Inclusion body myositis and misdiagnosis of polymyositis

Dr Matt Parton
British Rheumatology Society  May 2012

No interests to declare
A not uncommon referral

Dear colleague,

Thank you for seeing this 69 year old who has complained of aching muscles for a few months and who finds it harder to get out of a chair. I checked the CK and it was raised. I have stopped simvastatin but without improvement. Could this be polymyositis?

Yours sincerely...
A not uncommon referral

- Often older patient, male or female
- On a statin (who isn’t?)
- Myalgia (?really)
- Proximal weakness (?really)
- Raised CK (?how much)
- ?Polymyositis (?really)
A not uncommon referral

• Is this a muscle problem?
  – Overweight, arthritis, endocrine, depression...

• Is this a myositis?
  – Inflammation versus other problem

• Investigation: does this need a biopsy?
  – Will biopsy change management?
  – Could I miss anything if I don’t?

• Does this need treatment?
  – Steroids, immunosuppressants, side effects...
Mrs F – a case in point

- 69 year old, Black-Caribbean female
- IHD, NIDDM, hypertension. No Family history.
- Two years of painful muscles
- Hard to stand from sitting, later difficult to carry shopping or open jars.
- Normal voice & swallow. No rash.
- CK raised up to 1500
  - Statin discontinued – no change (1200-1500)
Mrs F – a case in point

Examination:

• Mild facial and neck flexion weakness
• Thinning of hands and thighs
• Arms: minimal biceps weakness, all wrist and hand muscles slightly weak
• Legs: moderate weakness at hips and ankles, worse of knee extension
• No skin or joint abnormalities
Mrs F – a case in point

Muscle biopsy:

• Marked increase of variation of fibre size
• Occasional eosinophilic inclusions
• Mild inflammation: no particular or focal pattern
• Several fibres show vacuoles, some of which rimmed
• No RRF; normal COX and other enzyme stains
• Immunohistochemistry:
  – many fibres positive for neonatal myosin
  – inclusions positive for p62, TDP43, myotilin
  – Dystrophy panel otherwise normal
Mrs F – a case in point

• Myalgia and progressive weakness
  – Mild of face and neck
  – Mild wrist and hand (including finger flexion)
  – Moderate all leg muscles, worst of knee extension
• No rash/arthritis. No effect of stopping statin
• CK 1500
• Biopsy: minimal inflammation, rimmed vacuoles and p62 and TDP43 +ve inclusions
Mrs F – a case in point

- Myalgia and progressive weakness
  - Mild of face and neck
  - Mild wrist and hand (including finger flexion)
  - Moderate all leg muscles, worst of knee extension
- No rash/arthritis. No effect of stopping statin
- CK 1500
- Biopsy: minimal inflammation, rimmed vacuoles and p62 and TDP43 +ve inclusions
- Diagnosis: INCLUSION BODY MYOSITIS
IBM: The fuzzy reality
IBM: What it isn’t

• Dermatomyositis
  – Humorally mediated autoimmune disorder:
    • complement-dependent
    • attack of capillaries in muscle and other tissues
    • unknown trigger
  – Characteristic pathology
    • infarction and perifascicular atrophy
  – Clinical: more acute, more proximal, usually has typical rash
IBM: What it isn’t

• “Polymyositis”
  – Cell mediated immune phenomenon
    • CD8+ T cells
    • unknown muscle antigen
    • invade and destroy non-necrotic muscle fibres expressing MHC-1
  – Clinically: more rapid onset, more proximal, more inflammatory than IBM
IBM: What it isn’t

• Polymyositis
  – Cell mediated immune phenomenon
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  – Clinically: more rapid onset, more proximal, more inflammatory than IBM
Muscle necrosis – most scattered in PM

DM – perifascicular atrophy

IBM – inclusions and vacuoles
sIBM: What it isn’t

- Myofibrillar myopathy
  - Focal degradation of myofibrils, +/- rimmed vacuoles, +/- inclusion bodies
  - AR or AD inheritance
  - Proximal / distal / respiratory muscle weakness / cardiomyopathy
  - Several genetic causes (desmin, myotilin, ZASP, alpha-beta crystallin, unknown)
sIBM: What it isn’t

• Inclusion body myopathy with Paget disease of bone and frontotemporal dementia
  – Rimmed vacuoles and inclusion bodies
  – AD mutations in VCP (valosin containing peptide, 9p12; myotube formation)
  – Variable phenotype
    • IBM-like 90%, Paget 43%, FTD 37%, also CMP
sIBM: What it isn’t

• Hereditary inclusion body myopathy (IBM2)
  – Rimmed vacuoles and inclusion bodies
  – AR mutations in GNE (UDP-N-acetyl-glucosamine 2-epimerase; 9p12)
  – Younger onset: footdrop and hip weakness
  – Sparing of quadriceps
IBM: The fundamentals
Epidemiology of IBM

• Most prevalent acquired muscle disease developing in those over 50
• Males > Females (2:1)
• Caucasians > other ethnicities
# Epidemiology of IBM

