Approach to the Patient With Asymptomatic Elevation in Serum Muscle Enzymes

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Overview of the talk

• Define “Asymptomatic HyperCKemia”
• Differentiate between normal CK vs. HyperCKemia
  ▪ Variation in CK by age, gender, ethnicity
• When to initiate the work up
• Non-neuromuscular and neuromuscular causes of “Asymptomatic HyperCKemia”
• Utility of EMG and muscle biopsy
• Work up of “Asymptomatic HyperCKemia”

Asymptomatic HyperCKemia

Persistent elevation of CK without muscle weakness or other muscle symptoms

What is CK?

• This reaction is critical for cellular energy generation and metabolism
• Iso-enzymes:
  ▪ CK-MM (skeletal muscle)
  ▪ CK-MB (cardiac muscle)
  ▪ CK-BB (brain)
• Rule out cardiac etiology by ordering troponin

Note that although this lecture mostly deals with serum CK, there are really 5 muscle enzymes: CK, AST, ALT, LDH and aldolase

All of them may be ‘proportionately’ elevated in the same fashion as the CK
Problems With “Normal” CK Value

- What is an abnormal CK?
- Clinical laboratory normals:
  - Reference range = central 95% of observations in Caucasians
  - Assumption of Gaussian distribution (bell-shaped curve)
  - “Normal” CK = 0 to 200 U/L
- At this level – 10-20% males and 3-5% females will have “HyperCKemia”

Distribution of CK in Healthy Males and Females

CK in a healthy population is markedly skewed toward higher values and is non-Gaussian

CK Distribution in Males:
97.5 percentile cut off preferred given skewed distribution

Normal CK by Age, Gender and Ethnicity

CK decreases with age

Physical Activity Increases CK

- Transient rise after exercise
- Up to 10-30 x ULN
- Slow decline over 7 days
- Degree of elevation depends on type/duration of exercise

Initial step in evaluating Asymptomatic HyperCKemia:
- Is the CK truly abnormal?

Initial step in assessing HyperCKemia
- Avoid exercise for 1 week
- Repeat CK
- 70% patients will normalize with this simple step
European Federation of Neurological Society Guidelines

- 97.5% CK for age, gender and race
- Repeat CK after 7 days of rest
- For work up - practical cut-off of 1.5 x ULN should be used

<table>
<thead>
<tr>
<th>Percentage of normal individuals with CK above ULN</th>
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<tbody>
<tr>
<td>White Female</td>
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<tr>
<td>1.0 ULN (97.5%)</td>
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<tr>
<td>1.5 ULN</td>
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<tr>
<td>2.0 ULN</td>
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Using this cut-off: Unnecessary investigations cut in half with only small reduction in sensitivity

So what we have learned thus far?

Asymptomatic HyperCKemia:

- ELEVATED CK
- No muscle symptoms
- Normal muscle exam

Repeat CK after 7 days, avoiding exercise

Normal CK ➔ Stop / Observe

CK level > 1.5-2x ULN for gender and race:
- Black male >1200
- Black female >650
- Non-black male >500
- Non-black female >325

Yes ➔ Continue work-up for non-NM causes

No ➔ Stop / Observe

Non-Neuromuscular Causes: Asymptomatic HyperCKemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
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<tbody>
<tr>
<td>Endocrine Disorders</td>
<td>Hyperthyroidism, Hypothyroidism, Hyperparathyroidism</td>
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<tr>
<td>Cardiac Disease</td>
<td>Hypertension, Malignancy</td>
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<tr>
<td>Acute Kidney Disease</td>
<td>Acute Kidney Injury</td>
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<tr>
<td>Viral Illness</td>
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<td>Pregnancy</td>
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<td>Enteric Disease</td>
<td>Intestinal Infections</td>
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<tr>
<td>Infections</td>
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<tr>
<td>Seizure</td>
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<tr>
<td>Medications</td>
<td>HMG-CoA Reductase Inhibitors (Statins), Fibrates, Beta-Blockers, Glucocorticoids, Antagonist Receptor Blocking Agents, Hydroxychloroquine, Isotretinoin</td>
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<tr>
<td>Surgical</td>
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<tr>
<td>Proliferative</td>
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<tr>
<td>Systemic</td>
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<tr>
<td>Myasthenia</td>
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<tr>
<td>Myositis</td>
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<td>Macro CK</td>
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Macro CK as Cause of HyperCKemia

- CK enzyme complex with higher molecular mass than usual CK
- Complex enzyme: CK + Immunoglobulin
- Reduced clearance – higher CK
- CK assays – not able to differentiate CK vs. Macro CK
- Asymptomatic HyperCKemia: 4% ‘Macro CK’
- Most common is ‘Macro CK’ type 1: associated with autoimmune diseases
- Macro CK type 1 (prevalence): 0.4–1.2%
- Diagnosis: Order CK electrophoresis
Statins
- Common cause of CK elevation
- Myalgias, myopathy, and rhabdomyolysis or ‘asymptomatic HyperCKemia’
- Incidence of CK elevations: 0.9% to 4.9%
- General elevations 2 – 10 x ULN

