MH-Related Diseases

Who Really Needs a Non-triggering Technique?

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Disclosures.....
Lecture Overview

✓ SHORT MH REVIEW

✓ WHO REALLY NEEDS A NON-TRIGGERING TECHNIQUE?

✓ DIAGNOSTIC TESTING
Important MH Principles
MH Pathophysiology

Exposure to Triggering Anesthetic Agent
Volatile Inhalational Anesthetic Gases
Succinylcholine

SKELETAL MUSCLE CELL

Depolarization

Sarcolemma
Transverse (T) Tubule
Terminal Clefts of SR
Sarcoplasmic Reticulum (SR)

1. Depolarization
2. Activation
3. Activation
4. Increased Intracellular Ca²⁺
5. Prolonged Open State of RYR1

Dantrolene Sodium

Sustained Muscle Cell Activation and Contraction
Increased Aerobic and Anaerobic Metabolism

Heat Production
Muscle Cell Hypoxia and Death

Malignant Hyperthermia Syndrome
Metabolic and Respiratory Acidosis
Muscular Rigidity
Rhabdomyolysis
Hyperthermia
Exposure to Triggering Anesthetic Agent
Volatile Inhalational Anesthetic Gases
Suxamethonium

Depolarization

Sarcolemma
Transverse (T) Tubule
Terminal Cisterns of SR
Sarcoplasmic Reticulum (SR)

1. Depolarization
2. Activation
3. Activation
4. Prolonged Open State of RYR1

Increased Intracellular Ca^{2+}

Dantrolene Sodium

SR Lumen

Sustained Muscle Cell Activation and Contraction
Increased Aerobic and Anaerobic Metabolism

Heat Production
Muscle Cell Hypoxia and Death

Malignant Hyperthermia Syndrome
Metabolic and Respiratory Acidosis
Muscular Rigidity
Rhabdomyolysis
Hyperthermia
MH Mortality in ASC

Cheerleader’s death highlights rare surgical risk
High school senior dies after undergoing cosmetic breast surgery

By Mike Celizic
TODAYShow.com contributor
updated 10:19 a.m. ET, Wed., March 26, 2008

Stephanie Kuleba’s friends called her “Sunshine” because that was the perfect nickname for the outgoing and bubbly girl who was everybody’s friend, the cheerleader with the near-perfect grade-point average who was too nice and too perfect for anybody to resent.

“She was just the kind of girl that everyone loved,” a friend, Dayna Mercer, told NBC News. “There was nothing bad about her.”

But the 18-year-old high school senior, who was headed to college and then medical school, felt...
MH-Associated Diseases

3 categories

1. Definitely linked to MHS
2. Rhabdomyolysis but not MH
3. Unproven and unconvincing
Genetic Basis of MH

RYR 1

3D ryanodine from Max Planck Society
Central Core Myopathy

RYR 1

transmembrane assembly

1 2 A
6 7
13 14 D
19 20 F

A
King-Denborough Syndrome

RYR 1

[Diagram showing genetic information and images of a person]
Obscure RYR1 Myopathies

- MmD with external ophthalmoplegia
- Multiminicore myopathy
- Congenital myopathy w cores/rods
- Central nuclear myopathy
- NMD w uniform type 1 fibers
- Congenital fiber type disproportion
Clinical Report

Native American Myopathy:
Congenital Myopathy With Cleft Palate, Skeletal Anomalies, and Susceptibility to Malignant Hyperthermia

Demetra S. Stamm,1,2 Arthur S. Aylsworth,3,4 Jeffrey M. Stajich,2 Stephen G. Kahler,5 Leigh B. Thorne,6 Marcy C. Speer,2† and Cynthia M. Powell3,4,*

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2Center for Human Genetics, Duke University, Durham, North Carolina
3Department of Pediatrics, Division of Genetics and Metabolism, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
4Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
5Department of Pediatrics, Section of Genetics, University of Arkansas for Medical Sciences, Little Rock, Arkansas
6Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Received 24 July 2007; Accepted 7 April 2008
Hypokalemic Periodic Paralysis

CACNL1A3

Malignant-Hyperthermia Susceptibility Is Associated with a Mutation of the α1-Subunit of the Human Dihydropyridine-Sensitive L-Type Voltage-Dependent Calcium-Channel Receptor in Skeletal Muscle

