ENDORAMA:
An 18 Year Old Man with Weakness

Laura Dickens
February 14, 2019
Objectives

1. Discuss the differential diagnosis for endocrine causes of muscle weakness
2. Evaluate for endocrine causes of muscle weakness
3. Discuss treatment for endocrine causes of muscle weakness
Chief complaint

18 year old man presenting to the ER with weakness
HPI

• He awoke yesterday with “tightness” in his arms and legs and attributed it to muscle soreness from a soccer match.
• Initially he was able to stand and walk across the room, then he sat down and was unable to stand again due to weakness in his legs > arms.
• Denies fever, infectious symptoms, sick contacts. Denies difficulty speaking or swallowing. Denies N/V, diarrhea, constipation, weight change. Denies chest pain, palpitations, leg swelling. Denies neck pain, joint pain.
• Denies taking any medications or using illicit drugs.
• No recent travel. No recent vaccines. No unusual food or animal exposures.
HPI

• Similar ED presentation 5 months ago to Comer:
  – Awoke with proximal muscle weakness which worsened over a few hours to the point where he could not walk
  – Denied recent exertion. Only change in routine was a large meal at Hooter’s the night before.
  – Labs showed elevated CK, electrolyte derangements
  – Weakness improved with supportive care and hydration in the ED
  – Neurology consulted, suspected viral myositis
• Muscle strength returned to baseline
• No further episodes until current presentation
<table>
<thead>
<tr>
<th>PMH:</th>
<th>Meds:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild, intermittent asthma</td>
<td>Albuterol PRN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PSH:</th>
<th>Allergies:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsillectomy (age 4-5)</td>
<td>NKDA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ROS:</th>
<th>Social:</th>
</tr>
</thead>
<tbody>
<tr>
<td>+weakness</td>
<td>Lives with mom, high school student. Born in the US, both parents are Mexican</td>
</tr>
<tr>
<td>+myalgias</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-contributory</td>
</tr>
</tbody>
</table>
Physical exam

VITALS: BP 104/51, HR 80, RR 18, O2 sat 97%, 5’3”, 160lbs, BMI 28.3 (94%)

Constitutional: He is oriented to person, place, and time. He appears well-developed and well-nourished. No distress.

HENT: Normocephalic and atraumatic. Oropharynx is clear and moist.
Eyes: Conjunctivae and EOM are normal. No proptosis or lid lag
Cardiovascular: Normal rate, regular rhythm. No murmur heard.
Pulmonary/Chest: Effort normal and breath sounds normal. No wheezes.
Musculoskeletal: He exhibits no edema or deformity.
Neurological: He is alert and oriented x3. **Strength 4+/5 in hip flexors, otherwise 5/5. Normal reflexes. Sensation intact.** Note initial general medicine exam described 2/5 strength in shoulders and hips and diminished reflexes.
Skin: Skin is warm and dry. No rash noted.
Psychiatric: He has a normal mood and affect.
Differential diagnosis? Endocrine causes?

- Causes of acute muscle weakness:
  - Myasthenia gravis crisis
  - Guillian-barre syndrome
  - Transverse myelitis
  - Periodic paralysis
  - Tick paralysis
  - Botulism
Admission Labs

CK = 640
High sensitivity troponin <6
CRP <3
ESR 5
HbA1c 4.8
Urine tox negative

Neutrophils 82%

Ca 9.4
Mg 1.9
Ph 2.5

6.4 3.9
0.3 0.1
29 53
162
15.3
10.8
333
Endocrine causes of weakness?

• Causes of acute muscle weakness:
  - Myasthenia gravis crisis
  - Guillian-Barré syndrome
  - Transverse myelitis
  - Periodic paralysis
  - Tick paralysis
  - Botulism

How does this change your differential?
Periodic paralysis?

Subtypes

• Hypokalemic periodic paralysis
  – Transient thyrotoxic paralysis
  – Andersen syndrome
• Hyperkalemic periodic paralysis
• Normokalemic periodic paralysis

Periodic paralysis

- Most commonly hereditary with AD inheritance
- Muscle diseases due to channelopathies
- Hypokalemic and hyperkalemic forms
- Clinically present as painless muscle weakness precipitated by heavy exercise or high-carbohydrate meals (hypoK) or cold, fasting, rest after exercise (hyperK)
- Respiratory, bulbar, and cardiovascular systems rarely involved

Genetic mutations in periodic paralysis

Figure 1.2. Mutations in the muscle calcium (CACNA1S), sodium (SCN4A), and potassium (KCNJ2) genes causing periodic paralyses.
Periodic paralyses: summary of subtypes