Note: Statins can and should be used if medically necessary – We know the CK is elevated so monitor CK and follow patient clinically
Extensive Work Up Leads to Diagnosis In Minority of Cases

- 114 patients with muscle biopsy and EMG after ruling out non-neuromuscular causes of HyperCKemia
- Diagnosis in 20% after extensive evaluation
- Definite diagnosis in 11%
  - Mostly dystrophinopathies, metabolic myopathies or rare non-inflammatory myopathies
- Probable diagnosis in 8-9%
  - 4 CPT (partial) deficiencies
  - 3 malignant hyperthermia
  - 2 rare inherited disorders
- Abnormal EMG/Muscle biopsy has higher chance of finding a definitive diagnosis: 22% vs. 8% (if muscle bx and EMG normal)

Occult or Latent Neuromuscular causes of ‘Asymptomatic HyperCKemia’

<table>
<thead>
<tr>
<th>Neuromuscular Dx in Asymptomatic (pauci-symptomatic) HyperCKemia</th>
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<tbody>
<tr>
<td>Dystrophies:</td>
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<tr>
<td>- Duchenne/Becker</td>
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<td>- Limb Girdle</td>
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<tr>
<td>- Others</td>
</tr>
<tr>
<td>- myotubular/desmin/myotonic</td>
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<tr>
<td>Metabolic/Mitochondrial</td>
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<tr>
<td>- CPT2 deficiency</td>
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<tr>
<td>- McArdle's disease</td>
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<tr>
<td>- Myoadenylate deaminase</td>
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<tr>
<td>- Mitochondrial</td>
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<tr>
<td>- Pompe's</td>
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<tr>
<td>Other</td>
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<tr>
<td>- Familial</td>
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<tr>
<td>- Sarcoïd</td>
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<tr>
<td>- Thyroid myopathy</td>
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<tr>
<td>- Congenital</td>
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<tr>
<td>Inflammatory</td>
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<tr>
<td>- IBM</td>
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<tr>
<td>- Autoimmune ILD/anti-synthetase</td>
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Idiopathic Inflammatory Myopathies

- Rarely associated with ‘Asymptomatic HyperCKemia’
  - Up to 5% cases
- Hypomyopathic DM
  - Subtle DM rash
  - Mild CK elevation
- IBM
  - Early disease given insidious onset/slow progression
- Anti-Synthetase syndrome
  - Subclinical myopathy with ILD-dominant features

IIM is important to recognize given need for treatment
**Idiopathic HyperCKemia (< 1%)**

Persistent elevation of serum CK despite normal neurologic examinations and investigative studies, including EMG and muscle biopsy

- Persistent CK elevation (after 7 days of rest)
- No cardiac disease (ni troponin/EKG)
- No symptoms or non-specific symptoms
- Negative family history for NM diseases
- No clinical/EMG or biopsy evidence of NM disease
- No other causes of HyperCKemia
  - malignancy, alcohol, drugs (e.g. statins), metabolic, endocrine etc.

**European Federation of Neurological Society: Guidelines on muscle biopsy for 'Asymptomatic HyperCKemia'**

- Perform muscle biopsy for following:
  - Abnormal (myopathic) EMG
  - CK > 3 times ULN
  - Patients < 25 years of age
  - Exercised-induced pain or exercise intolerance
- Women with CK < 3 times normal
  - Possibility of Duchenne/Becker mutation carrier
  - Lymphocytic DNA analysis
    - will identify 70% of carriers

**Benign Prognosis of Idiopathic HyperCKemia**

- 55 patients followed for 7.5 (4-15) years
- CK normalized (n=12) or decreased (n=24) in most pts
- Most remain asymptomatic or with minimal symptoms
- Most patient still had persistent CK elevations
- 80% (43/55) remained dx as Idiopathic HyperCKemia
  - 10 % diagnosed with neuromuscular disorder
  - 10% were diagnosed with cancer

**Diagnostic Workup of Asymptomatic HyperCKemia**

- Repeat CK after 7 days
- Avoid exercise
- CK > 1.5 x ULN for gender and race:
  - Black male >1200
  - Black female >550
  - Non-black male >100
  - Non-black female >325
- Rule out non-neuromuscular causes
  - Discuss with patient re utility of future workup:
    - 25-30% yield
    - Limited treatment
- EMG and muscle biopsy
  - Normal EMG/Biopsy
  - Idiopathic HyperCKemia
- Rule out neuromuscular causes
  - Malignancy
  - Endocrinopathies
  - Drugs (e.g. statins)
  - Inflammatory /other

**Summary: Asymptomatic HyperCKemia**

- Repeat CK after rest
- Consider gender, race and 97.5% cut off
- Proceed with work-up if CK > 1.5 x ULN
- Rule out non-neuromuscular causes
- Macro CK, endocrinopathies and drugs (e.g. statins) are important causes
- EMG/Muscle biopsy after discussion with patient
- Rule out neuromuscular causes
  - Dystrophies and metabolic myopathies
- EMG/Muscle biopsy yield = 25-30%
- 'Idiopathic HyperCKemia' has good prognosis with nl EMG/biopsy
Thank You