Muscle Disease: When is it not myositis?

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Disclosure Statement

• I have no conflicts of interest to report

• I do not have financial or other relationships with any commercial interest

• I will not be discussing off label use of pharmaceuticals or devices

"Under disclosure rules, I'm required to tell you I own stock in the company whose drug I'm prescribing."
Overview

- Diagnostic approach
- Usefulness and pitfalls of diagnostic tools
- Snakes, frogs, and chameleons

Diagnostic criteria: Bohan & Peter 1975

- Polymyositis
  - Definite: All criteria
  - Probable: Three criteria
  - Possible: Two criteria

- Limitations
  - Muscle biopsy normal in 10-15%
  - Criteria does not distinguish IBM, toxic, necrotizing, or dystrophy with inflammation
Proposed diagnostic criteria

• ENMC proposed major subtypes of IIM (2004):
  1. Inclusion body myositis
  2. Polymyositis
  3. Dermatomyositis
  4. Non-specific myositis (non-specific perimysial/perivascular infiltrates)
  5. Immune mediated necrotizing myopathy
  6. Amyopathic DM
  7. Possible DM sine dermatitis

ENMC proposed classification criteria, 2004 (exclude IBM)

- Clinical criteria
  - Inclusion: age > 18 (except DM or non-specific myositis), subacute, symmetric proximal > distal, neck flexor > neck extensor, rash typical of DM
  - Exclusion: clinical features of IBM; ocular or isolated bulbar weakness; neck extensor > flexor weakness, toxic, endocrine, amyloid myopathy; family history muscular dystrophy or proximal motor neuropathies

- Elevated CK

- Other laboratory criteria
  - Electromyography
  - MRI: diffuse or patchy increased signal on STIR
  - MSA in serum
• Muscle biopsy
  • Endomysial inflammatory cell (CD8+) infiltrate surrounding and/or invading non-necrotic muscle fibers or ubiquitous MHC 1 expression
  • Perifascicular atrophy
  • MAC depositions on small blood vessels, or reduced capillary density, or tubuloreticular inclusions in endothelial cells on EM, or MHC 1 expression in perifascicular fibers
  • Perivascular, perimysial inflammatory cell infiltrate
  • Scattered endomysial CD8+ T cells
  • Many necrotic fibers and sparse or slight perivascular inflammatory cells
  • Rimmed vacuoles, ragged red fibers, COX negative fibers
  • MAC deposition on the sarcolemma of non-necrotic fibers and other findings of muscular dystrophy
Diagnostic challenge

- Heterogeneous group of disorders
  - Age of symptom onset (i.e. juvenile DM versus IBM)
  - Rate of symptom progression
  - Multiple organ involvement (i.e. skin, heart, lung, GI)
  - Association with underlying cancer
  - Severity and distribution of muscular symptoms (i.e. hypomyopathic DM)
  - Laboratory findings (i.e. MSA, CPK, and markers of inflammation)
  - Response to treatment

Importance of the correct diagnosis

- Incorrect treatment
  - Risk for medication side effects
  - Cost of medication (i.e. annual cost of rituximab per patient is $37,000 for RA)

- Unnecessary diagnostic tests
  - Imaging for cancer screening, interstitial lung disease

- Screening for other systemic disorder

- Family planning and counseling
Approach to a patient with muscle weakness

• Clinical history and examination
• Laboratory studies
• Electrophysiological testing
• Imaging (ultrasound and MRI)
• Pathology

• How helpful are these studies in making the diagnosis of inflammatory myopathy?

Case 1

• 48-year-old black man with a history of osteoarthritis was noted to have CPK of 1280 IU/L
• He took ibuprofen as needed for his joint pains
• Examination findings:
  • General examination was normal
  • Neurological examination showed normal muscle bulk and give way weakness at the hip flexors due to hip pain
  • Sensory examination and reflexes were normal
• He was told that he had “inflammation of the muscle” and to see a neurologist
Is CK a good predictor of myopathy?

Brewster, et al. 2007

| Table 1. Distribution of serum CK in different population groups |
|-----------------|----------------|----------------|----------------|
|                 | Sex and        | Age | BMI | 2.5th percentile | Median | 97.5th percentile | >ULN (N%) |
|                 | ancestry       |     |     |                 |        |                 |          |
| All subjects    |                |     |     |                 |        |                 |          |
| Women           | 1411           | 45  | 27  | 40              | 111    | 460             | 508 (34) |
| Men             | 831            | 45  | 28  | 36              | 95     | 349             | 304 (37) |
| White subjects  |                |     |     |                 |        |                 |          |
| Women           | 503            | 48  | 26  | 35              | 88     | 286             | 64 (13)  |
| Men             | 252            | 47  | 26  | 29              | 72     | 201             | 21 (8)   |
| South Asian     |                |     |     |                 |        |                 |          |
| Women           | 147            | 45  | 27  | 37              | 87     | 313             | 23 (16)  |
| Men             | 193            | 44  | 26  | 47              | 143    | 641             | 38 (12)  |
| Black subjects  |                |     |     |                 |        |                 |          |
| Women           | 387            | 43  | 29  | 48              | 124    | 414             | 164 (42) |
| Men             | 183            | 44  | 26  | 71              | 213    | 801             | 11 (62)  |

