I. Clinical Evaluation:
   A. History/Symptoms:
      1. Onset birth-third decade or over a period of several years.
         a) Hereditary Myopathy: Muscular dystrophies, Congenital myopathies, Myotonias, Channelopathies (periodic paralysis), Metabolic and Mitochondrial myopathies
      2. Onset of symptoms over a few weeks, months, or a couple of years
         a) Acquired Myopathy: Inflammatory myopathies, Myopathies with systemic illness (critical illness myopathy), Endocrine myopathies, Drug-induced myopathies, Toxic myopathies
      3. Weakness?
         a) Proximal - Difficulty arising from a seated position, including motor vehicle and the toilet or from a squat/kneeling position, raising arms above head to place object on shelf, comb hair.
         b) Distal - opening jars, unscrewing bottle top, turning a key in ignition/door, foot drop
         c) Dysarthria, Dysphagia, Ptosis, Orthopnea and Dyspnea on exertion
      4. Associated Symptoms?
         a) Stiffness (myotonia) worse with exercise ->paramyotonia congenita or better with exercise->myotonic muscular dystrophy; Stiffness (myotonia) worse with cold ->paramyotonia congenita and myotonic muscular dystrophy
         b) Myoglobinuria: Dark red/brown-Coke or tea colored (not just a darker shade of yellow)
         c) Episodic or provoking factors of weakness
            (1) Exercise- metabolic myopathy-glycogen storage
            (2) Fever- metabolic myopathy- CPT deficiency
            (3) Cold – paramyotonia
(4) Recent toxin/drug use- ETOH, IV Drugs

d) Pain- unlikely secondary to a myopathy and more likely related to a musculoskeletal, rheumatologic, or pain disorder, particularly if pain is constant

e) Cramps- more often benign, systemic condition (electrolytes, endocrine), or neurogenic disorder (motor neuron disease) than a myopathy

5. Family History: Autosomal dominant, recessive or X-linked, or Maternal-Mitochondrial

B. Physical Examination:

1. Assess for Weakness

   a) Manual Muscle testing

   (1) Cranial/Bulbar: Ptosis, Forced eye closure, Extraocular movement, Lip pursing/holding air in cheeks, Tongue protrusion and lateral tongue movements to resistance, Speech- Lips-Pa (Ba if weak), Tongue-Ta (Da if weak), Posterior Tongue/Soft palate-Ka (Ga-if weak)

   (2) Limbs: Assess one side and compare to other side before moving on to next muscle group

   (3) Upper Limb: Shoulder abduction, external and internal rotation, elbow flexion and extension, wrist flexion and extension, thumb and finger extension, flexion and abduction

   (4) Lower Limb: Hip flexion, extension and abduction, Knee flexion and extension, ankle dorsiflexion and plantarflexion, inversion, eversion, and Toe extension and flexion.

   (5) Ideally test perpendicular to gravity: Hip flexion and Knee extension while seated, Knee flexion and Neck extension prone and Hip abduction in lateral decubitus, and Neck flexors supine

   (6) Expanded Medical Research Council (MRC) scale
(a) 5 Normal strength
(b) 5- Equivocal, barely detectable weakness
(c) 4+ Definite, but slight weakness to resistance
(d) 4 Move against some resistance
(e) 4- Minimal resistance
(f) 3+ Transient resistance but collapses
(g) 3 Active movement against gravity only
(h) 3- Movement against gravity but not full range
(i) 2 Able to move with gravity eliminated
(j) 1 Trace muscle contraction
(k) 0 No contraction

b) Functional Assessment of muscle weakness
(1) Useful when subjects have give-away weakness with manual strength testing or with children.
(2) Facial: Inability to bury eyelids=orbicularis oculi, Horizontal smile=lower facial/zygomaticus weakness, Inability to whistle= orbicularis oris weakness
(3) Ocular: Dysconjugate gaze, ptosis=levator palpebrae or tarsal muscle
(4) Bulbar: Speech, weak cry, poor suck, nasal regurgitation, aspiration pneumonia, coughing while eating
(5) Neck: Poor head control
(6) Trunk: Scoliosis, Increased lumbar lordosis, protuberant abdomen, difficulty sitting up from supine or staying upright while sitting
(7) Shoulder girdle: Extending arm over head (with or without object), scapular winging
(8) Forearm/Hand: Finger/wrist drop, Inability to make tight fist (flexors)

(9) Pelvic girdle: Difficulty going up a step(s), waddling gait, Unable to arise from a seated position without using arms, Gower’s sign

(10) Leg/Foot: Foot/toe drop, Inability to walk on heels or toes

(11) Respiratory: Use of accessory/neck muscles to speak or with exertion, Unable to lay supine without shortness of breath

2. Atrophy or Hypertrophy

   a) Hypertrophy: Paramyotonia congenita, reported in amyloid, sarcoid and hypothyroid

   b) Pseudohypertrophy: Replacement by fat/connective tissue in the Calf (posterior lower limb)

   (1) Duchenne and Becker dystrophin muscular dystrophy, Sarcoglycanopathies (LGMD 2C-F), FKR (LGMD-2I), telethonopathy (LGMD 2G)

   (2) Tendon rupture (Biceps brachii, Achilles) may disrupt muscle belly and mimic hypertrophy, occasionally partial, chronic denervation in CMT or radiculopathy may cause hypertrophy, rare: tumor

   c) Atrophy: Easy to miss if you don’t look, as often mild and gradual and not noticed by the patient.

      (1) Look for prominent tendons, joints, bone edges given loss of muscle bulk;

      (2) Focal convexities (divots) focal lipodystrophy often confused as muscle atrophy

3. Assess for Clinical Myotonia or Rippling muscles

C. Distribution of Weakness
1. In General Myopathy will result in symmetrical proximal limb weakness. Specific patterns of weakness: asymmetry, distal weakness, respiratory weakness and facial/ocular weakness narrow the differential diagnosis.

2. Facial/Ocular and Extraocular muscle weakness
   a) Mitochondrial Myopathy – chronic progressive external ophthalmoplegia (CPEO)
   b) Oculopharyngeal Muscular Dystrophy- prominent bulbar/dysphagia
   c) Oculopharyngodistal distal myopathy
   d) Neuromuscular Junction Disorder (MG, Botulism)

3. Facial/Ocular weakness (no extraocular weakness)
   a) Myotonic Muscular Dystrophy (MMD)
   b) Desmin (Myofibrillary) Myopathy
   c) Congenital Myopathies: Centronuclear, Nemaline, Central Core
   d) Facioscapulohumeral Muscular Dystrophy (FSH MD)

   a) FSH MD- should have facial muscle weakness, and asymmetrical limb weakness
   b) Emery-Dreifuss humeroperoneal dystrophy (EDMD)
   c) Calpainopathy- LGMD 2A
   d) Congenital Myopathy- Centronuclear
   e) Acid Maltase Deficiency (Pompe)
   f) Laminopathies- LGMD 1B
   g) Sarcoglycanopathies-LGMD 2C-F
   h) Scapuloperoneal MD with Hyaline bodies
5. Distal Arm (wrist and finger flexors) and Proximal Lower limb/Pelvic girdle Weakness
   a) Inclusion Body Myositis- often asymmetric weakness
   b) Uncommon- MMD

6. Distal Weakness predominate
   a) Myotonic Muscular Dystrophy (MMD) Type 1
   b) Inclusion Body Myositis (wrist and finger flexors, ankle dorsiflexor)
   c) Myofibrillar Myopathy
   d) Scapuloperoneal Myopathies with significant distal lower limb weakness
      (1) FSH MD, EDMD, Oculopharyngodistal distal myopathy,
      (2) Glycogenosis (Acid Maltase, phosphorylase b kinase, debranching enzyme)
      (3) Congenital Myopathy (Nemaline rod myopathy, central core, and centronuclear)
   e) Distal Myopathies
      (1) Late adult onset distal myopathy type 1 (Welander), type 2 (Markesbery/Udd)
      (2) Early adult onset distal myopathy type 1 (Nonaka), type 2 (Miyoshi), type 3 (Laing)

7. Neck Extensor Weakness: Clinically have head (drop) ptosis
   a) Inflammatory myopathies: IBM, PM (brachial-cervical inflammatory myopathy), DM
   b) Muscular dystrophy: FSH MD, MMD
   c) Metabolic myopathy: Carnitine deficiency, Acid Maltase deficiency
   d) Congenital myopathy
   e) Non-Myopathy: ALS, MG, Hyperparathyroidism, Hypothyroidism
f) Isolated Neck extensor myopathy, Bent Spine syndrome

8. Respiratory Weakness

a) Muscular Dystrophy: Duchenne, Becker, Emery-Dreifuss, LGMD 2A (Calpain) and 2I (FKRP), Myotonic (central hypoventilation), congenital MD-Ullrich

b) Metabolic Myopathies: Acid Maltase, Debrancher, & Carnitine deficiency

c) Myofibrillar myopathies: desmin, alpha-beta crystallin

d) Congenital Myopathy: Nemaline rod & Centronuclear, Congenital fiber type disproportionate with TPM3 mutation

e) Mitochondrial Myopathies: PEO, Leigh’s

f) Polymyositis-interstitial lung disease, Sarcoid: lung disease

g) ALS and MG

D. Associated Symptoms

1. Cardiac Dysfunction

a) Arrhythmias

(1) Myotonic MD and Emery-Dreifuss (X-linked & AD Lamin A/C) LGMD 1B (Lamin A/C), 2C-F (sarcoglycans), 2G (telethonin), Myofibrillar myopathy (particularly, ZASP mutation)

