MRI as an outcome measure in clinical trials

Volker Straub
Newcastle University, UK
NMR (MRI and MRS) as an outcome measure

With the development of quantitative approaches in imaging techniques for neuromuscular diseases, the possibility of using magnetic resonance imaging and spectroscopy as a non-invasive outcome measure to assess treatment response is becoming a reality. For this to be a realistic option in future trials, cross-centre comparability of results will be a prerequisite. In work led by Pierre Carlier’s group at the Institut de Myologie, standard operating procedures (SOPs) for certain quantitative techniques have been developed by a multinational (and multi-platform) working group. A manuscript has been prepared for publication, and SOPs for the following techniques:

- Acquisition of T1w images for qualitative evaluation of muscle involvement and topography of lesions in neuromuscular diseases
- Quantification of muscle fat infiltration in neuromuscular diseases using Nuclear Magnetic Resonance imaging 3-point Dixon or spectrally selective excitation techniques.
- Quantitative evaluation of muscle edema or inflammation in neuromuscular diseases using nuclear magnetic resonance T2 measurement techniques

will appear in a special supplement edition of Neuroromuscular Disorders in the near future.
MRI is a tool for different applications

Pattern recognition → e.g. T1w
outcome measures → quantitative MRI, e.g. Dixon technique, T2

Pathophysiology → contrast agents, Diffusion tensor imaging

texture analysis → algorithms
Muscles for Analysis
Analysis

Scaled values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>655</td>
</tr>
<tr>
<td>Image intensity</td>
<td>0 / 4256.7</td>
</tr>
<tr>
<td>Mean</td>
<td>699.05</td>
</tr>
<tr>
<td>SD</td>
<td>60.291</td>
</tr>
</tbody>
</table>

Median: 684.41  Mean: 6203.7  Mode: 684.41
T₁-w Signal Intensity

Hollingsworth K., Muscle & Nerve 2013
LGMD2I project

- Multicentre study including:

- Assessments:
  - medical history
  - cardiac and respiratory assessment
  - myometrium and timed tests

- MR investigations:
  - MRI (T₁ weighted images and 3 point Dixon)
  - phosphorous MRS

5 hours
38 patients with a mutation in the FKRP gene \((\text{Leu276Ile})\)
19 male, 19 female

the scanners:
Newcastle:
Philips 3T Intera Achieva
London, Paris, Copenhagen:
Siemens 3T Trio
Physical assessment in LGMD2I

Assessments

• **FVC** in sitting and lying
• **Myometry**: hip flexors, abductors, adductors, knee flexors, extensors, ankle dorsiflexors
• **Timed tests** including 6 point graded quality of movement: Timed up and go, 10 m walk/run, stair climb and descend and the timed rise from a chair, 6 minute walk distance
• An adapted **Northstar scale** for LGMD2I
Quantification with the 3 point Dixon technique

- Can look for sensitive changes not visible on T1w

19.6% (1.2%)
9.6% (1.1%)
51.9% (1.1%)
67.8% (3.6%)
7.0% (2.2%)
5.1% (2.9%)
67.1% (2.1%)
53.6% (2.1%)
Quantification with the 3 point Dixon technique

The median and IQ ranges for all muscles

- **BFLH**: 4
- **ST**: 3
- **SM**: 3
- **BFSH**: 2b
- **SARTORIUS**: 2b
- **MV**: 2b
- **GRACILIS**: 2a
- **LV**: 2b
- **RF**: 2b
- **MG**: 2b
- **LG**: 2b
- **PL**: 2b
- **SOL**: 2a
- **TA**: 2a

**Fat Percentage**
muscle assessment in LGMD2I

Change in total score on adapted NSAA over 12 month period

- Baseline
- 6 months
- 12 months
muscle assessment in LGMD2I

Distanced covered in 6 minute walk test. Change over a 12 month period
no significant changes in muscle strength and function over 12 months time in LGMD2I

