HyperCKemia

Nicholas J. Silvestri, M.D.
Assistant Professor of Neurology
INVITED REVIEW

ASYMPTOMATIC/PAUCI-SYMPTOMATIC CREATINE KINASE
ELEVATIONS (HYPERCKEMIA)

NICHOLAS J. SILVESTRI, MD and GIL I. WOLFE, MD

Department of Neurology, University at Buffalo, Buffalo General Medical Center,
100 High Street, Buffalo, New York 14203-1126, USA

Accepted 10 December 2012

ABSTRACT: Neuromuscular clinicians are frequently asked to evaluate patients referred for asymptomatic elevations in creatine kinase (CK), a catalytic enzyme that combines creatine and ATP to form phosphocreatine and ADP. This reaction is crucial for cellular energy generation and metabolism. This laboratory finding, often referred to in simplified lexicon as asymptomatic hyperCKemia, continues to generate controversy at several levels, including definition, the extent of evaluation, and the yield of diagnostic testing. In this review, we summarize the literature based on series of patients with asymptomatic hyperCKemia and provide a rational clinical approach to reveal identifiable underlying causes.


fraction may be seen in patients with sizable strokes. In a study of common causes of CK elevations in a medical ward, most elevations were found to be due to cardiac disease. Neuromuscular disease was rarely encountered.

In this review we focus on asymptomatic and pauci-symptomatic elevations of the CK-MM isoenzyme, which are traditionally associated with neuromuscular disorders, particularly myopathies. We define pauci-symptomatic as patients with nonspecific symptoms, such as mild myalgias, cramps, or
Outline

• Defining HyperCKemia
• Causes of HyperCKemia
• Diagnostic Evaluation of HyperCKemia
• Risk of Malignant Hyperthermia
• Recommended Evaluation of HyperCKemia
Creatine Kinase

Creatine

\[
\text{ATP} \rightleftharpoons \text{ADP} \quad \text{creatinine kinase}
\]

Phosphocreatine
Definitions

• Asymptomatic or pauci-symptomatic elevations in CK

• Pauci-Symptomatic:
  – Non-specific symptoms
    • mild myalgias, cramps, fatigue
  – Absence of severe exercise intolerance
  – No evidence of weakness on examination

• HyperCKemia: How high is too high?
CK levels vary by race and gender
Wong, et al.

- “High CK” group
  - black men
  - mean CK level 237.8 U/L (SD 492.1 U/L)
- “Intermediate CK” group
  - non-black men and black women
  - mean CK levels ranging between 109.3-149.7 U/L
- “Low CK” group
  - white women
  - mean CK levels ranging between 64.6-79.8 U/L

**Distribution of creatine kinase in the general population: Implications for statin therapy**

Lizzy M. Brewster, MD, a Gideon Mairuhu, MD, c August Sturk, PhD, b and Gert A. van Montfrans, MD, PhD

Amsterdam and Nieuwegein, The Netherlands

<table>
<thead>
<tr>
<th>Sex and ancestry</th>
<th>N</th>
<th>Age (SD)</th>
<th>BMI (SD)</th>
<th>2.5th percentile</th>
<th>Median</th>
<th>97.5th percentile</th>
<th>&gt;ULN (N%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects †</td>
<td>1411</td>
<td>45 (7)</td>
<td>27 (5)</td>
<td>40</td>
<td>111</td>
<td>460</td>
<td>508 (36)</td>
</tr>
<tr>
<td>Women</td>
<td>831</td>
<td>45 (7)</td>
<td>28 (6)</td>
<td>36</td>
<td>95</td>
<td>349</td>
<td>304 (37)</td>
</tr>
<tr>
<td>Men</td>
<td>580</td>
<td>46 (7)</td>
<td>26 (4)</td>
<td>51</td>
<td>143</td>
<td>616</td>
<td>204 (35)</td>
</tr>
<tr>
<td>White subjects</td>
<td>503</td>
<td>48 (7)</td>
<td>26 (5)</td>
<td>35</td>
<td>88</td>
<td>286</td>
<td>64 (13)</td>
</tr>
<tr>
<td>Women</td>
<td>252</td>
<td>47 (7)</td>
<td>26 (5)</td>
<td>29</td>
<td>72</td>
<td>201</td>
<td>21 (8)</td>
</tr>
<tr>
<td>Men</td>
<td>251</td>
<td>48 (7)</td>
<td>26 (4)</td>
<td>47</td>
<td>110</td>
<td>322</td>
<td>43 (17)</td>
</tr>
<tr>
<td>South Asian subjects</td>
<td>270</td>
<td>44 (6)</td>
<td>27 (5)</td>
<td>40</td>
<td>104</td>
<td>382</td>
<td>62 (23)</td>
</tr>
<tr>
<td>Women</td>
<td>147</td>
<td>45 (6)</td>
<td>27 (5)</td>
<td>37</td>
<td>87</td>
<td>313</td>
<td>23 (16)</td>
</tr>
<tr>
<td>Men</td>
<td>123</td>
<td>44 (6)</td>
<td>26 (5)</td>
<td>47</td>
<td>143</td>
<td>648</td>
<td>39 (32)</td>
</tr>
<tr>
<td>Black subjects</td>
<td>570</td>
<td>44 (6)</td>
<td>28 (5)</td>
<td>51</td>
<td>149</td>
<td>627</td>
<td>278 (49)</td>
</tr>
<tr>
<td>Women</td>
<td>387</td>
<td>43 (6)</td>
<td>29 (6)</td>
<td>48</td>
<td>124</td>
<td>414</td>
<td>164 (42)</td>
</tr>
<tr>
<td>Men</td>
<td>183</td>
<td>44 (6)</td>
<td>26 (4)</td>
<td>71</td>
<td>213</td>
<td>801</td>
<td>114 (62)</td>
</tr>
</tbody>
</table>