(2) Kearns-Sayre (mitochondria), Anderson’s syndrome (K+ channelopathy), Polymyositis with SRP (signal recognition protein) antibody

b) Congestive heart failure

(1) Muscular Dystrophy: Duchenne, Becker, LGMD 1B (Lamin A/C), 2C-F (sarcoglycans), Emery-Dreifuss, Myofibrillar myopathies
(2) Acid-Maltase deficiency, Carnitine Deficiency, Nemaline myopathy, Danon disease (X-linked, Lamp-2 lysosomal storage disorder), Polymyositis with SRP

2. Episodic Weakness with pain and myoglobinuria
   a) Triggered by exercise: Glycogenoses (McArdle, Tarui’s, etc.), Lipid disorders (CPT deficiency), Poorly conditioned individual with sudden significant exercise-not Neuromuscular disease
   b) Not related to exercise (often not neuromuscular disease related), Malignant hyperthermia, Drugs/toxins, Trauma, Infections, Neuroleptic malignant syndrome, Seizure
   c) A single episode of myoglobinuria with normal examination does not necessarily require an expensive investigation with muscle biopsy/gene tests, but recurrent episodes of myoglobinuria likely represent neuromuscular disease

3. Episodic Weakness
   a) Periodic Paralysis: Channelopathies
      (1) Na++ channelopathies: Hyperkalemic PP often with myotonia
      (2) Ca++ channelopathies: Hypokalemic PP, dihydropyridine receptor
      (3) Andersen’s syndrome: PP with cardiac arrhythmia, dysmorphic features
      (4) Secondary PP (thyrotoxicosis)
   b) Psychiatric disease: conversion disorder, depression, etc.

4. Stiffness/Inability to relax
   a) With fixed limb weakness: Myotonic Muscular Dystrophy type 1 (distal weakness) type 2 (proximal weakness), Becker’s disease (AR, Chloride channelopathy)
   b) Improves with exercise: Myotonia- Na+, Cl- channelopathy
c) Worsens with exercise/cold- Paramyotonia Na+ channelopathy, Brody’s disease (Calcium-ATPase, no myotonia)

d) Other: Rippling Muscle disease (visualize muscle mounding on exam, Caveolin); Malignant Hyperthermia (Ryanodine receptor, anesthesia induced delayed relaxation); Neuromyotonia; Stiff-Person (anti-GAD Ab)

II. Laboratory Evaluation

A. Creatine Kinase (CK)

1. Not always specific for myopathy, and may be mildly elevated <1000 IU/dl with:
   a) Neurogenic disorders with denervation and myofiber degeneration: ALS, CMT, SMA, post-polio;
   b) Medications; thyroid and hypoparathyroidism
   c) Trauma: IM/SQ injections, needle EMG, strenuous exercise;
   d) Increased muscle mass, race, gender,
   e) Idiopathic CKemia

2. Degree of elevation may differentiate muscle disease: Duchenne MD, LGMD 1C (caveolinopathy), 2A (calpainopathy), and 2B (dysferlinopathy) may have marked elevation x10-100 times normal. Untreated polymyositis CK is quite high; >10x normal while IBM is <12x normal.

3. When the diagnosis of polymyositis or dermatomyositis has been established monitoring CK may be useful in guiding immune suppression therapy.

4. It is unlikely that a slight CK elevation, x3 fold or less (<600), is associated with a myopathy in the absence of objective muscle weakness on physical examination.
5. Elevated AST and ALT are not specific for the liver and may be elevated secondary to myopathy. When attempting to assess liver function, particularly in setting of immune suppression agent at risk for hepatotoxicity, assess specific liver enzyme gamma glutamic transferase (GGT).

6. CK isoenzymes (CK-MM and CK-MB) are not useful in assessing muscle dz. However, CK-MB may be elevated in muscle disease and not represent cardiac disease.

B. Electrodiagnostic (EDX) testing- Often done as part of initial diagnosis

1. Excludes conditions with only motor weakness: motor neuron disease and neuromuscular junction disorders in addition to assessing for neuropathy/radiculopathy that may be superimposed or confused if sensory exam unreliable.

2. Motor NCS often normal unless muscle not electrically excitable (critical illness myopathy) or muscle severely affected (atrophy).

3. Needle EMG:
   a) Identifies: Myotonia (myotonic MD, paramyotonia congenital), Pseudomyotonia (Acid-Maltase deficiency)
   b) Myopathic MUAP (motor unit action potentials) identify patter of muscle involvement and determine site of biopsy
   c) Abnormal spontaneous activity (p-waves and fibrillation potentials) associated with active myofiber degeneration, narrows differential diagnosis:
      (1) Inflammatory myopathies (polymyositis, dermatomyositis and inclusion body myositis)
      (2) Infiltrative myopathy (sarcoid, amyloid)
      (3) Muscular Dystrophies (certain types, NOT ALL muscular dystrophies: Duchenne, Becker, Myotonic, and certain limb-girdle)
      (4) Metabolic Myopathies (glycogen storage-acid-maltase)
(5) Congenital Myopathies (again certain types: myotubular, late onset rod myopathy)

(6) Infectious Myopathy-rare (viral myositis, trichinosis)

(7) Rhabdomyolysis and Muscle Trauma

C. Gene testing

1. In general requires a medical insurance prior authorization before ordering, and may not be a covered benefit.

2. In general Muscular dystrophies with facial weakness/ptosis should (if possible) start with gene testing before muscle biopsy: Myotonic Muscular Dystrophy type 1 and 2, Oculopharyngeal Muscular Dystrophy, Facioscapulohumeral Muscular Dystrophy.

3. Certain LGMD caused by enzyme abnormalities FKRP (LGMD 2I), dysferlin (LGMD 2A) best to be gene tested as immunohistochemistry and western blot testing of muscle enzymes may not be reliable. However, may still need muscle biopsy to determine muscular dystrophy vs alternative myopathy.

4. Others: Duchenne and Becker MD (if immunohistochemistry is inconclusive can sequence the gene), LGMD 1B (Lamin A and C), 2C-F (sarcoglycans-immunohistochemistry unlikely to specify sarcoglycan type), Mitochondrial myopathy MERRF, MELAS, Myotubular Myopathy (MTM1), Nemaline myopathy (ACTA1), Nonaka distal myopathy, Congenital Muscular Dystrophy (FKRP, FCMD, MEB, POMT1), Chloride and Sodium channelopathies

D. Muscle Biopsy

1. Performed if clinical and/or EMG evaluation suggests a myopathy, should confirm if a myopathy is present.

2. Closed or Open (needle) muscle biopsy can be performed; Needle biopsy advantage as minimally invasive, easier to sample multiple sites, but muscle biopsy in blind fashion so may biopsy near tendon.
3. Appropriate Muscle to biopsy is key:
   
a) Affected muscle by examination or EMG but not severely affected or end-stage, avoid muscles with MRC <3 and select those MRC=4

b) Avoid muscles recently studied by needle EMG may have artifact from trauma.

c) Each muscle has a specific pattern of Type1 and 2 fibers, therefore, choose muscles with familiar patterns: Deltoid, Biceps, Vastus Medialis or Lateralis; Gastrocnemius should be avoided given significant tendon insertion throughout muscle.

4. Muscle Fiber Types

a) Type 1- red, slow twitch, has high oxidative and low glycolytic activity

b) Type 2- white, fast twitch, have low oxidative and high glycolytic activity

c) Type 2C is an immature muscle fiber type

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2A</th>
<th>Type 2B</th>
<th>Type 2C</th>
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<td>Color</td>
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<td>White</td>
<td>White</td>
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<td>Twitch speed</td>
<td>Slow</td>
<td>Fast</td>
<td>Fast</td>
<td></td>
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<tr>
<td>Fatigability</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Sensitive</td>
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<tr>
<td>Twitch + Oxidative glycolytic capacity</td>
<td>Slow oxidative</td>
<td>Fast oxidative glycolytic</td>
<td>Fast glycolytic</td>
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<tr>
<td>ATPase 9.4 (adenosine triphosphatase)</td>
<td>Light</td>
<td>Dark</td>
<td>Dark</td>
<td>Dark</td>
</tr>
<tr>
<td>ATPase 4.6 (distinguish 2A from 2B, and from type 1)</td>
<td>Dark</td>
<td>No stain</td>
<td>Medium dark</td>
<td>Dark</td>
</tr>
<tr>
<td>ATPase 4.3 (to distinguish 2C)</td>
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<td>No stain</td>
<td>No stain</td>
<td>Medium Dark/Dark</td>
</tr>
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<td>NADH-TR (nicotinamide adenine dinucleotide-tetrazolium reductase)</td>
<td>Dark</td>
<td>Medium Dark</td>
<td>Light</td>
<td>Medium Dark/Dark</td>
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<tr>
<td>Cytochrome oxidase (COX)</td>
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<td>Light</td>
<td>Light</td>
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<tr>
<td>Succinic dehydrogenase (SDH)</td>
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<td>Light</td>
<td>Medium Dark</td>
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<td>Phosphorylase</td>
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<tr>
<td>Periodic acid-Schiff (PAS)</td>
<td>Light</td>
<td>Dark</td>
<td>Medium Dark</td>
<td>Medium Dark</td>
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<tr>
<td>Oil red-O lipid droplets</td>
<td>Many</td>
<td>Medium/Many</td>
<td>Few</td>
<td></td>
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</tbody>
</table>
5. Histopathology

a) Hematoxylin and Eosin (H&E)

