A 50-YEAR OLD WOMAN & A 40 YEAR-OLD MAN WITH BIPOLAR DISORDER

Meltem Zeytinoglu, MD

PATIENT 1

History of the Present Illness

50 year-old female with prior medical history of bipolar disorder, hypothyroidism, and hyperthyroidism presents to establish care for management of thyroid disease.

PATIENT HISTORY

Past Medical History
Bipolar Disorder
Hypothyroidism
Hyperthyroidism
Hypertension
Mitral Valve Prolapse
Seasonal Allergies

Past Surgical History
None

Pertinent Family Hx
Mom – hypothyroidism
Mom – CVA (age 56)
Mom- Hypertension
Mom- ESRD on HD

Current Medications
Methimazole 10 mg bid
Telmisartan 80 mg
Fluticasone
Fexofenadine
Lithium
Multivitamin
Fish Oil
Vitamin C

Social History
Works for a Wellness Program in a local school corporation
No tobacco, alcohol, or illicit drug use

RELEVANT PRIOR HISTORY

2010- Routine Evaluation by PCP – TSH 5.41 → Levothyroxine 50 mcg daily.

Dose gradually titrated to 100 mcg daily, which she was on for > 1 year.

No prior history of irradiation to head, neck, or chest.

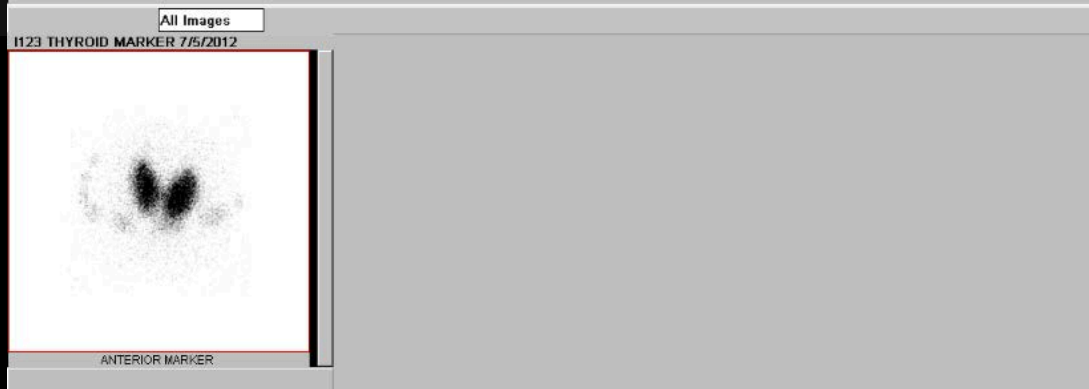
PRIOR TO EVALUATION MANAGEMENT

Date	TSH	Free T4	Free T3	Intervention
6/11/2012	< 0.01	3.8 (Ref range 0.8-1.8 ng/dL)	14.6 (Ref range 2.3-4.2 pg/ml)	Decreased LT4 to 75 mcg
9/20/2012	< 0.01			Decreased LT4 to 25 mcg
11/27/2012	< 0.01			Started on Methimazole 5mg tid → 10 mg bid
3/7/2013	28.35			Methimazole stopped
5/3/2013	< 0.01			Methimazole 10 mg daily
7/9/2013	< 0.01			Methimazole 10 mg bid

PERTINENT PRIOR EVALUATION

7/5/2012 – RAIU Scan
4 hour radioactive iodine uptake is 45%
24 hour radioactive iodine uptake is 73.6%

