Genetic Susceptibility to Statin-Induced Myopathy

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Goals of this Session

- To describe the extent of cholesterol-lowering drug use & adverse reactions in the U.S.
- To define severe statin myopathy
- To describe a candidate disease approach to risk assessment
At the conclusion of this presentation, participants should be able to

- Understand the prevalence of severe statin myopathy in the U.S.
- Be aware of the extent of persistent symptoms that may exist post-therapy
- Appreciate the candidate disease approach
- Realize the potential benefits of genetic risk assessment
Short History of the Guthrie Laboratory

1984 - present
The Robert Guthrie Biochemical & Molecular Genetics Laboratory

www.rgbmgl.org

- Performs biochemical & molecular diagnostic testing for inborn errors of metabolism with a primary interest in metabolic muscle diseases
- Approx. 6,000 tests/yr on blood or muscle biopsies; receives ~700 biopsies/yr
The Robert Guthrie Biochemical & Molecular Genetics Laboratory

- Biochemical analysis of muscle includes
  - Mitochondrial myopathies
  - Glycogen storage diseases
  - Lipid storage myopathies
  - Defects in purine metabolism
The Robert Guthrie Biochemical Genetics Laboratory

- Molecular testing for triggerable metabolic myopathies
  - Carnitine palmitoyltransferase (CPT) II deficiency
  - McArdle disease (myophosphorylase deficiency)
  - Myoadenylate deaminase deficiency
  - Exercise Intolerance Mutation Profile
Common Features of Triggerable Myopathies

- Exercise intolerance
- Rhabdomyolysis with myoglobinuria
- Elevated serum CK
- Autosomal recessive inheritance
- Manifesting carriers exist
- Muscle biopsies may be histochemically normal
Some of the Triggers

- Strenuous exercise
- Fasting
- Dehydration
- Extremes in temperature
- Sleep deprivation
- Anesthesia
- Viral infection
- Certain medications (e.g., statins)
Increasing Referral of Statin Myopathy Cases

Muscle biopsies referred to Guthrie Laboratory for analysis between 1998 & 2006
Cholesterol-Lowering Drug Therapy

- More than 102 million Americans have total cholesterol levels >200 mg/dL
  - 41 million with total cholesterol >240 mg/dL
- In 2005, 29.7 million people in U.S. on statin therapy
- By 2010, approximately 39 million taking statins

Medical Expenditure Panel Survey (MEPS); Agency for Healthcare Research & Quality
Statin drug use in the past 30 days

**Men**

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>45-64 years</td>
<td>3</td>
<td>15</td>
<td>18</td>
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<tr>
<td>65-74 years</td>
<td>*</td>
<td>26</td>
<td>50</td>
</tr>
<tr>
<td>75 years and over</td>
<td>*</td>
<td>19</td>
<td>45</td>
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**Women**

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<tr>
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<tbody>
<tr>
<td>45-64 years</td>
<td>2</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>65-74 years</td>
<td>*5</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>75 years and over</td>
<td>*2</td>
<td>18</td>
<td>39</td>
</tr>
</tbody>
</table>

*Estimates are considered unreliable. Data preceded by an asterisk have a relative standard error (RSE) of 20%-30%. Data not shown have an RSE of greater than 30%.

SOURCE: CDC/NCHS, Health, United States, 2010, Figure 17. Data from the National Health and Nutrition Examination Survey.
Adverse Reactions to Statin Therapy

- 5-7% (1.95 – 2.73 million) develop muscle aches and pains
- 0.2% (78,000) develop severe rhabdomyolysis
  - Defined primarily by serum CK >10XULN (>10 times the upper limit of normal)

Consequences of Adverse Reactions to Statin Therapy

- Risk of statin therapy withdrawal from >2.3 million patients based on myalgias alone
- 30% (690,000) may develop earlier cardiovascular events secondary to withdrawal of statins
  - Statins reduce cardiovascular endpoint events by 30%

Endogenous Risk Factors for ADRs Associated with Statins

- Advanced age (>80 yrs)
- Small body frame & fragility
- Female sex
- Multisystem disease (e.g., renal function impairment, hypothyroidism, diabetes)
- History of metabolic muscle disease
- Medications metabolized through P-450 3A4

‘Statin Myopathy’

**Original Definition:**
Myalgias that develop with statin therapy accompanied by a serum CK activity >10XULN
Limitations of Definition

- Degrees of myositis + rhabdomyolysis occur in patients with <9XULN CK
- Increased serum CK may occur in asymptomatic patients
- Some patients with statin myopathy have normal serum CK

Updated Definitions of Statin Myopathy

- **Myalgia**: focal or diffuse muscle aches or weakness with normal CK (ACC/AHA/NHLBI)
- **Myopathy**:
  - Any disease of muscle (ACC/AHA/NHLBI)
  - Myalgia with CK $\geq 10\times$ULN (NLA & FDA)
- **Myositis**: muscle pain with CK elevation (ACC/AHA/NHLBI)
- **Rhabdomyolysis**: severe muscle damage with damage to another organ, e.g., kidney, and CK$\geq 10\times$ULN (ACC/AHA/NHLBI & NLA)
  - CK$>50\times$ULN + organ damage (FDA)

Joy TR, Hegele RA. Ann Intern Med 2009;150:858
What about severely affected patients with serum CK <10XULN?