(1) General histology including fiber size and contour
   (a) Fiber splitting, snake coils, random distribution of marked fiber size variability all represent myopathy
   (b) Atrophy of a group of fibers suggests denervation
   (c) Perifascicular atrophy likely ischemia seen in dermatomyositis

(2) Degenerating or regenerating muscle fibers
   (a) Necrotic (degenerating) fibers are pale with loss of striations
   (b) Basophilic fibers are regenerating because of increased RNA

(3) Perimysial and Endomysial abnormalities
   (a) Fibrosis or increased connective tissue and adipose seen in a chronic myopathy or muscular dystrophy
   (b) Inflammation with muscle fibers surround or invaded by lymphocytes (macrophages, eosinophils)

(4) Position of nuclei
   (a) >30% internalized nuclei think muscular dystrophy or >60% think myotonic muscular dystrophy (MMD)
   (b) Pyknotic nuclei: MMD type 2, denervation without reinnervation, and untreated MG
   (c) Single central nuclei: Centronuclear congenital myopathy

(5) Intramuscular nerve/spindles, blood vessels

b) Gomori trichrome
(1) Good for general histology and particularly good stain for mitochondria, inclusions, and vacuoles.

   (a) Mitochondria much darker stain red and may demonstrate ragged red fiber

   (b) Nemaline rods (blue/violet rods) and hyaline or spheroid bodies (blue/violet smudges) seen in myofibrillar myopathies

   (c) Vacuoles stain reddish and may have rim

   (d) Define excessive connective tissue, and necrotic fibers are pale

c) NADH, SDH, COX and combined NADH/COX:

   (1) Stain Mitochondria, SDH= Nuclear encoded proteins and COX=mitochondrial encoded proteins

   (2) NADH: disruption of myofibrillar network creates altered pattern of mitochondria staining

       (a) Cores: congenital myopathies and muscular dystrophies

       (b) Moth-eaten (non-specific myopathy)

       (c) Targets: denervation and reinnervation

       (d) Coarse: immature or regenerating fiber

       (e) Tubular aggregates: (dark blob) certain myopathies and hypokalemic periodic paralysis

       (f) Lobulated: calpain LGMD, congenital MD but non-specific for myopathy

       (g) Ring fiber: ring of striations perpendicular to periphery of fiber

   (3) Disruption of mitochondria
(a) Fibers devoid of mitochondrial staining such as COX negative fibers (appear dark blue) on a combined NADH/COX stain seen in IBM

(b) SDH increased stain of mitochondria most sensitive and specific for mitochondrial proliferation: mitochondrial disease or regenerating fiber
   (i) SDH + vessels suggests MELAS
   (ii) SDH + fibers & ragged-red (trichrome) and lipid accumulation suggest Co-Q-10 deficiency

(c) COX may be increased (like SDH) or deficient, less sensitive for mitochondrial disorders then SDH
   (i) COX – and +/- ragged red fibers suggests mitochondrial DNA mutation including COX I, II, III genes
   (ii) COX diffusely reduced including vessels suggests LEIGH syndrome
   (iii) COX + and SDH + suggests nuclear gene defects for mitochondrial proteins including MELAS, Cytochrome b, PEO

d) ATPase (9.4, 4.6, 4.3):
   (1) Demonstrates distribution of muscle fiber types
   (2) Fiber type grouping in neurogenic disorders with chronic denervation and reinnervation
   (3) Type 1 fiber atrophy seen in congenital myopathies and Emery-Dreifuss, myotonic muscular dystrophy
   (4) Type 2 fiber atrophy non-specific and may not even represent neuromuscular disease as seen in disuse or steroid therapy
(5) Type 1 fiber predominance more common in congenital myopathy and muscular dystrophy (sometimes CIDP but would have fiber grouping as well)

(6) Type 2 fiber predominance associated with motor neuron disease

e) Acid Phosphatase:
(1) Stain necrotic fibers red
(2) Stain in lysosomal storage disorders
(3) Stain macrophages

f) Alkaline Phosphatase:
(1) Stains (black) blood vessels (capillaries) in inflammatory myopathies, dermatomyositis
(2) Highlight regenerating muscle fibers

g) Non-Specific Esterase:
(1) Also stains macrophages and lysosomes
(2) Stain neuromuscular and myotendinous junctions
(3) Small angular fibers (denervated)

h) Congo Red:
(1) Beta-amyloid deposition in IBM or acquired amyloid disorder

i) PAS:
(1) For glycogen storage disorders, acid-maltase deficiency stain excess glycogen,
(2) May have ring fibers suggests chronic myopathy, LGMD, Myotonic MD

j) Oil red-O:
(1) Increase lipid droplets may represent lipid storage disease such as carnitine deficiency
k) Phosphorylase (myophosphorylase):
   (1) Absent staining in McArdle type V glycogenosis

l) Phosphofructokinase:
   (1) Absent staining in Tarui’s type VII glycogenosis

m) Adenylate deaminase:
   (1) Absent/deficient in exertional myalgia syndrome
       myoadenylate deaminase deficiency
   (2) Not specific may need to tests enzyme to confirm
       deficiency

6. Immunohistochemistry
   a) Testing uses antibodies to determine if muscle fibers are missing
      certain proteins associated with a specific muscular dystrophy or
      congenital myopathy.

   b) Testing does not work for all myopathies as some proteins are
      decreased secondary to another myopathy and not directly
      related to the myopathic disorder of interest.

   c) Extracellular proteins:
      (1) Laminin α2 (Merosin):
          (a) Merosin deficient Congenital muscular dystrophy
          (b) Can be secondarily reduced in FKRP (LGMD 2I),
              MEB (muscle-eye-brain) muscular dystrophy,
              Walker-Warburg syndrome

      (2) Laminin β1
          (a) Reduced in Bethlem myopathy, while Collagen VI
              normal

      (3) Collagen VI
          (a) Ulrich’s congenital muscular dystrophy reduced
              collagen VI in muscle and capillaries
d) Sarcolemma-related proteins:

(1) Dystrophin: large protein, three antibodies to: N-terminal, rod and C-terminal of protein

   (a) Duchenne MD: often all 3 absent, C-terminal always absent
   
   (b) Becker MD: patchy loss with C-terminal preserved, normal immunohistochemistry staining does not exclude Becker dystrophin disorder

(2) Alpha-Dystroglycan:

   (a) Secondarily reduced in congenital myopathies (Fukuyama, MEB, Walker-Warburg, POMT 1, 2)
   
   (b) Reduction may be secondarily reduced in FKRP (LGMD 2I)

(3) Sarcoglycans:

   (a) Reduction in one may cause secondary reduction in others
   
   (b) Reduction while other testing negative indicates sarcoglycanopathy, but not specific type

(4) Dysferlin:

   (a) Absence has specificity for LGMD 2B
   
   (b) Reduction may be secondary to dystrophin, sarcoglycan, calpain or caveolin associated muscular dystrophy

(5) Caveolin-3

   (a) Specific for LGMD 1C (autosomal dominant)

e) Cytoplasmic Proteins (soluble) and Myofibrillar:

(1) Actin: can confirm intra myofiber inclusions are actin in nemaline rod congenital myopathy vs alternative inclusion (SLONAM)
(2) Myotilin (and desmin) intra fiber inclusion staining in some myofibrillar myopathies

(3) Calpain and Titan not useful with immunohistochemistry

f) Nuclear Proteins:

(1) Emerin: absent staining specific for EDMD type 1 (X-linked)

(2) Lamin A/C: immunohistochemistry no useful, Western blot may demonstrate reduction associated with EDMD type 2 (LGMD 1B)

E. Forearm Exercise Test

1. Perform test with Isometric contractions of the hand with a dynamometer for 1.5 seconds with rests of 0.5 seconds for 1 minute. Resting venous lactate and ammonia obtained at baseline and 2, 4, 6 and 10 minutes via IV and kept on ice.

