A 27 year old, post-partum, with nausea, vomiting, and hypercalcemia

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Endorama

September 10, 2020

ZOOM

AT THE FOREFRONT
UChicago Medicine

*I have no conflicts of interest to disclose.

Learning Objectives

- Discuss evaluation for post-partum patient with multiple endocrine abnormalities
- Review diagnostic considerations in pituitary dysfunction
- Discuss clinical management and follow up
- (Attempt to connect endocrine and neuromuscular findings if time allows)

27 year old female with a PMH of depression and possible cyclic vomiting syndrome presents to UC after multiple admissions for dehydration. She reports several months of vomiting and decreased appetite since the birth of her second child. The pregnancy and delivery were uncomplicated. Has lost about 20lbs over the last 2 months. She feels globally weak. No cough, fever, or difficulty swallowing. No sexual activity since childbirth and no menses. Unable to breastfeed. She has been told her potassium and magnesium have been low, but could not fill supplement prescriptions due to pharmacy closures. It appears she may have been started on methimazole for hyperthyroidism, but she did not fill the prescription.

Initial vitals and pertinent exam: Temp 36.7, BP 101/73, HR 101, SO_2 99%
Appears fatigued. Neck supple. No tenderness or thyromegaly. Normal weight. Reflexes unremarkable. No conjunctival redness or proptosis. Non-obese. No lower extremity edema. Skin very dry.

Feb 2020: normal birth after uncomplicated pregnancy, full term

April: OSH admission for n/v

calcium at 14.1, PTH <6,

TSH < 0.1

May: OSH admission

Ca at 13.0, PTH < 6

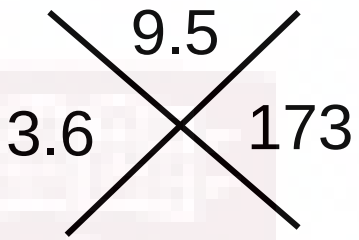
TSH < 0.1, FT4 1.4, FT3 4.7

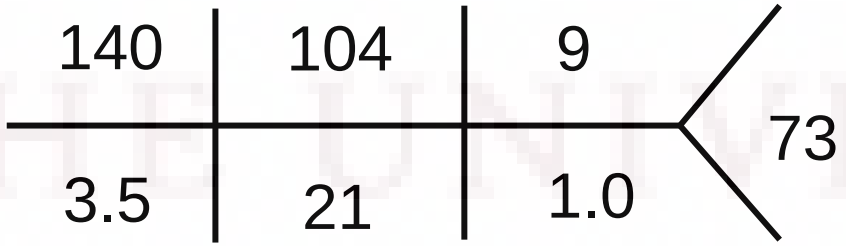
June: UC admission

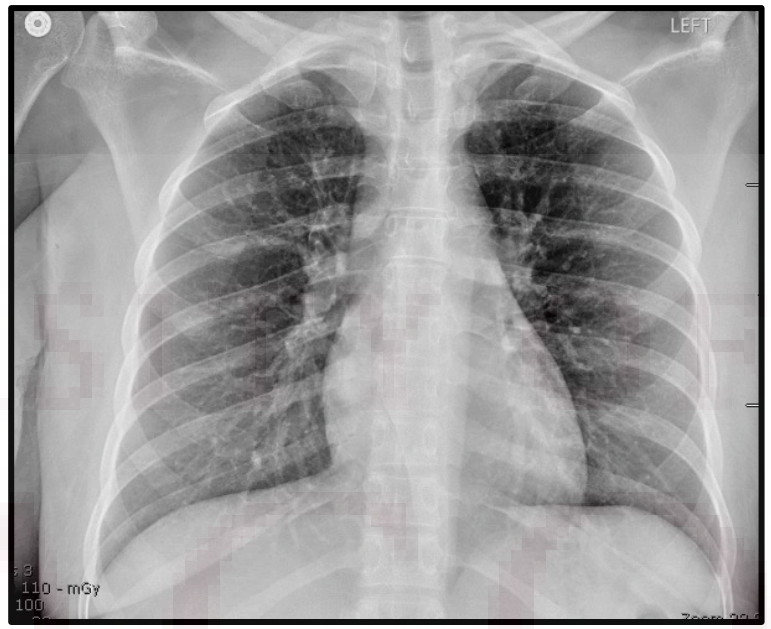
Ca 14.4, Cr 1.2, Mag 1.3, PTH 5

TSH 0.01, FT4 0.93, TT3 128

After initial fluid resuscitation, 18 hours after presentation:







Unremarkable. No hilar adenopathy.