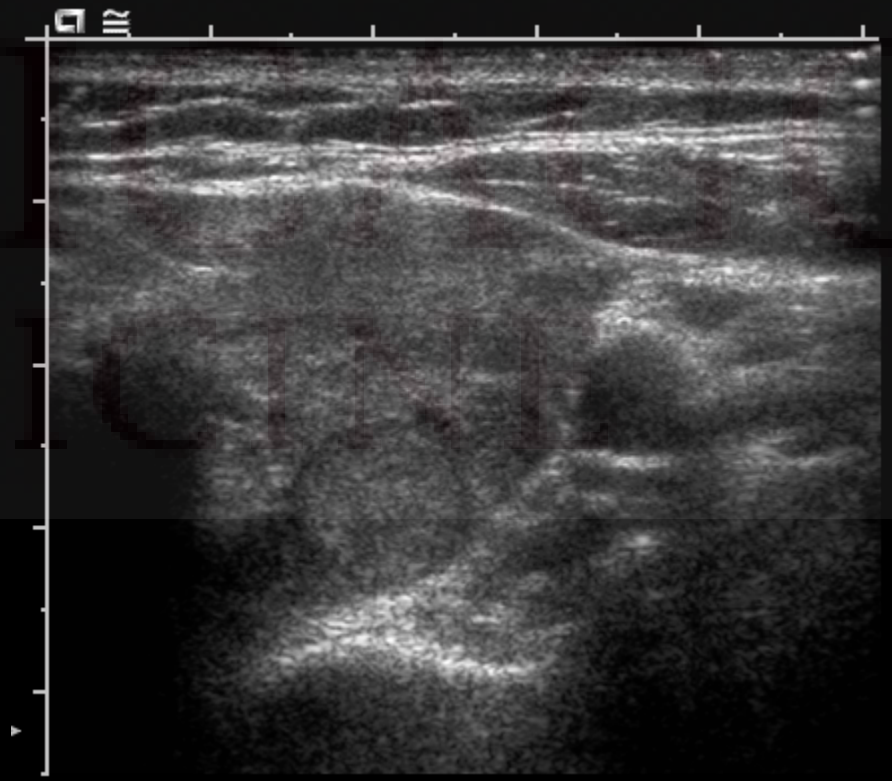
Thyroid stimulating immunoglobulin (TSI) was not checked.



PERTINENT PRIOR EVALUATION

11/5/2012 – Thyroid Ultrasound
Right lobe 5.2 x 2.5 x 1.9 cm
Left lobe 5.4 x 2.7 x 2.8 cm
Focal area of altered echogenicity in the left upper pole measuring 1.0 x 1.2 x 0.9 cm which is fairly well encapsulated and concerning for a discrete nodule. Either close surveillance or biopsy should be considered.

Patient did not have this nodule biopsied.



REVIEW OF SYSTEMS

General: Denies fevers, chills, fatigue, unexpected weight change.
HEENT: **Occasional trouble swallowing with liquids and solids.** Denies hoarseness, change in voice, vision disturbances including blurriness, double vision, swelling around eyes.
Cardiovascular: Denies chest pain, dizziness, syncope, lower extremity edema. **Positive for palpitations.**
Respiratory: Denies cough, chest tightness. **Occasional exertional dyspnea.**
Gastrointestinal: Denies nausea, vomiting, abdominal pain or distension, appetite change. **Reports diarrhea and constipation.**
Genitourinary: Denies urinary frequency, difficulty urinating, abnormal periods. **Occasional nocturia.**
Musculoskeletal: **Diffuse myalgias, arthralgias.** Denies joint swelling.
Neurological: Denies dizziness, weakness, numbness, tingling. **Positive for tremors.**
Hematologic: Denies easy bruising or bleeding.
Skin: Denies rashes, excessive sweating or moisture.
Psychiatric: Mood fluctuates between dysphoria and mania but has been stable recently.