2. Normal is a 3 to 5 fold increase in lactate and ammonia by 5 minutes with return to baseline by 10-15 minutes

3. No increase in lactate, but increase in ammonia consistent with myophosphorylase or phosphofructokinase deficiency.

4. No increase in ammonia, but increase in lactate, consistent with myoadenylate deaminase deficiency

5. No increase in either lactate or ammonia is a failed test indicating inadequate exercise.

References:


2. AANEM course on Adult Onset Myopathies, Richard Barohn, MD, Quebec City, Canada, 2010

MYOTONIA

I. Myotonia

A. Definition

1. Myotonia - delayed muscle relaxation following activation by voluntary movement, a mechanical stimulus (percussion myotonia), or an electrical stimulus

B. Clinical characteristics

1. Painless
2. Aggravated by cold
3. Improves after a warm-up period

C. Electrical characteristics

1. Rhythmic discharges
2. Occurs with needle electrode insertion lasting long periods after stimulus occurs or mild voluntary contraction
3. Amplitude waxes and wanes - varies from 10 uV to 1 mV
4. Frequency varies from 50 to 150 impulses per second – “dive-bomber, chain saw, motorcycle”
5. Morphology - similar to positive waves or fibrillation potentials
6. Decrement to repetitive stimulation which does not repair

D. Pathophysiology

See Chapter on Non-Dystrophic Myotonic Disorders in Neuromuscular Disorders, Amato and Russell, McGraw-Hill Professional; 2008
II. Not Myotonia (Table I)

A. Positive sharp waves/Fibrillations
   1. Occur with needle insertion and spontaneously
   2. Fire rhythmically at regular intervals
   3. Stop abruptly without decrescendo

B. Complex repetitive discharges
   1. Abrupt onset and cessation
   2. Morphology maintained throughout discharge
      a) Amplitude - 50 uV to 1 mV; duration -50 to 100 ms
      b) May be polyphasic
   3. Frequency - 5 to 100 impulses per second;
   4. "Machine gun" sound - very regular

C. Myokymia
   1. "Grouped fasciculation"
   2. Brief tetanic contractions of repetitively discharging single or multiple motor units

D. Neuromyotonia (Isaacs)
   1. Sustained or repetitive spontaneous muscle fiber activity
   2. Provoking stimulus not necessary
   3. Motor unit potentials or fibrillations firing at high frequencies - 300 impulses per second
   4. Decrementing discharge - "pings", "musical"
   5. Painless

E. Cramp
   1. Painful or painless
   2. Spontaneous or exercise or ischemia-induced
   3. Lasts seconds to minutes
4. High frequency (200 to 300 impulses per second) motor unit discharge involving a large part of the muscle synchronously

F. Contracture
1. Intense mechanical muscle shortening in absence of action potentials - electrically silent
2. Myophosphorylase or phosphofructokinase deficiency
3. Cannot produce ATP - prohibits Ca\(^{++}\) reaccumulation by sarcoplasmic reticulum and muscle relaxation cannot occur

G. Tetanus
1. Continuous motor unit discharges

H. Electrical activity of Schwartz-Jampel Syndrome
1. Neuromyotonia or complex repetitive discharges
2. Does not wax and wane

I. Electrical activity, of Stiff-Man Syndrome
1. Painful sustained contraction
2. Sustained interference pattern consisting of normal motor unit potentials in agonistic and antagonist muscles
3. Resembles tetanus
**TABLE I: Characteristics of Cramp Syndromes**

<table>
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<tr>
<th>KIND OF CRAMP</th>
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III. Conditions in which myotonia is found

A. Common

1. Myotonic dystrophy
   a) Myopathic EMG
   b) Mildly slowed conduction velocities
   c) Distribution of electrical myotonia variable
   d) Onset: adolescence or early adult life
   e) Syndrome of hatchet-faced appearance, frontal baldness, cataracts, gynecomastia, testicular/ovarian atrophy, diabetes mellitus, cardiac arrhythmias, low intelligence, clinical myotonia and distal greater than proximal weakness
   f) Incomplete penetrance

2. Myotonia congenita
   a) Thomsen’s (dominant)-myotonia in infancy, remains mild
   b) Becker’s (recessive) - more severe
   c) Contracture-type (recessive) - painful contractures induced by exercise

3. Paramyotonia congenita
   a) Myotonia worse with exercise
   b) Cold-induced rigidity

B. Less common

1. Hyperkalemic periodic paralysis
2. Acid maltase deficiency
3. Hyperthyroidism
4. Malignant hyperthermia

C. Not seen - Congenital myotonic dystrophy in infancy
REFERENCES


INFLAMMATORY/METABOLIC MYOPATHIES

I. Polymyositis/Dermatomyositis

A. Definition: Inflammatory myopathy of unknown etiology. The term dermatomyositis is applied when the myopathy is associated with a characteristic skin rash.

B. Until recently, there were no generally accepted criteria for definitive diagnosis. Many clinical studies, therefore, included heterogenous groups.

1. Bohan and Peter (NEJM, 1975) proposed the following diagnostic scheme:
   a. Symmetrical weakness of limb-girdle and neck flexor muscles, progressing over weeks to months.
   b. Abnormal muscle enzymes, representing muscle necrosis and perhaps regeneration (immature muscle membrane "leaky"). Increased creatinine phosphokinase, aldolase, transaminases and lactic dehydrogenase.
   c. Electrodiagnosis findings of myopathy. Reduced proximal muscle evoked amplitudes. Brief, low amplitude, polyphasic motor unit action potentials with fibrillation potentials, positive waves, and complex repetitive discharges on needle electromyography.
   d. Characteristic muscle biopsy. Necrosis and regeneration, variation in fiber size, myophagia, perifascicular atrophy, infiltrate of mononuclear inflammatory cells in muscle and in a perivascular distribution.
   e. Dermatologic features.

2. The criteria are empirically derived and failure to meet all criteria does not exclude the diagnosis.

C. Diagnostic Exclusions.

1. Evidence of central nervous system or peripheral nerve disease (neuromuscular junction transmission abnormalities are common, presumably related to immature, regenerating muscle, and, therefore, do not exclude the diagnosis.

2. Slow (years) progression of weakness (more characteristic of dystrophy).

3. Muscle biopsy evidence of granulomatous myositis (sarcoid) or infectious myositis (trichinosis, toxoplasmosis, bacterial, etc).

4. Toxic myopathies (drug induced, ETOH).

5. Evidence of rhabdomyolysis. Suggestive of acute viral myositis, severe muscle trauma, or some metabolic myopathies.

6. Evidence of underlying metabolic disorder (e.g. endocrinopathy, McArdle's syndrome).

7. Immunologic or clinical evidence of myasthenia gravis (although the two disorders may co-exist, the combination is unusual).
D. Clinical Classification.

1. Primary idiopathic polymyositis.
2. Primary idiopathic dermatomyositis.
3. Polymyositis (or dermatomyositis) associated with neoplasm.
4. Childhood polymyositis associated with necrotizing vasculitis.
5. Polymyositis (or dermatomyositis) associated with underlying collagen-vascular disease (overlap syndromes exist when independent criteria are met for two separate processes).

E. Clinical Features of Polymyositis.

1. Symmetrical proximal weakness progressing over weeks to months.
   a. Distal strength relatively maintained.
   b. Predilection of neck flexor > neck extensor weakness.
   c. Early weakness disproportionate to atrophy, although atrophy may become severe related to decreased muscle mass.
2. Decline in strength associated with muscle breakdown (150 g/d).
3. Recovery associated with regeneration.

F. Laboratory Evaluation.

1. CK, CBC, absolute eosinophil count, electrolytes, ANA, ESR (limited value, except in overlap), TFT, urinalysis (myoglobin), CXR.
2. Ischemic exercise.

G. Electrodiagnostic Evaluation.

1. General evaluation as per weakness protocol (Table I).
2. Additional studies as per myopathy/myositis protocol (Table II).
3. General comments.
   a. Majority of findings symmetric and most prominent in proximal muscles.
   b. The only expected NCV abnormality is a borderline-low or reduced CMAP amplitude in proximal muscles.
   c. Needle EMG abnormalities most prominent in proximal muscles, particularly paraspinal.
   d. Classic EMG findings:
      (1) Abnormal insertional activity with fibrillation potentials, positive waves, complex repetitive discharges. Most prominent abnormalities proximal (e.g. paraspinal).
      (2) Abnormal MUAP recruitment (rapid recruitment with minimal effort).
      (3) MUAPs may be of reduced amplitude and duration, with an increased % polyphasia.
      (4) In chronic myopathy, MUAPs may be of increased amplitude, highly polyphasic, and of long duration.
      (5) Increased jitter (using conventional concentric electrode) suggests active disease.
II. Steroid Myopathy

A. Clinically resembles inflammatory myopathy.
   1. No CK elevation.
   2. Less systemic manifestations.
   3. Cushinoid appearance.

B. Electromechanical Uncoupling.
   2. No fibrillation potentials (in differentiating inadequately treated PM from steroid myopathy, presence or absence of fibrillation may be helpful.
   3. MUAPs often small (fiber atrophy) but usually not polyphasic.

III. Inclusion Body Myositis

A. A degenerative myopathy of unknown etiology that resembles PM/DM but often has unusual distribution.
   1. Sometimes distal > proximal.
   2. Good grip but unable to extend fingers.
   3. May resemble motoneuron disease.

B. Comparison to DM and polymyositis.

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<tr>
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<th>IBM</th>
<th>DM</th>
<th>PM</th>
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<td>1. M:F</td>
<td>4:1</td>
<td>1:2</td>
<td>1:1</td>
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<td>2. Onset</td>
<td>50-70</td>
<td>20-80</td>
<td>30-60</td>
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<td>3. Course</td>
<td>Chronic</td>
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<td>4. CK</td>
<td>Slight</td>
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<td>5. Rx</td>
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<td>6. Malignancy</td>
<td>None</td>
<td>20%</td>
<td>?</td>
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<td>7. Biopsy</td>
<td>Inclusions (not viral)</td>
<td>Blood vessel involvement</td>
<td>Lymphocyte mediated damage</td>
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IV. McArdles Disease

A. Phosphorylase deficiency.

B. Characteristic history:
   1. Progressive weakness age 40-50; slow onset even 10 years before.
   2. Painful cramps.
   3. Clinical findings similar to PM (proximal > distal).
   4. Never athletic.
   5. Prior complaints of muscle stiffness.
   6. May or may not have had episodes of dark urine (myoglobinuria).

C. Electromyography.
   1. Borderline-low CMAP amplitudes.
   2. No decrement.
   3. Increased recruitment (myopathic units).
4. Fibrillation potentials may have proximal predilection, but para-
spinal muscles may show less involvement.

