NEUROMUSCULAR DISEASE IN CHILDREN

Allison Conravey, MD
The Neuromuscular pathway
Signs and symptoms

- Hypotonia - not improved with irritation
- Failure to reach milestones
- Weakness
- Decreased reflexes
Muscle Diseases

- Duchene's/ Becker's Muscular Dystrophy
- Congenital muscular dystrophy
- Congenital Myopathies
- Myotonic dystrophy
- Inflammatory myopathies
- Metabolic myopathies
Muscular dystrophies

- 4 criteria- 1. primary myopathies  2. genetically  3. progressive  4. myofiber degeneration at some stage
- Duchene
- Becker
- Emery-Dreifess
- Facioscapulahumoral
- Limb Girdle
- Oculopharyngeal
- Distal
- congenital
Duchene's muscular dystrophy

- Most common (1 in 3500 boys)
- X-linked
- Becker’s is more mild form of disease
- Proximal weakness- usually presenting around age 3
- Waddling gait, Gower’s sign
- Muscle psuedohypertrophy
- Wheelchair bound around age 10
- Elevated CK (50-100 fold)
- Dilated cardiomyopathy
- Respiratory problems
- Scoliosis
- Cognitive issues
Gower’s sign
Dystrophin

- Mutation in dystrophin gene
- A cytoskeletal protein, critical in stabilizing the link between the sarcolemmal membrane and the extracellular matrix
- Without dystrophin, there is sarcolemma breakdown and then muscle cell death
Duchene's Muscular dystrophy

- Diagnosed by clinical picture and elevated CK
- Molecular diagnosis available
- Muscle biopsy usually not needed
- Treatment consists of physical therapy, orthopedics, cardiology and pulmonary therapies
- Corticosteroids can help preserve ambulation
- Gene therapy in future
Congenital muscular dystrophy

- Heterogeneous group of disorders
- Most are autosomal recessive
- Weakness and hyporeflexia in first year of life
- Elevated CK (not as high as Duchene's)
- Muscle biopsy shows signs of myofibrillar necrosis and regeneration, along with endomysial fibrosis and deposition of fat
- Some die in infancy and others may live into adulthood with minimal disability
- Merosin (alpha-2 chain of laminin2) positive or merosin deficient
- Many are associated with CNS abnormalities (cobblestone lissencephaly, MR, seizures, white matter changes)
- Fukyama type, Muscle-eye-brain disease, Walker-Warburg syndrome, Ulrich form
Congenital myopathies

- Onset in early life with hypotonia, hyporeflexia, generalized weakness that is more often proximal than distal, and poor muscle bulk
- Often with dysmorphic features that may be secondary to the weakness
- Relatively nonprogressive
- Hereditary
- Unique morphological features on histochemical or ultrastructural examination of the muscle biopsy sample that originate within the myofiber
- Myopathies with protein accumulation
  - Nemaline myopathy
  - Myosin storage myopathy
  - Cap disease
  - Reducing body myopathy
- Myopathies with cores
  - Central core disease
  - Core-rod myopathy
  - Multiminicore disease
- Myopathies with central nuclei
  - Myotubular myopathy
  - Centronuclear myopathy
- Myopathies with fiber size variation
  - Congenital fiber type disproportion
Most common form of muscular dystrophy among whites
Prevalence 3-5/100,000
Usually appears in late adolescence or early adult life
Can present at birth (congenital myotonic dystrophy) or during the first decade (juvenile myotonic dystrophy) (20%)
Myotonia with a dystrophic process of muscle with multisystem involvement
Caused by a CTG trinucleotide expansion on chromosome 19q13.3
Pathogenesis

- Gene is DMPK which encodes a serine-threonine protein kinase (myotonia protein kinase [DMK]).
- The trinucleotide repeat does not affect the coding portion of the gene (transcribed to RNA but not to protein).
- Explanation for clinical manifestations of DM1 is multifactorial.
- Study on mice showed abnormal accumulation of abnormally expanded RNA molecules resulted in defective splicing of the skeletal muscle chloride channel pre-mRNA (Mankodi et al, 2002).
- The loss of chloride channel protein from the sarcolemma may lead to channel dysfunction and membrane hyperexcitability, resulting in myotonia.
Genetics