Phos: 3.6
Mag: 2.1

ESR: 120
CRP: 37

Calcium: 13.5 **(14.5)**

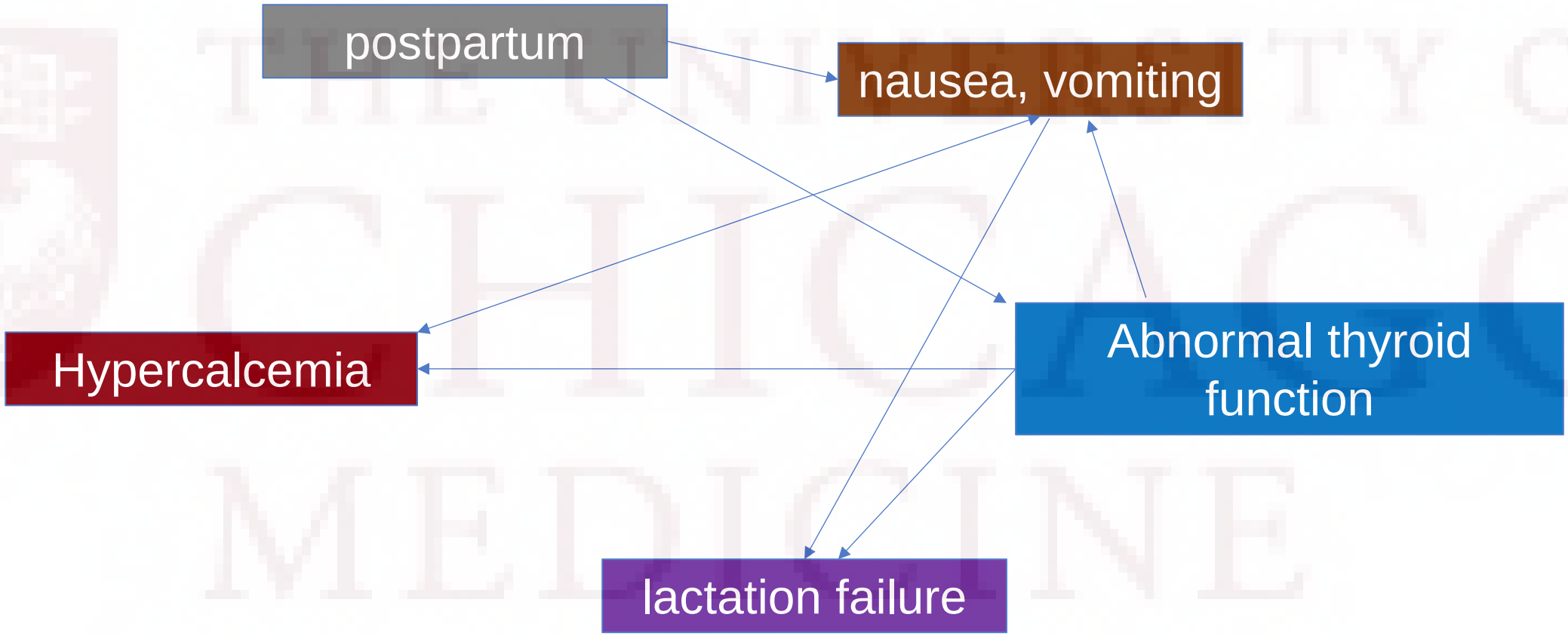
PTH: 5
Albumin: 2.7

TSH: 0.01
Total T3: 128
Free T4: 0.93
Total T4: 5.9

Endocrinology consulted.