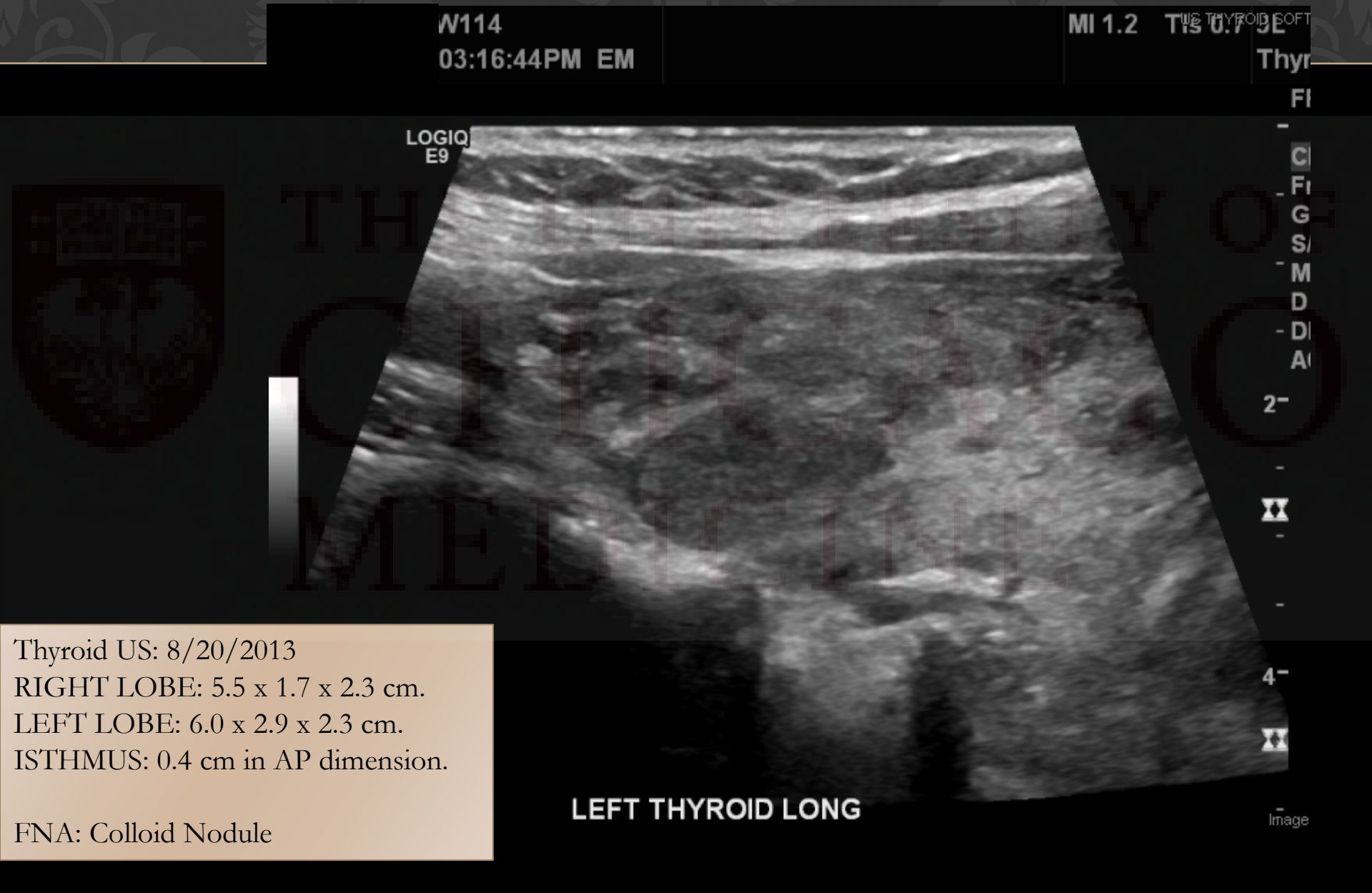
PHYSICAL EXAMINATION

BP 108/87 **P** 89 **R** 18 **WT** 119.5 kg **HT** 175.3 cm
General: Oriented to person, place, and time. Well-developed and well-nourished. No acute distress.
HEENT: Normocephalic and atraumatic.. Oropharynx is clear and moist. Conjunctivae normal and EOM are normal. Pupils are equal, round, and reactive to light. Hertle's exopthalmometer measurement - base of 96 R/L 21.5/21.5 (ULN < 18.5). **Mild periorbital edema inferior/bilaterally. Mild proptosis.** No injection.
Neck: Normal range of motion. Neck supple. No thyromegaly present. Symmetrically soft thyroid. No discrete nodules palpated.
Cardiovascular: Regular rate and rhythm. No murmurs, gallops, or rubs appreciated.
Pulmonary/Chest: Normal respiratory effort and breath sounds without wheezes or rales.
Abdominal: Soft, non-tender, non-distended with normal bowel sounds.
Musculoskeletal: Normal range of motion. No edema. 2 + distal peripheral pulses.
Neurological: Normal reflexes. No proximal muscle weakness.
Skin: Skin is warm and dry. Non-diaphoretic.
Psychiatric: Normal mood and affect.

DIAGNOSTIC EVALUATION & MANAGEMENT

TSH	< 0.01
Free T4	1.47
T3	198
TSI	4.1 Ref Range < 1.3

Anti-TPO and anti-TG antibodies negative.



Thyroid US: 8/20/2013
RIGHT LOBE: 5.5 x 1.7 x 2.3 cm.
LEFT LOBE: 6.0 x 2.9 x 2.3 cm.
ISTHMUS: 0.4 cm in AP dimension.