Gaussian Distribution

Normal Curve

Standard Deviation

![Gaussian Distribution Diagram](image)
Defining HyperCKemia

- **EFNS Guidelines**
  - Defined hyperCKemia as elevations > 1.5x ULN of values based on Brewster’s data
  - ULN defined as 97.5\textsuperscript{th} %tile

<table>
<thead>
<tr>
<th></th>
<th>Non-black Female</th>
<th>Non-black Male</th>
<th>Black Female</th>
<th>Black Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 ULN</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>1.5 ULN</td>
<td>1.5 (325)</td>
<td>1.0 (504)</td>
<td>1.3 (621)</td>
<td>0.5 (1201)</td>
</tr>
<tr>
<td>2.0 ULN</td>
<td>0.2</td>
<td>0.8</td>
<td>0.5</td>
<td>0</td>
</tr>
</tbody>
</table>

Not all elevations in CK level are due to neuromuscular disorders
Systemic Causes of HyperCKemia

• Connective tissue disorders
• Electrolyte disturbances
  – hyponatremia, hypokalemia, hypophosphatemia
• Endocrinopathies
  – hyper- or hypothyroidism, hyperparathyroidism
• Renal disease
• Cardiac disease
• Malignancy
Systemic Causes, Cont.

• Muscle trauma
  – e.g. crush injuries, generalized seizures, intramuscular injections, electromyography

• Pregnancy
Drug-Induced HyperCKemia

• **Statins**
  – Incidence 0.9-4.9% of patients

• Clozapine

• Beta blockers

• Isotretinoin

• Drugs of abuse: ethanol, cocaine, heroin

Thompson PD, Clarkson P, Karas RH. JAMA 2003;289:1681-1690
Physical Exertion and CK Levels

• In asymptomatic subjects, CK levels of 10x ULN have been observed following exercise
• If exercise particularly strenuous, muscle soreness, weakness, and in extreme cases, myoglobinuria, may ensue within 24-48 hours
• CK levels may ascend as high as 30x ULN within 24 hours of activity
  — levels slowly decline over the course of 7-10 days

Ehlers GG, Ball TE, Liston L. J Ath Train 2002;37:151-156
MacroCK

• Type 1
  – CK-IgG antibody complex
    • Usually CK-BB
  – Prevalence: 0.43-1.2%
  – often associated with an underlying autoimmune phenomenon (e.g. myositis)

• Type 2
  – oligomeric mitochondrial CK
  – Prevalence: 0.5-3.7%
  – often seen in patients with malignancy or hepatic disease

MacroCK

Myopathic Causes of HyperCKemia

- Muscular dystrophies
- Metabolic myopathies
- Congenital myopathies
- Inflammatory myopathies
Muscular Dystrophies

• Dystrophinopathy:
  – 37 cases described in 10 papers
  – Griggs et al: CK values were significantly higher in obligate female carriers of dystrophin mutation
    • Levels peaked in the first, second, and seventh decades

Limb Girdle Muscular Dystrophies

- Caveolin 3 (LGMD 1C): 10 cases, 5 papers
- Calpain (LGMD 2A): 12 cases, 3 papers
- Dysferlin (LGMD 2B): 10 cases, 5 papers
- α-sarcoglycan (LGMD 2D): 1 case
- FKRP (LGMD 2I): 6 cases, 2 papers
- ANO5 (LGMD2L): 3 cases, 2 papers
Other Muscular Dystrophies