What additional labs/eval/management do you predict were recommended?

COVID 19: (-) multiple


postpartum
nausea, vomiting
Hypercalcemia
Abnormal thyroid function
lactation failure

postpartum

nausea, vomiting

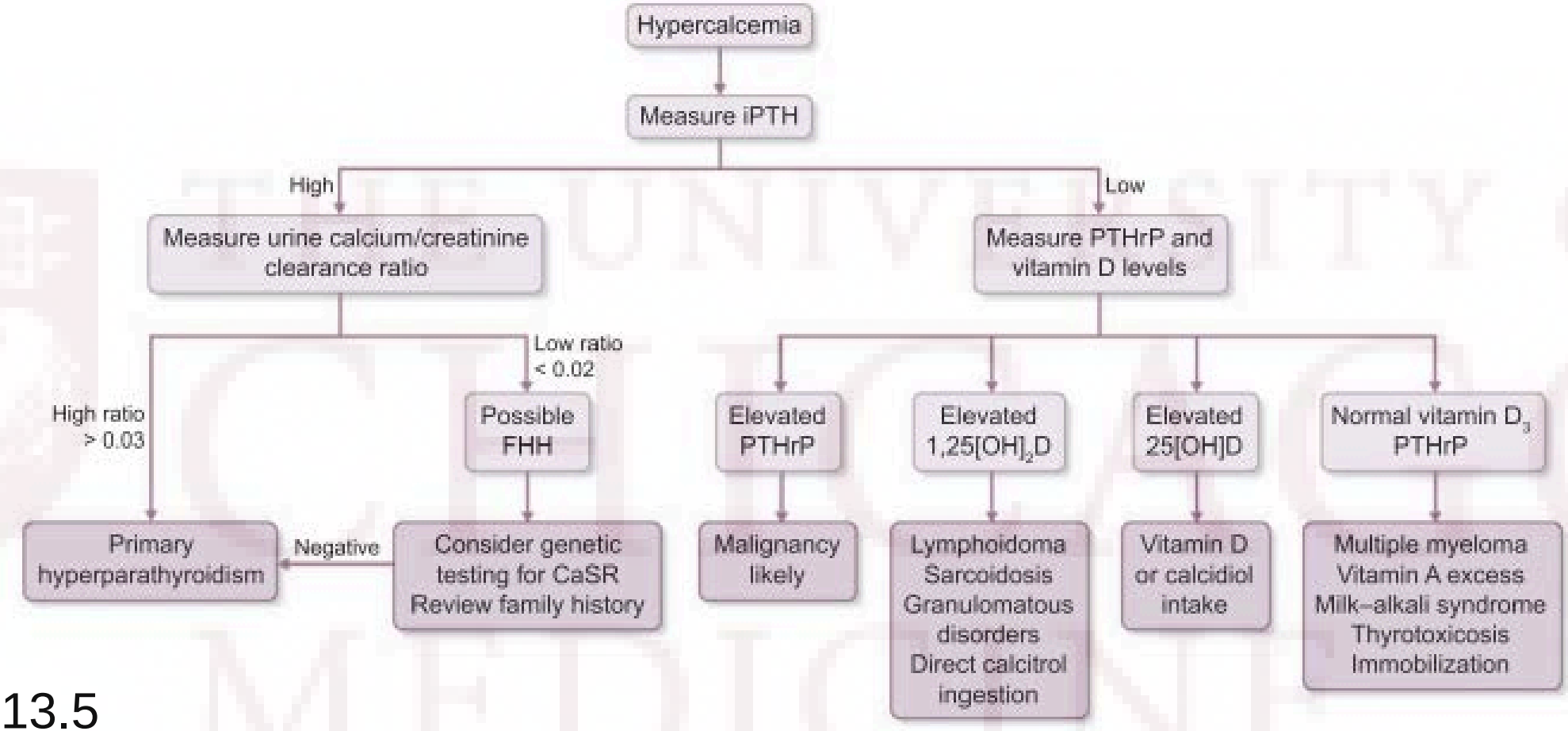
Hypercalcemia

Differential diagnosis?

