ENDORAMA:
An 18 Year Old Man with Weakness

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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

PMH:

Mild, intermittent asthma

PSH:

Tonsillectomy (age 4-5)

ROS:

+weakness

+myalgias

Meds:

Albuterol PRN

Allergies: NKDA

Social: Lives with mom, high school student. Born in the US, both parents are Mexican

Family: Non-contributory

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

Neck: Normal range of motion. Neck supple. No thyromegaly present.

Cardiovascular: Normal rate, regular rhythm. No murmur heard.

Pulmonary/Chest: Effort normal and breath sounds normal. No wheezes.

Abdominal: Soft. Bowel sounds are normal. Nontender.

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

141	108	9	128
2.1	21	0.6	

Ca 9.4
Mg 1.9
Ph 2.5

6.4	3.9
0.3	0.1
29	**53**

162

CK= 640
High sensitivity troponin <6
CRP <3
ESR 5

HbA1c 4.8

Urine tox negative

15.3	
10.8	333

Neutrophils 82%

Endocrine causes of weakness?

- Causes of acute muscle weakness:
  - [illegible]
  - [illegible]
  - 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

Fontaine et al. Adv Genet. 2008;63:3-23.

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

Fontaine et al. Adv Genet. 2008;63:3-23.

Genetic mutations in periodic paralysis

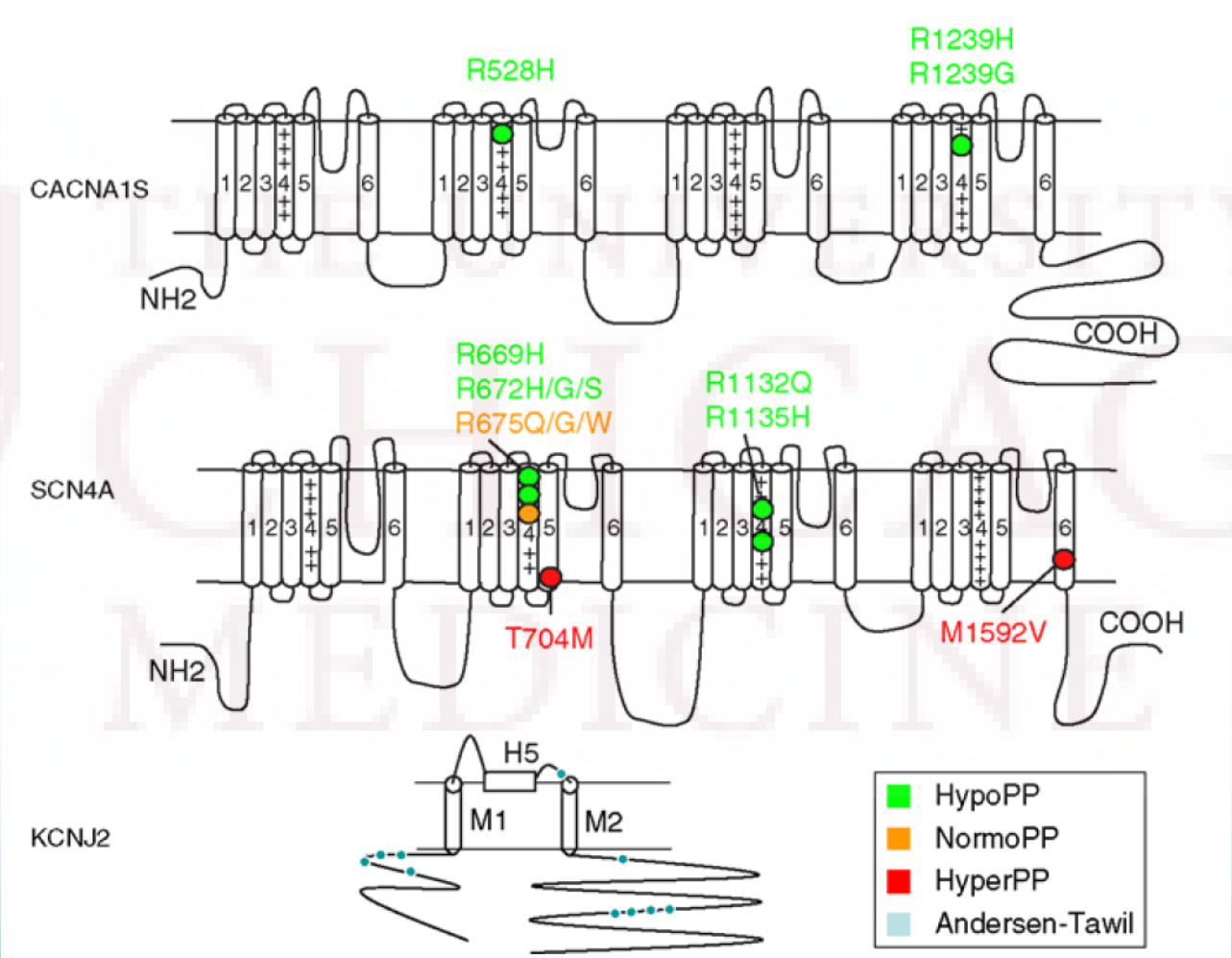


Figure 1.2. Mutations in the muscle calcium (*CACNA1S*), sodium (*SCN4A*), and potassium (*KCNJ2*) genes causing periodic paralyses.

Fontaine et al. Adv Genet. 2008;63:3-23.

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

Fontaine et al. Adv Genet. 2008;63:3-23.

For our patient, what additional labs would you check?

