McArdle Disease GSDV

- Incidence 1:100,000
- Autosomal recessive mutations in PYGM
- Absent or severely reduced muscle phosphorylase
- Failure to produce lactate during ischaemic exercise
<table>
<thead>
<tr>
<th>Features</th>
<th>N=59</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise Related Pain/ Fatigue</td>
<td>59</td>
<td>100</td>
</tr>
<tr>
<td>Second wind</td>
<td>51</td>
<td>86</td>
</tr>
<tr>
<td>Myoglobinuria</td>
<td>36</td>
<td>61</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Muscle Hypertrophy</td>
<td>24</td>
<td>41</td>
</tr>
<tr>
<td>Muscle wasting</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>Paraspinal, shoulder, Peri-scapular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle weakness MRC 4 Axial</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Shoulder girdle</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# McArdle Disease

<table>
<thead>
<tr>
<th>Age yrs</th>
<th>&lt;10</th>
<th>10-19</th>
<th>20-29</th>
<th>30-39</th>
<th>40-49</th>
<th>&gt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of symptoms, n=65</td>
<td>54 (87%)</td>
<td>6 (9.6%)</td>
<td>0</td>
<td>2 (3.2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, N=60</td>
<td>6 (10%)</td>
<td>11 (18.3%)</td>
<td>12 (20%)</td>
<td>12 (20%)</td>
<td>13 (21.6%)</td>
<td>7 (11.6%)</td>
</tr>
</tbody>
</table>

- 96% onset <20 years
- 28% diagnosed <20 years
Differential Diagnosis

- Other glycolytic disorders
- Muscular Dystrophies
- Fatty acid oxidation defects
- Mitochondrial disorders
Investigations

- Creatine kinase
  - Average 2,700 iu/l (range 230-13,000)
- Muscle biopsy
Muscle biopsy: caution

- Phosphorylase is unstable and fades quickly.
- Regenerating muscle expresses the foetal isoenzyme.
- Glycogen depletion (critical illness) phosphorylase histochemistry will not work.
- 18% of patients previously diagnosed by muscle biopsy did NOT have McArdle disease.
Ischaemic Lactate test: Equipment

- Cannula
- Sphygmomanometer cuff and bulb
- 8 Fluoride oxalate tubes (lactate)
- 8 EDTA tubes for (ammonia)
- Ice
- Fasting patient
Protocol

- Baseline Blood sample
  - Lactate
  - ammonia
- Inflate Sphygmomanometer cuff > systolic BP
- Patient rapidly grips repetitively for 1 minute (some protocols say 2 minutes)
- After two minutes, when patient fatigues cuff is deflated
- Blood is taken at 1, 2, 3, 5, 7, 10 and 12 minutes
  - Lactate
  - Ammonia
- Blood samples must be kept in ice
Normal result: 3-5 fold increase in lactate and ammonia

A failure for both Lactate and Ammonia to rise indicates a failed test
Problems with the test

- Protocol not standardised
- Healthy individuals can’t exercise for more than a minute
- GSD V patients often can’t exercise for a minute
- False results
  - Ipsilateral ante-cubital vein not used
  - Blood taken before cuff is deflated
  - If ammonia not simultaneously measured
  - Samples not put in ice
- Potential adverse events
  - Severe cramping/ discomfort
  - Myoglobinuria
  - Compartment syndrome
Non-ischaemic forearm exercise test
Hogrel et al Neurology 2001

- 26 healthy controls and 32 patients with a metabolic myopathy
- Aerobic forearm exercise at 70% maximum voluntary contraction for 30 seconds
- Discriminates GSDV from normal
Kasemi-Esfarjarni et al Ann Neurology 2002

- 9 GSDV patients and 1 phosphoglycerate mutase deficiency
- Identical protocol to ischaemic forearm test without ischaemia
- Similar results with both protocols
- No cramps with non-ischaemic test
- Four patients could not complete ischaemic forearm test
Diagnostic cycle test
Vising and Haller 2003

- 24 GSD V
- 17 normal controls
- 25 other metabolic myopathies
- Cycled at constant workload
- for 15 minutes
  Heart rate and respiratory gas exchange measured
- Second wind 7-15 minutes in McArdle subject
12 minute shuttle test