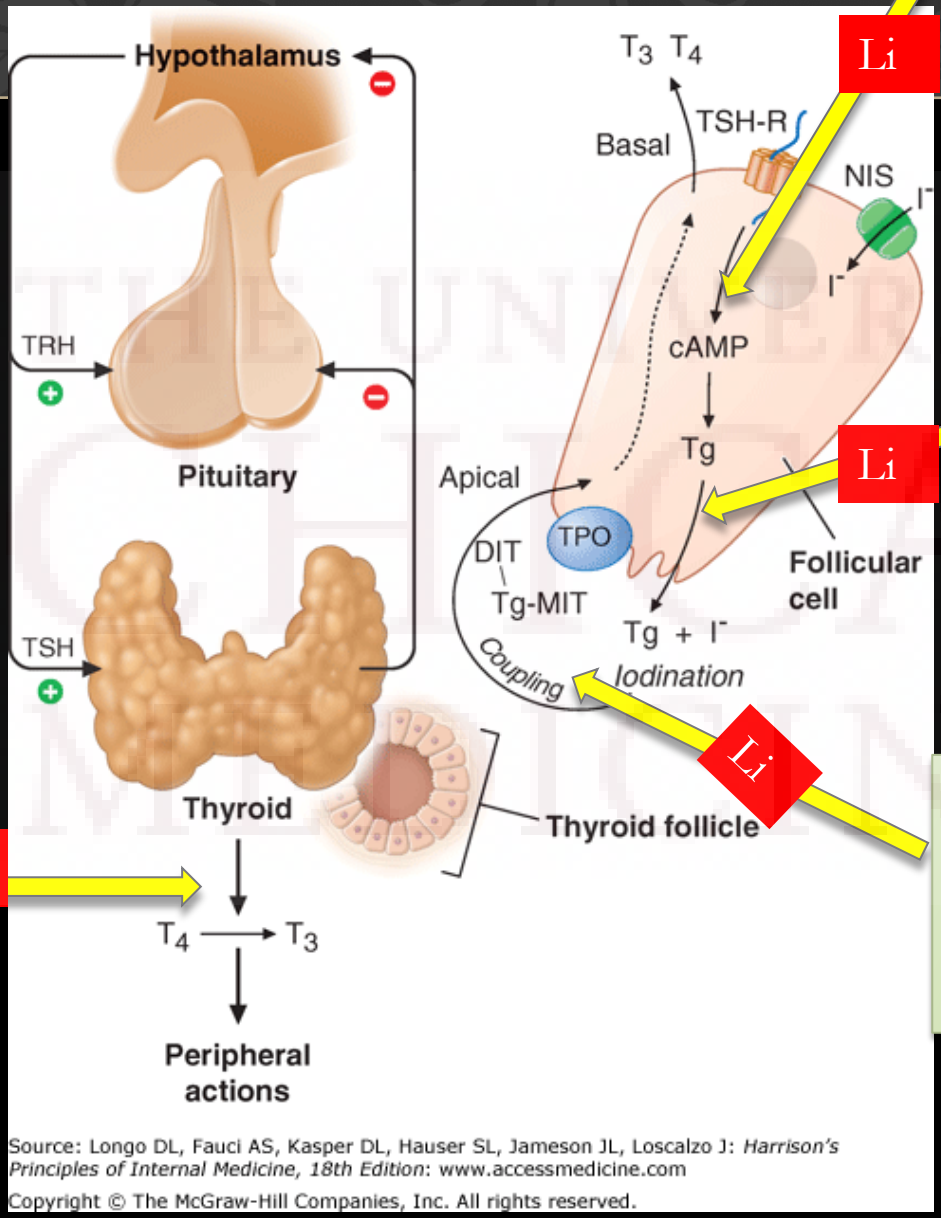
FNA: Colloid Nodule

CLINICAL QUESTION

Could her thyroid disease be lithium induced?

LITHIUM EFFECTS ON THYROID HORMONE SYNTHESIS

Lithium has been shown to be highly concentrated in thyroid cells



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

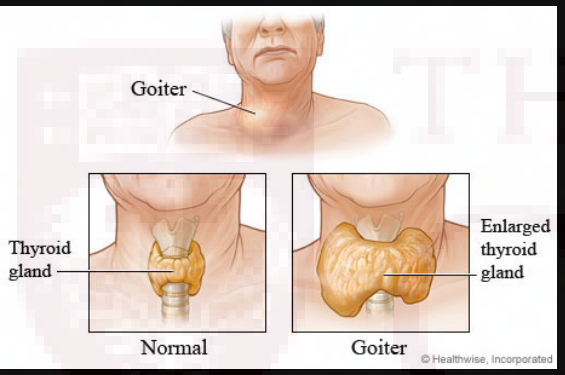
Inhibition of activity of TSH on cAMP

Increases intrathyroidal iodine content

Inhibits coupling of iodotyrosine residues to form iodothyronines (T4 and T3) by altering thyroglobulin structure

Inhibition of release of T4 and T3

LITHIUM AND THYROID DISEASE



Goiter: 40-50%

Inhibition of thyroid hormone secretion by lithium → decreased T4/T3 → Increased pituitary TSH secretion

Activation of pro-proliferative tyrosine kinase and Wnt/beta-catenin pathways

LITHIUM AND THYROID DISEASE

Subclinical Hypothyroidism & Hypothyroidism: 6-52%

Average duration of lithium use prior to onset ~18-24 months

Subclinical more common than overt hypothyroidism

Occurs in presence or absence of goiter

Risk increases with age > 45-50, female sex, and presence of family history of thyroid disease and thyroid auto-abs

Prevalence begins to approximate rates of general population after several years of lithium use

Lithium increases thyroid autoimmunity (+TPO) if present before therapy, but does not cause de novo synthesis of antibody

Basal TSH can be elevated in acute manic phase

With proper T4 therapy, <u>hypothyroidism is not a contraindication to lithium use</u>

Kibrige D, et al. Spectrum of lithium induced thyroid abnormalities: a current perspectivev. Thyroid Research. 2013;6(3):1-5.