Lab results

TSH <0.01

Free T4 3.42

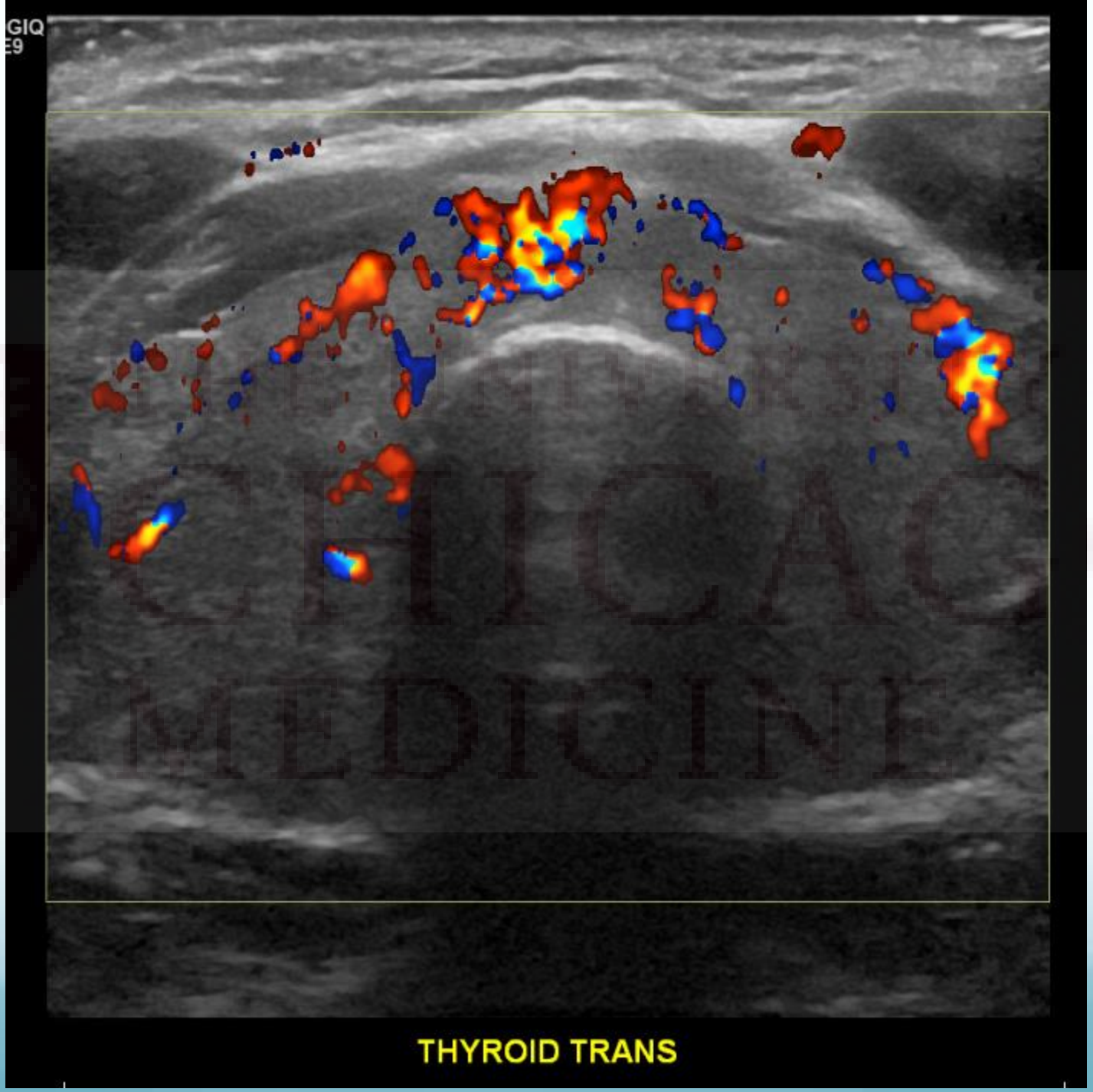
Total T3 275

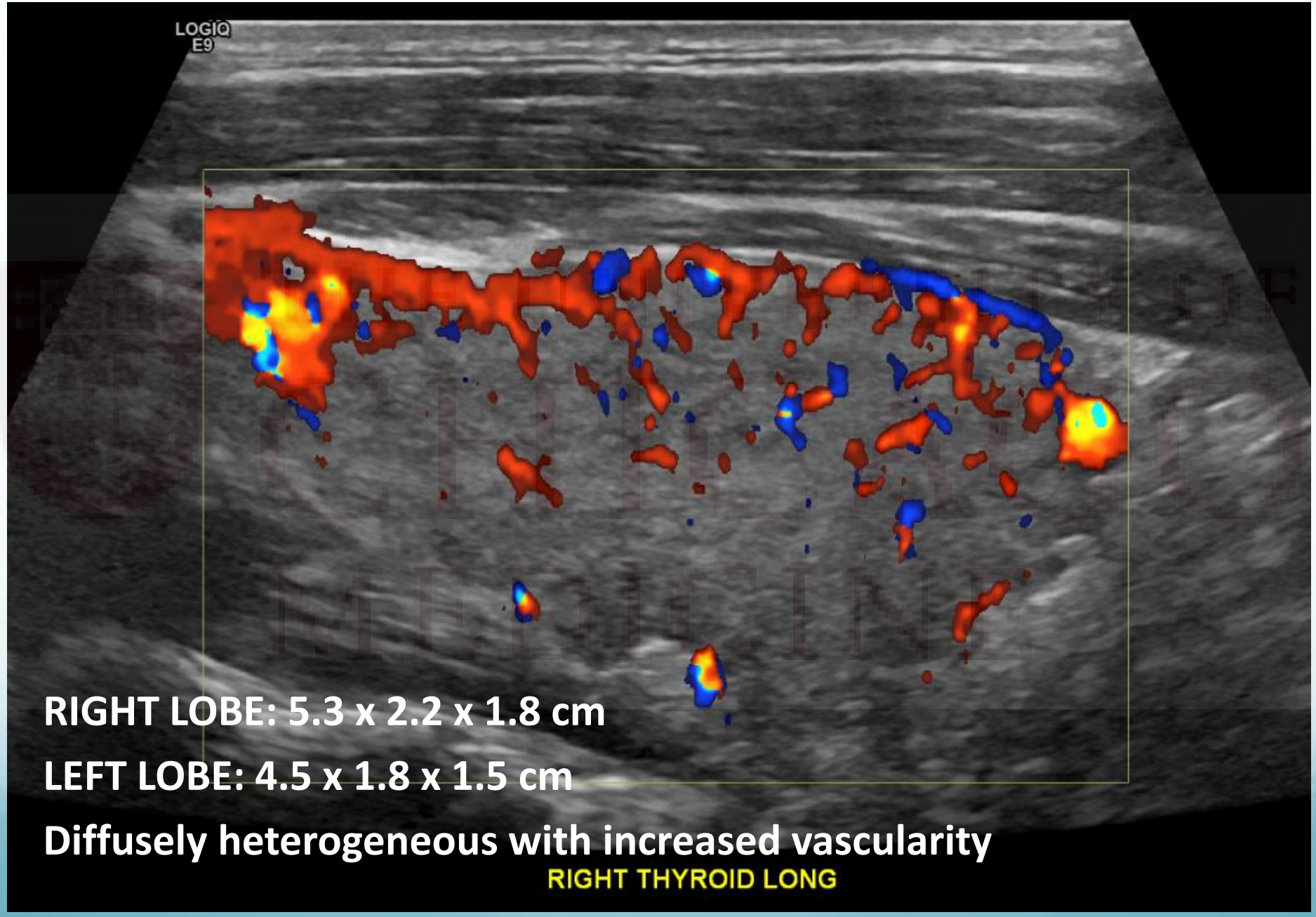
TSI positive

Anti-TPO, anti-TG positive

Neurology labs: Myositis antibody panel negative

Infectious labs: RVP negative, CMV IgG+ IgM-, EBV IgG+ IgM-, HIV negative


GIQ
E9
THYROID TRANS


LOGIQ
E9
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
RIGHT THYROID LONG

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 1. Clinical features of TPP

Feature
Adult young men
Sporadic
Recurrent acute paralysis with complete recovery
Limb > trunk involvement
Precipitated by heavy carbohydrate load, high-salt diet, alcohol, exertion
Family history of hyperthyroidism
Clinical features of hyperthyroidism
Hypokalemia
Normal acid-base balance
Low potassium excretion rate
Low phosphate excretion
EMG: low-amplitude compound muscle action potential with no change after epinephrine

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

TPP vs FHPP

TABLE 2. Distinguishing features between TPP and FHPP

	TPP	FHPP
Age (yr)	20–40	<20
Sex distribution	Predominantly male	Equal
Heredity	Sporadic	Autosomal dominant
Ethnicity	Asian, American Indian/Hispanic, Caucasian	Caucasian, Asian
Family history	History of thyrotoxicosis	History with hypokalemic paralysis
Clinical features of hyperthyroidism	Yes	No
Genetic predisposition	Associated with SNPs of $Ca_v1.1$ (−476A→G, intron 2 nt 57G→A, intron 26 nt 67A→G)	Mutations of $Ca_v1.1$ (R5258H, R1239H, R1239G), $Na_v1.4$ (R669H, R672G, R672H), $K_v3.4$ (R83H)

