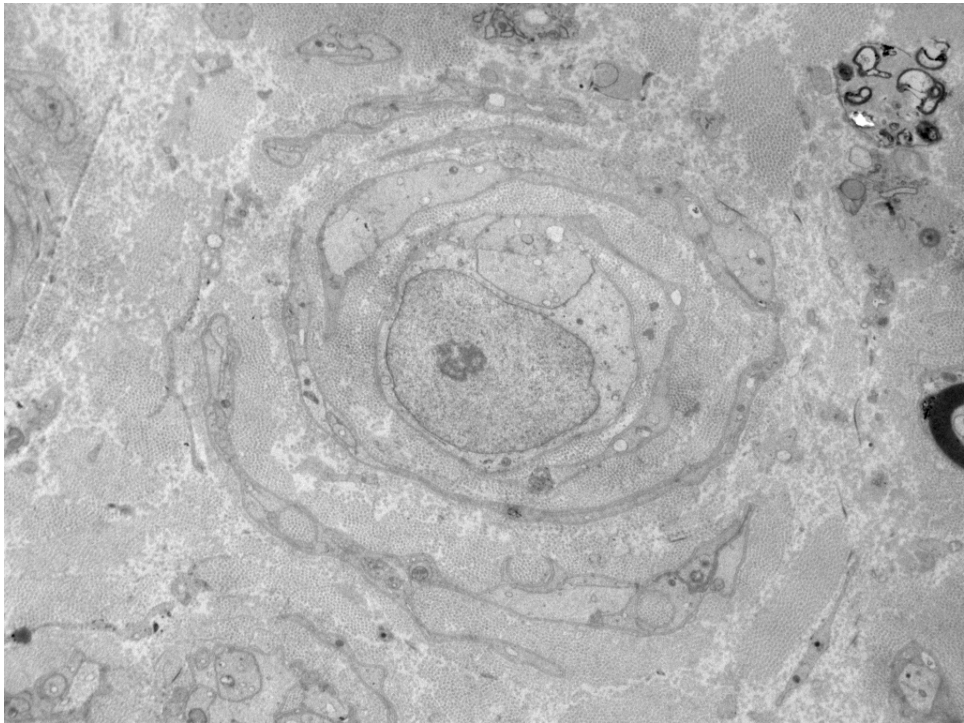


Further Discussion

1. Approach to further diagnostic testing
2. Revised differential diagnosis







Diagnostic Considerations

- Elevated CK
- Proximal and distal weakness
- Loss of reflexes
- Markedly decreased nerve conduction velocity
- Presence of foot deformities

Diagnoses

- Dystrophinopathy most consistent with Duchenne muscular dystrophy
  - *DMD*: duplication of exon 63
- Charcot-Marie-Tooth disease type 1
  - *PMP22*: duplication of exons 1-5