LITHIUM AND THYROID DISEASE

Hyperthyroidism

Much less common than hypothyroidism

Frequency 2-3 x greater than that of hyperthyroidism in the general population

Most commonly due to transient, painless thyroiditis → toxic effect of lithium on thyroid with direct release of thyroglobulin and thyroid hormone into circulation

In one study of 300 patients w/Graves' + 100 patients with painless thyroiditis → odds of lithium exposure was 4.7 (95%CI 1.3-17.1) x greater in patients with painless thyroiditis

Graves, though less frequent can be lithium-related. 14 cases of lithium associated thyrotoxicosis, 8 had Graves' disease. (3 with toxic MNG, 2 with painless thyroiditis).

Barclay ML, et al. Lithium associated thyrotoxicosis: a report of 14 cases, with statistical analysis of incidence. Clin Endocrinol. 1994;40:759.

Miller KK, Daniels CH. Association between lithium use and thyrotoxicosis caused by silent thyroiditis. Clin Endocrinol. 2001;55:501-508.

PATIENT 2

History of the Present Illness

40 year-old white male with past medical history remarkable for bipolar disorder (dependent on lithium) and hyperparathyroidism presents to establish care in the Bone clinic.

PATIENT HISTORY

Past Medical History
Bipolar Disorder
Hyperparathyroidism
Hypothyroidism
Hypogonadism
Nephroogenic Diabetes Insipidus
Hypertension
Chronic Interstitial Nephritis
Obesity

Past Surgical History
Subtotal parathyroidectomy

Pertinent Family Hx
Patient adopted
Birth parent history:
Father – Leukemia
Father – Alcoholism
Mother – Bipolar Disorder

Current Medications
Levothyroxine 62.5 mcg qd
Lithium 1800 mg qd
Paricalcitol 1 mcg qd
Androgel 1.62% - 3 pumps qd
Valsartan 80 mg qd
Amlodipine 10 mg qd
Thiothixene 3 mg bid

Social History
Recently moved from California
Married, lives with wife
First-grade teacher
Former tobacco user, drinks 2-3 drinks a few times per week

PRIOR HISTORY

Bipolar Disorder
Diagnosed in 1997 – has been on lithium therapy since that time

Multiple other therapeutic regimens tired; has never tolerated being on lower doses or off of lithium therapy

Sees a Psychiatrist at Mayo where he has been enrolled in multiple clinical trials

Patient's hypothyroidism, hyperparathyroidism, diabetes insipidus, and chronic interstitial nephritis all previously thought secondary to lithium use

PATIENT 2

Hyperparathyroidism

Diagnosed 2010
↑ PTH (in 200s) with normal calcium on routine evaluation
Initial therapy with Cinacalcet 30 mg daily → ankle edema
4/2012 Subtotal parathyroidectomy, 3 glands removed (UCLA)
3/2013 started on Paricalcitol
No hypocalcemia following. Most recent PTH was 65
No history of osteoporosis, nephrolithiasis
Denies numbness, tingling, tetany, constipation

Nephrogenic Diabetes Insipidus

Wakes up to urinate at least 3x per night
Has never been on medical therapy for DI
24-hour urine collection at 1 time: 13.478 L