- Myofibrillar myopathy: 2 cases, 1 paper
- Desmin myopathy: 1 case
- Myotonic dystrophy type 2: 1 case
Metabolic Myopathies

- CPT2 deficiency: 5 cases, 2 papers
- McArdle’s: 16 cases, 3 papers
- Mitochondrial cytopathy: 4 cases, 3 papers
- α glucosidase deficiency: 14 cases, 2 papers
- MADA deficiency: 4 cases, 3 papers
- PBK deficiency: 3 cases, 1 paper
- PFK deficiency: 1 case
Congenital Myopathies

- Multicore: 1 case
- Central Core: 5 cases, 4 papers
- Tubular aggregate myopathy: 4 cases, 2 papers
- Centronuclear: 1 case
- Lobulated fiber: 2 cases, 1 paper
Inflammatory Myopathies

• Polymyositis: 12 cases, 3 papers
• IBM: 3 cases, 2 papers
• Macrophagic myositis: 5 cases, 1 paper
Idiopathic HyperCKemia

• Introduced by Rowland
  – “persistent elevation of serum CK despite normal neurological examinations and investigative studies, including EMG and muscle biopsy”
• Incidence 0.71% in one large study of 12,828 patients in Norway
• May be familial
• Diagnosis of exclusion

Diagnostic Evaluation

7 major studies have addressed this question (don’t worry...I’m only going to talk about 3)
ASYMPTOMATIC HYPER-CK-EMIA: AN ELECTROPHYSIOLOGIC AND HISTOPATHOLOGIC STUDY

JUAN L. JOY, MD, and SHIN J. OH, MD

• 19 patients (13 men)
• Age range 12-61 years
• EMG abnormal in 14/19 patients
• Biopsy abnormal in 15/19
• Diagnoses in 15/19 patients

Retrospective study of a large population of patients with asymptomatic or minimally symptomatic raised serum creatine kinase levels

- Retrospective study of 114 subjects (93 male)
- 57% asymptomatic, 43% pauci-symptomatic
- Mean CK value 1410 U/L
- EMG abnormal in 57/100 patients
- Biopsy abnormal in 44/100 patients
- Diagnosis discovered in 21 patients (18.4%)
  - Likelihood of making diagnosis greater in subjects < 24 years, and higher CK levels (> 1039 U/L)

Prelle, et al.

<table>
<thead>
<tr>
<th>Performed biopsies</th>
<th>Routine results</th>
<th>Diagnoses</th>
</tr>
</thead>
</table>
| 70 Normal biopsies | Normal histology/histochemistry | 2 Dystrophinopathies  
3 Partial CPT Deficiency  
2 MH susceptibilities  
1 Myotonia fluctuans |
| 44 Pathological biopsies | 19 Mild nonspecific patterns  
14 Neurogenic patterns  
7 Primary myopathic patterns  
2 Mitochondriopathies  
1 Tubular Aggregates  
1 Central Core | 3 Dystrophinopathies  
1 Partial CPT Deficiency  
1 Dysferlinopathy  
1 Adenylate Deaminase Deficiency  
1 Mild Limb Girdle Dystrophy  
1 MH susceptibility  
1 Desminopathy  
1 Multiple Deletions  
1 Undiagnosed  
1 Tubular Aggregates Myopathy  
1 Central Core Myopathy |

• Evaluated 104 subjects (74 men)
  – Mean age 40 years (range 4-79 years)
• 50 asymptomatic, 54 pauci-symptomatic
• CK levels above 500 U/L on 2 occasions
• EMG abnormal 23/57 patients
  – Abnormal in 61% patients with abnormal biopsy
• Muscle biopsy abnormal in 83/104
  – 51/83 biopsies diagnostic

Fernandez, et al.

- Probable or definitive diagnosis made in 57 patients (55%)
- Higher probability of determining diagnosis in patients under 15 years

Fernandez, et al.

- McArdle disease (15)
- Dystrophinopathy (9)
- Alpha glucosidase deficiency (9)
- Polymyositis (6)
- Macrophagic myositis (5)
- FKRP mutation (2)
- Myofibrillar myopathy (2)
- Inclusion body myositis (2)
- Dysferlinopathy (1)
- Caveolinopathy (1)
- Calpainopathy (1)
- Mitochondrial (1)
- Glycogenesis without enzyme deficiency (1)
Asymptomatic or Minimally Symptomatic HyperCKemia: Histopathologic Correlates

Ron Dabby MD¹, Menachem Sadeh MD¹, Oscar Herman MD², Esther Berger PhD³, Nathan Watemberg MD⁴, Shlomo Hayek MD⁵, Joseph Jossiphov MD⁶ and Yoram Nevo MD⁷