D. Diagnostic Muscle Biopsy.

V. Periodic Paralysis

A. Hypokalemic.

1. Inheritance.
   a. Usually AD, occasionally sporadic.
   b. Males > females, 3:1 ratio.
   c. Incidence 8x10.

2. Clinical manifestations.
   a. Onset late childhood or adolescence.
   b. Episodes are initially infrequent but may eventually recur
daily.
   c. Typical attack.
      (1) Occurrence: during sleep, after strenuous exercise,
      following high carbohydrate meal.
      (2) Duration: 1-96 hours, average 12 hours.
      (3) Frequency: 1-200 per year.
      (4) Distribution of paralysis: limbs > trunk, proximal >
distal, LE > UE, rarely, see eyes, face, tongue, pharynx or
diaphragm involved.
      (5) Myotonic lid lag—other myotonia is rare.

3. Laboratory findings.
   a. Hypokalemia during attacks.
   b. Urinary retention of sodium, potassium, chloride and water.

4. Electrocardiogram.
   a. Sinus bradycardia.
   b. Signs of hypokalemia: U-waves in leads II, V-2, V-3 and V-4;
progressive flattening of T-waves and depression of ST segment.

5. EMG.
   a. During severe paralytic episodes:
      (1) Reduction in recruitment.
      (2) Decreased muscle excitability to electrical stimulation
      with absence of muscle action potentials.
   b. During less severe cases: decreased amplitude of compound
muscle action potential proportional to degree of weakness.
   c. Repetitive nerve stimulation at 10-25/sec may produce mild
increment in mildly weak muscles. No change in marked weakness.

6. Pathologic Changes.
   1. Nervous system is entirely normal.
   2. Muscle fibers:
      (a) Relatively large; similar size.
      (b) Vacuolization of sarcoplasm.

B. Thyrotoxic Periodic Paralysis.

1. Inheritance.
   a. Autosomal dominance.
c. Orientals, especially Japanese.

2. Clinical Manifestations.
   a. Similar in most respects to hypokalemic periodic paralysis and
      associated with hypokalemia.
   c. Greater liability to cardiac irregularity.

3. Treatment.
   a. Acute therapy: KCl; propranolol.
   b. Restoration of euthyroid state, via medical or radioactive
      suppression or surgical ablation of thyroid.

C. Primary Potassium-sensitive periodic paralysis (hyperkalemic periodic
paralysis, Adynamia Episodica Hereditaria of Gamstorp).

1. Inheritance.
   a. Autosomal dominant.
   b. Affects males and females equally.
   c. Incidence: $2 \times 10^{-6}$.

2. Clinical manifestations.
   a. Onset: infancy or early childhood (average-age 6).
   b. Sudden weakness following a short period of rest after exercise,
      exposure to cold, fasting, emotional upset, or administration of
      potassium.
   a. Duration: typically about one hour.
   b. Frequency: once per week; usually during the day. May decrease
      with age.
   c. Aching of muscles, circumoral tingling and paresthesias.
   d. Myotonia: lid lag; percussion myotonia.
   e. Distribution: paresis begins in LEs and low back, spreads to
      UEs and shoulders.

3. Laboratory Findings.
   a. Modest rise in serum K+; may remain within normal range.
   b. No reduction in renal excretion of K+.

4. EMG.
   a. Between attacks: increased insertional activity, CRDs and
      myotonic discharges.
   b. During an attack: increased myotonic discharges and muscle
      irritability but reversible inexcitability of the muscle with
      electrical stimulation.
   c. Abundant low amplitude, short duration MUAPs with early recruit-
      ment.
   d. With prominent myotonia, repetitive stimulation causes a decre-
      ment (enhanced with cooling).

D. Normokalemic Periodic Paralysis (possibly a variant of Potassium-sensi-
tive periodic paralysis).

1. Inheritance.
   a. Autosomal dominant.
   b. Affects males and females equally (complete penetrance).

2. Clinical manifestations.
   a. Onset: first decade, frequently as infants presenting with
      flaccid quadriplegia and normal serum K+.
   b. Frequency of attacks: every 1-3 months.
c. Duration: 2 days to 3 weeks.
d. Provoking factors.
   (1) Rest after exertion.
   (2) Sitting still.
   (3) Sleeping late.
   (4) Alcohol.
   (5) Cold.
   (6) Emotional stress.
e. Severity: often complete paralysis including jaw and cough reflex.
f. Awaken paralyzed.
3. Laboratory findings.
a. Normal serum potassium.
b. Increased sodium excretion and potassium retention during attacks.
4. EMG.
a. Reduced duration and amplitude of MUAPs.
b. No spontaneous myotonic discharges.

E. Paramyotonia with Periodic Paralysis.

1. Inheritance.
a. Autosomal dominant inheritance.
b. Affects both sexes equally.
2. Clinical manifestations.
a. Paradoxical myotonia (i.e., myotonia worse with repeated activity).
b. Onset: birth or early childhood.
c. Does not improve with age.
d. Markedly exacerbated by cold with stiffness of tongue, eyelid, face and extremity muscles.
e. Occasional generalized weakness associated with exposure to cold.
f. Frequent muscle hypertrophy.
3. Types of Paramyotonia.
a. Paramyotonia Congenita of Van Eulenberg:
   (1) Associated with hypokalemia.
   (2) Provoked by exercise.
   (3) Attacks often severe, lasting 6-24 hours.
b. Paralysis Periodica Paramyotonia.
   (1) Associated with hyperkalemia.
   (2) Attacks usually mild, lasting 1/2-6 hours.
4. EMG.
a. Myotonic discharges with myopathic MUAP.
b. Decrementing response to repetitive stimulation.
c. During episodes of paralysis, stimulation of nerve fails to elicit muscle action potentials.
d. Nerve conduction studies are normal between attacks.
TABLE I

Weakness Protocol

A. Conduction Studies.

1. Sural sensory (ankle); stimulate 14 cm proximal to recording electrode.

2. If sural equivocal or technically difficult:
   a. Opposite sural
   b. Medial sensory

3. Ulnar motor (hypothenar); stimulate at wrist and elbow and record F-response latency. Repetitive supramaximal stimulation at wrist (2 Hz x 4 stimuli) before and immediately after 5 seconds of maximal voluntary exercise. (Fingers should be restrained or taped together).

4. If proximal weakness predominates: Musculocutaneous motor (biceps brachii); stimulate at axilla with repetitive supramaximal stimulation as in item 3.

5. If legs weaker: Peroneal nerve (EDB); stimulate at ankle. Record F-response latency and repetitive stimulation.

6. Abnormality in any of the above requires further evaluation of suspected disorder (e.g., polyradiculopathy, myopathy, neuromuscular transmission abnormality, etc).

B. Needle Examination.

1. Examine selected distal and proximal muscles, in upper and lower limbs, including paraspinal.

2. For example, biceps brachii, first dorsal interosseous (hand); vastus lateralis; anterior tibialis; medial gastrocnemius; lumbar paraspinal muscles.
## TABLE II

Myopathy/Myositis Protocol

(Supplement to Weakness Protocol)

A. **Conduction Studies.**

1. Conduction studies as indicated under Weakness Protocol.

2. Musculocutaneous motor (biceps); stimulating at axilla including repetitive supramaximal stimulation (2 Hz x 4 stimuli).

3. Spinal accessory motor (trapezius) stimulating at posterior border of sternomastoid muscle.

B. **Needle Examination.**

1. Primarily unilateral examination, although one or two muscles may be examined on the opposite side to demonstrate symmetry as long as they are not likely muscles for biopsy.

2. Biceps brachii, triceps, first dorsal interosseous (hand), infraspinatus, vastus lateralis, anterior tibial, and lumbar paraspinal muscles.

3. If weakness is focal or selective, involved muscles should be sampled; e.g., brachioradialis, sternocleidomastoid, facial.

4. If findings are uncertain or unusual, quantitative MUAP measurements should be obtained from a proximal muscle (biceps brachii).
CONGENITAL/STORAGE MYOPATHIES

I. General Characteristics

A. Common Clinical Findings
   1. Marked generalized hypotonia at birth.
   2. Skeletal abnormalities - high arched palate, long face, congenital
      hip dislocation, pes cavus, contractures.
   3. Delayed motor milestones - never able to run or jump.
   4. No or slow progression.
   5. Thinness or decreased muscle bulk, decreased or absent muscle
      stretch reflexes (MSR).
   6. Widespread muscle weakness - usually worse proximally.
   7. Occasionally facial weakness and extra-ocular muscle involvement.

B. Laboratory
   1. CPK - normal or mild increase.
   2. EMG - short duration, small amplitude, polyphasic potentials with
      normal motor nerve conduction velocity and possible decreased
      amplitude.
   3. Muscle biopsy - Type I fiber predominance or Type II fiber paucity.

