

# 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](mailto:Ingrid.tein@sickkids.ca)

# Disclosures

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Heart and Stroke Foundation

Rare Diseases Foundation

Myositis Association

Foundation for Prader Willi Research

# Learning Objectives

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- To define the Clinical Syndrome of Myoglobinuria
- Metabolic Myopathies: Recurrent Hereditary 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  $\text{PO}_4$ , increased or decreased  $\text{Ca}^{2+}$  level; if renal failure, serum  $\text{K}^+$  and  $\text{Ca}^{2+}$  levels increase

# Myoglobinuria: Definition of Clinical Disorder

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

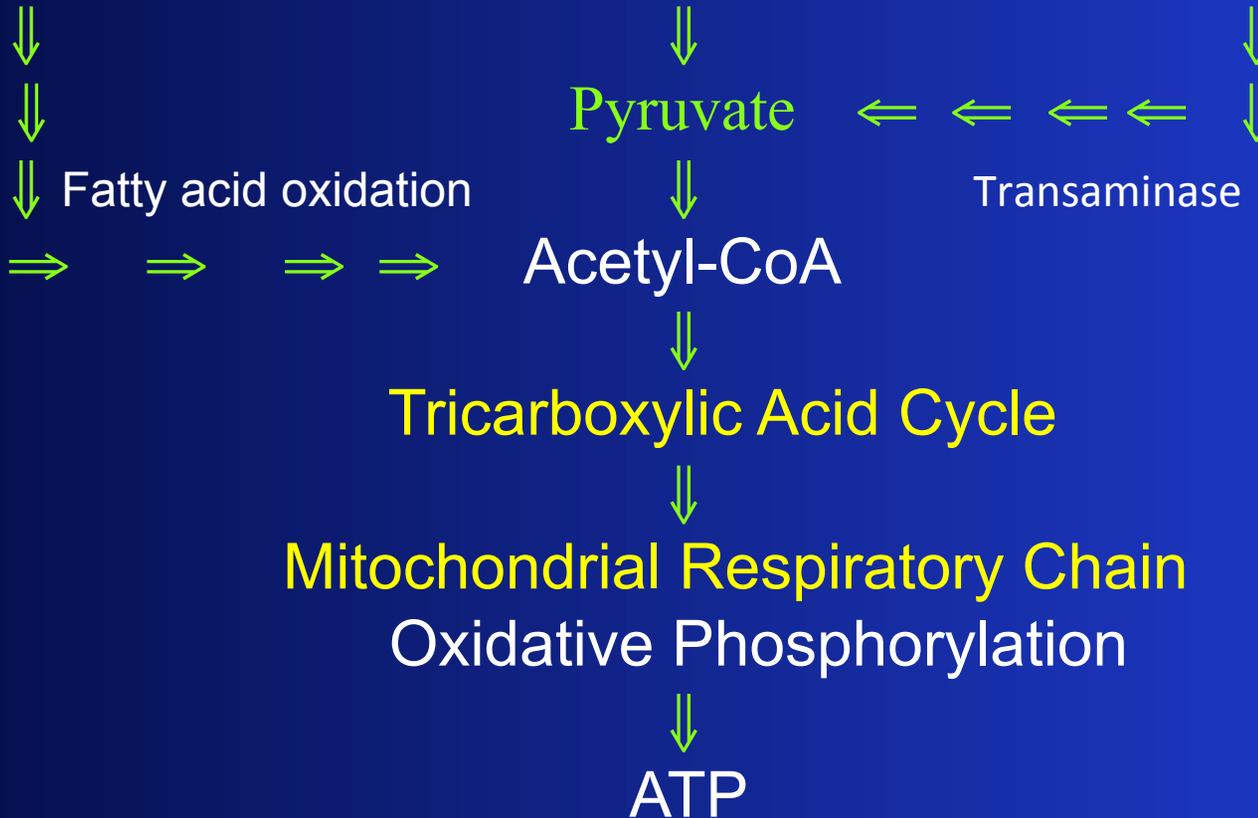
# Overview of Bioenergetic Metabolism

Fatty acids

Carbohydrates

Amino Acids

Glycolysis/Glycogenolysis



# 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<sup>+</sup>, Ca<sup>++</sup>
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 → K<sup>+</sup>, Ca<sup>++</sup>, PO<sub>4</sub><sup>-</sup>, albumin  
BUN, Creatinine, Uric Acid

## CRITICAL METABOLIC STUDIES

Glucose → if normal, consider defect other than FAO disorder  
→ if low, check Free fatty acid: Ketone ratio → if 1:1 → not FAOD



If > 2:1 → check serum carnitine total and free + acylcarnitine



If low total and free carnitine + increased acylcarnitines



FAO disorder

Lactate → if normal, consider glycolytic defect, etc.  
→ if elevated → Lactate/pyruvate ratio → if low → PDP1 defect  
→ if high → mitochondrial

# Hereditary 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

# Hereditary 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) \*

# Hereditary Causes of Metabolic Myopathy and Myoglobinuria

## 4. Purine Nucleotide Cycle

- (1) Myoadenylate deaminase (Hyser, 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  $\geq 1 / 5000$

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

$\sim 1/200$  infants found to harbour one of the 10 most common pathogenic point mutations

# “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 ( $\beta$ -oxidation  
gluconeogenesis, TCA cycle) by FFA/metabolites