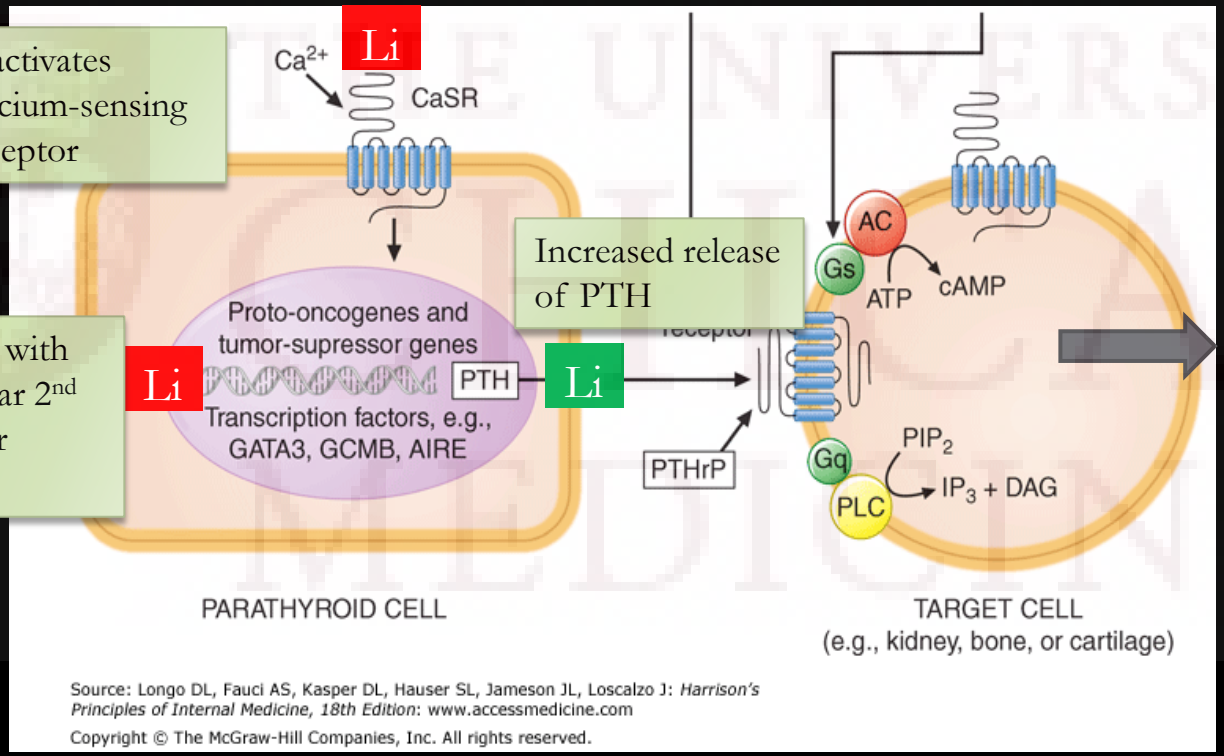
Hypothyroidism

Diagnosed 2008
Levothyroxine 50 mcg
Most recent TFTS – normal
Euthyroid by history & exam
Psychiatrist increasing LT4 with goal of getting TSH to lowest level of normal

HYPERPARATHYROIDISM WITH LITHIUM

Inactivates calcium-sensing receptor

Interferes with intracellular 2nd messenger signaling



Lancet Meta-Analysis 60 studies reporting effects of lithium on PTH

Calcium and PTH were increased by 10%compared with normal values in patients given lithium

Ca +0·09 mmol/L, (95% CI 0·02–0·17, p=0·009)
PTH +7·32 pg/mL, (95% CI 3·42–11·23, p<0·0001)

McKnight RF, et al. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012;379:721-28.

Saunders BD, et al. Lithium therapy and hyperparathyroidism: an evidence-based assessment. World J Surg. 2009;33:2314-2323.

GENETIC ANALYSIS OF LITHIUM-ASSOCIATED PARATHYROID TUMORS

Genetic analysis of 12 parathyroid tumors in 9 patients with lithium-associated hyperparathyroidism.

Comparative genomic hybridization (CGH), loss of heterozygosity, and multiple endocrine neoplasia type 1 gene (MEN1) mutation analysis were used in above patients.
CGH was also used in a non-lithium associated group of 13 sporadic parathyroid tumors

Lithium-associated parathyroid tumors had fewer genetic alterations compared with sporadic parathyroid tumors.
Tumorigenic pathway of lithium tumors thought independent of MEN1 and genes at 1p34.3-pter and 1q21-q32
Mechanism of lithium associated tumors →suspected increased parathyroid cell proliferation
Increased prevalence of multi-glandular disease occurring in lithium patients