II. Congenital Myopathies

A. Central Core - Shy, Magee, 1956 - autosomal dominant or sporadic.
   1. Clinical Features.
      a. Hypotonia, marked delay in motor milestones.
      b. Weak - legs > arms; proximal > distal; facial weakness occasion-
         ally.
      c. Skeletal abnormalities - kyphoscoliosis, lumbar lordosis, pes
         planus, pes cavus; congenital hip dislocation common.
      d. MSRs normal, decreased or absent.
      e. Progression - mild; persists into adult life; associated with
         malignant hyperthermia.
   2. Laboratory Evaluation.
      a. CPK - normal.
      b. Urinary - creatine increased; creatinine decreased.
   3. Electrodagnostic Evaluation - normal or slight changes only.
      a. Nerve conduction - normal or decreased motor amplitude; normal or
      mildly slowed CV,
      b. EMG - normal, short duration, long duration polyphasic units
         have all been described.
      a. Cores - central ( or peripheral); devoid of oxidative enzyme and
         phosphorylase and glycogen; decreased mitochondria.
      b. Type I fiber predominance with cores usually seen in Type I
         fibers.
      c. May be multiple cores in a single fiber.
B. **Nemaline** - Shy, Engel, Somers, Wanko, 1963 - Most sporadic, some autosomal dominant or autosomal recessive.

1. Clinical Features.
   a. Decreased fetal movements - floppy at birth; respiratory distress, poor suck and swallow; may be severe - infant death.
   c. Weak - proximal, axial, ankle dorsiflexors.
   d. MSRs - decreased or absent.
   e. Progression - often slowly progressive.

2. Laboratory Evaluation.
   a. CPK - normal or rarely increased.

3. Electrodiagnostic Evaluation.
   a. Nerve conduction - normal or decreased motor nerve evoked amplitude.
   b. EMG - rapid recruitment or short duration, polyphasic, small amplitude potentials.

   a. Rods - subsarcolemmal and central; red with trichrome stain; arranged in palisades or irregular; actin; Z-band material; are nonspecific.
   b. Type I fiber predominance.
   c. Rods, seen near vesicular nuclei with prominent nucleoli.
   d. N.b., nemaline rods are not specific for the congenital myopathy; may see with CVD, central core disease, tenotomy, glycosylation.

C. **Myotubular (centronuclear)** - Spiro, Shy, Gonatas, 1966 - X-linked recessive (Dutch)/Autosomal dominant; genetically heterogeneous.

1. Clinical Features.
   a. 2/3 hypotonic at birth; 1/3 later onset - childhood.
   b. Extra-ocular and facial weakness.
   c. Proximal and axial weakness > distal.
   d. MSRs - absent.
   e. Progression - little or none; X-linked cases severe - death in infancy.

2. Laboratory Evaluation.
   a. CPK - normal or slight increase in older patients.

3. Electrodiagnostic Evaluation.
   a. Nerve conduction - normal
   b. EMG - abnormal spontaneous activity with fibrillation potentials and positive waves. Small, short duration, polyphasic motor units.

   a. Type I fiber atrophy with central nuclei in both fiber types.
   b. Nuclei surrounded by clear areas - resemble (but are not) fetal myotubes at ten weeks after conception. Negative ATPase reaction; increased oxidative enzyme stain.
D. Mitochondrial Myopathies - A variety of disorders that have in common mitochondrial abnormalities, including abundant mitochondria, bizarrely shaped mitochondria, giant mitochondria, and mitochondria with inclusion bodies.

1. Muscle Biopsy.
   a. "Ragged red fibers". Increased oxidative enzyme activity corresponding to mitochondrial aggregates in the subsarcolemmal space; may be inclusions, lipid droplets.
   b. Usually Type I fiber involvement predominates.
   c. Also abnormal mitochondria in cerebellum, liver, etc.

2. Clinical features usually include progressive external ophthalmoplegia (PEO); part of many diverse syndromes, either familial or sporadic. Two common forms:
   a. Ocular or ocular pharyngeal myopathies.
      (1) starts with unilateral of bilateral ptosis, followed by limitation of ocular movements (and sometimes pharyngeal movement) and progressive, mild extremity weakness.
      (2) autosomal dominant; predilection in French-Canadian kinship for oculopharyngeal myopathy.
      (3) may resemble oculobulbar myasthenia gravis.
   b. Kearns-Sayre syndrome; described 1958; apparent lack of genetic transmission.
      (1) main features; PEO, pigmentary retinopathy, complete heart block, onset < 20 years of age.
      (2) short stature, neurosensory hearing loss, MR, CSF protein > 100 mg/dl, EEG abnormal, calcifications of CT (? hypoparathyroidism).

3. Electrodiagnostic Evaluation.
   a. Nerve conduction. Facial CMAP amplitude reduced (distinguishing this from MG), without evidence of a decremental response.
   b. Mild myopathic changes in proximal muscles.
   c. Normal jitter; increased muscle fiber density.
   d. ? of borderline-low sural amplitude in some patients.

E. Congenital Fiber Type Disproportion - Brooke, 1973; genetics unclear, ? AR or AD.

1. Clinical Features.
   a. Present at birth or shortly after with hypotonia and weakness.
   b. Muscle contractures, kyphoscoliosis, hip dislocations, pes cavus, and high arched palate.
   c. Weak - proximal = distal; legs > arms.
   d. Course - reaches worst point by age 2 then improves.

2. Laboratory Evaluation.
   a. CPK - occasionally elevated.

3. Electrodiagnostic Evaluation.
   b. EMG - usually normal or mildly myopathic; rarely see spontaneous activity.

   a. Small Type I fibers and large Type II fibers.
   b. Type I fiber predominance.
c. Occasionally - moth-eaten fibers, internal nuclei.

F. Other - multicore, finger print, reducing body, sarcotubular, zebra body.

1. Benign Congenital Hypotonia.
   a. Hypotonic at birth or soon after.
   b. Retain active limb movements and DTRs.
   c. Delayed motor development but improves.
   d. Enzymes, biopsy, EMG all normal.

III. Glycogen Storage Diseases

A. Type II Infantile Glycogenosis - Pompe's Disease (acid maltase deficiency) - deficiency of alpha-1,4-glucosidase - autosomal recessive.

1. Clinical features of infantile, generalized form.
   a. Onset few months after birth.
   b. Weakness, marked hypotonia, poor suck, weak cry.
   c. Cardiomegaly, hepatomegaly, enlarged tongue.
   d. May involve anterior horn cells.
   e. Severe - most die in first year of life; childhood onset - most die by end of second decade.

2. Laboratory Evaluation.
   a. EKG - short PR interval, high QRS, LVH.
   b. CPI - increased.

3. Electrodiagnostic Evaluation.
   b. Widespread spontaneous activity; may see myotonic discharges, abundant complex repetitive discharges.
   c. Small, short duration, polyphasic motor unit potentials with rapid recruitment.

   a. Massive deposits of glycogen.
   b. Type I fibers most involved - vacuolar myopathy.

B. Type II Adult Glycogenosis (Acid Maltase Deficiency)

1. Clinical Features.
   b. Slowly progressive - proximal > distal - mimics polymyositis or limb-girdle dystrophy.
   c. May present with respiratory difficulty (35%) and all eventually die of respiratory failure.
   d. Cardiac muscle spared.

2. Laboratory Evaluation.
   a. CPK - increased < 10 times upper limit of normal

3. Electrodiagnostic Evaluation.
   a. Same as infantile form but less widespread; involves proximal muscles only. Abundant complex repetitive discharges.

4. Muscle Biopsy - as above.
C. Type III Glycogenosis - Debrancher Enzyme Deficiency - amyo-1,6-glucodlsacase deficiency, autosomal recessive.

1. Clinical Features.
   a. Infants - hypotonia and weakness, hypoglycemia, ketosis.
   b. Children - psychomotor retardation, hepatomegaly.
   c. Weakness - early fatigue
   d. Improves over time; usually benign disease of childhood.

2. Laboratory Evaluation.
   a. CKK - markedly increased.
   b. Ischemic exercise test negative.
   c. Glucose challenge - rise in blood lactate.
   d. Glucagon challenge after fast - no elevation of blood glucose.

3. Electrodiagnostic Evaluation.
   a. EMG - small, polyphasic, short duration motor units with abundant fibrillations and positive waves.

   a. Excessive glycogen deposition - subsarcolemmal.

D. Type V Glycogenosis - McArdle's (muscle phosphorylase deficiency) autosomal recessive.

1. Clinical Features.
   a. Progressive weakness - age 40-50 or as early as late 20's.
   b. Muscle pain, weakness, stiffness after moderate exercise, exercise "intolerance".
   c. Weak - proximal > distal resembling polymyositis (but may lack neck flexor predilection).
   d. Occasional myoglobinuria (dark urine).
   e. Forearm ischemia - electrically silent muscle contracture (not cramp).

2. Laboratory Evaluation.
   a. Ischemic exercise test - no rise in venous lactate levels after exercise.
   b. Enzymes - mild elevation at rest; increased after exercise.

3. Electrodiagnostic Evaluation.
   a. Nerve conduction - normal (proximal amplitudes not reduced).
   b. Repetitive stimulation - may show decrement - not consistently reported.
   c. EMG - may show some spontaneous activity at rest; contracture is electrically silent; motor units myopathic. Distribution atypical for inflammatory myopathy.

   a. Subsarcolemmal PAS-positive blebs.
   b. Absence of phosphorylase.

E. Type IV Glycogenosis - Branching Enzyme Deficiency - amyo-1,4-transglucosidase deficiency - autosomal recessive.

1. Clinical Features.
   a. Children die by age 4.
   b. Hypotonia, atrophic extremities, absent MSRs.
   c. Splenomegaly, hepatomegaly.
2. Electrodiagnostic Evaluation.
   a. "Myopathic".
   a. PAS positive material in muscle.