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

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

TPP: Pathogenesis

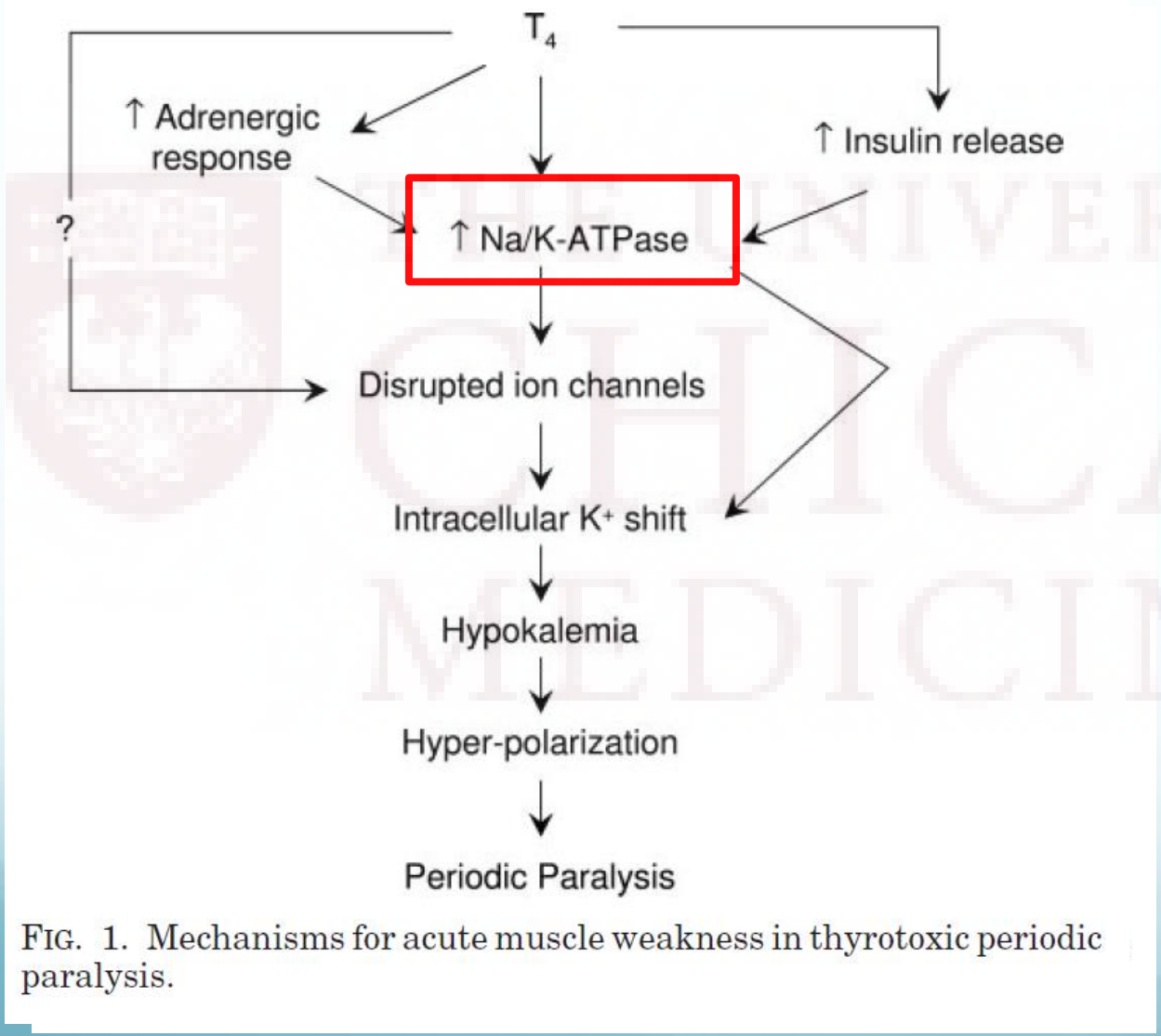
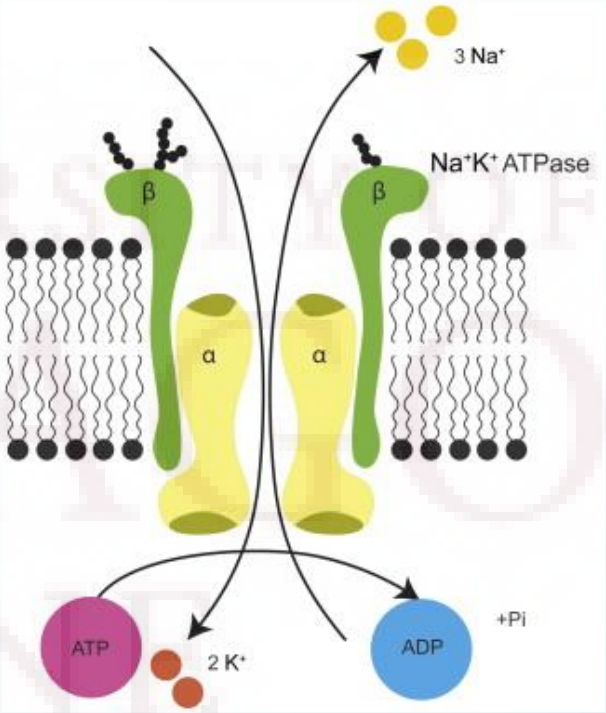


FIG. 1. Mechanisms for acute muscle weakness in thyrotoxic periodic paralysis.



Increased pump activity

1. T3
2. Catecholamines
3. Insulin

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

Chan et al. BMJ. 1991 Nov 2;303(6810):1096-9.