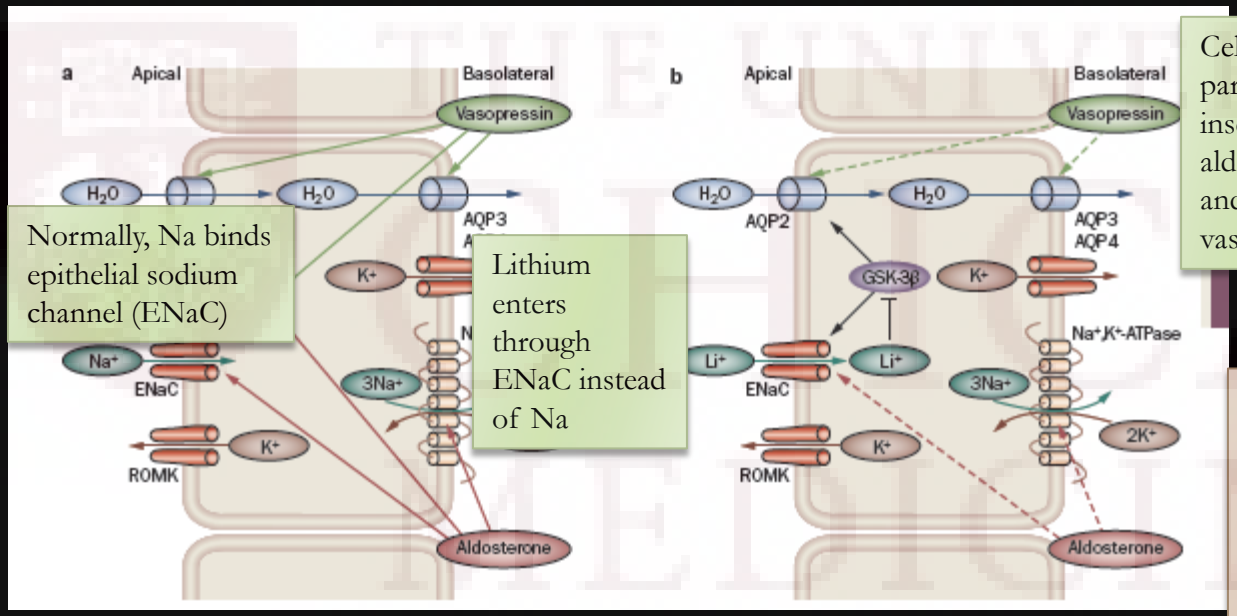
Table 1 Clinical and genetic data for the twelve lithium-associated parathyroid tumors from nine patients.

				Lithium therapy		Clinical data					CGH results		LOH results				
Patient	Age at operation (years)	Gender	Glands affected	Duration (years)	Dose (average mg/day)	SCa* (mmol/l)	Post-sCa* (mmol/l)	PTH†	Gland analyzed	Gland weight (g)	Losses	Gains	1p	1q	11q13	*MEN1* mutation analysis‡	*MEN1* polymorphisms
1	78	F	1	5	750	3.17	2.28	3.55	LA-1	8.06	1pcen-p31, 11q13-qter, 15q	—	+	+	+	—	—
2	52	M	4	16	180	2.97	2.35	2.83	LA-2	0.37	—	—	+	+	+	—	—
3	72	M	4	20+	500	2.81	2.54	3.07	LA-3	0.70	22911.2-q13	X	+	+	+	—	—
4	35	M	1	8–10	750	2.90	2.33	1.90	LA-4	na	11p14-p15, 11q22-q25	—	+	+	LOH	c.1193insTAC	—
5	64	F	2	20	1000	2.73	2.32	1.13	LA-5	0.12	—	—	+	+	+	—	—
6	52	F	1	0.5	500	2.80	2.12	1.68	LA-6	5.63	—	—	+	+	+	—	D418D‖
7	47	F	2	15+	750	2.93	2.35	4.56	LA-7	0.81	—	—	+	+	+	—	D418D
8	70	M	4	15	500	2.74	2.40	2.91	LA-8a	0.26	—	X	+	+	NI	—	D418D
									LA-8b	na	—	—	+	+	NI	—	D418D
9	68	F	4	12	750	2.65	2.43	1.07	LA-9a	0.08	—	—	+	+	+	—	D418D
									LA-9b	0.06	—	—	+	+	+	—	D418D
									LA-9c	0.03§	—	—	+	+	+	—	D418D

*Pre- and post-operative serum calcium (reference range 2.10–2.60 mmol/l); †pre-operative intact PTH in multiples of the upper normal limit; ‡confirmed somatic mutations; nucleotide numbering based on sequence obtained from EMBL Accession No. U93236; §even though this sample falls below the normal criteria for an abnormal gland (42), histopathologically this sample was found to be hyperplastic. —, none detected; ‖, nucleotide change – c.1364 C > T; +, retention of heterozygosity; na, not analysed/not available; NI, not informative (homozygous); LOH, loss of heterozygosity.

Dwight T. Genetic analysis of lithium-associated parathyroid tumors. European Journal of Endocrinology. 2002;146:619–627.