IV. Lipid Storage Diseases

A. Carnitine Deficiency - autosomal recessive.
   1. Clinical Features.
      a. Triad = progressive muscle weakness, lipid excess in muscle, and
         muscle carnitine deficiency.
      b. Onset - age 18 months to 38 years.
      c. Slowly progressive, proximal > distal.
      d. Hepatic insufficiency.
      e. Overlap with mitochondrial myopathies.
   2. Laboratory Evaluation.
      a. CPK - increased.
      b. Serum carnitine normal; muscle carnitine low.
   3. Electrodiagnostic Evaluation.
      a. EMG myopathic with spontaneous activity.
      b. Neuropathy may develop.
      a. Excess lipid droplets - Type I fibers.

B. Carnitine Palmityltransferase Deficiency - no lipid excess in muscle.
   Autosomal recessive, painful muscle cramps, onset in adolescence, weak
   after exercise with normal strength at rest; rhabdomyolysis with renal
   failure.
ABSTRACT: The presence of myotonia and paramyotonia on clinical examination and of myotonic discharges during electrodiagnostic (EDX) studies are important for the diagnosis of certain neuromuscular conditions. The increased muscle activity of myotonia produces muscle stiffness that improves with repeated activity. Paramyotonia produces a similar symptom, but the stiffness paradoxically increases with activity. Myotonic discharges are easily recognized on EDX testing because of the waxing and waning discharges. Myotonic dystrophy and myotonia congenita share both clinical and electrodiagnostic myotonia. Paramyotonia congenita and hyperkalemic periodic paralysis are associated with clinical paramyotonia and electrical myotonia. Acid maltase deficiency often produces myotonic potentials without clinical evidence of myotonia or paramyotonia. The differential diagnosis of these myotonic disorders is discussed.


DIFFERENTIAL DIAGNOSIS OF MYOTONIC DISORDERS

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Diff erential Diagnosis of Myotonic Disorders

Myotonia rarely presents clinically in isolation. It is often an additional clue to consider in a constellation of more prominent signs and symptoms associated with a disease such as myotonic dystrophy. On electromyographic (EMG) examination, myotonia presents frequently when unexpected either in apparent isolation or as part of a difficult neuromuscular case. This EMG finding often becomes a key element in the diagnosis. Myotonic potentials are one of the most specific potentials recognized on needle EMG. The aim of this review is to aid the reader in the differential diagnosis of myotonic disorders (Table 1). Genetic tests are available for many of these disorders, although in some cases they are only available in specialized laboratories.

Recognizing Myotonia Clinically. Myotonia is defined clinically as the occurrence of “delayed relaxation of muscle after voluntary contraction or percussion.”1 Patients with myotonia often complain of muscle stiffness that improves with repeated use of the muscle, the so-called “warm-up phenomenon.” On examination, myotonia may be apparent from the first handshake, presenting with a delayed release of the hand.8,31 This can also be appreciated by asking the patient to repeatedly grip and release the examiner’s fingers. Another helpful maneuver is to ask the patient to repeatedly close the eyes tightly. After the first closure, there may be lag in opening the eyes, but this will improve with repeated efforts (Fig. 1A). Patients with paramyotonia also complain of muscle stiffness, but the stiffness often is associated with exercise rather than improving with exercise, i.e., there is no warm-up phenomenon (Fig. 1B). Myotonia may be provoked by percussion of muscle, e.g., by percussion of the thenar eminence. The muscle stiffens, often adducting the thumb (Figs. 2, 3). Both paramyotonia and myotonia are associated with myotonic discharges on EMG. Myotonia and paramyotonia are usually not difficult to distinguish from muscle cramps that present with a sudden and painful focal muscle contracture. Myotonia and paramyotonia are typically painless.

Recognizing Myotonia on Electrodiagnostic Testing. Myotonia is often easier to define on EMG examination than on neurological examination (Fig. 4). Myotonic potentials are caused by chronically depolarized muscle membranes. They are spontaneous, painless discharges with a waxing and waning of both

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Abbreviations: CMAP, compound muscle action potential; CRD, complex repetitive discharge; EDX, electrodiagnostic; EMG, electromyographic; HyperKPP, hyperkalemic periodic paralysis; HypoKPP, hypokalemic periodic paralysis

Key words: myotonia; myotonia congenita; myotonic dystrophy; paramyotonia; periodic paralysis; Schwartz–Jampel syndrome

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amplitude and frequency, producing a characteristic audio profile often compared to a dive-bomber.\textsuperscript{1,2,15} These potentials are repetitive discharges with a rate of 20–80 Hz and are of two types: (1) biphasic spike potentials less than 5 ms in duration that resemble fibrillation potentials, and (2) positive waves, 5–20 ms in duration, that resemble positive sharp waves. A single myotonic potential may look and sound exactly like a fibrillation potential or positive sharp wave, but it is the multiple runs with the characteristic waxing and waning that distinguish the discharges as myotonic potentials. Needle insertion and movement, muscle contraction, or tapping the muscle will often provoke the myotonia. Although single myotonic potentials can resemble fibrillations or positive sharp waves, myotonic potentials are rarely confused with other discharges.

Waning discharges are easily distinguished from myotonic discharges because they lack the characteristic waxing that is part of the classic definition. However, these potentials may represent a subset of myotonia. Logigian et al.\textsuperscript{21} found that 4 of 17 patients with genetically confirmed proximal myotonic myopathy (DM2) had only waning discharges without evidence of classic myotonic discharges. As expected, all of the 16 patients with myotonic dystrophy (DM1) in their study had classic myotonic discharges.

Myokymic potentials are spontaneous potentials that have rhythmic firing of grouped motor unit action potentials. Typically the discharges are in groups of 2–10 at a frequency of 2–60 Hz, with a sound like marching soldiers. Neuromyotonic discharges are secondary to continuous muscle activity firing at 100–300 Hz. The potentials do not wax and wane, but may abruptly decrease in amplitude, producing a “ping” sound. Neuromyotonic discharges are not affected by voluntary activity, sleep, or anesthesia, but may be interrupted by a local blockade of peripheral nerve, the presumed generator of the discharges. Tapping on the nerve provokes neuromyotonia. Complex repetitive discharges (CRDs) are repetitive complex potentials with a sudden onset and cessation, resembling the sound of a motorboat or motorcycle. These potentials do not wax and wane like myotonia, although the waveform shape, amplitude, and frequency may change during discharge. Cramps are rarely captured on EMG, but may be distinguished by their sudden painful contraction accompanied by high-frequency discharges, which can be up to 150 Hz. The discharge frequency and the number of motor unit discharges increase gradually during the development of the cramp, and subside gradually as the cramp fades.

### Table 1. Differential diagnosis of myotonic disorders.

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**FIGURE 1. (A)** Myotonia of the orbicularis oculi. In this series of photographs the patient is initially looking straight ahead (left), then forcibly closing her eyes (center), and finally is attempting to open her eyes as wide as possible (right). Note that the patient is unable to open her eyes because of myotonia of the orbicularis oculi muscle. This figure demonstrates classic myotonia, in which the myotonia is most severe after the first contraction. If the patient had repeated the forcible eye closures the myotonia would have “warmed up” or lessened with repeated closures. (B) Paradoxical orbicularis oculi myotonia. In this series of photographs the patient has been asked to forcibly close her eyes and then to open them fully as quickly as possible. Each photograph was taken immediately after the patient was told to open her eyes. After the first forcible eye closure (left) the patient has no difficulty in opening her eyes. Note the progressive difficulty in fully opening her eyes. After the fourth forcible eye closure (right) the patient is unable to open her eyes. (Reproduced with permission from Pourmand R, editor: Neuromuscular diseases: expert clinicians’ views. Boston: Elsevier; 2001. © Elsevier.)
Electrodiagnostic Studies That May Aid Differential Diagnosis.

Myotonia is the most useful finding on standard EMG and nerve conduction examinations. However, several specialized tests may also aid in making or confirming the diagnosis of a disorder associated with myotonia: repetitive stimulation, the “short” and “long” exercise tests, and the provocative cold test.

Repetitive Stimulation. It has long been recognized that in myotonic syndromes repetitive stimulation at 5–10 Hz leads to a decrement in the compound muscle action potential (CMAP). This decrement has been attributed to transient inexcitability of the muscle membrane. Although consistent with a myotonic disorder, this finding is not specific.

Exercise Testing. In the “short” exercise test the patient is asked to exercise briefly (10–30 s). A CMAP is recorded and compared with the CMAP recorded prior to exercise. In patients with DM1, this brief period of exercise causes a decrease in the CMAP, whereas in DM2 there is no change.

In the “long” exercise test both the period of exercise and the subsequent time of recording are “long.” As first described by McManis et al., the CMAP is tested over a 30–45-min period following 5 min of sustained exercise. In all forms of periodic paralysis, both genetic and metabolic (e.g., thyro-toxic periodic paralysis), there is a decrease in CMAP over time. The CMAP decrement in patients with hypokalemic periodic paralysis (HypoKPP) and hyperkalemic periodic paralysis (HyperKPP) differs qualitatively from the decrement in those with paramyotonia congenita. In paramyotonia congenita, there is a rapid decline in CMAP amplitude followed by a slow increase back to baseline over the next 60 min. In HypoKPP and HyperKPP, the amplitude increases immediately after exercise and then declines slowly over the course of 15–30 min. Patients with myotonia congenita also may show a decrement on the exercise test, but this is not consistent.

