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

[Images of histological sections showing muscular tissues with different staining for dystrophin, utrophin, and nNOS]
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
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
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

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

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

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**

- **CMT + muscular dystrophy**

- **DMD + other rare genetic diseases**
Intramuscular nerve twig