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Baseline min</th>
<th>Baseline max</th>
<th>Baseline median</th>
<th>12 months min</th>
<th>12 months max</th>
<th>12 months median</th>
<th>Difference (sig)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Flex (pounds)</td>
<td>2.2</td>
<td>81.1</td>
<td>16.1</td>
<td>3.0</td>
<td>64.0</td>
<td>13.8</td>
<td>0.36</td>
</tr>
<tr>
<td>Hip Abd (pounds)</td>
<td>1.4</td>
<td>86.1</td>
<td>18.2</td>
<td>5.2</td>
<td>78.5</td>
<td>13.0</td>
<td>0.45</td>
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<tr>
<td>Hip Add (pounds)</td>
<td>1.6</td>
<td>58.9</td>
<td>14.1</td>
<td>4.0</td>
<td>74.8</td>
<td>9.1</td>
<td>0.11</td>
</tr>
<tr>
<td>Knee Flex (pounds)</td>
<td>1.9</td>
<td>66.1</td>
<td>18.6</td>
<td>0.0</td>
<td>70.5</td>
<td>17.7</td>
<td>0.10</td>
</tr>
<tr>
<td>Knee Ext (pounds)</td>
<td>4.3</td>
<td>156.6</td>
<td>26.3</td>
<td>4.4</td>
<td>142.3</td>
<td>20.5</td>
<td>0.82</td>
</tr>
<tr>
<td>Ankle DF (pounds)</td>
<td>5.6</td>
<td>86.3</td>
<td>38.0</td>
<td>4.0</td>
<td>93.6</td>
<td>46.0</td>
<td>0.16</td>
</tr>
<tr>
<td>Stair climb time (secs)</td>
<td>1.4</td>
<td>46.2</td>
<td>5.4</td>
<td>1.7</td>
<td>∞</td>
<td>6.4</td>
<td>0.08</td>
</tr>
<tr>
<td>Stair descend time (secs)</td>
<td>1.5</td>
<td>39.9</td>
<td>3.5</td>
<td>1.25</td>
<td>∞</td>
<td>4.5</td>
<td>0.24</td>
</tr>
<tr>
<td>Chair rise time (secs)</td>
<td>0.4</td>
<td>27.6</td>
<td>2.6</td>
<td>0.6</td>
<td>∞</td>
<td>3.3</td>
<td>0.55</td>
</tr>
<tr>
<td>TUG (secs)</td>
<td>4.3</td>
<td>50.5</td>
<td>12.0</td>
<td>4.1</td>
<td>∞</td>
<td>13.8</td>
<td>0.96</td>
</tr>
<tr>
<td>10 metre time (secs)</td>
<td>2.3</td>
<td>21.5</td>
<td>8.4</td>
<td>2.5</td>
<td>25.0</td>
<td>8.8</td>
<td>0.15</td>
</tr>
<tr>
<td>6MWD (metres)</td>
<td>67</td>
<td>625</td>
<td>312</td>
<td>50</td>
<td>718</td>
<td>353</td>
<td>0.77</td>
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<tr>
<td>FVC (sit) (%) predicted</td>
<td>51</td>
<td>107</td>
<td>81</td>
<td>48</td>
<td>100</td>
<td>76</td>
<td>0.001</td>
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<tr>
<td>FVC (lie) (%) predicted</td>
<td>36</td>
<td>105</td>
<td>71</td>
<td>28</td>
<td>100</td>
<td>66</td>
<td>0.02</td>
</tr>
</tbody>
</table>

except for FVC!

Willis T et al., PLOS ONE 2013
### Muscle MRI: Change in Fat % Over 12 Months in LGMD2I

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Baseline min</th>
<th>Baseline max</th>
<th>Baseline median</th>
<th>12 month min</th>
<th>12 month max</th>
<th>12 month median</th>
<th>Paired diff. (sig)</th>
</tr>
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<tbody>
<tr>
<td>BFLH§</td>
<td>1.5</td>
<td>97.3</td>
<td>71.6</td>
<td>2.2</td>
<td>94.4</td>
<td>75.2</td>
<td>0.004</td>
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<tr>
<td>ST§</td>
<td>2.3</td>
<td>100</td>
<td>55.7</td>
<td>2.1</td>
<td>96.1</td>
<td>59.7</td>
<td>0.021</td>
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<tr>
<td>SM§</td>
<td>2.6</td>
<td>94.1</td>
<td>49</td>
<td>2.9</td>
<td>95.6</td>
<td>54.2</td>
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<tr>
<td>BFSH</td>
<td>2.7</td>
<td>78.1</td>
<td>25.5</td>
<td>4.1</td>
<td>82.3</td>
<td>24.9</td>
<td>0.06</td>
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<tr>
<td>SAR§*</td>
<td>0.85</td>
<td>88.9</td>
<td>24.2</td>
<td>3.4</td>
<td>87.5</td>
<td>25.3</td>
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<td>VM</td>
<td>1.1</td>
<td>89.1</td>
<td>25.6</td>
<td>0.8</td>
<td>83.5</td>
<td>30.9</td>
<td>0.065</td>
</tr>
<tr>
<td>GRAC§*</td>
<td>2.3</td>
<td>81.7</td>
<td>25.3</td>
<td>3.9</td>
<td>84.2</td>
<td>26.6</td>
<td>0.018</td>
</tr>
<tr>
<td>VL§*</td>
<td>0.6</td>
<td>82.1</td>
<td>15.6</td>
<td>1.2</td>
<td>82.1</td>
<td>20.9</td>
<td>0.025</td>
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<tr>
<td>RF§*</td>
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<td>81.3</td>
<td>10.9</td>
<td>0.8</td>
<td>82.1</td>
<td>12.3</td>
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<td>MG§*</td>
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<td>90.3</td>
<td>21.7</td>
<td>1.3</td>
<td>90.3</td>
<td>22.6</td>
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<td>LG§</td>
<td>0.8</td>
<td>88.4</td>
<td>19.3</td>
<td>0.8</td>
<td>87.8</td>
<td>23.9</td>
<td>0.009</td>
</tr>
<tr>
<td>PL</td>
<td>2.8</td>
<td>55</td>
<td>15.1</td>
<td>3.2</td>
<td>61.8</td>
<td>14</td>
<td>0.896</td>
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<tr>
<td>SOL</td>
<td>1.5</td>
<td>84.9</td>
<td>9.1</td>
<td>2.1</td>
<td>86</td>
<td>10.9</td>
<td>0.246</td>
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<tr>
<td>TA</td>
<td>1.4</td>
<td>24.6</td>
<td>5.5</td>
<td>1.3</td>
<td>23.5</td>
<td>5.2</td>
<td>0.627</td>
</tr>
</tbody>
</table>