## 3. Respiratory Chain defects

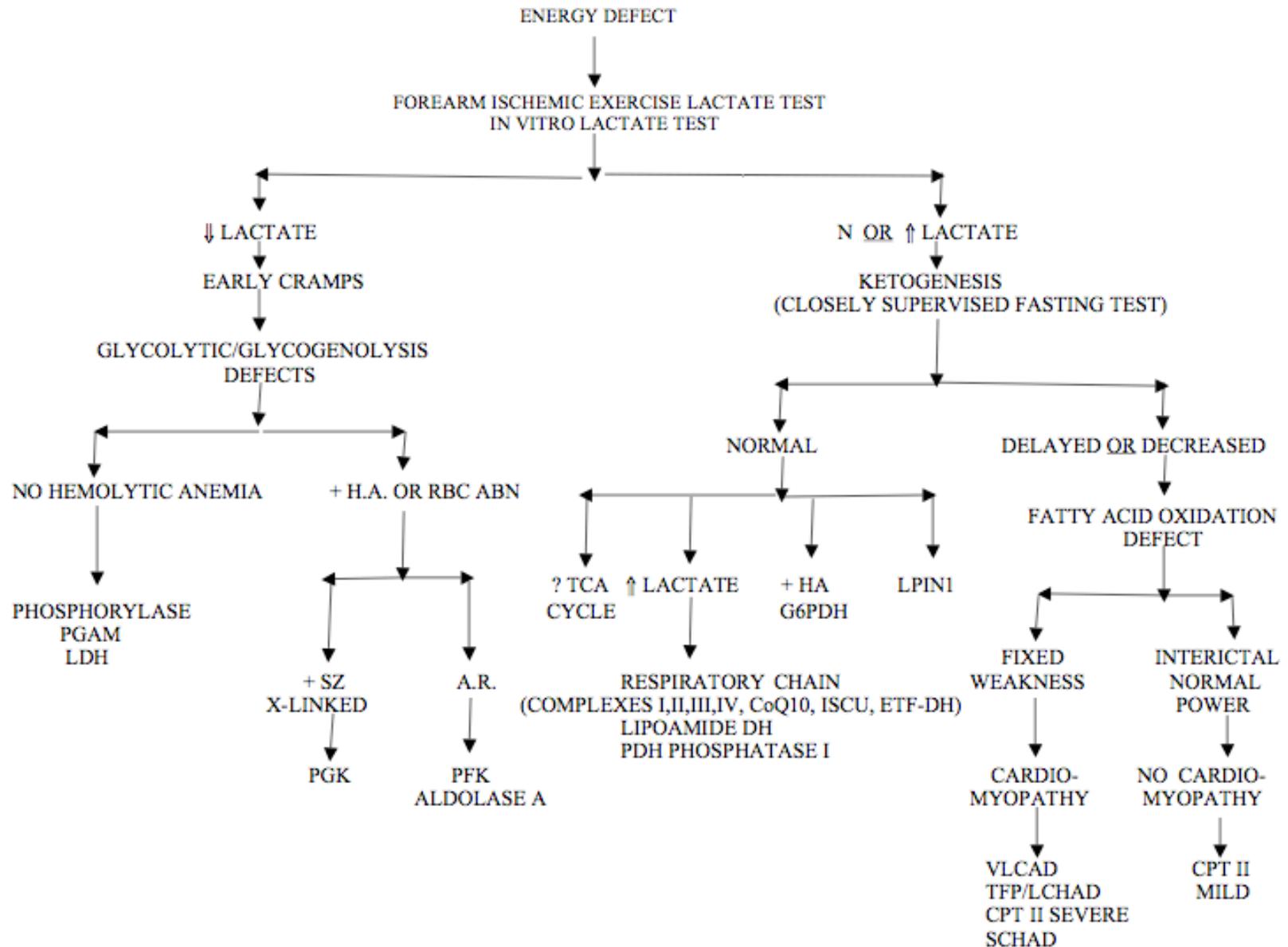
(a) Decreased ATP

# Differentiation Between Disorders of Glycogen vs Lipid Metabolism Resulting in Exercise Intolerance and/or Myoglobinuria

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

Modified from Tein I. 2003. Approach to Muscle Cramps, Exercise Intolerance and Recurrent Myoglobinuria. Proceedings of 38<sup>th</sup> Annual Meeting of the Canadian Congress of Neurosciences. Muscle Diseases Course. Quebec City (CME course)

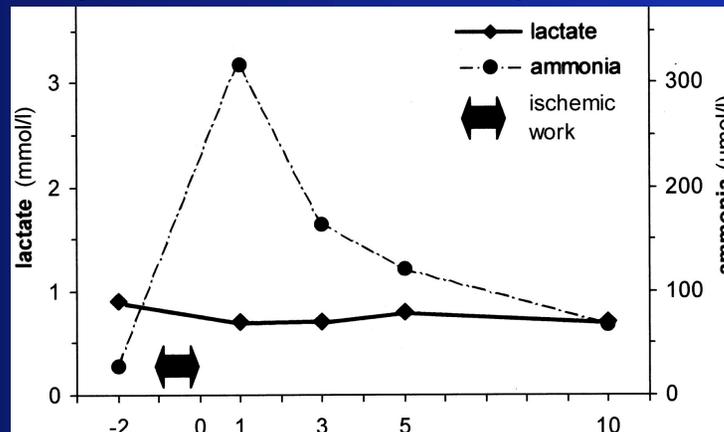
**FIG. 1 APPROACH TO INVESTIGATION OF HEREDITABLE RECURRENT MYOGLOBINURIA**



# 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

# 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

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