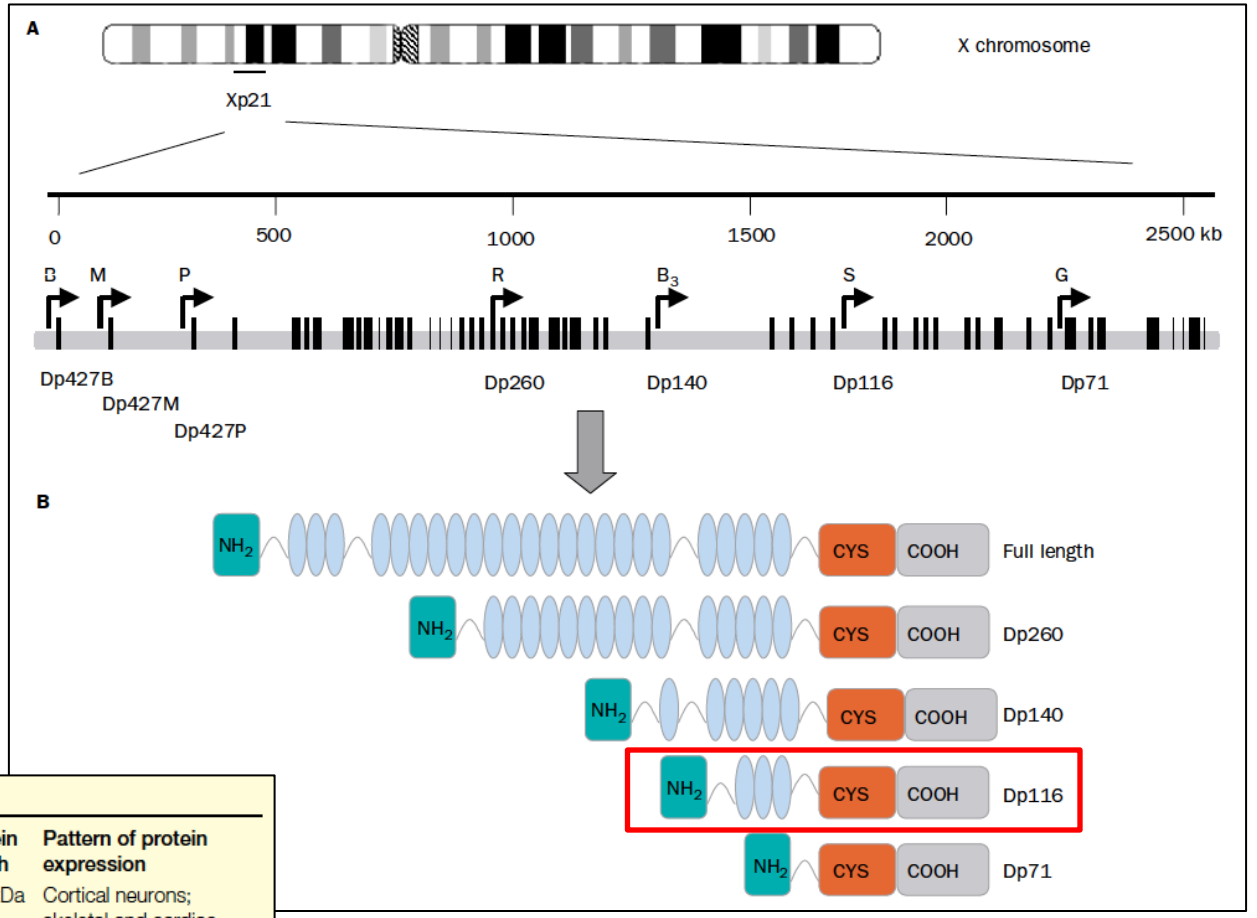
Learning Objectives: DMD

- Types of mutations known to cause dystrophinopathies
- 95% of dystrophinopathy patients diagnosed with deletion/duplication analysis, followed by sequencing of coding exons and exon-intron boundaries
  - Deletions usually worse than duplications phenotypically
- Muscle biopsy ultimately only necessary for patients with novel *DMD* variants of unknown significance, or mutations of deep intronic or regulatory regions
- Duplication of exon 63 is predicted to be out-of-frame, leading to early truncation of the transcript, transcript instability, and deficiency of dystrophin expression
  - Juan-Mateu, et al. DMD Mutations in 576 Dystrophinopathy Families. PLoS One. 2015 Aug 18;10(8).

Learning Objectives: CMT

- Subtypes of CMT (1, 2, intermediate, 4, X-linked) determined by nerve conduction studies, family history, mode of inheritance
- CMT1: Numerous genetic subtypes
  - Duplication of peripheral myelin protein 22 (*PMP22*; CMT 1A) and mutations in myelin protein zero (*MPZ*; CMT 1B) together account for 90% of cases
  - Genetic testing historically started with these two genes with subsequent analysis of less common subtypes if no mutation initially identified
  - Today: Increased availability of next generation sequencing from commercial labs offering multi-gene panels including *PMP22* and *MPZ* with genes of less common subtypes

- Markedly decreased nerve conduction velocity of 7 m/sec
- Schwann cell dystrophin (Dp116) starts with exon 56
- DMD: Duplication of exon 63



Isoforms of dystrophin protein

Symbol	Isoform	Promoter and unique first exon	Protein length	Pattern of protein expression
Dp427 B	Brain (or cortical)	5′ of the muscle promoter	427 kDa	Cortical neurons; skeletal and cardiac muscle
Dp427 M	Muscle	Between the brain promoter and intron 1	427 kDa	Skeletal and cardiac muscle; glial cells
Dp427 P	Purkinje cell	Between intron 1 and intron 2	427 kDa	Purkinje cerebellar neurons; (skeletal muscle)
Dp260	Retinal isoform	Intron 29	260 kDa	Retina; (brain and heart)
Dp140		Intron 44	140 kDa	CNS; kidney
Dp116	S-dystrophin	Intron 55	116 kDa	Schwann cells
Dp71	G-dystrophin	Intron 62	71 kDa	Brain; liver; cardiac muscle; (ubiquitously expressed in most other tissue but not skeletal muscle)

Expression is low in tissues in brackets.

Lancet Neurology 2:731-740, 2003

DMD combined with CMT

- Incidence in US (in the absence of a family history)
  - DMD/BMD: 1/7200
  - CMT: 1/3300
- Male patient: 1/24,000,000 chance of having both diseases

European Journal of Neurology 2007, **14:** 1182–1185 doi:10.1111/j.1468-1331.2007.01917.x