Our Experience
Creatine Kinase in Severe Statin Myopathy

n=166

Derived from Guthrie Laboratory research data during NIH funded study on genetic susceptibility to statin-induced myopathy
Severe Adverse Reactions to Statin Therapy

- 0.2% (78,000) develop severe rhabdomyolysis (CK>10XULN)
- Additional severe cases with CK ranging from normal to 9XULN brings total to 0.52% (~203,000)
Prominent Clinical Features of Severe Statin Myopathy: Our Experience (n=281)

- Persistent symptoms (up to 88%)
- Muscle pain (46%)
- Muscle weakness (46%)
- Fatigue (14%)
- Progressive course (11%)
- Muscle cramps (10%)
Laboratory Features of Severe Statin Myopathy (n=281)

- Elevated serum CK (85%)
  141 of 166 reported
- Myoglobinuria (78%)
  15 of 19 reported
- Abnormal EMG (66%)
  46 of 70 reported
Summary: Our Definition of Severe Statin Myopathy

Robert Guthrie Biochemical & Molecular Genetics Laboratory

- Muscle weakness and/or pain or cramps specifically associated with statin therapy
- Associated fatigue
- Persistent or progressive symptoms may be present for weeks, months or years post therapy
- Serum CK ranging from normal to >10XULN
  - 2/3 expected in the range of 4XULN to >10XULN
Spectrum of Statin Tolerance Leading to Muscle Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>(94.5%)</td>
</tr>
<tr>
<td>Mild Reversible Myalgias</td>
<td>(6%)</td>
</tr>
<tr>
<td>Severe Rhabdomyolysis</td>
<td>(0.5%)</td>
</tr>
</tbody>
</table>
Drug & Dose Dependence of Severe Statin Myopathy (n=155)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>%PerSx</th>
<th>Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atorvastatin (52%)</strong></td>
<td>10</td>
<td>97</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>83</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>100</td>
<td>18</td>
</tr>
<tr>
<td><strong>Pravastatin (5%)</strong></td>
<td>10</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>100</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>100</td>
<td>37</td>
</tr>
<tr>
<td><strong>Simvastatin (21%)</strong></td>
<td>10</td>
<td>67</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>78</td>
<td>33</td>
</tr>
<tr>
<td>Rosuvastatin (9%)</td>
<td>5</td>
<td>75</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>88</td>
<td>24</td>
</tr>
</tbody>
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Hypothesis

A higher proportion of individuals with statin myopathy will have underlying metabolic disorders than expected in the general population.
Preliminary Studies

- Test Group: 136 severe statin myopathy cases
- Controls:
  - 100 general population (no exposure to statins)
  - 116 statin tolerant
  - 106 non-statin myopathy
- Biochemical analysis of muscle biopsies
- Exercise Intolerance Mutation Profile
Biochemical Studies

- 52% of biopsies had significant biochemical deficiencies
  - 31% of these with multiple deficiencies
  - CK more likely ≥10XULN in patients with multiple deficiencies
- Coenzyme Q10 and CPT were most commonly reduced
  - 2.3-fold more men than women had muscle CoQ10 deficiency (P=0.009)
Conclusions from Molecular Studies

- 10% of myopathic patients had disease-causing mutations (3% with mutations among statin-tolerant controls)
- Carriers for CPT II deficiency and McArdle disease increased 12- and 20-fold, respectively, over general population
- Homozygotes for myoadenylate deaminase deficiency increased 3.25-fold
GENETIC RISK FACTORS ASSOCIATED WITH LIPID-LOWERING DRUG-INDUCED MYOPATHIES

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MARK TARNOPOLSKY, MD, PhD,3 WENDY L. PELTIER, MD,4 ALEXANDRU C. BARBOI, MD,4
NAGANAND SRIPATHI, MD,7 ROBERT L. WORTMANN, MD,6 and PAUL S. PHILLIPS, MD7
### Implications of Increased Carrier Status in Statin Myopathy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Carrier Frequency</th>
<th>Homozygote Frequency</th>
<th>-fold increase in risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT II deficiency*</td>
<td>1/270</td>
<td>1/300,000</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>McArdle disease**</td>
<td>1/170</td>
<td>1/100,000</td>
<td>&gt;500</td>
</tr>
</tbody>
</table>

*Derived from data generated in the Guthrie Laboratory

**Haller RG. Arch Neurol 2000;57:923-4
Toward Statin Myopathy Risk Assessment

- Carriers for additional metabolic myopathies may be prevalent among patients with severe statin myopathy
A Case of Severe Statin Myopathy

Case Report: 54-year-old man

- Onset of muscle pain & severe exercise intolerance 2 mos. following initiation of atorvastatin therapy
- Persistent symptoms post-therapy with no weakness or atrophy
- Serum CK 10XULN
54-year-old Man with Statin Myopathy

Mutation Analysis:

Carrier for the common R50X mutation in the *PYGM* gene causative for McArdle disease
Is the finding of genetic risk factors for statin myopathy good news for drug companies?
Yes!