• 40 patients (30 men)
• 19 asymptomatic, 21 pauci-symptomatic
• EMG abnormal in 8/40
• Biopsy abnormal in 22/40
  – 3 demonstrated abnormal dystrophin staining—these were the only diagnostic biopsies
• Overall yield of work-up in this study 8%

20 patients (14 men) with prior non-diagnostic EMGs

Mean CK level 399 U/L

Biopsy abnormal in 11
  - Non-specific findings in 6
  - Mild myopathic changes in 4
  - MAD deficiency in 1

Simmons Z, Peterlin BL, Boyer PJ, Towfighi J. Muscle Nerve 2003;27:242-244
Simmons et al.

- Biochemical analysis:
  - Partial PBK deficiency: 3
  - Partial CPT2 deficiency: 2

- Diagnostic yield 30% (6/20)

Simmons Z, Peterlin BL, Boyer PJ, Towfighi J. Muscle Nerve 2003;27:242-244
# Electromyography

<table>
<thead>
<tr>
<th>STUDY</th>
<th>ABNORMAL EMGs/TOTAL EMGs PERFORMED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brewster, et al.</td>
<td>4/14 (28.6%)</td>
</tr>
<tr>
<td>Dabby, et al.</td>
<td>8/27 (28.9%)</td>
</tr>
<tr>
<td>Fernandez, et al.</td>
<td>23/57 (40.4%)</td>
</tr>
<tr>
<td>Joy and Oh</td>
<td>14/19 (73.7%)</td>
</tr>
<tr>
<td>Malandrini, et al.</td>
<td>15/37 (40.5%)</td>
</tr>
<tr>
<td>Prelle, et al.</td>
<td>57/100 (57%)</td>
</tr>
<tr>
<td>Reijneveld, et al.</td>
<td>9/30 (30%)</td>
</tr>
<tr>
<td>Simmons, et al.</td>
<td>9/20 (45%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>139/304 (45.7%)</strong></td>
</tr>
</tbody>
</table>
Electromyography

• Should it be used as a screening tool?
• Abnormal in 51-93% of patients who went on to have an abnormal muscle biopsy
• Prelle, et al:
  – EMG normal in 11 of 43 patients (25.6%) who went on to have an abnormal biopsy
  – Sensitivity of EMG in their study was only 68.7%, and specificity was 53.8%

## Muscle Biopsy

<table>
<thead>
<tr>
<th>STUDY</th>
<th>ABNORMAL BIOPSIES/ TOTAL NUMBER OF BIOPSIES PERFORMED</th>
<th>DIAGNOSTIC BIOPSIES/ TOTAL NUMBER OF BIOPSIES PERFORMED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brewster, et al.</td>
<td>4/14 (28.6%)</td>
<td>0/14 (0%)</td>
</tr>
<tr>
<td>Dabby, et al.</td>
<td>22/40 (55%)</td>
<td>3/40 (7.5%)</td>
</tr>
<tr>
<td>Fernandez, et al.</td>
<td>83/104 (79.8%)</td>
<td>51/104 (49%)</td>
</tr>
<tr>
<td>Joy and Oh</td>
<td>15/19 (78.9%)</td>
<td>15/19 (78.9%)</td>
</tr>
<tr>
<td>Malandrini, et al.</td>
<td>34/37 (91.9%)</td>
<td>3/37 (8.1%)</td>
</tr>
<tr>
<td>Prelle, et al.</td>
<td>44/114 (38.6%)</td>
<td>20/114 (17.5%)</td>
</tr>
<tr>
<td>Reijneveld, et al.</td>
<td>24/31 (77.4%)</td>
<td>0/31 (0%)</td>
</tr>
<tr>
<td>Simmons, et al.</td>
<td>11/20 (55%)</td>
<td>6/20 (30%)</td>
</tr>
<tr>
<td>Filosto, et al.</td>
<td>83/105 (79%)</td>
<td>15/105 (14.3%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>320/484 (66.1%)</td>
<td>113/484 (23.3%)</td>
</tr>
</tbody>
</table>
“Non-specific Myopathy”

• 42.8% biopsies in these studies demonstrated non-specific myopathic findings

• What is the significance?
  – Yet-to-be discovered myopathies?
  – Should more rigorous genetic and/or biochemical testing have been done?
  – Skill of interpreting physician?
### Likelihood of Making a Diagnosis

