Approach to the Patient With Asymptomatic Elevation in Serum Muscle Enzymes

Association des medecins rhumatologues du Quebec (AMRQ) Quebec, Canada

Rohit Aggarwal, MD MS
Assistant Professor of Medicine
Co-Director Myositis Center
University of Pittsburgh
Disclosures

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aTyr Pharma : Advisory Board
Pfizer : Research Grant
Overview of the talk

• Define “Asymptomatic HyperCKemia”
• Differentiate between normal CK vs. HyperCKemia
• 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”
Q1. What CK levels should be considered abnormal?

A. CK levels above upper limit of normal (as per lab)?

B. CK levels above 95% of normal CK distribution in a healthy population

C. CK levels above 97.5% of normal CK distribution in a healthy population
Asymptomatic HyperCKemia

Persistent elevation of CK without muscle weakness or other muscle symptoms

Asymptomatic HyperCKemia

Non-Neuromuscular causes

- Normal CK for Age, Gender, Ethnicity
- Exercise Injury
- Drug Toxins
- Endocrine

Neuromuscular disorder

- Abnormal EMG, Muscle biopsy
- Diagnosis of Neuromuscular disorder

- Normal EMG, Muscle biopsy
- Idiopathic HyperCKemia
What is CK?

- 86 Kd dimeric enzyme; function to catalyze the combination of creatine and ATP to form phosphocreatine and ADP
- 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 Caucasiens
• 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”

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

97.5 percentile cut off:
532 (95% CI 384–738) for men
248 (95% CI 184–340) for women
Normal CK by Gender and Ethnicity

Race and Gender

CK levels: Black Male > Black Female > White Male > White Female

Lilleng et al. Neuromuscular disorders 2011
Normal CK by Age

Age (Female)

CK decreases with age

Lilleng et al. Neuromuscular disorders 2011
**Proposed Normal Cut-off for Serum CK**

*Initial step in evaluation of Asymptomatic HyperCKemia:*
- Is the CK truly abnormal?

<table>
<thead>
<tr>
<th>97.5\textsuperscript{th} percentile for serum CK</th>
<th>White Female</th>
<th>White Male</th>
<th>Black Female</th>
<th>Black Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK (IU/L)</td>
<td>217</td>
<td>336</td>
<td>414</td>
<td>801</td>
</tr>
</tbody>
</table>

Brewster et al., 2007
Q2. What is the first step after in evaluation of asymptomatic patient has abnormal CK?

A. Look for non-neuromuscular causes of abnormal CK
B. Repeat CK after 3 days
C. Look for non-neuromuscular and neuromuscular causes of abnormal CK
D. Repeat CK after 7 days
Physical Activity Increases CK

- Transient rise after exercise
- Especially after eccentric exercise or heavy labor or unaccustomed exercise
- Up to 10-30 x ULN within 24-48 hours of strenuous physical activity
- Slow decline over 7 days
- Degree of elevation depends on type/duration of exercise

Lilleng et al. Neuromuscular disorders 2011
Physical Activity Increases CK

Initial step in assessing HyperCKemia

- Avoid exercise for 1 week
- Repeat CK
- 70% patients will normalize with this simple step

Lilleng et al. Neuromuscular disorders 2011
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

### Percentage of normal individuals with CK above ULN

<table>
<thead>
<tr>
<th></th>
<th>White Female</th>
<th>White Male</th>
<th>Black Female</th>
<th>Black Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 ULN (97.5%)</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>

*Using this cut-off: Unnecessary investigations cut in half with only small reduction in sensitivity*

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Kyriakides T et al. Eur J Neurol 2010
So what we have learned thus far?

Asymptomatic HyperCKemia:

ELEVATED CK +
No muscle symptoms +
Normal muscle exam
So what we have learned thus far?

Asymptomatic HyperCKemia:
- ELEVATED CK
- No muscle symptoms
- Normal muscle exam

- Repeat CK after 7 days, avoiding exercise

If normal CK: Stop / Observe
So what we have learned thus far?