Data for age and body mass index (BMI) are means (SD). Data are rounded to the nearest integer. CK is expressed as international units per liter. *Number (percentage) of participants with a CK above the ULN, as recommended by the manufacturer (140 IU/L for women, 174 IU/L for men, with appropriately established reference intervals, 2.5% of the subjects are expected to have values above the ULN). (Including participants of “other” ancestry (n = 68), with the exclusion of outliers (n = 3, 1 South Asian and 2 black participants) and those using statins (n = 30, 21 South Asian, 8 black participants, and 1 of other ancestry).
Electrophysiological testing

Nerve conduction studies typically normal

Needle electromyography
- Fibrillation and positive: membrane irritability or "denervation"
- Myotonia
- Complex repetitive discharges
- Short duration and polyphasic motor unit potentials
- Early recruitment

Limitations:
- Reliability is not well established
- Interpretation depends on the skills of the electromyographer and the number of muscles tested
Limitations of electrophysiological testing

- Poor sensitivity
  - Sensitivity for detecting abnormal 50 to 74%
  - Sensitivity for detecting myopathy 46 to 75%
- Lack specificity for the diagnosis of inflammatory myopathy

Role of MR imaging
MRI

- Advantage
  - Direct muscle biopsy
  - No ionizing radiation exposure
  - Distinguish active disease from end stage muscle
  - Capture a detailed anatomical information
- Fat suppressed T2 weight or STIR (Short Tau Inversion Recovery) sequences preferred

Case 2

- 52 year old man who has had gradually progressive proximal weakness over 10 years with his legs more severely affected than his arms
- One year prior, his CPK was noted to be 1522 IU/L and MRI of his thighs showed atrophy and increased signal on STIR images
- Based on these findings, the diagnosis of inflammatory myopathy was made
MRI limitations

- Muscle T2 hyperintensity is non-specific: trauma, myonecrosis, infection, denervation, rhabdomyolysis, interstitial fluid overload and non-inflammatory myopathies all have similar appearance
- No objective quantification of disease
- MR imaging is not a feature of most diagnostic criteria
- Others: cost, availability, contraindications

Vlekkert et al, 2015

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>FNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI (n=48)</td>
<td>0.91 (0.77, 0.98)</td>
<td>0.69 (0.39, 0.91)</td>
<td>0.09</td>
</tr>
<tr>
<td>Muscle biopsy (n=47)*</td>
<td>0.77 (0.60, 0.90)</td>
<td>1.0 (0.74, 1.0)</td>
<td>0.23</td>
</tr>
<tr>
<td>Muscle biopsy after MRI as triage test (n=36)*</td>
<td>0.81 (0.64, 0.93)</td>
<td>1.0 (0.40, 1.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>MRI as add-on test to muscle biopsy (n=47)*</td>
<td>0.94 (0.81, 0.99)</td>
<td>0.67 (0.35, 0.90)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*All muscle biopsies.
*Muscle biopsies guided by an abnormal MRI.
†Results if 1 or both tests are positive.
FNR, false negative rate.
Role of muscle biopsy
Role of muscle biopsy

- History, laboratory studies, electrophysiological testing, and imaging studies are helpful to guide biopsy
- Sensitive muscle biopsy in diagnosing muscle disorder is isolation maybe low
  - 29/64 biopsy was diagnostic a muscle disease (Cardy and Potter, 2007)

De Bleecker et al, 2015

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Recommended list of IM diagnostic stains.</th>
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<tbody>
<tr>
<td>Required stains for muscle biopsies</td>
<td>Additional stains for suspected IM</td>
</tr>
<tr>
<td>HE</td>
<td>AK</td>
</tr>
<tr>
<td>ATPase/Mysin F/S</td>
<td>CD3, CD8, CD68</td>
</tr>
<tr>
<td>NADH</td>
<td>HLA-ABC/MHC-I</td>
</tr>
<tr>
<td>SDH</td>
<td>MAC (c,5b-8)</td>
</tr>
<tr>
<td>COX or COX/SDH</td>
<td>p62</td>
</tr>
<tr>
<td>Gomori</td>
<td>CD31</td>
</tr>
<tr>
<td>PAS</td>
<td>CD56/NCAM</td>
</tr>
<tr>
<td>vonWidau B.</td>
<td>AP</td>
</tr>
<tr>
<td>AP</td>
<td>Myosin-fetal</td>
</tr>
<tr>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Congo rd.</td>
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</table>

Abbreviations: alkaline phosphatase (AK), fast/slow (F/S), acid phosphatase (AP), cytochrome c oxidase (COX), hematoxylin–eosin (HE), membrane attack complex (MAC), non-specific esterase (NE), succinate dehydrogenase (SDH).