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<th>Incidence (per 100,000/yr)</th>
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Older, male, white (but not always); delayed diagnosis
# Epidemiology of IBM vs. DM

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<td>Olmsted, MN, USA</td>
<td>0.96 (0.60-1.31)</td>
<td>21.42 (13.07-29.77)</td>
<td>1:3</td>
<td>57 (30-95)</td>
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Aetiology of IBM

UNCERTAIN

• Inflammation:
  – Invasion of myocytes overexpressing MHC-I by CD8 positive T-lymphocytes

• Degeneration:
  – Deposition of amyloid
Inflammation vs. degeneration

"Come in, you're not the first to arrive."
Clinical features of IBM

“SPOT DIAGNOSIS”

• Insidious, progressive

• Quadriceps
  – Can’t maintain standing posture
  – Falls
  – Difficulty with inclines
Clinical features of IBM

- Finger flexors
  - Very specific finding
  - Can’t grip
- Asymmetry
- Dysphagia
Investigations of IBM

• Limited rise in CK (usually)
• Neurophysiology often unhelpful
  – Can be normal
  – Look for “neuropathic” findings
• No diagnostic antibody test (as yet?)
Pathology of IBM

A. Endomysial inflammation and rimmed vacuoles
B. Amyloid inclusions
C. COX-negative fibres
D. MHC-I over-expression
Inflammation in IBM

• Cytokine release (IL-1beta, TNF-alpha, etc)
• Increased pro-inflammatory chemokines (CXCL 9, CXCL10, CCL 3)
• Above promote CD8-positive T-lymphocytes to damage myofibres overexpressing MHC-I
Proposed immune mechanism in IBM

Dalakas Nat Clin Pract 2006
Proposed mechanism of myodegeneration in IBM

Askanas 2006
What links inflammation and degeneration in IBM?

Interrelation of inflammation and APP in sIBM: IL-1β induces accumulation of β-amyloid in skeletal muscle

Jens Schmidt, Konstanze Barthel, Arne Wrede, Mohammad Salajegheh, Mathias Bähr and Marinos C. Dalakas

• Various techniques comparing sIBM, PM, DM, normal, others (ALS, etc)
• Looks for role of IL-1beta and specificity to IBM
• Higher levels of inflammatory cytokines and chemokines in IBM

• Pattern of expression of above differs
  – IBM: more widely
  – PM: at areas of inflammation
  – DM: capillaries and perifascicular
• Similar increased levels of “degenerative molecules” in IBM and PM and DM

• Pattern of expression of above differs
  – IBM: more widely
  – PM: at areas of inflammation
  – DM: capillaries and perifasicular
• APP expression proportional to inflammation
  • More so in IBM than DM
  • Not in PM
• Myotube culture model:
  • No background production of chemokines/cytokines
  • Self-amplifying production on exposure (esp. IL-1beta)
  • Similar chemokine / cytokine expression to IBM fibres
  • If chemokines present:
    • More APP produced
    • More amyloid produced
    • More protein aggregation
Only in IBM do beta-amyloid and IL-1beta co-localise

Overall conclusions

• Argue for role of IL-1beta as link
• Don’t prove if inflammation is initial event
• Argue link of inflammation to degeneration is unique to IBM
  • Higher expression of inflammatory chemokines
  • Localisation of these to within myofibres
So, how can we treat IBM?
The drugs don’t work
The drugs don’t work

- Argues against immune basis?
(No) Evidence for treatment

• Cochrane review (Rose, unpublished)
  – Nine trials
    • 3 x IVIg, 2 x Interferon, 1 x MTX, 1 x oxandrolone, 2 x combinations
  – No benefit from any intervention in trials
    • Underpowered
    • Short duration
    • Usually single centre
    • Heterogeneity of individual response???
Management

• Pharmacological
  – Immunomodulatory
    • Steroids +/- other agents if highly inflammatory biopsy?
    • IVIg for dysphagia?
    • Antioxidants, anti-aggregation...

• Non-pharmacological
  – Multi-disciplinary supportive care
    • Physio, SALT, OT, respite, PEG feeding...
  – Exercise??
So, how can we diagnose IBM?
Clinical features of IBM vary, but there is a typical and distinctive picture.

Badrising, J Neurol 2005
Clinical features of IBM vary, but there is a typical and distinctive picture.
Onset in the quadriceps and slow progression are also typical.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Male</th>
<th>Female</th>
<th>p</th>
<th>p_c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Quadriceps</td>
<td>40</td>
<td>63</td>
<td>31</td>
<td>72</td>
<td>0.03</td>
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<tr>
<td>Finger flexors</td>
<td>9</td>
<td>14</td>
<td>5</td>
<td>12</td>
<td>0.46</td>
</tr>
<tr>
<td>Pharynx</td>
<td>6</td>
<td>9</td>
<td>2</td>
<td>5</td>
<td>0.08</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>14</td>
<td>5</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>100</td>
<td>43</td>
<td>12</td>
<td></td>
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</tbody>
</table>

n number; p, p-value for the frequency difference between sexes corrected for multiple comparisons; ns not significant.
Varied aspects of disability in IBM

- IBM-Functional Rating Scale: 26/40 (17-38, SD 5.9)
- Single Items

50% patients complain of dysphagia
Clinical features of IBM vary but overall a typical pattern can be recognised
Pathology

• Endomysial inflammation
  – CD8-positive T cells (and their distribution)
  – MHC-I overexpression

• Rimmed vacuoles
  – Non-specific result of misfolded protein
    • LGMD2I, SMA, myofibrillar myopathies...