Asymptomatic HyperCKemia:

- ELEVATED CK
- No muscle symptoms
- Normal muscle exam

Repeat CK after 7 days, avoiding exercise

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

Normal CK → Stop / Observe
Non-Neuromuscular Causes: Asymptomatic HyperCKemia

<table>
<thead>
<tr>
<th>Systemic causes of hyperCKemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine Disorders</strong></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td><strong>Cardiac Disease</strong></td>
</tr>
<tr>
<td>Acute Kidney Disease</td>
</tr>
<tr>
<td>Viral Illness</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Celiac Disease</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
</tr>
<tr>
<td>HMG-CoA Reductase Inhibitors</td>
</tr>
<tr>
<td>(Statins)</td>
</tr>
<tr>
<td>Fibrates</td>
</tr>
<tr>
<td>Anti-retrovirals (Zidovudine)</td>
</tr>
<tr>
<td>Beta-blockers</td>
</tr>
<tr>
<td>Anti-psychotic (Clozapine, etc)</td>
</tr>
<tr>
<td>Angiotensin Receptor Blocking</td>
</tr>
<tr>
<td>Agents</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td>Isotretinoin</td>
</tr>
<tr>
<td>Colchicine</td>
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</tbody>
</table>
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 ‘MacroCK’ 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
Risk of Malignant hyperthermia in asymptomatic hyperCKemia

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Testing</th>
<th>Result</th>
<th>Family history</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malandrini</td>
<td>37 (70% M)</td>
<td>In vitro contracture test with halothane-caffeine</td>
<td>1 MH susceptible (2.7%)</td>
<td>None</td>
<td>Very low risk of MH</td>
</tr>
<tr>
<td>Weglinski</td>
<td>49 (73% M)</td>
<td>In vitro contracture test with halothane-caffeine</td>
<td>24 MH susceptible (49%)</td>
<td>14 had FH of high CK levels; Most have had anesthesia without any MH</td>
<td>Possible risk, alert anesthesiologist about risk of MH</td>
</tr>
</tbody>
</table>

- Several older studies: CK levels are insensitive and nonspecific for risk for MH in the absence of a personal or family history of anesthetic complications.

Reasonable to inform about potential risk of MH before undergoing anesthesia, so that necessary precautions are put into place

Diagnostic Workup of Asymptomatic HyperCKemia

ELEVATED CK + No muscle symptoms + Normal muscle exam

Repeat CK after 7 days, avoid exercise

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

Normal CK
STOP

NO
STOP/observe
Diagnostic Workup of Asymptomatic HyperCKemia

ELEVATED CK
+ No muscle symptoms
+ Normal muscle exam

Repeat CK after 7 days, avoid exercise

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

Normal CK
STOP

NO
STOP/observe

Rule out non-neuromuscular causes

Discuss with patient re utility of future workup

EMG and muscle biopsy

• Endocrine
• CTD
• Cardiac/Renal
• Viral Illness
• Pregnancy
• Celiac Disease
• Medications
• Metabolic
• Surgery
• Malignancy
• MacroCK

STOP and treat causes
Q3. What is the diagnostic yield of doing EMG and muscle biopsy on patient with asymptomatic hyperCKemia after ruling out non-neuromuscular causes

B. 50%
C. 70%
D. 90%
Abnormal muscle biopsy: 2/3rd of cases
- Mostly non-specific and not diagnostic

Muscle biopsy will be diagnostic
- Only 20-25% cases
- Often requires extensive w/u for dystrophies and metabolic myopathies

<table>
<thead>
<tr>
<th>Study</th>
<th>Abnl /total # biopsies</th>
<th>Dx/total # biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brewster</td>
<td>4/14 (29%)</td>
<td>0/14 (0%)</td>
</tr>
<tr>
<td>Dabby</td>
<td>22/40 (55%)</td>
<td>3/40 (8%)</td>
</tr>
<tr>
<td>Fernandez</td>
<td>83/104 (80%)</td>
<td>51/104 (49%)</td>
</tr>
<tr>
<td>Joy and Oh</td>
<td>15/19 (79%)</td>
<td>15/19 (79%)</td>
</tr>
<tr>
<td>Malandrini</td>
<td>34/37 (92%)</td>
<td>3/37 (8%)</td>
</tr>
<tr>
<td>Prelle</td>
<td>44/114 (39%)</td>
<td>20/114 (18%)</td>
</tr>
<tr>
<td>Reijneveld</td>
<td>24/31 (77%)</td>
<td>0/31 (0%)</td>
</tr>
<tr>
<td>Simmons</td>
<td>11/20 (55%)</td>
<td>6/20 (30%)</td>
</tr>
<tr>
<td>Filosto</td>
<td>83/50 (79%)</td>
<td>15/105 (14%)</td>
</tr>
<tr>
<td>Total</td>
<td>320/484 (67%)</td>
<td>113/484 (23%)</td>
</tr>
</tbody>
</table>
Diagnostic Yield of EMG in Asymptomatic HyperCKemia

