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Electrical Impedance Myography as a Biomarker in Neuromuscular Disorders

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Neuromuscular disorders: some common, many rare

- **Common:**
  - Carpal tunnel syndrome, sciatica, diabetic neuropathy, statin-induced myopathy

- **Rare:**
  - **Muscle diseases:** Pompe’s disease, inclusion body myositis, Duchenne muscular dystrophy, Becker’s muscular dystrophy, myotonic dystrophy, dermatomyositis
  - **Nerve diseases:** Charcot-Marie-Tooth neuropathy, chronic inflammatory polyradiculoneuropathy, amyotrophic lateral sclerosis, spinal muscular atrophy
  - **Neuromuscular junction diseases:** Myasthenia gravis, Lambert-Eaton Myasthenic syndrome, botulism
Approaches to assessing disease status and the effect of therapy

- Strength measurements
- Functional assessments
  - Distance walked, timed tasks, complex performance batteries
- Questionnaires
- Imaging (MRI, CT of muscle)
  - Assess muscle size, signal characteristics
- Serologic biomarkers
  - Many currently being investigated
Limitations of current approaches

• Strength measurements
  – What apparatus to use? Variable depending on strength of examiner
  – Fatiguing
• Functional measurements
  – Generally not especially repeatable
  – Limited assessment of non-ambulatory cases, young children, or those who can’t follow directions
  – Fatiguing
• Questionnaires
  – Influenced by mood, generally insensitive
• Imaging
  – Expensive and often inconvenient
  – Difficult to assess multiple body regions
• Serologic markers
  – Very few identified, especially to follow disease status and response to therapy
Electrical impedance myography (EIM)

- Technique based on application of low-intensity, high frequency electrical current to localized areas of tissue and measurement of resulting voltages
Basic concept underlying EIM

Changes in composition and structure of muscle with disease impact the impedance of muscle in unique and reproducible ways.

Normal Muscle  Myopathy/Dystrophy  Neurogenic Atrophy
Advantages of EIM

• Looks at the relevant compartment (ie, the muscle itself)
• Fast and easy to apply
  – At the bedside
  – Requires minimal patient cooperation
• Can use in all age groups
  – From children to the elderly
• Can focus on area of disease activity
  – Proximal or distal muscles for example
• Requires relatively little training
  • Measurements could even be done at home by a caregiver
• Painless and non-invasive
EIM is repeatable and sensitive to change: ALS as an example

**SINGLE MUSCLE** repeatability in 30 normal subjects over a mean of about 2 weeks

15 ALS patients followed over time (average of muscles)

Summary of power analyses

*From Rutkove et al, 2007*

*From Rutkove et al, 2005*
Data in 50 subjects over 6 months in just completed ALS Association funded study

Coefficient of variation in rate of decline = 0.55

Coefficient of variation in rate of decline = 0.84

Coefficient of variation in rate of decline = 0.93
Numbers needed for clinical trial based on 6 month data

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Patients needed per study arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIM</td>
<td>95</td>
</tr>
<tr>
<td>HHD</td>
<td>266</td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>220</td>
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</tbody>
</table>

*Assuming a 6 month, placebo-controlled study, aiming to identify a 20% treatment effect with 80% power, one-tailed, p < 0.05

And EIM correlates to survival…with hazard ratio of 1.40, p = 0.035
Also correlates to rate of decline in HHD (r = 0.41) and ALSFRS (r = 0.43) over 1 year, p <0.001 for both
One challenge: how to get the best data

Based on off-the-shelf technology

Circa 2001

Circa 2004

2001-2009

MIT collaboration (2006-09)

Convergence Medical Devices, Inc

Dedicated EIM devices
Collecting data with our newest device
ALS data using latest device

Reactance of the Biceps \( (R^2 = 0.99) \)

Test

Retest

ALS Patients

Normal subjects

EveryLife Foundation for Rare Diseases
Limitations

• Not directly measuring molecular mechanisms
  – “Blunt tool”

• Discriminating primary muscle from primary nerve disease remains a challenge

• Exact significance of changes uncertain
  – Fat, connective tissue imposition? Loss of normal structure?
  – Animal research program underway to help sort that out

• Superimposed conditions could impact certain aspects of data
  – Obesity, congestive heart failure, kidney failure

• Still relatively new and unfamiliar to most investigators
Future directions/application

• Multiple studies in neuromuscular disease being planned
  – Studies in amyotrophic lateral sclerosis, spinal muscular atrophy, Duchenne muscular dystrophy, hereditary inclusion body myositis, facioscapulohumeral muscular dystrophy now ongoing or planned.

• Identification of best EIM indices

• Establishment of relationship between EIM data and other functional and meaningful outcomes
  – An example: correlation to survival in ALS

• Getting the technology in many people’s hands to increase familiarity and get feedback

• Continually improve and refine the technology
Collaborators and Funding

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