TPP Pathogenesis: Increased Na-K ATPase activity

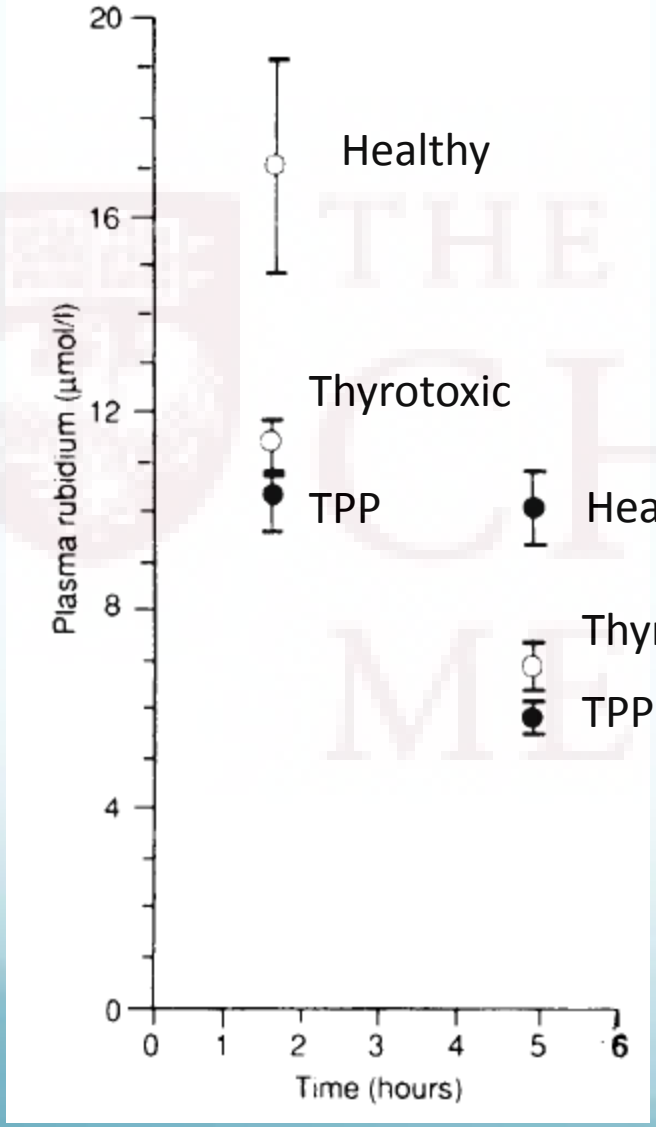
hyroxine concentrations and platelet Na^+, K^+-ATPase activity in healthy men and thyrotoxic men with re indicated

Healthy men (n=15)	Untreated thyrotoxic men (n=15)	Untreated men with periodic paralysis (n=12)	Treated thyrotoxic men (n=7)	Treated men with periodic paralysis (n=6)
35·1 (30·2 to 40·0)	41·4 (34·9 to 47·9)	33·1 (28·0 to 38·2)	41·0 (30·0 to 52·0)	34·8 (29·1 to 40·5)
2·3 (2·1 to 2·5)	<0·02	<0·02	1·6 (0·8 to 2·4)	
4·5 (3·7 to 5·3)	20·2 (15·1 to 25·3)*	19·6 (15·1 to 24·1)*	6·7 (5·7 to 7·7)*	6·6 (6·4 to 6·8)*
11·5 (9·3 to 13·7)	38·1 (32·4 to 43·8)*	45·5 (38·4 to 52·6)*	14·0 (12·0 to 16·0)*	17·6 (16·4 to 18·8)*
134 (81 to 180)	253 (169 to 821)†	374 (195 to 1196)†‡	148 (110 to 234)†‡	131 (86 to 173)

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

Chan et al. BMJ. 1991 Nov 2;303(6810):1096-9.

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

Chan et al. BMJ. 1991 Nov 2;303(6810):1096-9.