Abnormal thyroid function

lactation failure

Hypercalcemia



Calcium 13.5

PTH: 5

25-OH vitamin D: < 7

1, 25-OH vitamin D: < 8.0

PTH-rp: 0.5

No monoclonal activity on SPEP or UPEP (with immunofixation)

ACE level: 45 U/L (16 – 85 U/L)

Nephrol Dial Transplant (2018) 33: 549-551.

Hypercalcemia

	6/14/2020 1226	6/15/2020 0656	6/15/2020 1433	6/15/2020 1825	6/16/2020 0525	6/16/2020 1740	6/17/2020 0542	6/18/2020 1041	6/19/2020 0752	6/
BASIC & COMPREHENSIVE										
Calcium	*14.4 ** ⏫	*13.5 ** ⏫	*12.2* 🔺	*12.1* 🔺	*11.5* 🔺	*11.5* 🔺	*10.9* 🔺	*9.9*	*8.7*	

No calcitonin or bisphosphonates given.

postpartum

nausea, vomiting

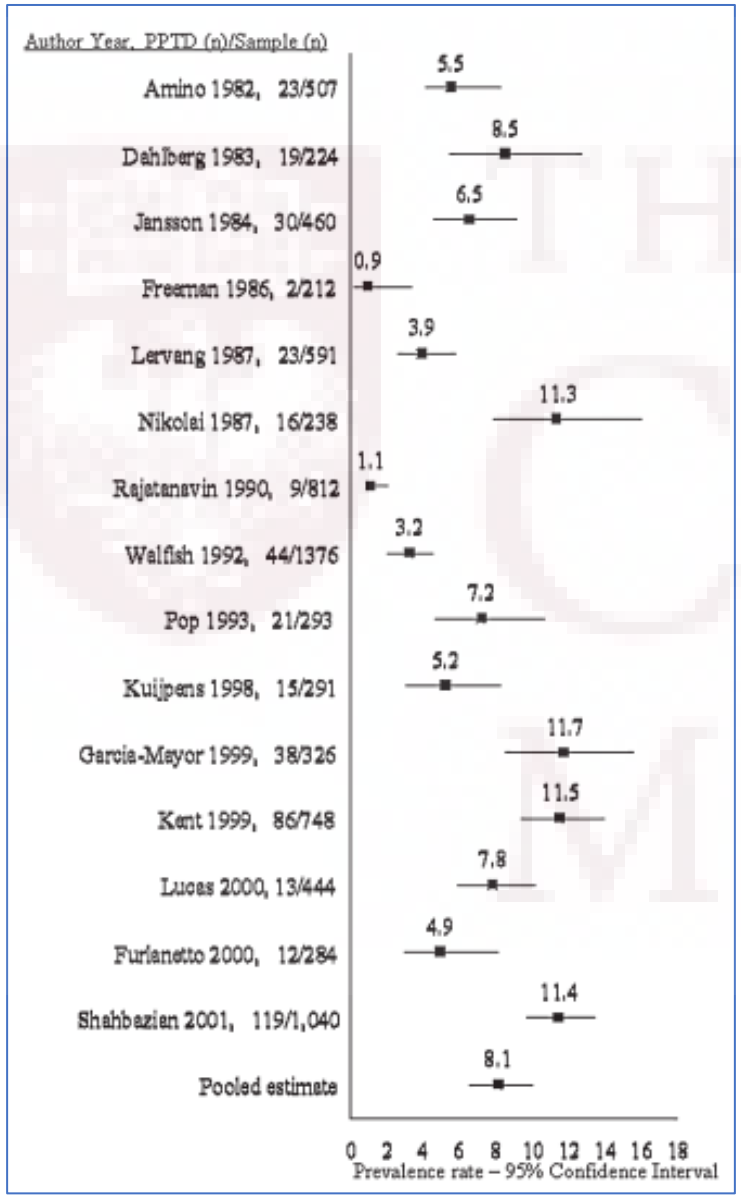
Hypercalcemia

Abnormal thyroid function

Differential diagnosis?

