RHABDOMYOLYTIC SYNDROME: DIAGNOSIS AND TREATMENT

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Consequences of myopathic process at contractile level

- less force generation/tissue unit
- muscles with myofibers parallel to tendon longitudinal axis lead to wide and quick displacement
- muscles with myofibers skewed to tendon longitudinal axis lead to great contraction force but slow and limited displacement

%MRC score for all subjects is shown as a time series curve plotted against age at each assessment. %MRC is the percentage of total muscle strength in 34 muscles

(Hyde et al, Neuromuscul Disord. 2001;11:165-70)
Hypothesized model (initial model) on dimensions to experienced fatigue in patients with three neuromuscular disorders (FSHD, MD, and HMSN)

Adjusted model of perpetuating factors of experienced fatigue in patients with neuromuscular disorders ($N=198$); error terms have been omitted in the figure. *$P<.001$, #$P<.05$.

(Kalkman JS et al, J Psychosom Res 2007)
Physiopathology of muscle fatigue and exercise intolerance in muscle diseases (Edwards, 1987)

- Alterations of sarcolemmal excitability
- Alterations of electro-mechanical coupling
- Metabolic exhaustion
- Reduction of myofiber volume/number
- Intersitial connective and vascular tissue alterations
Myalgia, defined as any pain perceived in muscle, is very common in the general population. It can be referred from ligaments, joints, bones, the peripheral and central nervous system. Sometimes myalgia can be the only presenting symptoms of a primary muscle disease.
Myalgia at rest, especially in the absence of weakness, is rarely due to a primary myopathy.

**Myalgia in relation to exercise:**

-- Pain experienced during (exertional) or immediately following (post-exertional) exercise. Myalgia associated with primary myopathies is commonly exertional.

-- Delayed muscle pain (delayed post-exertional) usually occurs 24–48 h after strenuous or eccentric exercise. Soreness is usually accompanied by loss of strength and elevated levels of serum creatine kinase (sCK) activity. It commonly occurs in unfit individuals undertaking unaccustomed exercise and is not a hallmark of primary muscle disease. It is thought to be due to microtrauma and local inflammation.
Myalgia in relation to exercise

**Muscle cramps:** per se are of heterogeneous origin and may be associated with specific neurogenic disorders

**Table 1. Common causes of muscle cramps**

- Idiopathic
- Familial
- Pregnancy
- Endocrine
- Electrolyte disturbances (e.g. dehydration)
- Neurogenic disorders
- Medications
- Metabolic

**Table 2. Neurogenic diseases associated with muscle cramps**

- Motor neuron disease
- Cramp-fasciculation syndrome
- Neuralgic amyotrophy
- Radiculopathy
- Peripheral neuropathy
- Isaac’s syndrome
- Post-polio syndrome
- Kennedy disease
- Satoyoshi syndrome
- Myokymia–hyperhidrosis syndrome
- Stiff person syndrome
Neuro and muscle degeneration and oxidative stress

Therapy?
When the rhabdomyolysis??

Term definition: destruction and disintegration of striated muscle:

- Muscle breakdown and myofiber necrosis
- Leakage of intracellular muscle constituents into the circulation and extracellular fluid

The basic clinical triad:
- Weakness
- Myalgia
- Tea-colored, red-black discoloration urine

Lab: CK>5000 U/L
Lab: myoglobinuria
Acute rhabdomyolysis is a serious, life-threatening complication often requiring critical care; it has many causes:

- Acute infections
- Systemic disease
- Toxins
- Trauma
- Inherited muscle disorders

- Exertional vs nonexertional
- Physical vs nonphysical causes

Myopathic diseases presenting with myalgias and cramps may be associated with an increased risk of acute rhabdomyolysis or progressive muscle weakness.
Rhabdomyolysis presentation

Muscular presentation:
- Myalgias
- Progressive muscle weakness
- “dark urine”

General presentation:
- Fever
- Tachycardia
- Nausea and vomiting

Early complications:
- Hyperkaliemia
- Elevated liver enzymes
- Hypocalcemia
- Dyshytmias or cardiac arrest

Late complications:
- Acute Renal insufficiency
- CID
Rhabdomyolysis - prognosis

- 10-50% develop ARF
- RhMy is the cause of 5-25% of ARF
- RhMy mortality rate in ARF 7-80%
- Patients with severe injury and RhMy-induced ARF have 20% mortality rate
Lab character- 1

