Approach to Muscle Cramps, Exercise Intolerance and Recurrent Myoglobinuria

WCN, Dubai 2019

Ingrid Tein MD

Division of Neurology
Dept. of Pediatrics, Laboratory Medicine and Pathobiology
Genetics and Genome Biology Program
The Hospital for Sick Children
The University of Toronto, Toronto, Canada
Ingrid.tein@sickkids.ca
Disclosures

Canadian Institutes of Health Research
Canadian Foundation of Innovation
United Mitochondrial Diseases Foundation
Physicians’ Services Incorporated Foundation
Heart and Stroke Foundation
Rare Diseases Foundation
Myositis Association
Foundation for Prader Willi Research
Learning Objectives

• To define the Clinical Syndrome of Myoglobinuria

• Metabolic Myopathies: Recurrent Hereditable Myoglobinuria
To acquire an understanding of the Etiologies and Pathophysiological Mechanisms

• To provide an Approach to Diagnosis

• To recognize the key differentiating features between disorders of glycogen and lipid metabolism

• To recognize mitochondrial disorders
Myoglobinuria: Definition of Clinical Disorder

1. If patient alert:

A. Myalgia or limb weakness
B. Pigmenturia
   1. Test in urine is positive but there are a few red blood cells in urine
   2. Identification as myoglobin by immunochemical method

C. Serum creatinine kinase (CK) and other sarcoplasmic enzyme levels usually > 100 times the upper normal limit during acute attack

D. Inconstant features: increased serum uric acid level, increased PO\(_4\), increased or decreased Ca\(^{2+}\) level; if renal failure, serum K\(^{+}\) and Ca\(^{2+}\) levels increase
2. If patient is comatose or in acute renal failure, there may be no muscular symptoms or signs, but:

A. Serum sarcoplasmic enzymes levels are 100 times normal

B. There is biochemical evidence of renal failure
Overview of Bioenergetic Metabolism

Fatty acids  Carbohydrates  Amino Acids
Glycolysis/Glycogenolysis

⇓  ⇓  ⇓
Pyruvate  ↔  ↔  ↔  ↔

⇓  Fatty acid oxidation

⇒  ⇒  ⇒  ⇒  Acetyl-CoA

⇓
Tricarboxylic Acid Cycle

⇓
Mitochondrial Respiratory Chain

Oxidative Phosphorylation

⇓
ATP
Approach to Acute Attack of Myoglobinuria

7 Key Points to Remember

1. Hydration/Diuresis if no renal failure
2. Provide Energy supply
3. Bed rest
4. Correct K+, Ca++
5. Monitor for cardiac arrhythmias
6. Watch for respiratory failure
7. Watch for renal failure

**Urine:** Hematest +, microscopy: no or few RBCs

⇓
Check for Ketones -> if high and serum glucose low -> not FAO defect

-> if low/moderate -> Urine OA -> if Dicarboxylicaciduria consider FAO defect

FAO= fatty acid oxidation
Approach to Acute Attack of Myoglobinuria

**Blood**
- CK, AST

**CORE TESTS**
- Glucose, Electrolytes $\rightarrow$ K+, Ca++, PO4 -, albumin
- BUN, Creatinine, Uric Acid

**CRITICAL METABOLIC STUDIES**
- Glucose $\rightarrow$ if normal, consider defect other than FAO disorder
  - $\rightarrow$ if low, check Free fatty acid: Ketone ratio $\rightarrow$ if 1:1 $\rightarrow$ not FAOD
  - $\Downarrow$
  - If $>2:1$ $\rightarrow$ check serum carnitine total and free + acylcarnitine
  - $\Downarrow$
  - If low total and free carnitine + increased acylcarnitines
  - $\Downarrow$
  - FAO disorder

- Lactate $\rightarrow$ if normal, consider glycolytic defect, etc.
  - $\rightarrow$ if elevated $\rightarrow$ Lactate/pyruvate ratio $\rightarrow$ if low $\rightarrow$ PDP1 defect
  - $\rightarrow$ if high $\rightarrow$ mitochondrial
Hereditable Causes of Metabolic Myopathy and Myoglobinuria

I. Biochemical Abnormality Known

1. **Glycolysis/Glycogenolysis**

   (1) Phosphorylase (McArdle, 1951) *
   (2) Phosphofructokinase (Tarui, Layzer, 1965) *
   (3) Phosphoglycerate kinase (DiMauro, 1981) *
   (4) Phosphoglycerate mutase (DiMauro, 1981) *
   (5) Lactate dehydrogenase (Kanno, 1980) *
   (6) Phosphorylase “b” kinase (Abarbanel, 1986)
   (7) Debrancher (Brown, 1986)
   (8) Aldolase A (Kreuder, 1996) *