DIABETES INSIPIDUS AND LITHIUM



Normally, Na binds epithelial sodium channel (ENaC)

Lithium enters through ENaC instead of Na

Cell becomes partially insensitive to aldosterone and vasopression

Nephrogenic DI is seen in 20-40% of patients on chronic lithium therapy.

Principal cells of collecting duct are primary target for lithium nephrotoxicity.

Therapy:
Discontinuation of lithium if possible.
If unable, amiloride, which blocks the ENaC may prevent nephrotoxic effects of lithium.

Grufield JP and Rossier BC. Lithium nephrotoxicity re-visited. Nat Rev Nephrol. 2009;5:270-76.

OPTIMAL ENDOCRINOLOGIC MANAGEMENT OF PATIENTS ON LITHIUM

Before starting lithium:
Baseline serum TSH, Calcium

During lithium therapy:
Monitor GFR, TSH, Calcium at least every 12, and possibly even more frequently (with personal or family history of endocrine disease)

Monitor for symptoms of acute onset of nocturia, polyuria, hypercalcemia, goiter

Repeat blood tests if there is a change in mood state (mania)

Monitor for changes in weight

CONCLUSIONS

The spectrum of endocrinopathies caused by lithium use is broad and includes diseases of the thyroid (subclinical or overt hypothyroidism), hyperthyroidism (painless thyroiditis or Graves'); parathyroid (hyperparathyroidism and hypercalcemia); and diseases affecting water and sodium balance (nephrogenic DI).

Close monitoring before and during lithium use is critical in preventing these endocrinopathies.

With close monitoring, lithium can often be continued with thyroid disease and parathyroid disease (where effects of drug continue after withdrawal).
However, it should be stopped, unless no other alternatives for mood disorder when nephrotoxicity, including DI, is apparent.

OBJECTIVE

Review of Systems

Constitutional: Positive for fatigue. Negative for fever, chills, diaphoresis, activity change, appetite change and unexpected weight change.

HENT: Negative for trouble swallowing and voice change.

Eyes: Negative.

Respiratory: Negative for cough and shortness of breath.

Cardiovascular: Negative for chest pain, palpitations and leg swelling.

Gastrointestinal: Negative for nausea, vomiting, abdominal pain, diarrhea, constipation and abdominal distention.

Genitourinary: Positive for frequency.

Musculoskeletal: Negative. Negative for back pain, joint swelling and arthralgias.

Skin: Negative.

Neurological: Negative for tremors, weakness, light-headedness and numbness.

Hematological: Negative.

Psychiatric/Behavioral: Positive for sleep disturbance and dysphoric mood. The patient is nervous/anxious.

Recently depression more predominant than manic symptoms.

BP 106/78 | Pulse 64 | Resp 16 | Ht 177.5 cm (5' 9.88") | Wt 103.692 kg (228 lb 9.6 oz) | BMI 32.91 kg/m2

Physical Exam

Vitals reviewed.

Constitutional: He is oriented to person, place, and time. He appears well-developed and well-nourished.

HENT:

Head: Normocephalic and atraumatic.

Eyes: Conjunctivae normal and EOM are normal. Pupils are equal, round, and reactive to light.

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

Thyroid is symmetric and does not appear to be enlarged. There are no palpable nodules appreciated on exam.

Cardiovascular: Normal rate, regular rhythm and normal heart sounds.

No murmur heard.

Pulmonary/Chest: Effort normal and breath sounds normal. No respiratory distress. He has no wheezes. He has no rales.

Abdominal: Soft. Bowel sounds are normal. He exhibits no distension. There is no tenderness.

Musculoskeletal: He exhibits no edema and no tenderness.

Neurological: He is alert and oriented to person, place, and time. He has normal reflexes.

No tremors. Chvostek's negative.

Skin: Skin is warm and dry.

Psychiatric: His behavior is normal. Judgment and thought content normal.

Affect is slightly flat.

LITHIUM IN THE MANAGEMENT OF THYROID DISEASE

Older studies, including an RCT, have looked at lithium in management of thyrotoxicosis. Results did not show superiority to thionamides, especially when considering adverse effects. However, in rare cases of thionamide intolerance may be considered.

Has been used as adjunct in therapy radioactive iodine therapy for hyperthyroidism. 2 large randomized trials showed that lithium enhanced I-131 effectiveness with more prompt and permanent control in patients with large goiters. Another study, has not confirmed these results.

Has also been used for thyroid cancer – increases iodine retention in a thyroid remnant. No significanat clinical benefit.

Kristensen O, et al. Lithium carbonate in the treatment of thyrotoxicosis. A controlled trial. Lancet. 1976;20:603-605.

Lazarus JH. Lithium and thyroid. Best Prac Clin Res Endocrinol. 2009;23:723-733.