Willis T et al., PLOS ONE 2013
Phosphorus spectroscopy in LGMD2I

Phosphorus spectra were acquired from the gastrocnemius and soleus.
DMD/LGMD2I project - Acknowledgements

**Newcastle:** Tracey Willis, Kieren G. Hollingsworth, Andrew M Blamire, Anna Mayhew, Michelle Eagle, staff at the Clinical Research Facility: Carol Smith, Louise Morris.

**Copenhagen:** Marie-Louise Sveen and John Vissing, Søren Andersen.

**Paris:** Pierre Carlier, Julie Vandenheede, Tania Stojkovic, Paulo Loureiro, Jean-Yves Hogrel, Claire Wary, Laurie Cabrol.

**London:** Jasper Morrow, Chris Sinclair, John Thornton, Tarek Yousry, Francesco Muntoni, Mike Hanna.

And most importantly the patients.
Workshop report

Towards harmonization of protocols for MRI outcome measures in skeletal muscle studies: Consensus recommendations from two TREAT-NMD NMR workshops, 2 May 2010, Stockholm, Sweden, 1–2 October 2009, Paris, France

Kieren G. Hollingsworth a, Paulo L. de Sousa b,c,d, Volker Straub c,* Pierre G. Carlier b,c,d
Clinical Outcome Study for Dysferlinopathy (COS)

Chief Investigator: Kate Bushby
Project Manager: Brigitta von Rekowski
Sponsor: NUTH NHS Foundation Trust
Funder: Jain Foundation

... and 14 study sites in Europe, USA, Japan, Australia...
COS Study Aims

Systematic long-term longitudinal study in a cohort of at least 150 genetically confirmed patients, to:

• Determine the clinical make-up/ sub-populations (?)
• Determine the natural history/ disease progression
• Determine the utility of OM’s across a broad spectrum of severity
• Collect biomaterial linked to clinical info for biomarker research
• Build an international network of trial-ready sites in dysferlinopathy

Newcastle
30 October – 1 November 2013
COS eligibility criteria and assessments

- Confirmed genetic diagnosis of dysferlinopathy
- \( \geq 10 \) years old
- Ambulant/non-Ambulant with ratio 2:1
- 6 visits over 3 years (screening, baseline, 6 months, 1yr, 2yrs, 3yrs)
- Medical assessments:
  - physical, neurological, respiratory, cardiac, lab tests on blood
- MRI: Dixon, T1w, T2 & B1 mapping (at 13 sites)
- MRS: 31P NMR spectroscopy (at 3 sites)

Newcastle
30 October – 1 November 2013
Thigh muscles; Dixon

Control

Patient

JAIN – Quantitative analysis

1.8%

7.3%

2.1%

86.9%
14 international COS sites

Status as of 30. September 2013

Tokyo: 13
Washington: 0
Columbus: 10
Saint Louis: 4
Charlotte: 11

Enrollment (11 sites): **116** (77%)
Amb. / non-Amb.: **82** / **34** (2.4:1)

Closing date (enrollment): **28. February 2014**

Newcastle: **38** (closed to enrollment)
Berlin: 2
Paris: 2
Munich: **10** (closed to enrollment)
Marseille: 0
Padova: 0
Barcelona: 14
Sevilla: 7
Sydney: 5

94 baseline visits:
86 MRI (9 sites); 34 MRS (Ncl)
67 blood (6 sites); 28 skin (5 sites)
Applications of MR imaging and spectroscopy techniques in neuromuscular disease: collaboration on outcome measures and pattern recognition for diagnostics and therapy development

Volker Straub
Newcastle University, UK

COST Domain - Biomedicine and Molecular Biosciences (BMBS)
Objectives of the network

1. Improve diagnosis and our understanding of muscle pathology → online atlas

2. Develop multicentric imaging outcome measures → SoPs

3. Explore new contrasts, targets and imaging techniques for NMD → clinical testing

4. Explore strategies for muscle imaging texture analysis → validated algorithms
A shadow stalks between the lines
Here in black and there in white,
A shadow falls between the breaths
To emerging lands of gray
Thank You

Institute of Genetic Medicine, Newcastle upon Tyne, UK