- **CK (CK-MM)** rises within 12 hours of the onset of muscle injury, peaks in 1-3 days, declines 3-5 days after muscle injury
- predictive (>5000 U/L) of renal failure
- half-life (1.5 days) longer than myoglobin (2-3 hrs)
- **myoglobin** early marker, in the urine at plasma level >1.5 mg/dL and red-brown color to urine when concentration >100-300 mg/dL (urine dipstick + at 0.3 mg/dL)
- **Other muscle markers:** carbonic anhydrase III, aldolase (specific), LDH, transaminases, troponin I and T
Electrolyte levels variably altered: illness severity, course stage and therapeutic intervention
- serum level of potassium and phosphate increase
- serum levels of calcium initially reduced as calcium moves into the cells, then gradually increase
- hyperuricemia
- Clotting studies (disseminated intravascular coagulation)
- Urinalysis: proteins, brown casts and uric acid, electrolyte wasting consistent with renal failure
Rhabdomyolysis results in the release of cell breakdown products into the bloodstream and extracellular space.

**Clinical picture** severe muscle pain and weakness, in more than 50% of patients “dark urine” is the initial clinical sign of rhabdomyolysis, fever, tachycardia, nausea and vomiting.

The **early complications** hyperkalemia, due to massive muscle breakdown, hypocalcemia, elevated liver enzymes, due to the release of proteases from injured muscle, and cardiac dysrhythmias or cardiac arrest due to hyperkalemic acidosis.

The **late complications** (after 12–72 hours) acute renal insufficiency and disseminated intravascular coagulation.

Serum CK levels are the most sensitive indicator of muscle damage; a level of 5000 U/l or greater is related to nephrotoxicity and renal failure -diffuse tubulopathy (Tamm-Horsfall protein reactivity) -direct citotoxicity, renal vasoconstriction -hypovolemia/dehydratation, aciduria
Management of Rhabdomyolysis

IF

Mild myoglobinuria and No systemic symptoms

Hydration

Muscle resting
Management of Rhabdomyolysis

IF

Severe episodes

Continuous Hydration

monitoring

hemodialysis

Analgesia

Antioxidant therapy
Management of rhabdomyolysis

- initial stabilization and resuscitation
- soon start fluid replacement with saline
- Mannitol infusion (glomerular blood flow, directly protective)
- bicarbonate infusion (acidic urine after restoration of normal renal perfusion)
- Free radical scavengers
- Dyalisis (daily hemodialysis or continuous hemofiltration: to remove urea and potassium
- Avoid calcium in the renal failure recovery phase
Rhabdomyolysis' causes

- Acute infections
- Metabolic myopathies
- Inflammatory myopathies
- Toxins
- Muscular dystrophies
- Trauma
- Systemic disease
- Mitochondrial diseases

**MUSCLE DISORDERS**
### Table 10  Laboratory investigations that may be performed prior to biopsy

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<thead>
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<th>Investigation</th>
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<td>Resting lactate (respiratory chain defect)</td>
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<td>Non-ischaemic forearm exercise test (glycolytic enzyme defects)</td>
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<td>Dry blood spot or acid maltase in leukocytes for GSDII</td>
</tr>
<tr>
<td>Fasting acyl carnitine blood spot profile (fatty acid oxidation defects)</td>
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<td>Magnetic resonance imaging (local and diffuse inflammatory myopathies)</td>
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<td>CPT II in leukocytes and cultured fibroblasts (CPT II deficiency)</td>
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<td>Genetic screening for common mutations of suspected myopathy</td>
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### Table 11  Possible muscle biopsy investigations

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<th>Investigation</th>
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<td>Histology and histochemistry</td>
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<tr>
<td>Haematoxylin and eosin, modified Gomori trichrome, Oil red O, periodic acid–Schiff, adenosine triphosphatase, combined succinate dehydrogenase–cytochrome c oxidase, NADH dehydrogenase, myophosphorylase, phosphofructokinase, acid phosphatase, Congo red</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
</tr>
<tr>
<td>Dystrophin, α-, β-, γ- and δ-sarcoglycans, dysferlin, caveolin-3, MHC-1, α-dystroglycan</td>
</tr>
<tr>
<td>Western blot (if indicated)</td>
</tr>
<tr>
<td>Dystrophin, calpain-3, dysferlin, α-sarcoglycan</td>
</tr>
<tr>
<td>Mitochondrial enzyme activity</td>
</tr>
<tr>
<td>CPT II activity</td>
</tr>
<tr>
<td>Glycolytic enzyme activities</td>
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</tbody>
</table>
Exercice protocol

Incremental exercise test on a computized cycloergometer

Calculate pnPOmax

• Steps of 3’ each, 60-70 rpm, interspaced with 2’ pauses
• Progressively 10% of pnPOmax incremental power output for each step, until exaustion (rPOmax)
• Venous blood withdrawal to measure plasmatic lactate and lipoperoxides at basal conditions, during 2’ inter-steps intervals and 20’ after the end of exercise
Sustained maximal voluntary contraction (MVC) with variable definitions. F, force produced voluntarily; Fm, maximally possible force; Fsx, force added by superimposed electrical stimulation; Fs, maximally possible force response on electrical stimulation; CAF, central activation failure.