* Etiologies documented to cause recurrent myoglobinuria beginning in childhood
Hereditable Causes of Metabolic Myopathy and Myoglobinuria

2. Fatty Acid Oxidation
   (1) Carnitine palmitoyltransferase II (DiMauro, 1973)
   (2) Long-chain acyl-CoA dehydrogenase (Roe, 1986)
   (3) Short-chain L-3-hydroxyacyl-CoA dehydrogenase (Tein, 1990)
   (4) Very long-chain acyl-CoA dehydrogenase (Turnbull, 1994)
   (5) Medium-chain acyl-CoA dehydrogenase (Ruitenbeek, 1995)
   (6) TFP/Long-chain L-3-hydroxyacyl-CoA DH (Tein, 1995)
   (7) Medium-chain 3-ketoacyl CoA thiolase (Kamijo et al., 1997)

3. Pentose Phosphate Pathway
   (1) G6PD (Bresolin, 1988)
Hereditable Causes of Metabolic Myopathy and Myoglobinuria

4. **Purine Nucleotide Cycle**
   (1) Myoadenylate deaminase (Hyster, 1989)

5. **Respiratory Chain**
   (1) Complex II and aconitase, ISCU (Haller, 1991)
   (2) Coenzyme Q10 deficiency (Ogasahara, 1989)
   (3) Multiple Mitochondrial DNA deletions (Ohno, 1991)
   (4) Complex I deficiency (de Lonlay-Debeney, 1999); ACAD9
   (5) Complex III deficiency (cytochrome b) (Andreu, 1999)
   (6) Complex IV deficiency (COX deficiency) (Keightley, 1996)
   (7) ETF-DH with muscle CoQ10 deficiency (Gempel, 2007)
   (8) mtDNA m.4281 A>G (Ile) with COX def. (Emmanuele 2011)

6. **Pyruvate Dehydrogenase Phosphatase 1 (PDP1)** (Maj, 2005)

7. **Lipoamide Dehydrogenase Deficiency** (Elpeleg, 1997)

8. **Muscle-specific phosphatidic acid phosphatase LPIN1** (Zeharia, 2008)
Mitochondrial Disorders

General Prevalence

\[ \geq \frac{1}{5000} \]

Most common inborn error of metabolism

nDNA encoded disorders

\[ \sim 80\% \]

> 1500 proteins

mtDNA encoded disorders

\[ \sim 15-20\% \]

encode 13 subunits OXPHOS

2 rRNAs (12S,16S) 22 tRNAs, and ncRNA

> 260 pathogenic mutations +120 large-scale rearrangements

\[ \sim \frac{1}{200} \] infants found to harbour one of the 10 most common pathogenic point mutations

Parikh et al., 2015; Schon et al 2012; Elliott et al., 2008
“Key Neurological Features”

- Ophthalmoplegia
- Stroke
- Seizures
- Ataxia
- Myoclonus
- Exercise intolerance fatigue
- Myopathy
- Rhabdomyolysis
- Mental regression
- Headache
- Cortical blindness
- Optic neuropathy
- Sensorineural hearing loss
- Dystonia
- Myelopathy
- Peripheral neuropathy
“Key Systemic Features”

- Retinitis pigmentosa
- Short stature
- Diabetes mellitus
- Hypertrophic cardiomyopathy
- Renal tubular acidosis
- Sideroblastic anemia
- Hypoparathyroidism
- Intestinal pseudo-obstruction
- Failure to thrive
Principles of Mt DNA

- **Maternal inheritance** - all mtDNA from oocyte

- **Heteroplasmy**
  - each cell has numerous mutant and wild-type mtDNA which at cell division, distribute randomly among daughter cells

- **Mitotic segregation**
  - At cell division, percentage of mutant to wild-type in daughter cells may shift from one generation to another and the phenotype may change

- **Threshold effect**
  - Minimum critical number of mutant mtDNA to cause mitochondrial dysfunction in an organ
  - Lower in tissues highly dependent on oxidative metabolism
Dependence of Skeletal Muscle on Different Metabolic Pathways

A. Resting State:

Heavy dependence on FFA’s and fatty acid oxidation

Glucose utilization ~ 10-15% of total body turnover and accounts for 10% of oxygen consumption
Dependence of Skeletal Muscle on Different Metabolic Pathways

B. Working State:

Dependent upon, type, intensity and duration of exercise

**Moderate exercise:**

1. High energy phosphates initially
2. Muscle glycogen for first 5-10 minutes ---> lactate
3. Muscle triglycerides and blood-borne fuels
4. After 90 minutes, FFA and glucose