- Autosomal dominant with variable penetrance
- Normal people have 5 to 37 repeats
- In families with DM1, there is amplification of the repeats in the next generation (anticipation)
- CTG repeat expansion occurs to a greater degree in egg than in sperm
- Borderline premutation- 38 to 49 copies (small possibility of expansion)
- Carrier premutation- 50 to 80 copies (mildly symptomatic or no symptoms)- no cardiac problems
- Full mutation- above 80 copies
- Positive correlation with increased number of repeats and earlier age of disease onset (not possible to predict age)
Clinical

- Myotonia- percussion and grip
- Stiffness that improves with repeated contractions
- Weakness (face, distal>proximal)
- Weakness progresses over time as myotonia improves
- Atrophy (face and sternocleidomastoid affected first)
- Hatchet face (long face with shrinkage of masseter and temporal muscles)
- Cheshire cat smile
- Dysarthria, swallowing difficulties and mild external ophthalmoplegia may be seen
Associated features

- Hearing loss
- Polyneuropathy (large myelinated fibers)
- Smooth muscle involvement of pharynx, esophagus and GI tract
- Myotonia of anal sphincter
- Excessive daytime sleepiness
- Cardiomyopathy and conduction defects-
  - prolonged PR interval (70%)
  - arrhythmias, mainly atrial flutter (15%)
- Immunologic abnormalities- increased catabolism of IgG (1/3)
Associated symptoms

- Endocrinopathies-
  - frontal baldness
  - loss of body hair
  - testicular atrophy, infertility
  - hypothyroidism
  - growth hormone secretion disturbances
  - insulin-resistant diabetes (6.5-20%)
- Ophthalmology- cataracts after age 10
- Cognitive deficits in 80%
- Older adults have frontal and temporal lobe cognitive decline
Myotonic Dystrophy

- Frontal balding
- “Hatchet” facies due to atrophy of temporalis muscle
- Ptosis and drooping mouth due to weakness of facial muscles
- Wasting of sternocleidomastoid muscle

Cataracts

Gynecomastia
Congenital myotonic dystrophy

- Almost always transmitted by mother (15-20%)
- The greater the CTG expansion in the mother, the higher the probability of the offspring being affected (>100 copies=62% risk)
- GTG repeats usually >730 copies
- Polyhydramnios
- Prematurity (50%)
- Arthrogryposis
- Perinatal asphyxia common
- Weak suck
Congenital Myotonic Dystrophy

- Hypotonia, especially involving neck muscles
- Facial diplegia (87%)
- Delayed motor development (87%)
- Mental retardation (68%)
- Clinical myotonia is absent in 1st year - 12% of 1 to 5 year old children
- In 1st year - respiratory insufficiency, dysphagia and aspiration, and problems with GI motility (16% mortality)
- After 1st year - appear to improve for a few years, only to deteriorate gradually with features of the adult form of disease
Inflammatory Myopathies

- Associated with a presumed immunologic attack
- Polymyositis, Dermatomyositis and infectious myositis
- Elevated CK with muscle weakness and pain
Dermatomyositis

- Muscle pain and weakness associated with rash
- Can be acute or insidious
- Erythematosus, scaly discoloration of eyelids which then spreads to cheeks and extensor surfaces of joints (Grotton rash), elbows and knees
- Increased ESR and WBC
- May have positive ANA
- MRI- increased signal in T2 with normal T1
- Treatment- prednisone or other immunosuppressives
Polymyositis

- Uncommon in children
- Chronic inflammatory process of muscles
- Cell mediated disease with abnormal T lymphocytes
- Can begin as early as 1yo
- Can look like muscular dystrophy- more rapid onset
- Antibodies to myosin in 90%
- Course is generally downhill
Metabolic myopathies