Incremental exercise protocol in BMD (9 pts, 24-44 yrs)

Exercise protocol:
- 0.75Hz repetitive plantar flexions (3 bites per RT)
- starting with 20% MVC workload and, by subsequent 10% increments each 30 seconds, till: exhaustion

MRS spectra revealed each 8 sec

Metabolites on 31P-MRS
Quantification of 64 signals relative to Pi e PCr amplitudes in the last 72 seconds of exercise and during recovery (until complete for PCr)
Metabolic myopathies

Hereditary myopathies due to an impairment of muscle carbohydrate and fat metabolism

Clinical manifestations:
- Muscle pain
- Exercise-intollerance
- Contractures
- Dark urine
- Muscular cramps

Mitochondrial diseases
Glycogen Storage Disease
Disorders of fatty acid oxidation
## Typical differences among metabolic myopathies

<table>
<thead>
<tr>
<th>McArdle’s disease</th>
<th>CPT II deficiency</th>
<th>Mitochondrial myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise-induced cramps</td>
<td>Exercise-induced pain/stiffness</td>
<td>• No exercise-induced pain</td>
</tr>
<tr>
<td>Symptoms early in exercise</td>
<td>Symptoms late in exercise</td>
<td>• Out-of-breath experience</td>
</tr>
<tr>
<td>CK constantly elevated</td>
<td>CK normal between attacks</td>
<td>• Symptoms early and late in exercise</td>
</tr>
<tr>
<td>Low maximal VO2</td>
<td>Near normal VO2max</td>
<td>• CK normal/mildly elevated</td>
</tr>
<tr>
<td>Second wind phenomenon</td>
<td>No second wind phenomenon</td>
<td>• Low maximal VO2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No second wind phenomenon</td>
</tr>
</tbody>
</table>
Disorders of glycogen metabolism

Glycogen

- **Alpha-1,4-Glucosidase (GSD II)**

Glucose

Lysosome

- **Phosphorylase Kinase Alpha-2 (GSD VIII and IX, X-linked)**
- **Liver Phosphorylase (GSD VI)**
- **Muscle Phosphorylase (GSD V)**

**Glycogen Synthase**

**Branching Enzyme (GSD IV)**

**UDPG**

**Glycogen**

**Debranching Enzyme (GSD III)**

**Glucose-1-P**

- **In liver: Glucose-6-Phosphatase (GSD I)**
- **In brain and muscle: Phosphofructokinase (GSD VII)**

**Fructose-6-P**

**Fructose-1,6-P**

**To blood**

- **Glucose-6-Phosphate Transporter (GSD IB)**

- **Phosphoglucomutase**
Mc Ardle’s Disease

Transmitted as autosomal recessive trait
chromosome 11q12
Myophosphorylase deficiency
Young-adult/onset

Clinical features:
Exercise intollerance, muscle cramps
“Second wind” phenomenon
Recurrent episodes of myoglobinuria after exercise
High level of CPK
Disorders of fatty acid oxidation

Fatty acids are the major substrate at rest and in prolonged low-intensity exercise.

Myalgia occurs later along the exercise compared to glycolitic defects.

Myoglobinuria exercise-related is common.

**Infantil forms**
- Episodes of hypoglycaemia
- Liver and cardiac involvement

**Adult forms**
- Myalgia
- Exercise intolerance

**Figure 1.** Scheme of selected metabolic pathways of lipid. (OCTN2: plasma membrane sodium-dependent carnitine transporter; TG: triglycerides; DG: diglycerides; ATGL: adipose triglyceride lipase; CGI-58: comparative gene identification-58; CPTI: carnitine palmitoyltransferase I; CACT: carnitine-acylcarnitine translocase; CPTII: carnitine palmitoyltransferase II; VLCAD: very long-chain acyl-CoA dehydrogenase; MTP: mitochondrial trifunctional protein; SCAD/MCAD: short-chain/medium-chain acyl-CoA dehydrogenases; ETF: electron-transfer flavoprotein; ETFDH: ETF-dehydrogenase; Q: coenzyme Q; C: cytochrome c).
Carnitine Palmitoyl Transferase II (CPT II)