lactation failure

Abnormal thyroid function



Pooled prevalence study of postpartum thyroiditis

TABLE 6. PREVALENCE OF POSTPARTUM THYROID DYSFUNCTION IN SUBGROUPS AND POOLED ESTIMATES FROM SEVEN STUDIES

Subgroups	*First author*	*Publication year*	*Country*	*Total sample*	*No. with PPTD*	*Prevalence*	*95% CI*
Type 1 DM	Alvarez-Marfany (14)	1994	US	28	7	25	12.7–43.4
	Gerstein (17)	1993	Canada	40	9	22.5	12.3–37.5
	Bech (19)	1991	Denmark	57	6	11	4.9–21.1
Totals				125	22	—	—
Pooled estimate						19.6	19.5–19.7
Family history	Furlanetto (28)	2000	Brazil	52	5	9.6	4.2–20.6
	Alvarez-Marfany (14)	2000	US	12	4	33.3	13.8–60.9
Totals				64	9	—	—
Pooled estimate						22.3	21.7–22.9
Prior thyroid disease	Lazarus (30)	1997	UK	13	9	69.2	42.3–87.3
	Tada (16)	1994	Japan	92	37	40.2	30.8–50.4
	Othman (21)	1990	UK	5	5	100	56.5–100
Totals				110	51	—	—
Pooled estimate						43.2	43.0–43.3

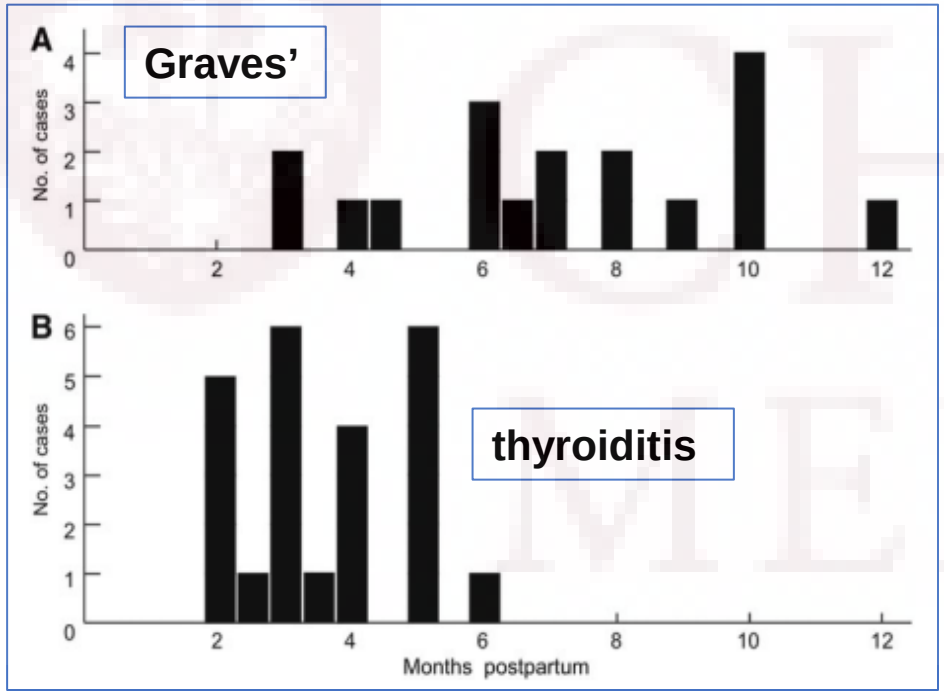
Pooled prevalence in general population is **8%**.