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

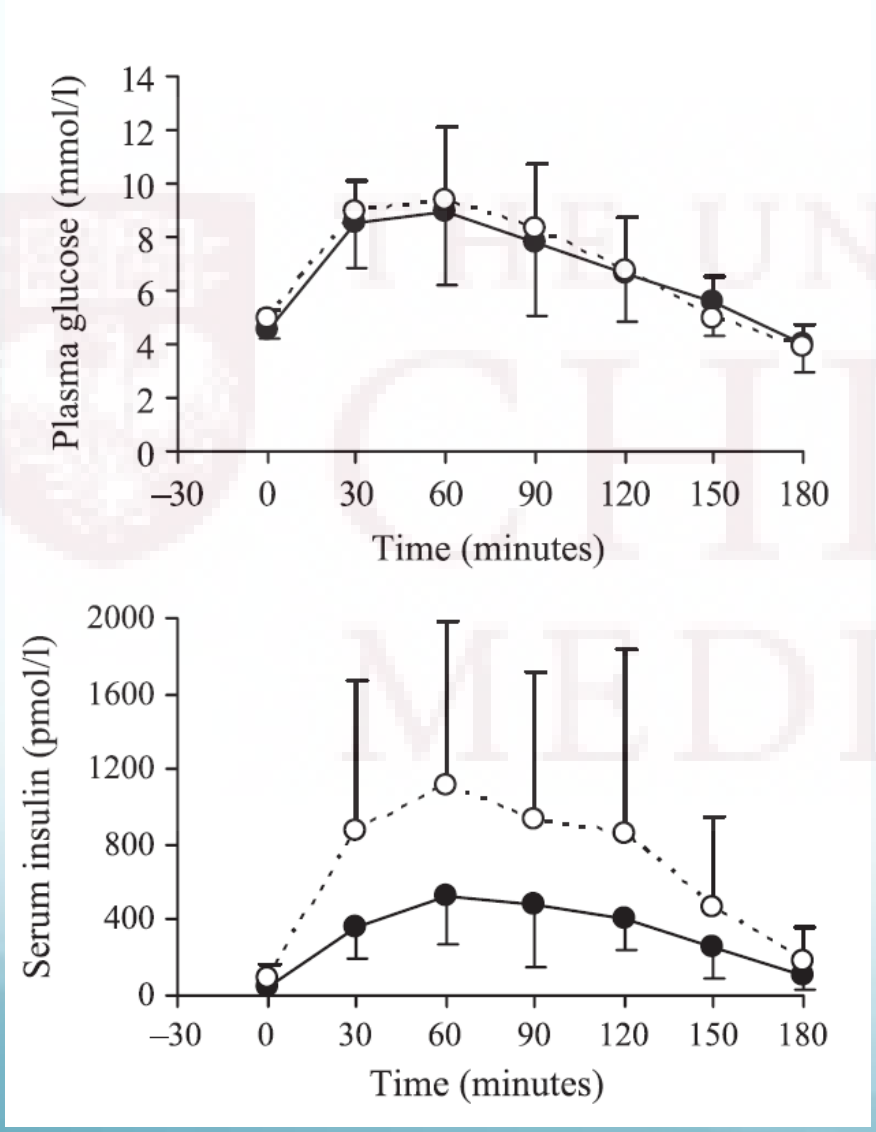
	TPP group ($n = 10$)	Control group ($n = 10$)	P
Age (year)	38 ± 9	42 ± 7	0·348
Duration after diagnosis (year)	4·4 ± 4·1	5·6 ± 2·6	0·470
BMI (kg/m^2)	26·56 ± 5·28	21·98 ± 2·27	0·021
Waist circumference (cm)	88·7 ± 11·1	77·2 ± 8·2	0·022
Hip circumference (cm)	97·5 ± 10·1	90·1 ± 5·5	0·066