- ADRs are not necessarily due to statins
- ADRs may be due, in large part, to genetic susceptibility for muscle disease
- Alteration of dosage or statin type may help reduce or prevent symptoms
Is the finding of genetic risk factors for statin myopathy good news for physicians?
Yes!

- Selected testing of high risk individuals will identify many of those at risk for ADRs and allow better medical management
Serum Creatine Kinase Monitoring During Statin Therapy

- Important to know baseline CK
- Racial variation exists
  - African Amer males (800-1,000 U/L)
- Gender differences
  - CK > in males than females
- Asymptomatic familial HyperCKemia exists (Baker & Samjoo, Can J Neurol, 2008)
  - Elevated CK may persist post-therapy
Indications That Qualify Patients for Genetic Testing Prior to Statin Therapy

- History of muscle disease
- Idiopathic hyperCKemia
- Multi-system disease
Testing of High Risk Groups

- Baseline CK at least for anyone with the core endogenous risk factors
- Mutation panel for common metabolic myopathies
  - McArdle disease
  - CPT II deficiency
  - Myoadenylate deaminase deficiency
  - Additional disorders to be included
Statin Myopathy
Project Collaborators

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University at Buffalo
Paul J. Isackson, Ph.D.
Edward Fine, M.D.
Comprehensive Genotyping for Susceptibility to Metabolic Muscle Disease

Funding Source: STTR Grant Phase I NHLBI
Comprehensive Genotyping: Categories of Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of Genes</th>
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<tr>
<td>Fatty Acid Oxidation</td>
<td>7</td>
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<tr>
<td>CoQ10 deficiency</td>
<td>5</td>
</tr>
<tr>
<td>Glycogen Storage Disease</td>
<td>3</td>
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<tr>
<td>Muscular Dystrophies</td>
<td>4</td>
</tr>
<tr>
<td>Purine Cycle Defect</td>
<td>1</td>
</tr>
<tr>
<td>Malignant Hyperthermia</td>
<td>1</td>
</tr>
<tr>
<td>Mitochondrial Disease</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>33</strong></td>
</tr>
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</table>
Comprehensive Genotyping for Susceptibility to Metabolic Muscle Disease

Test & Control Groups
Clinical Unknown Myopathy Group (n=392)
Severe Statin Myopathy Group (n=197)
Mild Statin Myopathy Group (n=163)
Statin-Tolerant Control Group (n=133)
## Results of Genotyping

### Variants & Mutations Detected (%)

<table>
<thead>
<tr>
<th>Disorder Category</th>
<th>Severe Statin Myopathy</th>
<th>Non-Statin Myopathy</th>
<th>Statin-Tolerant Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant Hyperthermia</td>
<td>1.5</td>
<td>2.1</td>
<td>0</td>
</tr>
<tr>
<td>Fatty Acid Oxidation Defects</td>
<td>13.5</td>
<td>7.0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>12.1</td>
<td>3.8</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>27.1</strong></td>
<td><strong>12.9</strong></td>
<td><strong>1.8</strong></td>
</tr>
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</table>
Mutations in Ryanodine Receptor Gene (\textit{RYR1}) Cause Malignant Hyperthermia (MH)

- 30 dominantly inherited causative mutations
  - Account for 50-60\% of causative mutations
- Prevalence 1 in 5,000 to 1 in 50,000 with incomplete penetrance
Comprehensive Genotyping for Susceptibility to Metabolic Muscle Disease

- STTR Grant Phase II
- NHLBI
Risk Groups Eligible for Metabolic Muscle Disease Testing

- Evidence for MH
  - FH, CHCT(+), EPI

- Exercise Intolerance + Rhabdomyolysis
  - McArdle disease
  - CPT II deficiency
  - Myoadenylate deaminase deficiency
  - Very-Long-Chain Acyl-CoA dehydrogenase deficiency

- Other Clinical Entities
  - Viral-induced myositis
  - Inflammatory myositis
  - Muscular dystrophies
  - Muscle weakness
  - Hyper-CK-emia

- Multi-Trigger Exposure
  - Extreme exertion
  - Extremes in temperature
  - Drug exposure (e.g., statins)
  - Fasting
  - Anesthesia
  - Sleep deprivation
  - Viral infection

- Armed Services Personnel
- Individuals taking statins
Statin Myopathy Study

5-yr RO1 NHLBI

Cathy Kern – Research Coordinator

ckern@buffalo.edu

www.rgbmgl.org