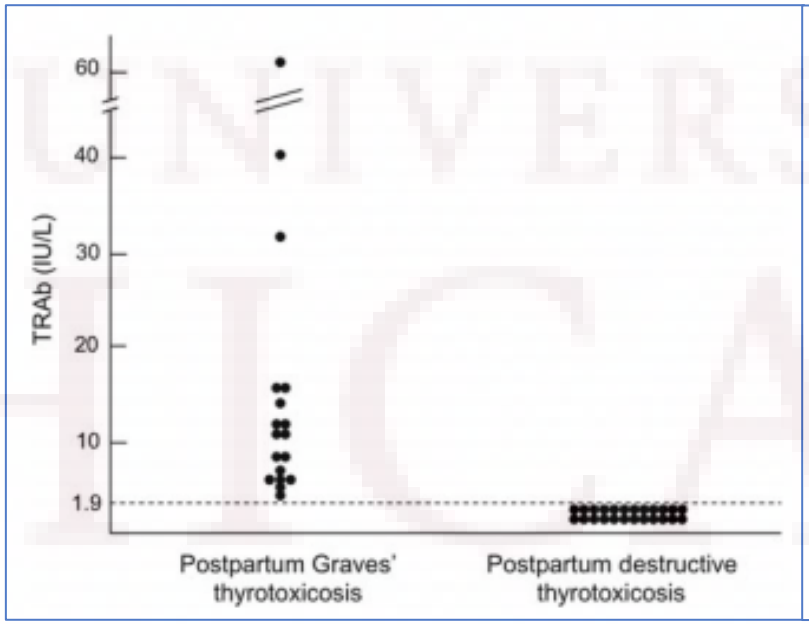
Prevalence increased with prior disease, family history, and history of type I DM.

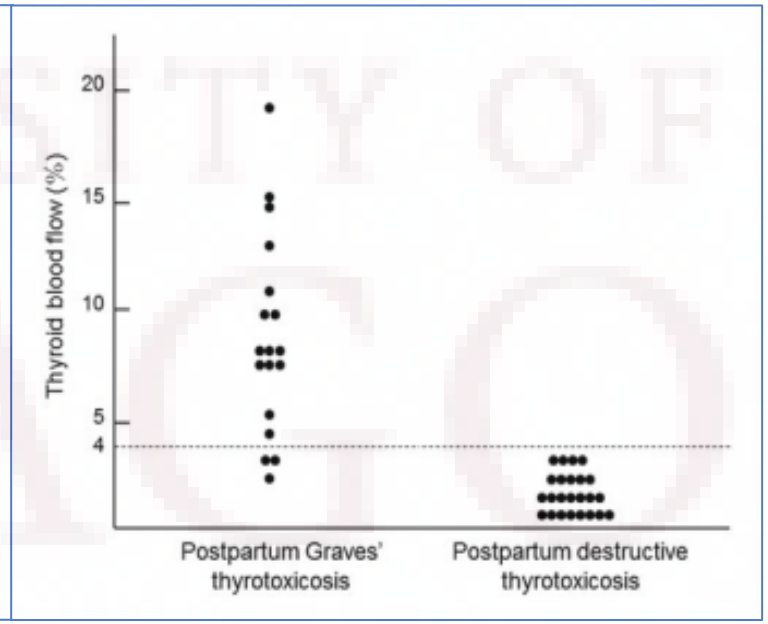
Thyroid. 2006;16(6):573-582.

Abnormal thyroid function

Differentiation of thyrotoxicosis from thyroiditis and Graves' disease







Thyrotoxicosis from Graves' more likely to present later after pregnancy, with positive thyroid receptor antibodies and more blood flow on thyroid US

Thyroid. 2014;24(6):1027-1031.

Abnormal thyroid function

	6/14/2020 1514	6/15/2020 0656	6/19/2020 0752	6/20/2020 0421	6/25/2020 1242	6/26/2020 0451	7/1/2020 1439	7/2/2020 0530	7/2/2020 1359	7/8/2020 0457	7
THYROID FUNCTION											
Thyroxine, Free	0.93 *		0.59 *	0.66 *		0.41 *		0.37 *	0.37 *	0.56 *	
Thyroglobulin Ab		<0.4									
Thyroid Perox. Ab		<0.4									
Thyroid Stimulatin...	0.01 *		0.02 *	0.02 *	0.57 *					4.59 *	
Triiodothyronine		128 *	66 *	54 *	35 *						
Thyroxine		5.9 *			3.9 *		3.6 *				