Nicole Monnier,1 Vincent Procaccio,1,3 Paul Stieglitz,2 and Joël Lunardi1,3

1Laboratoire de Biochimie de l’ADN and 2Département d’Anesthésie, CHU Grenoble, and 3Laboratoire BECP, EA 2019 UJF, DBMS-CEA Grenoble, Grenoble

MH-Associated Diseases

3 categories

1. Definitely linked to MHS
2. Rhabdomyolysis but not MH
3. Unproven and unconvincing
Muscular dystrophies
McArdle’s disease
CPT-2 deficiency
Myoadenylate deaminase deficiency

Rhabdomyolysis
Muscular Dystrophies

- Duchenne type – X-linked
- Becker type – X-linked
- Limb-girdle
- Emery-Dreifuss
- Facioscapulohumeral
- Oculopharyngeal
- Congenital
- Myotonic
Duchenne Muscular Dystrophy

- Extracellular matrix
- Dystrophin-associated glycoprotein complex
- Sarcolemma
- C-terminus
- Dystrophin
- Actin-binding region
- α helix
- Linking proteins
- Actin filaments
Duchenne Muscular Dystrophy

Recommendations:

- Succinylcholine **absolutely contraindicated**
- Volatile agents **relatively contraindicated**
- Pre-op screening
Surgery and Anesthesia

EndDuchenne.org

CONNECT

Email

SIGN UP

HOW WE HELP

Parent Project
Muscular Dystrophy
LEADING THE FIGHT TO END DUCHEENNE
Heat Stroke and MH

- 12 year old child has acute MH in OR
- CHCT shows MH susceptibility
- 8 mos later: dies after football practice: T 108 F
- RYR-1 mutation detected in pt and relatives

Tobin et al. JAMA, 286, 2001
Clinical update

Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management

### Box 1  Risk factors for statin-associated muscle symptoms. Adapted from Mancini et al.9

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropometric</td>
<td>Age &gt; 80 years old (general caution advised for age &gt; 75)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>Low body mass index</td>
</tr>
<tr>
<td></td>
<td>Asian descent</td>
</tr>
<tr>
<td>Concurrent</td>
<td>Acute infection</td>
</tr>
<tr>
<td>conditions</td>
<td>Hypothyroidism (untreated or undertreated)</td>
</tr>
<tr>
<td></td>
<td>Impaired renal (chronic kidney disease classification 3, 4, and 5) or hepatic function</td>
</tr>
<tr>
<td></td>
<td>Biliary tree obstruction</td>
</tr>
<tr>
<td></td>
<td>Organ transplant recipients</td>
</tr>
<tr>
<td></td>
<td>Severe trauma</td>
</tr>
<tr>
<td></td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Vitamin D deficiency</td>
</tr>
<tr>
<td>Surgery</td>
<td>Surgery with high metabolic demands. The American Heart Association recommends temporary cessation of statins prior to major surgery10</td>
</tr>
<tr>
<td>Related history</td>
<td>History of creatine kinase elevation, especially &gt; 10 × the upper limit of the normal range</td>
</tr>
<tr>
<td></td>
<td>History of pre-existing/unexplained muscle/joint/tendon pain</td>
</tr>
<tr>
<td></td>
<td>Inflammatory or inherited metabolic, neuromuscular/muscle defects (e.g. McArdle disease, carnitine palmitoyl transferase II deficiency, myoadenylate deaminase deficiency, and malignant hyperthermia)</td>
</tr>
<tr>
<td></td>
<td>Previous statin-induced myotoxicity</td>
</tr>
<tr>
<td></td>
<td>History of myopathy while receiving another lipid-lowering therapy</td>
</tr>
</tbody>
</table>
Awake MH?

Identical de novo Mutation in the Type 1 Ryanodine Receptor Gene Associated with Fatal, Stress-induced Malignant Hyperthermia in Two Unrelated Families

Linda Groom, B.Sc.,* Sheila M. Muldoon, M.D.,† Zhen Zhi Tang, Ph.D.,‡ Barbara W. Brandom, M.D.,§ Munkhuu Bayarsaikhan, Ph.D.,∥ Saiid Bina, Ph.D.,# Hee-Suk Lee, M.D.,** Xing Qiu, Ph.D.,†† Nyamkhishig Sambuughin, Ph.D.,‡‡ Robert T. Dirksen, Ph.D.§§