<table>
<thead>
<tr>
<th>STUDY</th>
<th>NUMBER OF PATIENTS DIAGNOSED/TOTAL NUMBER OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brewster, et al.</td>
<td>10/14 (71.4%)</td>
</tr>
<tr>
<td>Dabby, et al.</td>
<td>3/40 (7.5%)</td>
</tr>
<tr>
<td>D’Adda, et al.</td>
<td>6/55 (10.9%)</td>
</tr>
<tr>
<td>Fernandez, et al.</td>
<td>57/104 (54.8%)</td>
</tr>
<tr>
<td>Joy and Oh</td>
<td>15/19 (78.9%)</td>
</tr>
<tr>
<td>Lilleng, et al.</td>
<td>4/97 (4.1%)</td>
</tr>
<tr>
<td>Malandrini, et al.</td>
<td>3/37 (8.1%)</td>
</tr>
<tr>
<td>Prelle, et al.</td>
<td>21/114 (18.4%)</td>
</tr>
<tr>
<td>Simmons, et al.</td>
<td>6/20 (30%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>125/445 (28.1%)</strong></td>
</tr>
</tbody>
</table>
What is the prognosis when the work-up is non-diagnostic?
Follow-up of a large population of asymptomatic/oligosymptomatic hyperCKemic subjects

- Longer term follow-up of 55 of 93 unclassified patients in Prelle et al. study
  - Mean 7.47 years (range 4-15 years)
- CK levels persistently elevated in 43/55 patients
  - Mean CK level 616 U/L
- 3 further diagnoses made:
  - 1 LGMD (unclassified)
  - 1 dystrophin mutation carrier
  - 1 SMN1 mutation carrier

BENIGN PROGNOSIS IN IDIOPATHIC HYPER-CK-EMIA

JAAP C. REIJNEVELD, MD,¹ NICOLETTE C. NOTERMANS, MD, PhD,¹
WIM H.J.P. LINSSEN, MD, PhD,² and JOHN H.J. WOKKE, MD, PhD¹

• Followed up 23 subjects at a mean of 7.2 years after initial non-diagnostic work-up
• CK levels stable over time
• 1 patient diagnosed with polyneuropathy, 2 subsequently found to have CAV3 mutations
• Concluded that long term follow-up with in patients with normal initial evaluation unnecessary

# Malignant Hyperthermia

<table>
<thead>
<tr>
<th>STUDY</th>
<th>ABNORMAL IN VITRO CONTRACTURE TEST/ TOTAL NUMBER IN VITRO CONTRACTURE TESTS PERFORMED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malandrini, et al.</td>
<td>2/37 (5.4%)</td>
</tr>
<tr>
<td>Sunohara, et al.</td>
<td>2/3 (67%)</td>
</tr>
<tr>
<td>Weglinski, et al.</td>
<td>25/49 (51%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>29/89 (32.6%)</strong></td>
</tr>
</tbody>
</table>

Weglinski MR, Wedel DJ, Engel AW. Anesth Analg 1997;84:1038-1041
**Recommended Diagnostic Algorithm**

1. Elevated CK level and normal physical examination
2. Repeat CK, fractionate into isoenzymes to ensure MM is elevated
   - Exclude strenuous physical activity (re-draw CK level after 7 days of rest)
   - Exclude non-neuromuscular causes
3. Asymptomatic or non-exertional symptoms
4. CK level is > 1.5 times the ULN for gender and race?
   - Non-black female > 325 U/L
   - Non-black male > 504 U/L
   - Black female > 621 U/L
   - Black male > 1201 U/L
**Recommended Diagnostic Algorithm**

**Exercise Intolerance**

- CK level is > 1.5 times the ULN for gender and race?
  - Non-black female > 325 U/L
  - Non-black male > 504 U/L
  - Black female > 621 U/L
  - Black male > 1201 U/L

**No**
- **Observe**

**Yes**
- **EMG to rule-out rare causes (e.g. motor neuron disease, myotonic disorders)**
  - **Abnormal**
    - **Diagnosis**
  - **Normal**
    - **Appropriate metabolic testing**
      - Abnormal
        - Forearm Exercise Testing
          - **Abnormal**
            - Exercise Intolerance

**Exercise Intolerance**
Recommended Diagnostic Algorithm

**EMG**

Non-diagnostic or myopathic findings

- **Diagnosis**
  - Abnormal
    - Muscle biopsy with biochemical analysis and staining for dystrophin, α/β/γ sarcoglycan, CAV3, dysferlin, MHC-1, α dystroglycan; Western blot for dystrophin, dysferlin, calpain
  - Non-diagnostic
    - Consider genetic testing for dystrophin, dysferlin, calpain, CAV3, FKRP
  - Normal
    - Idiopathic HyperCKemia
Thank You