• Inclusions
  – Overlap with myofibrillar myopathies

• Congophilia
  • Variation with methods, non-specific but sensitive

• EM for tubulofilaments?
Pathological features of IBM vary but overall a typical pattern can be recognised.
• 107 cases: 27 PM, 64 IBM, **16 overlap**
  – Latter: biopsy diagnosis of PM but clinical features of IBM

• Questions:
  – Frequency of autoimmune disease / markers?
  – Is PM always associated with autoimmune disease or marker?
  – Can muscle biopsy reliably distinguish PM and IBM?
<table>
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<th>IBM</th>
<th>PM/IBM</th>
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<tr>
<td>n</td>
<td>27</td>
<td>64</td>
<td>16</td>
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<tr>
<td>Mean CK</td>
<td>2199</td>
<td>546</td>
<td>570</td>
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<tr>
<td>Other autoimmune disease</td>
<td>14.8%</td>
<td>12.5%</td>
<td>6.25%</td>
</tr>
<tr>
<td>Autoimmune marker positive</td>
<td>20%</td>
<td>35.3%</td>
<td>35.7%</td>
</tr>
<tr>
<td>Improvement with Rx</td>
<td>63%</td>
<td>6.25%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Monocyte invasion of non-necrotic fibre</td>
<td>63%</td>
<td>100%</td>
<td>81.25%</td>
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- Differentiation needs combined clinical / pathological approach
- Cases with key clinical features of IBM can lack canonical pathology
So, how do we diagnose IBM?
Griggs criteria

Principally pathological:
• Invasion of non-necrotic fibres
• Rimmed vacuoles
• Intracellular amyloid or tubulofilaments on EM
All 3: “definite IBM”
If only 2...

Clinical
• > 6 months’ duration
• > 30 years old
• Proximal and distal of arm and leg and 1 of
  – Finger flexors weak
  – Wrist fl > ex weak
  – Quads weak
...then “Probable IBM”
<table>
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<th>Pathologically defined IBM</th>
<th>Clinical</th>
<th>Pathological</th>
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<td>• Clinical and laboratory findings consistent with IBM</td>
<td>• Endomysial exudate</td>
<td>• Rimmed vacuoles</td>
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<tr>
<td></td>
<td></td>
<td>• Partial inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Congo red positive or SMI-31 or tubulofilaments on EM</td>
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<th>Clinically defined IBM</th>
<th>Clinical</th>
<th>Pathological</th>
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<tr>
<td>• Over 6 months duration</td>
<td>• Endomysial exudate or increased MHC-I expression</td>
<td></td>
</tr>
<tr>
<td>• Over 30 years old</td>
<td>• NO Congo red positive nor SMI-31 nor EM showing tubulofilaments</td>
<td></td>
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<td>• EMG consistent</td>
<td></td>
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<tr>
<td>• Quads weaker than hip flexors AND finger flexors weaker than shoulder abductors</td>
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<th>Possible IBM</th>
<th>Clinical</th>
<th>Pathological</th>
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<tr>
<td>• As clinically defined IBM but</td>
<td>• As clinically defined IBM</td>
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<td>• Quads weaker than hip flexors OR finger flexors weaker than shoulder abductors</td>
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Thanks to David Hilton-Jones
Immunoblots against normal human muscle of plasma from

- 25 IBM
- 25 other immune disease (10 DM, 10 PM, 10 Myasthenia)
- 15 healthy controls

- 52% sensitivity of IBM cases (13/25) to unknown 43kD protein
- 100% specificity of IBM cases
  - Unrelated to age, any treatment received, disease duration, race or sex
Conclusion

- No 100% reliable distinguishing individual criterion for IBM vs. PM
- Combined clinical and pathological assessment essential
- Keep in mind all possibilities
- Target and tailor best possible management
“I shall not today attempt further to define the kinds of material I understand to be embraced within that shorthand description; and perhaps I could never succeed in intelligibly doing so. But I know it when I see it”.

US Supreme Court Justice Potter Stewart (on defining hard core pornography!)
Queen Square Centre for Neuromuscular Diseases

Thank you
Myxovirus-Like Structures
in a Case of Human Chronic Polymyositis

Abstract. Intranuclear and intracytoplasmic aggregates of filaments with tubular structures and transverse striations occurred in muscle tissues biopsied from a patient with chronic polymyositis. The filamentous tubules bear a close resemblance to the incomplete form of myxovirus in which the envelope is missing. Three biopsies from the same patient, taken during a period of 1½ years, all revealed these structures. This finding provides presumptive evidence that a chronic persistent viral infection may be involved in the pathogenesis of chronic polymyositis.