- The most common form
- Young Adult-Onset

**Clinical Presentation:**
- Recurrent myoglobinuria
- Muscle pain
- Stiffness induced by prologed aerobic exercise, fasting, infections, emotional stress

During attacks
- Rhabdomyolysis is severe
- Myoglobinuria
- CPK: 100000

Between attacks
- Oligosymptomatic
- Neurological examination is negative

Renal Dialysis
Mitochondrial Diseases

OXPHOS is a metabolic pathway that uses energy released by the oxidation of nutrients to produce adenosine triphosphate (ATP).
Mitochondrial diseases

Skeletal muscle heteroplasmy (%)

VO\textsubscript{2max} (L/min)

$0$ $20$ $40$ $60$ $80$ $100$

$0$ $1$ $2$ $3$ $4$

$r = 0.98$

$p < 0.0001$

Fig. 2 The relationship between peak workload and oxygen uptake during cycle exercise in patients with MM (filled circles) and control individuals (open circles). The regression line for patients ($r^2 = 0.94$) is shown.

Jeppesen TD et al, Ann Neurol 2003

No symptoms

Symptomatic

$\tau = 0.98$

$p < 0.0001$
MUSCULAR DYSTROPHIES

Sometimes exercise-induced cramps may be the only presenting symptom and muscle histopathology may show mild abnormalities.

Although the majority of muscle dystrophies does not commonly exhibit myalgia, exertional muscle pain can be a presentation of some entities, such as myotonic dystrophy 2, limb-girdle muscular dystrophy 2I (LGMD 2I), LGMD2B and LGMD 2L.

Weakness, myotonia, rippling muscle disease, muscle atrophy/hypertrophy, hyperCKemia or a history of myoglobinuria are accompanying clinical features.
Limb girdle muscular dystrophy type 2I (LGMD2I): affected individuals can be paucisymptomatic at onset, and exertional myalgia and/or rhabdomyolysis can be the presenting features of FKRP deficiency.

Another limb girdle muscular dystrophy which appears to be frequently associated with exertional myalgia is LGMD2B secondary to recessive mutations in the dysferlin gene, often with a marked inflammatory component.

In addition, rhabdomyolysis has been reported in individuals presenting with beta- and gamma-sarcoglycanopathies and in patients carrying of mutations in anoctamin 5 gene.
Exertional myalgia is an important feature in myopathies due to **RYR1 mutations**, for which exercise intolerance and rhabdomyolysis associated with malignant hyperthermia susceptibility has been described in several reports, in addition to a close relation with fever rhabdomyolysis and increased risk of heat stroke.

### Table 1

Main clinical and histopathological features in core myopathies due to mutations in the skeletal muscle ryanodine receptor (RYR1) and the selenoprotein N (SEPN1) genes and genetically distinct congenital myopathies (3)

<table>
<thead>
<tr>
<th>Gene</th>
<th>RYR1 ad</th>
<th>RYR1 ar</th>
<th>SEPN1</th>
<th>MTM1</th>
<th>DNM2</th>
<th>NEB</th>
<th>ACTA1</th>
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<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
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<tr>
<td><strong>Onset</strong></td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
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<tr>
<td><strong>Infancy</strong></td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
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<tr>
<td><strong>Childhood</strong></td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>–</td>
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<tr>
<td><strong>Adolescence/adulthood</strong></td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td><strong>Clinical features</strong></td>
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<tr>
<td><strong>External ophthalmoplegia</strong></td>
<td>+</td>
<td>+++</td>
<td>–</td>
<td>+++</td>
<td>+++</td>
<td>–</td>
<td>–</td>
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<tr>
<td><strong>Bulbar involvement</strong></td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
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<tr>
<td><strong>Respiratory involvement</strong></td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
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<tr>
<td><strong>Cardiac involvement</strong></td>
<td>–</td>
<td>+</td>
<td>++a</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
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<tr>
<td><strong>Myalgia</strong></td>
<td>+++</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Malignant hyperthermia</strong></td>
<td>+++</td>
<td>++b</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td><strong>Histopathology</strong></td>
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<tr>
<td><strong>Cores</strong></td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td><strong>FTD</strong></td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
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<tr>
<td><strong>Connective tissue/fat</strong></td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<td><strong>Central nuclei</strong></td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<tr>
<td><strong>Nemaline rods</strong></td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

**MTM1**, myotubularin gene; **DNM2**, dynamin 2 gene; **NEB**, nebulin gene; **ACTA1**, skeletal muscle α-actin gene; **RYR1 ad**, **RYR1** autosomal dominant; **RYR1 ar**, **RYR1** autosomal recessive; –, not reported; +, infrequent; ++, common; ++++, very common.