- Muscle phosphorylase deficiency (McArdle’s)- onset in childhood with painful muscle cramps and weakness after exertion
- Congenital defect of phosphofructokinase (Glycogenosis type VII)- easy fatigability and weakness of stiffness induced by exertion
- Phosphoglyceromutase deficiency- life long history of muscle pain, cramps and weakness after exercise and MR
- Aldolase A deficiency- unexplained episodes of jaundice and anemia and markedly elevated CK
Disorders of neuromuscular junction

- Myasthenia gravis
- Botulism
- Lambert-Eaton
Myasthenia Gravis

- Autoimmune disease in which antibodies are directed against acetylcholine receptor antibodies which impair neuromuscular transmission and produce weakness.
Types

- Neonatal - transplacental passage of antibodies to baby
- Juvenile - <18yo, F>M
- Adult onset (early or late)
- Congenital - not autoimmune
  - defects in proteins at NMJ
  - can be presynaptic, synaptic or postsynaptic
Generalized Myasthenia Gravis

- Eye findings (ptosis or extraocular muscle weakness) most common - 50% at presentation and 90% at some time during illness
- Double vision
- Pupil is always spared
- Bulbar symptoms are the next most common symptom
- Nasal speech
- Dysphagia
- Jaw weakness
Muscle weakness

- Fluctuates and progressively worsens over the course of the day
- Fatigability
- Painless
- Variable distribution and severity (may be asymmetric)
- Distal weakness less common
- Legs usually affected later
- Most common muscles - jaw closure, neck flexors, deltoids, triceps
- Respiratory muscles may be affected
- Bowel and bladder spared
Physical exam

- Pupils unaffected
- Fatigability- sustained upgaze, count to 100, repetitively testing proximal limb or neck flexors
- Subtle weakness- functional testing
- Ice bag test
- DTRs preserved
- No sensory findings
Fatigability
MG treatment

- Anticholinesterase inhibitors
- Remission induction - steroids, IVIG, plasmaphoresis, immunosuppressives
- Thymectomy
A number of drugs have the potential to impair neuromuscular transmission and worsen MG

- Antirheumatic: Penicillamine, chloroquine
- Antibiotics: aminoglycosides > macrolides, fluoroquinolones
- Antiarrythmics: beta blockers, calcium channel blockers, procainamide
- Anesthetic agents: Non-depolarizing agents (vecuronium, pancuronium), succinylcholine
- Magnesium
- Phenytoin
- Carnitine
- Ace inhibitors
Infantile Botulism

- caused by a neurotoxin produced by the spore-forming, anaerobic, gram-positive bacilli *Clostridium botulinum*, which is found globally in soil
- The toxin irreversibly binds to presynaptic cholinergic receptors at motor nerve terminals and is subsequently internalized.
- Once inside the cytosol, the toxin behaves as a protease, damaging an integral membrane protein of acetylcholine-containing vesicles, disrupting exocytosis and inhibiting the release of the acetylcholine that is needed to excite muscle
- Soil and honey contamination are the two recognized sources of botulinum spores (A history of honey consumption is seen in 15 percent of the botulism cases reported to the CDC)
- Presents at 6 weeks to 6 months
Infantile botulism

<table>
<thead>
<tr>
<th>Sign and Symptom</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness or floppiness</td>
<td>88</td>
</tr>
<tr>
<td>Poor feeding</td>
<td>79</td>
</tr>
<tr>
<td>Constipation</td>
<td>65</td>
</tr>
<tr>
<td>Lethargy/decreased activity</td>
<td>60</td>
</tr>
<tr>
<td>Weak cry</td>
<td>18</td>
</tr>
<tr>
<td>Irritability</td>
<td>18</td>
</tr>
<tr>
<td>Respiratory difficulties</td>
<td>11</td>
</tr>
<tr>
<td>Seizures</td>
<td>2</td>
</tr>
</tbody>
</table>