Cardy and Potter, 2007

Is a combination of studies more sensitive and specific?

| Table 1. Predictive values of screening investigations for abnormal muscle biopsy |
|----------------------------------|-------------------------------|-----------------|----------------|----------------|----------------|
| Screening test(s)               | n (%)                        | Sensitivity (95% CI) | Specificity (95% CI) | LR⁺ | LR⁻ |
| CK > 1000 IU/l                  | 64 (100)                     | 48 (30-66)         | 94 (87-102)      | 8.0 | 0.6 |
| CK > 500 IU/l                   | 64 (100)                     | 66 (48-83)         | 77 (63-91)       | 2.9 | 0.4 |
| Abnormal EMG                    | 50 (76)                      | 74 (56-92)         | 67 (49-84)       | 2.2 | 0.4 |
| Abnormal MRI                    | 21 (33)                      | 92 (76-107)        | 89 (68-109)      | 8.4 | 0.1 |
| CK > 1000 IU/1 OR Abnormal MRI  | 21 (33)                      | 92 (76-107)        | 89 (68-109)      | 8.4 | 0.1 |
| Abnormal EMG OR Abnormal MRI    | 17 (27)                      | 89 (68-109)        | 88 (65-110)      | 7.4 | 0.1 |
| Abnormal EMG OR Abnormal MRI    | 17 (27)                      | 89 (68-109)        | 88 (65-110)      | 7.4 | 0.1 |

n: number of patients undergoing screening test; LR⁺, positive likelihood ratio; LR⁻, negative likelihood ratio.
Case 3

- A 19 year old young man was found to have an elevated CK of 8950 IU/L after he complained of not being able to keep up with his peers while running
- He was treated with a course of oral prednisone with no improvement in his symptoms and his CK decreased to high 6000’s
- Physical examination showed mild weakness in the hamstring muscles and asymmetric moderate weakness of the gastrocnemius muscle, with the left more severely affected than the right
Case 4

- 16 year old girl has a 5 year history of progress proximal arm weakness and difficulty climbing the steps
- There is no family history of muscle disease
- Physical examination showed bilateral winging of the scapula, facial weakness, arm extension and flexion weakness, and ankle dorsiflexion weakness
- CPK was 410 IU/L
- EMG showed short duration and low amplitude motor unit potentials and membrane irritability
Case 5

- 40 year old complains of a 6 month history of progressive proximal weakness that has worsened over the past month resulting in her having difficulty climbing the stairs
- She has a history of Graves disease and her hyperthyroidism is well controlled
- She has two sons who were diagnosed with DMD
- Physical examination showed proximal muscle weakness
- CK was 2436 IU/L
- She was treated with prednisone and azathioprine with no improvement in her symptoms
Case 6

• 49 year old woman has a 10 year history of progressive proximal muscle weakness and occasional myalgias and muscle cramps
• Physical examination showed proximal (3/5) more than distal weakness (4/5)
• Electrophysiological testing showed widespread myopathic changes and her CPK was 660 IU/L
Case 1: Healthy individual
Case 2: Kennedy’s disease
Case 3: LGMD 2b (dysferlinopathy)
Case 4: FSHD (fascioscapulohumeral muscular dystrophy)
Case 5: Female carrier, dystrophinopathy
Case 6: Myotonic dystrophy, type 2 (proximal myotonic myopathy)
Differential diagnosis to consider

- Inherited myopathy
  - Metabolic myopathy
  - Muscular dystrophy
- Toxic myopathy
- Endocrine myopathy

Can IIM mimic muscular dystrophy?

- 17 of 51 (33%) anti-HMGCR myopathy initially suspected of having limb girdle muscular dystrophy
- All patient underwent genetics testing for LGMD (dystrophin, dysferlin, sarcoglycans, calpain-3, caveolin-3, anoctamin 5, fukutin-related protein) and other inherited myopathies (acid maltase deficiency)
- All characterized by prolonged disease course, asymptomatic or oligosymptomatic hyperCKemia, exercise intolerance, or myalgia
2018 ACR/EULAR classification criteria

- **Goals:**
  - Establish criteria to distinguish idiopathic inflammatory myopathies (IIM) from mimickers
  - Categorize IIMs in major subgroup
  - Consensus method used for study design, definition of possible criteria candidates, and selection of IIM subgroups and comparators
2018 ACR/EULAR classification criteria