Waist : hip ratio	0·91 ± 0·05	0·86 ± 0·06	0·046
Systolic blood pressure (mmHg)	127 ± 17	127 ± 9	0·911
Diastolic blood pressure (mmHg)	78 ± 13	75 ± 5	0·508
FT4 (pmol/l)†	16·60 ± 3·39	16·94 ± 3·08	0·820
TSH (mIU/l)†	3·32 ± 3·24	3·31 ± 2·45	0·994

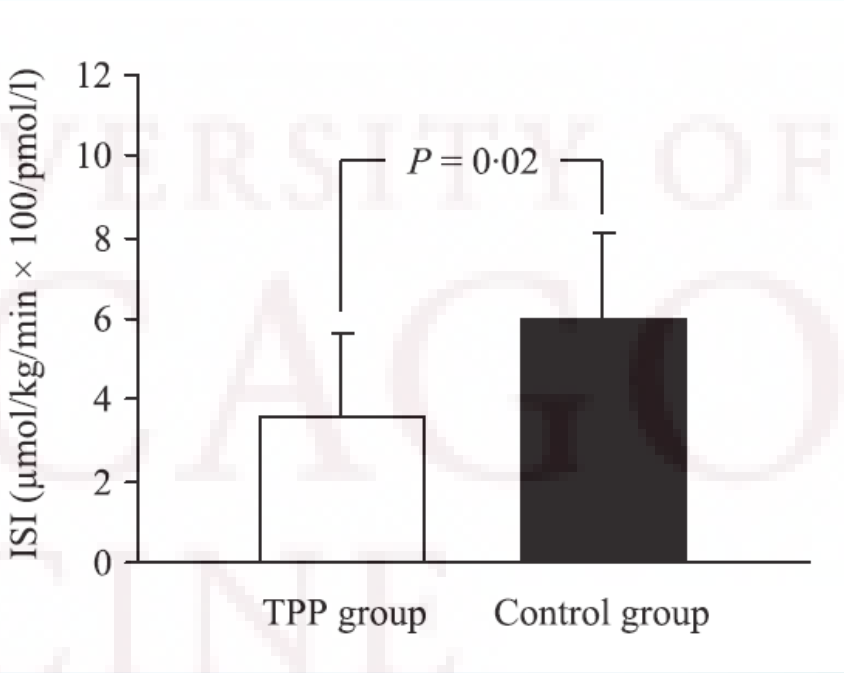
90% overweight

†Reference range: 9·03–22·57 pmol/l for FT4, 0·25–4·00 mIU/l for TSH.