**Mild-Moderate prolonged exercise:**

1. Between 1-4 hours, FFA uptake increases 70%
2. After 4 hours, FFA utilized 2X carbohydrates
Proposed Mechanisms for Myoglobinuria

1. **Glycolytic disorders**
   (a) Decreased ATP

2. **Fatty acid oxidation disorders**
   (a) Decreased ATP
   (b) Detergent properties of LCFA’s on membranes
       predisposing to free radical lipid membrane peroxidation
   (c) Inhibition of key metabolic pathways (β-oxidation, gluconeogenesis, TCA cycle) by FFA/metabolites

3. **Respiratory Chain defects**
   (a) Decreased ATP
## Differentiation Between Disorders of Glycogen vs Lipid Metabolism Resulting in Exercise Intolerance and/or Myoglobinuria

<table>
<thead>
<tr>
<th></th>
<th>Glycolytic/Glycogenolytic Myophosphorylase Deficiency</th>
<th>Fatty Acid Oxidation Carnitine Palmitoyltransferase II Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>Muscle cramps</td>
<td>Muscle stiffness</td>
</tr>
<tr>
<td>Fixed weakness</td>
<td>More common – proximal</td>
<td>Less common</td>
</tr>
<tr>
<td>Symptom onset in exercise</td>
<td>Early (first few minutes)</td>
<td>Late (usually after 1 hour or several hours later)</td>
</tr>
<tr>
<td>Second wind phenomenon</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td>Abnormal forearm ischemic lactate test</td>
<td>+</td>
<td>Normal</td>
</tr>
<tr>
<td>Delayed ketogenesis on fasting</td>
<td>None</td>
<td>+</td>
</tr>
<tr>
<td>Muscle Biopsy</td>
<td>+/- Glycogen storage</td>
<td>+/- Microvesicular lipid storage</td>
</tr>
</tbody>
</table>

FIG. 1 APPROACH TO INVESTIGATION OF HEREDITABLE RECURRENT MYOGLOBINURIA

ENERGY DEFECT

FOREARM ISCHEMIC EXERCISE LACTATE TEST
IN VITRO LACTATE TEST

↓ LACTATE
EARLY CRAMPS

GLYCOLYTIC/GLYCOGENOLYSIS DEFECTS

NO HEMOLYTIC ANEMIA + H.A. OR RBC ABN

PHOSPHORYLASE PGAM
LDH

+ SZ X-LINKED
PGK

A.R. + TCA CYCLE
PFK
ALDOLASE A

RESPIRATORY CHAIN
(COMPLEXES I,II,III,IV, CoQ10, ISCUI, ETF-DH)
LIPOAMIDE DH
PDH PHOSPHATASE I

? LACTATE

+ HA G6PDH
LPIN1

NORMAL

DELAYED OR DECREASED

FATTY ACID OXIDATION DEFECT

FIXED WEAKNESS
CARDIOMYOPATHY

INTERICTAL NORMAL POWER
CARDIOMYOPATHY

NO CARDIOMYOPATHY

CPT II MILD

Ischemic Forearm Lactate Test in McArdle’s Disease

- IV catheter in antecubital vein
- Cuff occlusion of arterial flow in upper arm
- Isometric hand grip contractions 1s on/1s off X 1-2 min of dynamometer (* stop immediately if pain or contracture)

Results

- Pressure transducer indicates rapid decrease in maximum voluntary contraction (MVC) at 40 sec
- Blunted rise in lactate (< 2 X vs 4-5 X) at 1 min
- Exaggerated rise in ammonia (10 X vs 4-5 X) at 1 min
ETF-DH Deficiency

- Exercise intolerance
- Fatigue
- Proximal myopathy
- Elevated serum CPK
- Lipid storage myopathy

- Lab
  - Isolated muscle Coenzyme Q10 deficiency
  - Markedly decreased Complex I and II-III
  - Moderately decreased Complex IV

- Treatment: CoQ10 + Riboflavin

Gempel K et al. Brain 2007; 130:2037-44
Muscle-specific phosphatidic acid phosphatase - LPIN1

- LPIN1 gene encodes muscle-specific phosphatidic acid phosphatase
- Key enzyme in triglyceride and membrane phospholipid biosynthesis
- Pathology: accumulation of phosphatidic acid and lysophospholipids in muscle
- Clinical presentation:
  - Onset ages 2-7 years
  - Recurrent myoglobinuria precipitated by febrile illness and episodes lasting 7-10 days
  - CNS and heart are spared
  - One of six individuals with statin-induced myopathy was a carrier for Glu769Gly pathogenic mutation in LPIN1 gene
  - Normal neuromuscular exam and CK between episodes

References