**Hypokalemic PP**
- Primary
  - Hereditary
  - Thyrotoxic PP
- Secondary
  - Renal K losses
  - GI K losses
- Treatment (hereditary)
  - Acute: KCl
  - Chronic: KCl, +/- acetazolamide

**Normokalemic PP**
- Differentiate from hyperPP presenting with normal K
- Prone to hypoPP with certain triggers (steroids, hyperthyroidism)

**Hyperkalemic PP**
- Primary
  - Hereditary
- Secondary
  - Renal and endocrine hyperK
- Treatment (hereditary)
  - Acute: thiazide, inhaled beta agonist, IV Ca
  - Chronic: dichlorphenamide (proven in RCT), acetazolamide, thiazide

For our patient, what additional labs would you check?
Lab results

TSH <0.01
Free T4 3.42
Total T3 275
TSI positive
Anti-TPO, anti-TG positive

Neurology labs: Myositis antibody panel negative

Infectious labs: RVP negative, CMV IgG+ IgM-, EBV IgG+ IgM-, HIV negative
RIGHT LOBE: 5.3 x 2.2 x 1.8 cm
LEFT LOBE: 4.5 x 1.8 x 1.5 cm
Diffusely heterogeneous with increased vascularity
Thyrotoxic Periodic Paralysis (TPP)

• Known complication of thyrotoxicosis
  – Chinese: 1.8% of all thyrotoxic patients, **13% of male thyrotoxic patients**
  – Japanese: 1.9% of all thyrotoxic patients, **4.3% of male thyrotoxic patients**
  – North America: 0.1-0.2% thyrotoxic patients
• Male to female ratio 1:17 to 1:20
• Typical age of presentation is 20-40 years
• Any cause of thyrotoxicosis can present with TPP (GD, toxic MNG, LT4 abuse or overtreatment)

Kung et al. JCEM. 2006 Jul;91(7):2490-5.
TPP clinical features

- Recurrent, transient attacks of muscle weakness ranging from mild to complete paralysis
- Prodrome of muscle aches, cramps, stiffness
- Lower limbs affected first, then girdle muscles, then upper limbs
- Bowel and bladder function unaffected
- Respiratory, bulbar, and ocular muscles rarely involved
- Attacks last a few hours to 72 hours

<table>
<thead>
<tr>
<th>TABLE 1. Clinical features of TPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult young men</td>
</tr>
<tr>
<td>Sporadic</td>
</tr>
<tr>
<td>Recurrent acute paralysis with complete recovery</td>
</tr>
<tr>
<td>Limb &gt; trunk involvement</td>
</tr>
<tr>
<td>Precipitated by heavy carbohydrate load, high-salt diet, alcohol, exertion</td>
</tr>
<tr>
<td>Family history of hyperthyroidism</td>
</tr>
<tr>
<td>Clinical features of hyperthyroidism</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Normal acid-base balance</td>
</tr>
<tr>
<td>Low potassium excretion rate</td>
</tr>
<tr>
<td>Low phosphate excretion</td>
</tr>
<tr>
<td>EMG: low-amplitude compound muscle action potential with no change after epinephrine</td>
</tr>
</tbody>
</table>

Kung et al. JCEM. 2006 Jul;91(7):2490-5.
TPP vs FHPP

- TPP: older age, male, Asian, history of thyrotoxicosis
- FHPP: younger age, AD inheritance, no hyperthyroidism

**TABLE 2. Distinguishing features between TPP and FHPP**

<table>
<thead>
<tr>
<th>Feature</th>
<th>TPP</th>
<th>FHPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>20–40</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Sex distribution</td>
<td>Predominantly male</td>
<td>Equal</td>
</tr>
<tr>
<td>Heredity</td>
<td>Sporadic</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Asian, American Indian/Hispanic, Caucasian</td>
<td>Caucasian, Asian</td>
</tr>
<tr>
<td>Family history</td>
<td>History of thyrotoxicosis</td>
<td>History with hypokalemic paralysis</td>
</tr>
<tr>
<td>Clinical features of hyperthyroidism</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
| Genetic predisposition                        | Associated with SNPs of Ca,
|                                             |   1.1 (–476A→G,                                           | Mutations of Ca,
|                                             |   intron 2 nt 57G→A, intron 26 nt 67A→G)                |   1.1 (R5258H, R1239H, R1239G), Na,
|                                             |                                                          |   1.4 (R669H, R672G, R672H), K,
|                                             |                                                          |   3.4 (R83H)                                           |

Kung et al. JCEM. 2006 Jul;91(7):2490-5.
TPP: Pathogenesis

Increased pump activity
1. T3
2. Catecholamines
3. Insulin

Fig. 1. Mechanisms for acute muscle weakness in thyrotoxic periodic paralysis.