Anesthesiology 2011; 115:938

7 reported cases
MH-Associated Diseases

3 categories

1. Definitely linked to MHS
2. Rhabdomyolysis but not MH
3. Unproven and unconvincing
Noonan’s Syndrome
Osteogenesis Imperfecta
Arthrogryposis
Kearns-Sayre syndrome (KSS)
Leigh's syndrome
Mitochondrial DNA depletion syndrome (MDS)
Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)
Myoclonus epilepsy with ragged red fibers (MERRF)
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
Neuropathy, ataxia and retinitis pigmentosa (NARP)
Pearson syndrome
Progressive external ophthalmoplegia (PEO)
Mitochondrial Myopathies

No association with MH Susceptibility
Summary

Definitely associated with MH

- Central Core myopathy
- Multiminicore myopathy
- King-Denborough syndrome
- Any Ryanodine Myopathy
- Native American Myopathy
- Hypokalemic Periodic Paralysis

RYR1
Central Core Myopathy
Multiminicore Myopathy
King-Denborough Syndrome
Any Ryanodine Myopathy
Native American Myopathy
Hypokalemic Periodic Paralysis

STAC3
Summary

Definitely associated with MH

- Central Core myopathy
- Multiminicore myopathy
- King-Denborough syndrome
- Any Ryanodine Myopathy
- Native American Myopathy
- Hypokalemic Periodic Paralysis

CACNL1A3
MH Susceptibility in Some Patients

Heat Stroke rhabdomyolysis

Exercise-induced rhabdomyolysis
Diseases Not associated with MH Susceptibility

Arthrogryposis

O.I.

Noonan’s

Duchenne’s
Volatile Agent-induced Rhabdomyolysis

- Dystrophinopathies
- McArdle’s disease
- Myoadenylate deaminase deficiency
- CPT-2 deficiency
- Exaggerated rhabdo after heat, exercise, or statins
STOP

To protect private Patient Information

Only (1) family allowed at the desk at a time

Last name appears on monitor when prescription is ready

Thank You.
MHAUS GUIDELINES

Testing for Malignant Hyperthermia (MH) Susceptibility:

How do I counsel my patients?
Muscle Contracture Testing (CHCT)
CHCT Testing, U.S. and Canada

University of Minnesota
Minneapolis, MN
Paul A. Iaizzo, PhD
(612) 624-7912 or -3959

Uniformed Services University
of the Health Sciences
Bethesda, MD
(Military & Civilian)
Sheila M. Muldoon, MD

University of California
Davis, CA
Timothy Tautz, MD

Wake Forest University
Winston-Salem, NC
Joseph R. Tobin, MD

Toronto General Hospital
Toronto, Ontario
Julian Loke, MD, FRCPC
Genetic Testing: RYR1 Gene Sequencing

RYR1: gene structure and mutational spots

Myoplasmic domain

Transmembrane

NH$_2$

C35, R614

D2129, R2458

R4214, R4914

COOH

DHPR binding

Calmodulin binding
MALIGNANT HYPERThERMIA SUSCEPTIBILITY NEXTGEN SEQUENCING (NGS) PANEL

TEST METHODS

- NEXTGEN SEQUENCING
- DELETION/DUPLICATION TESTING VIA ARRAY COMPARATIVE GENOMIC HYBRIDIZATION

NEXTGEN SEQUENCING

<table>
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<tr>
<th>Test Number</th>
<th>Test</th>
<th>Price</th>
<th>CPT Code(s)</th>
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</thead>
<tbody>
<tr>
<td>1383</td>
<td>NextGen Sequencing (3 genes)</td>
<td>$1,590</td>
<td>81479 (x2), 81408</td>
</tr>
</tbody>
</table>

In addition, Targeted Familial Mutation testing via Sanger sequencing is available for any gene in the panel:

<table>
<thead>
<tr>
<th>Test Number</th>
<th>Test</th>
<th>Price</th>
<th>CPT Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Targeted Familial Mutations - Single Exon Sequencing</td>
<td>$250</td>
<td>81479</td>
</tr>
<tr>
<td>200</td>
<td>Targeted Familial Mutations - Double Exon Sequencing</td>
<td>$370</td>
<td>81479</td>
</tr>
<tr>
<td>300</td>
<td>Targeted Familial Mutations - Triple Exon Sequencing</td>
<td>$440</td>
<td>81479</td>
</tr>
</tbody>
</table>
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