- **Abnormal EMG:**
  - 50% cases
  - Mostly non-specific changes
- **EMG:**
  - Sensitivity 69%
  - Specificity 54%

- Normal EMG: Doesn’t rule out
- Abnormal EMG: Doesn’t rule in

- **EMG uses:**
  - Guide for muscle biopsy
  - Occasional neurologic dx

<table>
<thead>
<tr>
<th>Study</th>
<th>Abnormal EMGs/total EMGs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brewster</td>
<td>4/14 (29%)</td>
</tr>
<tr>
<td>Dabby</td>
<td>8/27 (29%)</td>
</tr>
<tr>
<td>Fernandez</td>
<td>23/57 (40%)</td>
</tr>
<tr>
<td>Joy and Oh</td>
<td>14/19 (74%)</td>
</tr>
<tr>
<td>Malandrini</td>
<td>15/37 (41%)</td>
</tr>
<tr>
<td>Prelle</td>
<td>57/100 (57%)</td>
</tr>
<tr>
<td>Reijneveld</td>
<td>9/30 (30%)</td>
</tr>
<tr>
<td>Simmons</td>
<td>9/20 (45%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>139/304 (46%)</strong></td>
</tr>
</tbody>
</table>

Prelle et al. J Neurol 2002
Diagnostic Yield of EMG and Muscle Biopsy

• Yield of EMG + Muscle biopsy:
  ▪ 30% chance of neuromuscular dx

• Most EMG + muscle biopsy:
  ▪ Non-specific
  ▪ 30-40%

• Normal EMG + Muscle biopsy:
  ▪ 30-40%
  ▪ Idiopathic HyperCKemia

HyperCKemia literature: Diagnosis by EMG and muscle biopsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients diagnosed/total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brewster</td>
<td>10/14 (71%)</td>
</tr>
<tr>
<td>Dabby</td>
<td>3/40 (8%)</td>
</tr>
<tr>
<td>D’Adda</td>
<td>6/55 (11%)</td>
</tr>
<tr>
<td>Fernandez</td>
<td>57/104 (55%)</td>
</tr>
<tr>
<td>Joy and Oh</td>
<td>15/19 (79%)</td>
</tr>
<tr>
<td>Malandrini</td>
<td>4/97 (4%)</td>
</tr>
<tr>
<td>Malandrini</td>
<td>3/37 (8%)</td>
</tr>
<tr>
<td>Prelle</td>
<td>21/114 (18%)</td>
</tr>
<tr>
<td>Simmons</td>
<td>6/20 (30%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>125/445 (28%)</strong></td>
</tr>
</tbody>
</table>
Extensive Work Up Leads to Diagnosis In Minority of Cases

• 114 Caucasian patients (93 males; 21 females; age 3-70) were evaluated 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)

Prelle et al. J Neurol 2002
Likelihood of diagnosis based on CK and Age

CK level not predictive of neuromuscular diagnosis on EMG/Biopsy, except when very high CK levels >7-10 x ULN

| Diagnosis or pathologic biopsy vs. normal (Odds Ratio) |
|---------------------------------|-----------------|-----------------|-----------------|
| CK                             | Age ≤ 24 y      | Age 25 – 39 y   | Age ≥ 40 y      |
| < 554 U/L                      | 1 (reference)   | 2               | 11              |
| 555-1038 U/L                   | 5               | 6               | 7               |
| > 1039 U/L                     | 28              | 17              | 4               |

| Diagnosis vs. Non-Diagnosis (Odds Ratio) |
|---------------------------------|-----------------|-----------------|-----------------|
| CK                             | Age ≤ 24 y      | Age 25 – 39 y   | Age ≥ 40 y      |
| < 554 U/L                      | 1 (reference)   | 7               | 27              |
| 555-1038 U/L                   | 7               | 10              | 8               |
| > 1039 U/L                     | 81              | 15              | 2               |

CK and Age together can help in likelihood of neuromuscular diagnosis

Occult or Latent Neuromuscular causes of ‘Asymptomatic HyperCKemia’