Infantile Botulism

- Treatment is supportive
- Use of botulinum immune globulin in infants has successfully reduced the time spent in the hospital and the need for mechanical ventilation and tube feeding
- Prognosis is excellent, with a case-fatality rate of less than 2 percent
- Recovery results from the regeneration of nerve terminals and motor endplates.
- Diaphragmatic function returns before peripheral muscle recovery.
Peripheral Neuropathies

- Guillain- Barre syndrome (AIDP)
- CIDP
- Hereditary motor and sensory neuropathy (CMT)
Guillian-Barre syndrome (AIDP)

- Acquired, immune mediated polyradiculoneuropathy causing dysfunction, segmental demyelination and/or axonal degeneration is peripheral nerves, spinal sensory and motor nerve roots, and cranial nerves
- 1-2/100,000 per year
- Previous infection in 2/3 of children (URI or AGE)
- Most frequent between ages 4 and 9
- Associated with pain and parasthesias
- Usually symmetric ascending paralysis
- Ataxia (44%)
- CN involvement
GBS

- Can have papilledema
- Can have impaired vital capacity
- Dysautonomia
- Sphincter disturbances in 1/3
- Decreases or absent reflexes
- Increased CSF protein - may have small increase in WBC
- EMG - conduction block and prolonged F-waves
- Treatment - IVIG or plasma exchange
- Recovery usually is 2 months - may take up to 18 months
CIDP

- Childhood incidence of 0.5/100,000 per year
- Like GBS but slower progression
- CSF- albumino-cytologic dissociation
- Treatment- steroids, IVIG, plasma exchange, immunosuppressives
Hereditary motor and sensory neuropathy

- Also called Charcot-Marie-Tooth disease (CMT)
- Peroneal muscular atrophy
  - CMT1- AD
    - extensive segmental demyelination and remyelination of peripheral nerves
    - thickening of peripheral nerves
  - CMT2- less common axonal form
  - CMT3 (Dejerine-Sottas syndrome)- most severe demyelinating form
CMT 1

- Bimodal age distribution - 1\textsuperscript{st} 2 decades or after 5\textsuperscript{th} decade
- Can have sx before age 1
- Peroneal muscles affected 1\textsuperscript{st}
- Pes cavus, scoliosis, contractures, absent ankle jerks
- Decreased sensation
- Increased CSF protein
- Decreased NCVs
- Slowly progressive
CMT 2

- Genetically heterogeneous
- Axonal degeneration of peripheral nerves
- Clinical picture similar to CMT 1 with slower progression
CMT 3 (Dejerine-Sottas Disease)

- Onset of sx in infancy or early childhood progressing to severe disability
- AD or AR
- Hypotonia, muscle atrophy and weakness
- Facial weakness
- Very slow NCVs
Anterior horn cell disease

- Spinal Muscular Atrophy
- Infection (polio, enteroviruses, rabies)
Spinal Muscular Atrophy

- AR
- 1 in 10,000-25,000
- Mutation in SMN1- 2 copies
- SMA 1 (Wednig-Hoffman)- ¼
- SMA 2- ½
- SMA 3 (Kugleburg Welander)
- Symmetric proximal weakness
- Atrophy
- Diaphragm spared until late
- Cardiac and smooth muscle spared
- Tongue fasciculation
- Absent DTR’s
- Some sensory symptoms

- Blood marker for SMN1 gene
- CK- normal or mild elevation
- EMG- fibrils and facsics
- Biopsy- dennervation atrophy
SMA 1

- Acute and rapidly progressive
- Almost always fatal by 3yo
SMA 2

- Symptoms by 18 months
- Tremor in upper extremities
- CK increased up to 5x normal
- May have gastroc hypertrophy
SMA 3

- Present 18 months to adult
- Proximal muscle weakness
- Impaired joint mobility
Poliomyelitis

- Affects motor units of spinal cord and brain
- Mostly affects anterior horns cells
- Clinically ranges from non specific febrile illness to a severe and potentially fatal paralytic disease
- Paralytic polio follows aseptic meningitis
- Pain, fasciculations, twitching and decreased DTR’s
- Polio-like syndrome- seen with west nile virus and other viruses