Brislin and Theroux, Pediatric Anesthesia 2013
Autosomal dominant hypermetabolic condition that occurs in genetically predisposed subjects during general anesthesia, induced by commonly used volatile anesthetics and/or the neuromuscular blocking agent succinylcholine.

Triggers cause an altered intracellular calcium regulation. An MH attack, unless immediately recognized and treated, is often fatal. Clinical symptoms of a classic MH attack are accelerated muscle metabolism, muscle contractions, metabolic acidosis, tachycardia, and hyperthermia.

These symptoms are correlated with some altered biochemical parameters, such as metabolic acidosis with increased pCO2 and lactate production and release of potassium and muscle proteins, as creatine kinase and myoglobin, into the blood.

Myopathies with cores

Ryr1 gene (chr 19) mutations
Inflammatory myopathies

Muscle pain is uncommon in idiopathic inflammatory myopathies, with the exception of some more florid cases of dermatomyositis and some cases of sporadic inclusion body myositis. Muscle pain has more frequently been reported in localized forms of myositis. Myalgia generally occurs at rest and it can be exacerbated by exercise, even if typical exertional myalgia is rare.

Occurrence of rhabdomyolysis, with subacute severe proximal myopathy, has to be considered for the necrotizing autoimmune myopathy, a rare but probably underdiagnosed (NM) disorder defined on muscle biopsy features of marked muscle necrosis with regeneration, with negligible inflammatory infiltrate. This disease is closely associated to some forms of toxic myopathies, for instance statin myopathy, connective tissue disease or malignancy.

Case report- 1

Male, 27 yr-old

strenuous physical exertion (3 km running upstream on a hill and carrying on a lift on the shoulders) late morning at summer time under condition of high temperature and humidity

*admission*: diffuse myalgias, weakness, CK 13000, coca cola urine, mild hypokalemia
Case report- 1: muscle biopsy

ATPase 9.4 20x

NADH 20x

COX 20x
Case report- 1

Pathogenesis of RhMy in severe exertion:

Combination of mechanical and thermal muscle injury
ATP depletion
Concurrent hypokalemia
Case report- 2

Female, 80 yr-old

On admission: subacute severe weakness at lower limbs, with muscle pain and pressure aching, myoglobinuria

On examination: severe paraparesis, manly proximal, deep tendon hyporeflexia at lower limbs

Lab: CK 7845 U/L

Electromiography: myogenic without denervation activity

TC total body (26/3): pneumoperitoneum and colon diverticulosis

muscle biopsy: tri 20x
Case report- 2: clinical course

Conservative treatment, antibiotics and no surgery

- Mild one month steroid therapy (starting with prednisone 25 mg x day)
- CK normalize after 3 months
Case report- 3

Male, 63 yr-old

On admission: chronic dyarrhea, malabsorption, subacute severe weakness at lower limbs, with muscle pain and pressure aching, myoglobinuria

On examination: severe paraparesis, manly proximal, deep tendon hyporeflexia at lower limbs

Lab: CK >6000 U/L, hypokalemia, hypocalcemia, secondary hyperparathyroidism, metabolic alkalosis

Electromiography: myogenic without denervation activity

TC total body (26/3): thyroid goitre

muscle biopsy HE 20x
Case report- 4

Male, 63 yr-old
PLOS Genetics A thermolabile aldolase A mutant causes fever-induced recurrent rhabdomyolysis without hemolytic anemia (Asmaa Mamoune et al.)

Aldolase A deficiency has been reported as a rare cause of hemolytic anemia occasionally associated with myopathy.

-a deleterious homozygous mutation in the ALDOA gene in 3 siblings with episodic rhabdomyolysis without hemolytic anemia. Myoglobinuria was always triggered by febrile illnesses.

- the underlying mechanism involves an exacerbation of aldolase A deficiency at high temperatures, which was rescued by arginine supplementation in vitro and lipid droplets, accumulated in patient myoblasts, reduced by dexamethasone.
All 3 affected patients harbored the homozygous ALDOA gene c.839 C>T (p.Ala279Val, NM_000034) mutation.