SHORT COMMUNICATION

Charcot-Marie-Tooth neuropathy type 1A combined with Duchenne muscular dystrophy

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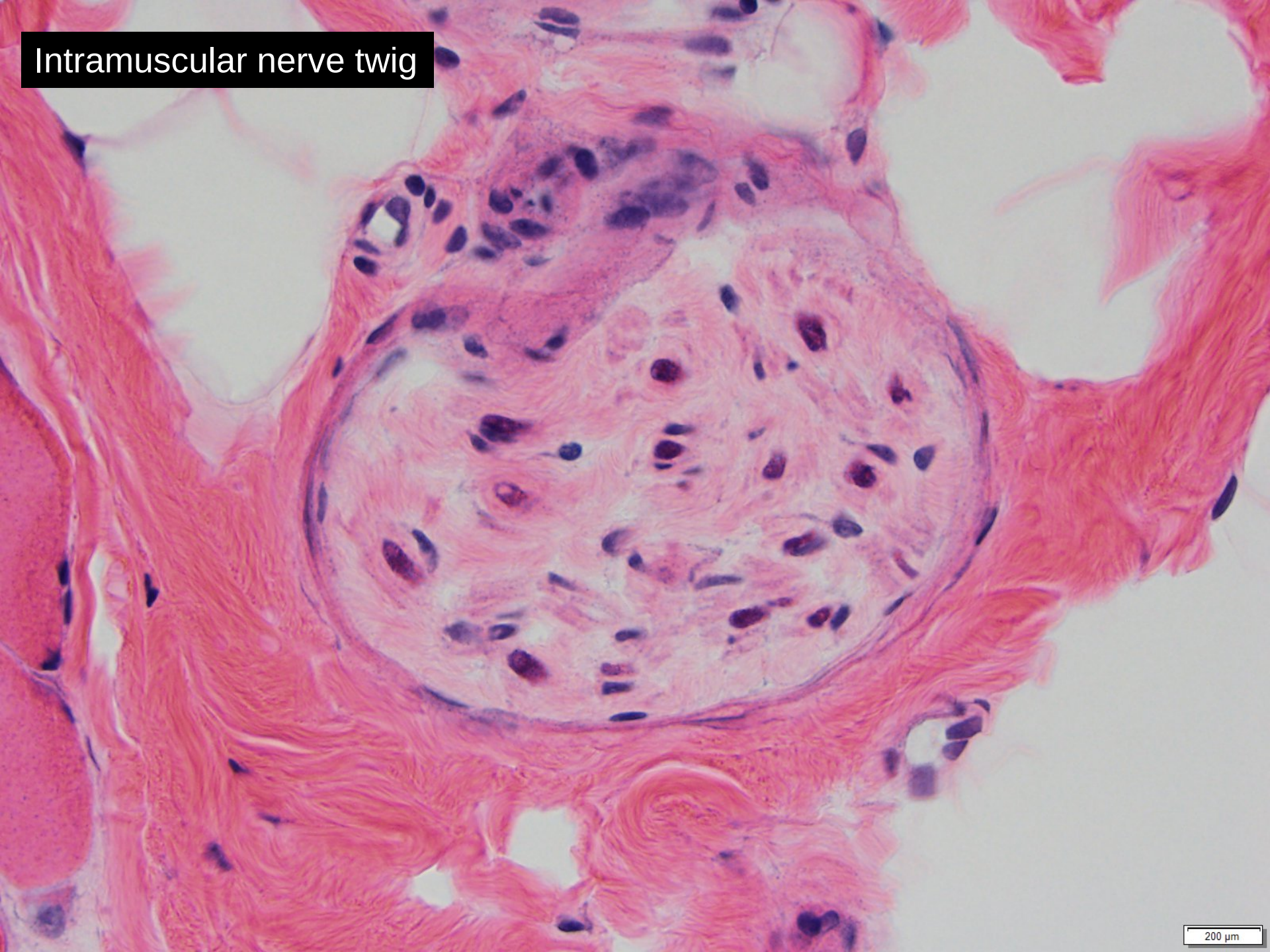
Keywords:
Charcot-Marie-Tooth disease, CMT1A, Duchenne muscular

We report a 24-year-old male with an unusual combination of two inherited neuromuscular disorders – Charcot-Marie-Tooth (CMT) disease type 1A and Duchenne muscular dystrophy (DMD). A phenotypic presentation of this patient included features of both these disorders. Nerve conduction studies revealed demyelinating

“Double Trouble”

- DMD/BMD + CMT
  - Bergmann C, Senderek J, Hermanns B, Jauch A, Janssen B, Schröder JM, Karch D. **Becker muscular dystrophy combined with X-linked Charcot-Marie-Tooth neuropathy.** Muscle Nerve. 2000 May;23(5):818-23.
- CMT + muscular dystrophy
  - Bütefisch CM, Lang DF, Gutmann L**. The devastating combination of Charcot-Marie-Tooth disease and facioscapulohumeral muscular dystrophy.** Muscle Nerve. 1998 Jun;21(6):788-91.
- DMD + other rare genetic diseases
  - Donkervoort S, Schindler A, Tesi-Rocha C, Schreiber A, Leach ME, Dastgir J, Hu Y, Mankodi A, Wagner KR, Friedman NR, Bönnemann CG. **'Double trouble': diagnostic challenges in Duchenne muscular dystrophy in patients with an additional hereditary skeletal dysplasia.** Neuromuscul Disord. 2013 Dec;23(12):955-61. doi: 10.1016/j.nmd.2013.08.003. Epub 2013 Aug 11.


Intramuscular nerve twig
200 µm