Cooling Test. Cold provokes the symptom of weakness in patients with paramyotonia congenita. This cold effect may be reproduced in the EDX laboratory by recording the CMAP for an individual muscle before and after cooling the limb for 15–30 min at 15°C. The CMAP decrement in paramyotonia congenita patients is typically greater than 75%. Cooling may initially provoke myotonia in pa-
patients with paramyotonia congenita, but after prolonged cooling there will be a decrease in electrical activity.

**DISORDERS WITH BOTH CLINICAL AND ELECTRICAL MYOTONIA**

**Myotonic Dystrophy.** Myotonia congenita, DM1, and DM2 all share prominent clinical classic myotonia and electrical myotonia.

The best-known myotonic disorder is DM1. The characteristics of this CTG-repeat disorder include cranial muscle wasting/weakness and distal-predominant limb weakness. The small temporalis muscles, ptosis, and a long, lean face produce a characteristic facial appearance. Cranial muscle abnormalities may also include dysphagia, dysarthria, and sometimes eye-movement abnormalities. The limb muscle weakness affects distal muscles to a greater degree than proximal muscles. Along with inclusion-body myositis, this muscle disease has the distinction of prominent finger-flexor weakness. Reflexes are depressed in proportion to weakness. The rate of disease progression is slow; longevity is not affected in many patients, but overall life expectancy is reduced secondary to respiratory diseases, cardiovascular diseases, neoplasms, and sudden deaths presumably from cardiac arrhythmias. The manifestations outside of the nervous system are also characteristic and include frontal balding, cataracts, and cardiac abnormalities. Cataracts eventually develop in nearly all patients. Frontal baldness is also universal. Diabetes is more common in DM1, although it is not seen in all patients. Cardiac abnormalities are apparent on echocardiogram with evidence of first-degree heart block or bundle branch block.

Clinically, the myotonia is usually simple to demonstrate both by percussion and by asking the patient to perform physical tasks such as squeezing a hand or opening the eyes. Sometimes the myotonic grip of a parent is a hint in diagnosing childhood myotonic dystrophy, which may be more severe in children because of the phenomenon of anticipation whereby triplet repeat instability in the gametes leads to an increased expansion of the triplet repeat. In DM1 this may be pronounced, with a nearly asymptomatic mother giving birth to a child with a greatly expanded CTG repeat and congenital myotonic dystrophy, manifested by developmental delay and severe limb weakness.

The diagnosis is confirmed by genetic analysis, which is performed widely. Disease onset varies from infancy to young adulthood. Incidence is 12–14 per 100,000.

**Proximal Myotonic Myopathy.** DM2, known as proximal myotonic myopathy in Europe, is another triplet repeat disorder that shares many of the features of myotonic dystrophy. The CCTG expansion mutation in intron 1 of the zinc finger protein 9 gene causes DM2. DM2 is an adult-onset muscular dystrophy associated with myotonia, proximal weakness, cataracts, cardiac arrhythmias, insulin resistance, and other multisystemic features of adult-onset DM1. The major distinction of DM2 is the later onset and predominant proximal weakness. Myotonia is also prominent in this disorder both clinically and on EMG. Congenital DM2 does not occur.

**Myotonia Congenita.** Myotonia is the prominent clinical symptom of myotonia congenita. The severe classic myotonia causes stiffness especially when first starting an activity. Once these patients have warmed up, they may perform activities at a normal or advanced level, including competitive sports. The disorder presents in early childhood and may be described by the parents as weakness and clumsiness in addition to or instead of stiffness. Despite the reported difficulties, affected children appear “athletic,” with increased muscle bulk, presumably because of the sustained muscle activity. The myotonic symptoms often improve with age but do not completely disappear.

Myotonia congenita is secondary to a mutation in the CICN1 chloride channel, and may be transmitted either dominantly or recessively. Curiously, a particular mutation may be recessive in some families and dominant in others. The reasons for this are not clear. Recessively inherited myotonia congenita is referred to as Becker’s myotonia congenita and dominantly inherited disease as Thomsen’s myotonia congenita. The chloride channel defect leads to an elevation of the resting membrane potential and thus a tendency toward repeated muscle contractions. Genetic testing for myotonia congenita may be performed in some specialized centers, many of which are best located at www.genetests.org.
Schwartz–Jampel Syndrome. Schwartz–Jampel syndrome, also known as chondrodystrophic myotonia, is associated with severe myotonia as well as short stature, muscular hypertrophy, diffuse bone disease, ocular and facial abnormalities, and joint contractures.27,43 Muscle stiffness is one of the first symptoms that presents in childhood. There is no warm-up phenomenon for the myotonia. The EMG findings of this rare disorder more closely resemble neuromyotonia or CRDs. Unlike typical myotonia, the repetitive, high-frequency discharges in this disorder do not wax and wane. Schwartz–Jampel syndrome is caused by loss-of-function mutation in the HSPG2 gene, which encodes perlecan, a heparan sulfate proteoglycan secreted into basement membranes.26

DISORDERS WITH CLINICAL PARAMYOTONIA AND ELECTRICAL MYOTONIA

Both HyperKPP and paramyotonia congenita are characterized by attacks of weakness and paramyotonia. Both of these dominantly inherited diseases present in infancy or childhood and are associated with sodium channel mutations. In HyperKPP the attacks of weakness dominate the clinical picture. These attacks are often provoked by resting after exercise, skipping meals, or eating foods containing a high potassium content.10,25,34 The attacks occur relatively frequently (one per day to one per week), are short-lived (minutes to hours), and usually are not completely disabling. Some patients complain of stiffness with exercise and demonstrate paramyotonia on examination. EMG studies show myotonia in ~75% of HyperKPP patients.25 During the attack, the serum potassium level is often elevated. Muscle biopsy shows a vacuolar myopathy. Patients with paramyotonia congenita mainly complain of stiffness, but also have attacks similar to those of HyperKPP. One of the major factors provoking stiffness in these patients is cold temperature. EMG demonstrates myotonia in all paramyotonia congenita patients. In both HyperKPP and paramyotonia congenita the paramyotonia and attacks of weakness decrease in middle age. In cases where periodic paralysis or paramyotonia congenita are being questioned, the exercise test and cooling test may be particularly helpful. Nearly all cases of periodic paralysis are associated with mild to moderate weakness in later adult life.6,18,19,25

Both HyperKPP and paramyotonia congenita are secondary to mutations in the sodium-channel SCN4A gene. T704M and M1592V are the most common mutations in HyperKPP. In paramyotonia congenita, R1448C and T1313M are the most common residues affected. These mutations cause a chronically depolarized muscle membrane. Genetic testing is available for these disorders in specialized centers.

Potassium-aggravated myotonia is also linked to a sodium-channel mutation.32 In this disorder, potassium administration “aggravates” or brings on myotonia. These patients also experience episodic myotonia. They do not have attacks of weakness. The myotonia is not sensitive to cold and is most prominent ~20 minutes after exercise.

When considering HyperKPP or paramyotonia congenita, the main differential consideration is HypoKPP,10,34 which does not show any paramyotonia clinically or myotonia on EMG.25 Attacks of weakness are more prolonged in HypoKPP (lasting hours to days) and are more severe, often leaving the patient unable to walk. Inherited forms of HypoKPP are secondary to calcium-channel mutations. Metabolic causes are most often secondary to hyperthyroidism, although chronic potassium wasting (e.g., renal tubular acidosis) may also cause episodic muscle weakness. Andersen–Tawil syndrome, which is associated with mutations in KCNJ2,30 consists of the triad of cardiac arrhythmias, dysmorphic features, and periodic paralysis; there is no myotonia.

MYOTONIA ONLY ON EMG, NOT PHYSICAL EXAMINATION

Myotonia on clinical examination is always associated with myotonic discharges on EMG. The converse is also nearly always true, with one notable exception. Acid maltase disease consistently shows myotonic potentials on EMG with absent clinical myotonia.28,35 Adult-onset acid maltase deficiency (glycogenosis type II) is a glycogen storage disease that presents with truncal and proximal limb weakness that is slowly progressive over the years. Death is usually caused by weakness of respiratory muscles. Occasionally, the presenting weakness is diaphragmatic. Unlike certain other glycogen storage diseases, the heart and liver are not enlarged. Serum creatine kinase levels are increased. EMG shows evidence of multiple spontaneous discharges including myotonic discharges, fibrillation potentials, positive sharp waves, CRDs, and small motor unit action potentials. Diagnosis is confirmed by muscle biopsy with periodic acid–Schiff positive vacuoles. A more malignant form of the disease may present in infancy with heart muscle and neuronal involvement.

OTHER DISORDERS

There are other disorders in which myotonia is occasionally recognized, although usually not as a pre-
dominant or essential part of the presentation. Muscle diseases such as polymyositis and inclusion-body myositis, or severe active denervation are rarely associated with myotonic potentials. In some of these cases, CRDs may be mistaken for myotonic potentials. Fibrillation potentials, positive sharp waves, and myotonic discharges have been reported previously in hypothyroid patients, but the myotonic discharges are not common. Electrical myotonia may also be seen with some drugs: 20,25-diazacholesterol, chloroquine, colchicine, and hydroxy methylglutaryl coenzyme A reductase inhibitors.

CONCLUSIONS

Recognizing the associated clinical and EMG characteristics of myotonia and paramyotonia greatly aids neuromuscular diagnosis. During routine EDX testing a few additional historical details and a brief physical examination are likely to provide the correct diagnosis or suggest further investigations.

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