- Patient walks as far as possible in 12 minutes
- Borg RPP must not exceed 4
- Every one minute record
  - Heart rate
  - RPP
  - Distance travelled (walking speed)
12 minute walk test
Quinlivan et al JNNP 2010

- 36 patients studied on more than one occasion for baseline assessment
- Second wind identified in 100%
  - For some it was the first time
- Pain and heart rate increase at 2-3 minutes
- Pain and Heart rate ratio peak at 5 – 6 minutes
- Second wind at 6-8 minutes
### 12 minute walking assessment

<table>
<thead>
<tr>
<th>Minutes</th>
<th>Heart Rate</th>
<th>Walking speed km/hr</th>
<th>RPP</th>
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<tbody>
<tr>
<td>1</td>
<td>90</td>
<td>4.0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>117</td>
<td>5.5</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>140</td>
<td>5.5</td>
<td>5.0</td>
</tr>
<tr>
<td>4</td>
<td>144</td>
<td>4.5</td>
<td>3.0</td>
</tr>
<tr>
<td>5</td>
<td>142</td>
<td>4.5</td>
<td>3.0</td>
</tr>
<tr>
<td>6</td>
<td>152</td>
<td>4.5</td>
<td>3.0</td>
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<tr>
<td>7</td>
<td>143</td>
<td>4.5</td>
<td>3.0</td>
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<tr>
<td>8</td>
<td>134</td>
<td>4.5</td>
<td>2.0</td>
</tr>
<tr>
<td>9</td>
<td>116</td>
<td>4.5</td>
<td>2.0</td>
</tr>
<tr>
<td>10</td>
<td>122</td>
<td>5.5</td>
<td>2.0</td>
</tr>
<tr>
<td>11</td>
<td>131</td>
<td>5.5</td>
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</tr>
<tr>
<td>12</td>
<td>133</td>
<td>5.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

- 0  Nothing at all   "No P"
- 0.3 Extremely weak Just noticeable
- 1  Very weak
- 1.5 Weak  Light
- 2  Moderate
- 2.5 Strong  Heavy
- 3  Very strong
- 4  
- 5  Extremely strong "Max P"
- 6  
- 7  
- 8  
- 9  Absolute maximum  Highest possible

Borg CR10 scale
Rating of Pain as a ratio to walking speed
Group Mean (n = 20) (John Buckley)
<table>
<thead>
<tr>
<th></th>
<th>R50X/R50X</th>
<th>R50X/other</th>
<th>R50X/G205s</th>
<th>G205s/G205s</th>
<th>Other</th>
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<tbody>
<tr>
<td>41/75</td>
<td>21/75</td>
<td>9/75</td>
<td>2/75</td>
<td>4/75</td>
<td>Pakistani male: Homozygous exon 1 c.14delT</td>
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<tr>
<td></td>
<td>c2430C&gt;T,G810G</td>
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<td></td>
<td>C2386_2387delG</td>
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<td>c1129A&gt;T,N377Y</td>
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<td></td>
<td>c808C&gt;T, R270X</td>
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<td>c1345G&gt;A,A449G</td>
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<td>c2465C&gt;A,G133R</td>
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<td></td>
<td>c2465C&gt;A,A822D</td>
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<tr>
<td></td>
<td>c403G&gt;A,A822D</td>
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<td>c403G&gt;A,G133R</td>
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<td>c279C&gt;T,R94W</td>
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<td>c1466C&gt;G, P489R</td>
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<td></td>
<td>c107T&gt;C, L36P</td>
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<tr>
<td></td>
<td>3xPro489Arg</td>
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<tr>
<td>54.6%</td>
<td>28%</td>
<td>12%</td>
<td>2.6%</td>
<td>5.3%</td>
<td></td>
</tr>
</tbody>
</table>

R50X, G205S 70% diagnostic, 95% at least one allele mutated
Summary

- Forearm exercise test is not essential for the diagnosis of McArdle disease
- Ischaemia is not necessary
- Protocol must be standardised open to error
- The test should not be performed by inexperienced individuals without supervision
- Useful test normal result excludes glycolytic disorder
- Other forms of exercise testing may be more useful for patients with suspected McArdle disease
Acknowledgements

- John Buckley, Chester University
- Association for Glycogen Storage Disorders