Kung et al. JCEM. 2006 Jul;91(7):2490-5.
TPP Pathogenesis: Increased Na-K ATPase activity

• In vivo and in vitro assessment of Na-K ATPase activity in TPP and controls

• Subjects
  – 21 healthy patients
  – 23 untreated thyrotoxic patients
  – 13 untreated TPP patients
  – 7 treated thyrotoxic patients
  – 6 treated TPP patients

• Outcomes
  – Platelet Na-K ATPase activity
  – Plasma rubidium concentration after oral loading

TPP Pathogenesis: Increased Na-K ATPase activity

<table>
<thead>
<tr>
<th></th>
<th>Healthy men (n=15)</th>
<th>Untreated thyrotoxic men (n=15)</th>
<th>Untreated men with periodic paralysis (n=12)</th>
<th>Treated thyrotoxic men (n=7)</th>
<th>Treated men with periodic paralysis (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Na+, K⁺-ATPase activity (umol/h/g protein)</td>
<td>35·1 (30·2 to 40·0)</td>
<td>41·4 (34·9 to 47·9)</td>
<td>33·1 (28·0 to 38·2)</td>
<td>41·0 (30·0 to 52·0)</td>
<td>34·8 (29·1 to 40·5)</td>
</tr>
<tr>
<td></td>
<td>2·3 (2·1 to 2·5)</td>
<td>&lt;0·02</td>
<td>&lt;0·02</td>
<td>1·6 (0·8 to 2·4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4·5 (3·7 to 5·3)</td>
<td>20·2 (15·1 to 25·3)*</td>
<td>19·6 (15·1 to 24·1)*</td>
<td>6·7 (5·7 to 7·7)*</td>
<td>6·6 (6·4 to 6·8)*</td>
</tr>
<tr>
<td></td>
<td>11·5 (9·3 to 13·7)</td>
<td>38·1 (32·4 to 43·8)*</td>
<td>45·5 (38·4 to 52·6)*</td>
<td>14·0 (12·0 to 16·0)*</td>
<td>17·6 (16·4 to 18·8)*</td>
</tr>
<tr>
<td></td>
<td>134 (81 to 180)</td>
<td>253 (169 to 821)†</td>
<td>374 (195 to 1196)†‡</td>
<td>148 (110 to 234)†‡</td>
<td>131 (86 to 173)†‡</td>
</tr>
</tbody>
</table>

Platelet Na+, K⁺-ATPase activity (umol/h/g protein)

TPP Pathogenesis: Increased Na-K ATPase activity

- Plasma rubidium five hours after oral load
  - Healthy: 10.2 umol/l
  - Thyrotoxic: 7.0 umol/l
  - TPP: 6.0 umol/l
- Lower rubidium concentration indicates that sodium pump activity is increased in TPP compared to thyrotoxicosis alone

TTP Pathogenesis: Insulin Resistance

- Study in Thailand comparing insulin sensitivity in 10 men with TPP compared to 10 age and sex-matched men with simple thyrotoxicosis

Table 1. Characteristics at time of study

<table>
<thead>
<tr>
<th></th>
<th>TPP group (n = 10)</th>
<th>Control group (n = 10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>38 ± 9</td>
<td>42 ± 7</td>
<td>0.348</td>
</tr>
<tr>
<td>Duration after diagnosis (year)</td>
<td>4.4 ± 4.1</td>
<td>5.6 ± 2.6</td>
<td>0.470</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.56 ± 5.28</td>
<td>21.98 ± 2.27</td>
<td>0.021</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>88.7 ± 11.1</td>
<td>77.2 ± 8.2</td>
<td>0.022</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>97.5 ± 10.1</td>
<td>90.1 ± 5.5</td>
<td>0.066</td>
</tr>
<tr>
<td>Waist : hip ratio</td>
<td>0.91 ± 0.05</td>
<td>0.86 ± 0.06</td>
<td>0.046</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127 ± 17</td>
<td>127 ± 9</td>
<td>0.911</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78 ± 13</td>
<td>75 ± 5</td>
<td>0.508</td>
</tr>
<tr>
<td>FT4 (pmol/l)†</td>
<td>16.60 ± 3.39</td>
<td>16.94 ± 3.08</td>
<td>0.820</td>
</tr>
<tr>
<td>TSH (mIU/l)†</td>
<td>3.32 ± 3.24</td>
<td>3.31 ± 2.45</td>
<td>0.994</td>
</tr>
</tbody>
</table>

†Reference range: 9.03–22.57 pmol/l for FT4, 0.25–4.00 mIU/l for TSH.