Thermolabile mutation could be likely the cause of the clinical phenotype of the patient. The decrease of Aldolase A activity was enhanced at high temperature and could explain the fever induced rhabdomyolysis. The enzyme thermolability was rescued by arginine supplementation in vitro.
Diagnostic algorithm for investigations of rhabdomyolysis.

- **Heat**
  - Fatty acid oxidation or other metabolic defect
  - Acyl carnitines
  - Fasting organic acids
  - Skin biopsy
  - Muscle biopsy
  - RYR1
  - LPIN1
  - Genetics

- **Fever**
  - McArdle disease
  - Genetics
  - Muscle biopsy

- **Fasting**
  - Glycerolytic disorder
  - Muscle biopsy
  - RYR1
  - Muscle biopsy

- **Trigger**
  - Exercise
    - Short
      - CK raised
    - Prolonged
      - Second wind +
    - Variable
      - CK normal
      - CK raised

- **Exercise**
  - Second wind -

- **Genetics**
  - Muscular dystrophy
  - Genetics
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Genetics</th>
<th>Inheritance</th>
<th>Key clinical features</th>
<th>Diagnostic investigations</th>
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<td>Muscular dystrophies</td>
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<tr>
<td>DMD/BMD</td>
<td>DYS</td>
<td>X-linked</td>
<td>Exercise Mild</td>
<td>Genetics, muscle biopsy (IHC: dystrophin)</td>
<td>Manifesting females</td>
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<tr>
<td>LGMD2B</td>
<td>DYSF</td>
<td>AR</td>
<td>Exercise Mild</td>
<td>Genetics, muscle biopsy (IHC: dysferlin)</td>
<td>Inflammatory component</td>
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<tr>
<td>LGMD2I</td>
<td>FKRP</td>
<td>AR</td>
<td>Exercise Moderate</td>
<td>Genetics, muscle biopsy (IHC: α-DG)</td>
<td>Common C826A mutation</td>
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<td>Disorders of glycolysis metabolism</td>
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<tr>
<td>McArdle disease</td>
<td>PYGM</td>
<td>AR</td>
<td>Exercise within minutes Severe (ARF)</td>
<td>Muscle biopsy, genetics</td>
<td>‘Second wind’</td>
</tr>
<tr>
<td>Tarui disease</td>
<td>PFKAB</td>
<td>AR</td>
<td>Exercise within minutes Severe (ARF)</td>
<td>Muscle biopsy, genetics</td>
<td>Haemolytic anaemia</td>
</tr>
<tr>
<td>Disorders of fatty acid metabolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPTII deficiency</td>
<td>CPTII</td>
<td>AR</td>
<td>Exercise (prolonged), fasting, fever Severe (ARF)</td>
<td>Acyl carnitines, CPTII activity (fibroblasts), genetics</td>
<td>Triggers include exercise, fasting, infection, stress</td>
</tr>
<tr>
<td>VLCAD deficiency</td>
<td>ACADVL</td>
<td>AR</td>
<td>Exercise (prolonged), fasting, fever Severe (ARF)</td>
<td>Acyl carnitines, muscle biopsy, genetics</td>
<td>Similar to CPTII deficiency</td>
</tr>
<tr>
<td>Mitochondrial trifunctional protein</td>
<td>HDHA,</td>
<td>AR</td>
<td>Variable</td>
<td>Acyl carnitines, muscle biopsy, genetics</td>
<td>Associated neuropathy</td>
</tr>
<tr>
<td>deficiency</td>
<td>HDHB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphatidic acid phosphatase deficiency</td>
<td>LPIN1</td>
<td>AR</td>
<td>Infections Moderate</td>
<td>Acyl carnitines, muscle biopsy, genetics</td>
<td>Early onset</td>
</tr>
<tr>
<td>Congenital myopathies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CCD, MmD)</td>
<td>RYR1</td>
<td>AD, AR</td>
<td>Exercise Moderate</td>
<td>Muscle biopsy, genetics</td>
<td>Associated MH risk</td>
</tr>
</tbody>
</table>

IHC: immunohistochemistry; AR: autosomal recessive; AD: autosomal dominant; CK: creatine kinase; ARF: acute renal failure.
Conclusion

Myalgia associated with exercise intolerance can be the presenting feature of a metabolic or myopathic disorder. A careful history and examination should prompt the clinician to perform the first-line investigations. An accurate diagnosis is necessary in order to provide a long-term follow-up, including prevention of rhabdomyolysis and genetic counselling.
Our group

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