- 93 variables identified: previous criteria and expert suggestion
- 976 IIM and 624 non-IIM cases from 47 centers
- Two models generated: with or without muscle biopsy
- 16 variables identified that could discriminate IIMs cases were weight and included in the final criteria
- Web-based calculator provide a score representing the probably of a patient having IIM
2018 ACR/EULAR classification criteria limitation

- Few patients from rare subtypes were recruited (IMNM, hypomyopathic DM)
- Only one MSA, anti-Jo1 antibody, was included because other antibodies were not widely documented
- Muscle MRI only available in 38 percent of patients and excluded from the analysis
Summary

- Not all myositis is inflammatory myopathy
- A good history and examination is an essential to diagnosed inflammatory myopathy
- Laboratory testing (including MSA), electrophysiology, imaging, and muscle biopsy all contribute to the diagnosis of IIM
<table>
<thead>
<tr>
<th>Variable</th>
<th>Score points</th>
<th>Definition</th>
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</table>
| Age of onset | Without muscle biopsy 1.3
Age of onset of first symptom assumed to be related to the disease ≥18 years and ≤40 years 2.1 | 18 ≤ age (years) at onset of first symptom assumed to be related to the disease <40 Age (years) at onset of first symptom assumed to be related to the disease ≥40 |
| Muscle weakness | Without muscle biopsy 0.7
Objective symmetric weakness, usually progressive, of the proximal upper extremities 0.8
Objective symmetric weakness, usually progressive, of the proximal lower extremities | Weakness of proximal upper extremities as defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time Weakness of proximal lower extremities as defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time |
| Neck flexors are relatively weaker than neck extensors | Without muscle biopsy 1.9 | Muscle grades for neck flexors are relatively lower than neck extensors as defined by manual muscle testing or other objective strength testing |
| In the legs, proximal muscles are relatively weaker than distal muscles | Without muscle biopsy 0.9 | Muscle grades for proximal muscles in the legs are relatively lower than distal muscles in the legs as defined by manual muscle testing or other objective strength testing |
| Skin manifestations | Without muscle biopsy 3.1
Heliotrope rash 2.1 | Purple, bluish-colored, or erythematous patches over the eyelids or in a peri-orbital distribution, often associated with periorbital edema Erythematous to violaceous papules over the extensor surfaces of joints, which are sometimes swollen. May occur over the finger joints, elbows, knees, malleoli, and toes |
| Gottron’s papules | Without muscle biopsy 3.5 | Erythematous to violaceous papules over the extensor surfaces of joints, which are not palpable |
| Gottron’s sign | Without muscle biopsy 0.7 | Difficulty in swallowing or objective evidence of abnormal motility of the esophagus |

Lundberg et al, 2018
Table 2. The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for adult and juvenile idiopathic inflammatory myopathies (IBM)

When no better explanation for the symptoms and signs exist, these classification criteria can be used

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without muscle biopsy</th>
<th>With muscle biopsy</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Jo-1 (anti-b-helix- transfer RNA synthetase) autoantibody present</td>
<td>3.9</td>
<td>3.8</td>
<td>Autoantibody testing in serum performed with standardized and validated test, showing positive result</td>
</tr>
<tr>
<td>Elevated serum levels of creatine kinase (CK)* or lactate dehydrogenase (LDH)* or aspartate aminotransferase (ASAT/AST)* or alanine aminotransferase (ALAT/AET)*</td>
<td>1.3</td>
<td>1.4</td>
<td>The most abnormal test values during the disease course (highest absolute level of enzymes) above the relevant upper limit of normal</td>
</tr>
<tr>
<td>Muscle biopsy features—presence of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers</td>
<td>1.7</td>
<td></td>
<td>Muscle biopsy reveals endomysial mononuclear cells abutting the sarcolemma of otherwise healthy, non-necrotic muscle fibers, but there is no clear invasion of the muscle fibers</td>
</tr>
<tr>
<td>Perimysial and/or perivascular infiltration of mononuclear cells</td>
<td>1.2</td>
<td></td>
<td>Mononuclear cells are located in the perimysium and/or located around blood vessels (in either perimysial or endomysial vessels)</td>
</tr>
<tr>
<td>Perifascicular atrophy</td>
<td>1.9</td>
<td></td>
<td>Muscle biopsy reveals several rows of muscle fibers, which are smaller in the perifascicular region than fibers more centrally located</td>
</tr>
<tr>
<td>Rimmed vacuoles</td>
<td>3.1</td>
<td></td>
<td>Rimmed vacuoles are bluish by hematoxylin and eosin staining and reddish by modified Gomori trichrome stain</td>
</tr>
</tbody>
</table>

* Serum levels above the upper limit of normal.