TTP Pathogenesis: Insulin Resistance

Our patient:
BMI 28.3 (94%)
A1c 4.8

TPP treatment

• Acute attacks
  – Potassium
    • **Oral** – one protocol suggests 30 mEq q2 hours until improvement
    • **IV** – limit to <10mmol/hr unless cardiopulmonary compromise
    • Recovery in ~6 hours
    • Monitor for rebound hyperkalemia (up to 40% incidence)
  – Propranolol

• Chronic management
  – Treat hyperthyroidism
    • Restoring euthyroidism eliminates attacks
  – Beta blocker
    • Propranolol 40-120mg daily
  – Avoid triggers
Propranolol for Acute TPP

- Case series show efficacy of propranolol alone in TPP attacks
- Dosing regimens studied:
  - 3mg/kg PO propranolol x1
  - 1mg IV propranolol q10 minutes (up to 3mg)
- Also effective for prophylaxis against future attacks

Clinical course

• Weakness resolved with K repletion
• CK trended down with hydration
• Graves’ treatment:
  – Methimazole 20mg daily
  – Atenolol 25mg daily*
• Follow up labs in 2 weeks (no show despite reminder...), clinic follow up 4 weeks
TPP treatment

What treatment would you recommend for this patient when he comes to clinic?
A. Methimazole for one year
B. Radioactive iodine
C. Thyroidectomy
D. B or C
E. A, B, or C
What treatment would you recommend for this patient?

A. Methimazole for one year  
B. Radioactive iodine  
C. Thyroidectomy  
D. B or C  
E. A, B, or C

---

**Table 5. Clinical Situations That Favor a Particular Modality as Treatment for Graves’ Hyperthyroidism**

<table>
<thead>
<tr>
<th>Clinical situations</th>
<th>RAI</th>
<th>ATD</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>x</td>
<td>√√ / !</td>
<td>√ / !</td>
</tr>
<tr>
<td>Comorbidities with increased surgical risk and/or limited life expectancy</td>
<td>√√</td>
<td>√</td>
<td>x</td>
</tr>
<tr>
<td>Inactive GO</td>
<td>√</td>
<td></td>
<td>!</td>
</tr>
<tr>
<td>Active GO</td>
<td>b</td>
<td>√√</td>
<td>!</td>
</tr>
<tr>
<td>Liver disease</td>
<td>√√</td>
<td>!</td>
<td>!</td>
</tr>
<tr>
<td>Major adverse reactions to ATDs</td>
<td>√√</td>
<td>x</td>
<td>!</td>
</tr>
<tr>
<td>Patients with previously operated or externally irradiated necks</td>
<td>√√</td>
<td>√</td>
<td>!</td>
</tr>
<tr>
<td>Lack of access to a high-volume thyroid surgeon</td>
<td>√√</td>
<td>!</td>
<td>!</td>
</tr>
<tr>
<td>Patients with high likelihood of remission (especially women, with mild disease, small goiters, and negative or low titer TRAbs)</td>
<td>√</td>
<td>√√</td>
<td>!</td>
</tr>
<tr>
<td>Patients with periodic paralysis</td>
<td>√√</td>
<td>!</td>
<td>√√</td>
</tr>
<tr>
<td>Patients with right pulmonary hypertension, or congestive heart failure</td>
<td>√√</td>
<td>!</td>
<td>!</td>
</tr>
<tr>
<td>Elderly with comorbidities</td>
<td>√</td>
<td></td>
<td>!</td>
</tr>
<tr>
<td>Thyroid malignancy confirmed or suspected</td>
<td>x</td>
<td>-</td>
<td>√√</td>
</tr>
<tr>
<td>One of more large thyroid nodules</td>
<td>-</td>
<td>√</td>
<td>√√</td>
</tr>
<tr>
<td>Coexisting primary hyperparathyroidism requiring surgery</td>
<td>-</td>
<td>-</td>
<td>√√</td>
</tr>
</tbody>
</table>

<sup>a</sup>For women considering a pregnancy within 6 months, see discussion in Section [T2].

<sup>b</sup>Table 14 describes the use of RAI in GO in detail, considering disease activity, severity, and other risk factors for GO progression.
Questions?

Thank you!
References


• UpToDate. Thyrotoxic Periodic Paralysis.