Soonthornpun et al. Clin Endocrinol (Oxf). 2009 May;70(5):794-7.

TTP Pathogenesis: Insulin Resistance



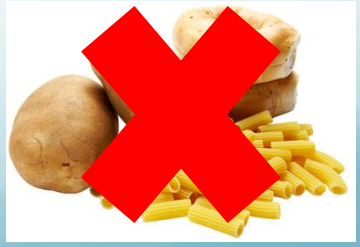


Our patient:
BMI 28.3 (94%)
A1c 4.8

Soonthornpun et al. Clin Endocrinol (Oxf). 2009 May;70(5):794-7.

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



UpToDate. Thyrotoxic Periodic Paralysis.

Propranolol for Acute TPP

3mg/kg PO propranolol

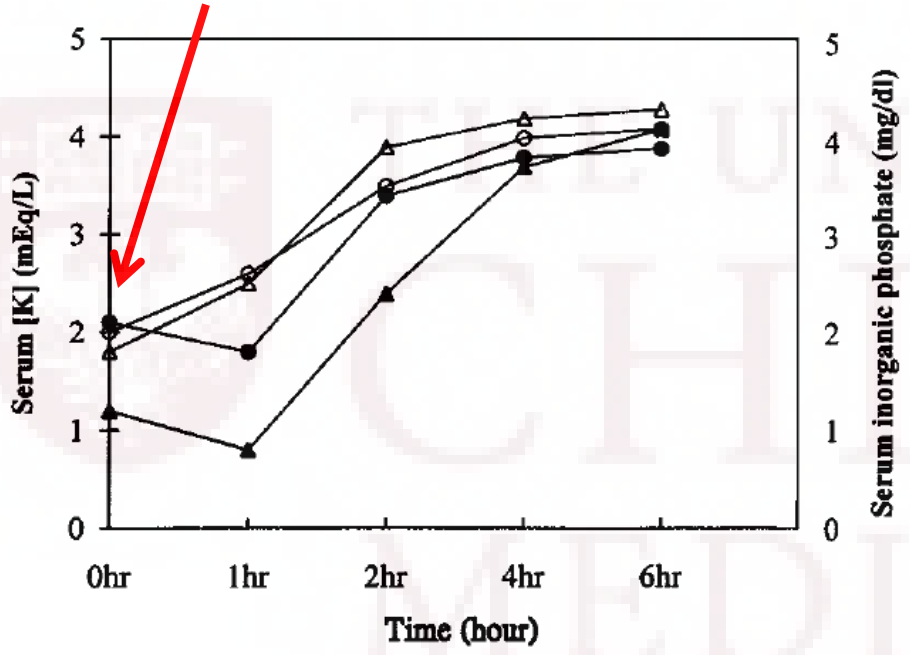


Fig 1. Changes in serum potassium and phosphate concentrations after the administration of oral propranolol. Solid symbols, case 1; open symbols, case 2; circles, potassium; triangles, inorganic phosphate. Serum potassium and inorganic phosphate concentrations increased within 2 hours. There was no rebound hyperkalemia or hyperphosphatemia in the 48 hours of observation.

- 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

Lin et al. Am J Kidney Dis. 2001 Mar;37(3):620-3.

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

TABLE 5. CLINICAL SITUATIONS THAT FAVOR A PARTICULAR MODALITY AS TREATMENT FOR GRAVES' HYPERTHYROIDISM

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

√√ = preferred therapy; √ = acceptable therapy; ! = cautious use; - = not first-line therapy but may be acceptable depending on the clinical circumstances; X = contraindication.

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

[b]Table 14 describes the use of RAI in GO in detail, considering disease activity, severity, and other risk factors for GO progression.

Ross et al. Thyroid. 2016 Oct;26(10):1343-1421.
Chang et al. Int J Endocrinol. 2014;2014:949068.

Questions?

Thank you!

References

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