Neuromuscular Dx in Asymptomatic (pauci-symptomatic) HyperCKemia

**Dystrophies**
- Duchenne/Becker (dystrophinopathy)
- Limb Girdle
- Others
  - myofibrillar/desmin/myotonic

**Metabolic/Mitochondrial**
- CPT2 deficiency
- McArdle’s disease
- Myoadenylate deaminase
- Mitochondrial
- Pompe’s

**Other**
- Neurogenic causes
- Familial
- Sarcoid
- Thyroid myopathy
- Congenital

**Inflammatory**
- IBM
- Amyopathic DM
- Autoimmune ILD/anti-synthetase
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*
We must recognize that in most cases where a specific diagnosis is made (e.g. adult dystrophies or metabolic myopathies)

1. No Treatment Exists in most cases
2. Course is Often Benign if presentation is asymptomatic
Diagnostic Workup of Asymptomatic HyperCKemia

1. **ELEVATED CK**
   - No muscle symptoms
   - Normal muscle exam

2. Repeat CK after 7 days, avoid exercise

   - **Normal CK**
     - STOP
   - **NO**
     - STOP/observe

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

4. Rule out non-neuromuscular causes

5. Discuss with patient re utility of future workup

   - EMG and muscle biopsy

   - STOP and treat causes

   - Endocrine
   - CTD
   - Cardiac/Renal
   - Viral Illness
   - Pregnancy
   - Celiac Disease
   - Medications
   - Metabolic
   - Surgery
   - Malignancy
   - MacroCK
Diagnostic Workup of Asymptomatic HyperCKemia

**ELEVATED CK**
- No muscle symptoms
- Normal muscle exam

Repeat CK after 7 days, avoid exercise

- Normal CK
  - STOP

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

Rule out non-neuromuscular causes

- NO
  - STOP/observe

Discuss with patient re utility of future workup

- EMG and muscle biopsy

Normal EMG/Biopsy

- Rule out neuromuscular causes

Idiopathic HyperCKemia

STOP and treat causes

- Endocrine
- CTD
- Cardiac/Renal
- Viral Illness
- Pregnancy
- Celiac Disease
- Medications
- Metabolic
- Surgery
- Malignancy
- MacroCK

- Dystrophies
- Metabolic
- Congenital
- Inflammatory
- Other
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 (nl 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, exercise, pregnancy, etc.

Q4. What is the prognosis of idiopathic hyperCKemia?

A. Always have benign course on long term follow up

C. 50% of patients will progress on long term follow up to develop neuromuscular symptoms

D. 90% of patients will normalize their CK overtime
Benign Prognosis of Idiopathic HyperCKemia

- 55 patients with idiopathic hyperCKemia were 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
  - 2 diagnosed with neuromuscular disorder (1 case of LGMD with weakness, dystrophinopathy carrier)
  - 3 with thyroid abnormality
  - 5 were diagnosed with cancer

Other studies showed even better long term prognosis of asymptomatic hyperCKemia

D'Adda J Neurol 2006; Reijneveld JC Muscle Nerve 2000
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

T. Kyriakides  EJN 2010
Diagnostic Workup of Asymptomatic HyperCKemia

ELEVATED CK + No muscle symptoms + Normal muscle exam

Repeat CK after 7 days, avoid exercise

Normal CK STOP

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

NO STOP/observe

Rule out non-neuromuscular causes

Discuss with patient re utility of future workup:
• 25-30% yield
• limited treatment

EMG and muscle biopsy with biochemical test

Normal EMG/Biopsy

Idiopathic HyperCKemia

Rule out neuromuscular causes

STOP and treat causes

- Endocrine
- CTD
- Cardiac/Renal
- Viral Illness
- Pregnancy
- Celiac Disease
- Medications
- Metabolic
- Surgery
- Malignancy
- MacroCK

- Dystrophies
- Metabolic
- Congenital
- Inflammatory
- Other
Diagnostic Workup of Asymptomatic HyperCKemia

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- No muscle symptoms
- Normal muscle exam

Repeat CK after 7 days, avoid exercise

CK level > 1.5-2x ULN for gender and race:
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Rule out non-neuromuscular causes

Discuss with patient re utility of future workup:
- 25-30% yield
- limited treatment

EMG and muscle biopsy with biochemical test

Normal EMG/Biopsy

Idiopathic HyperCKemia

Course is benign in 80%

STOP and treat causes

NO

STOP/observe

STOP
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

We appreciate any questions/comments:

aggarwalr@upmc.edu