levothyroxine started

- Graves' hyperthyroidism
- thyroiditis
- central hypothyroidism

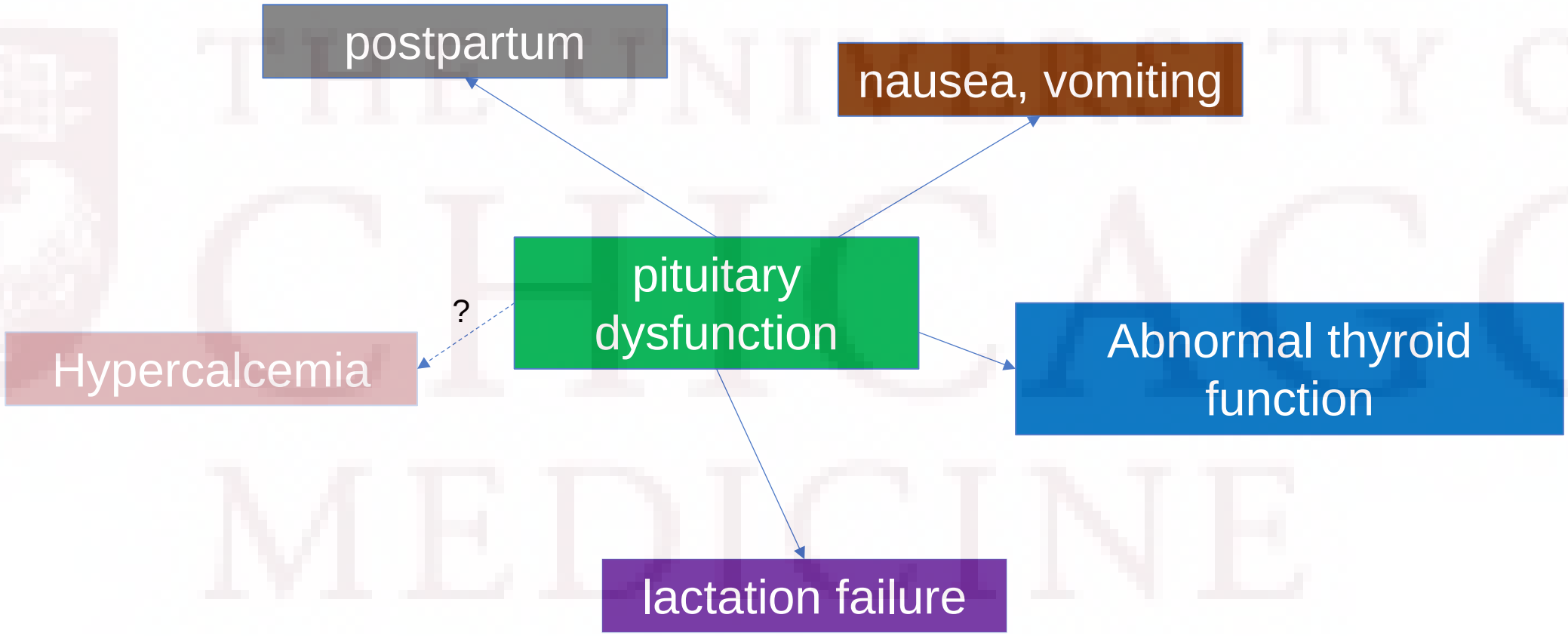
postpartum

nausea, vomiting

Hypercalcemia

Abnormal thyroid function

lactation failure


postpartum
nausea, vomiting
pituitary dysfunction
?
Hypercalcemia
Abnormal thyroid function
lactation failure

pituitary dysfunction

	6/16/2020 0525	6/17/2020 0957	6/17/2020 1452	6/17/2020 1800
ENDOCRINOLOGY				
BHCG, Plasma, Quant.				
Cortisol	*<1.0 **			
FSH				*3.6 **
Luteinizing Hormone				*1.8 **
Pregnancy Test, Ur			*Negative **	
Prolactin				*70.27 **
FSH				*3.6 **
ACTH		*1.6 **		
IGF1 LC MS				

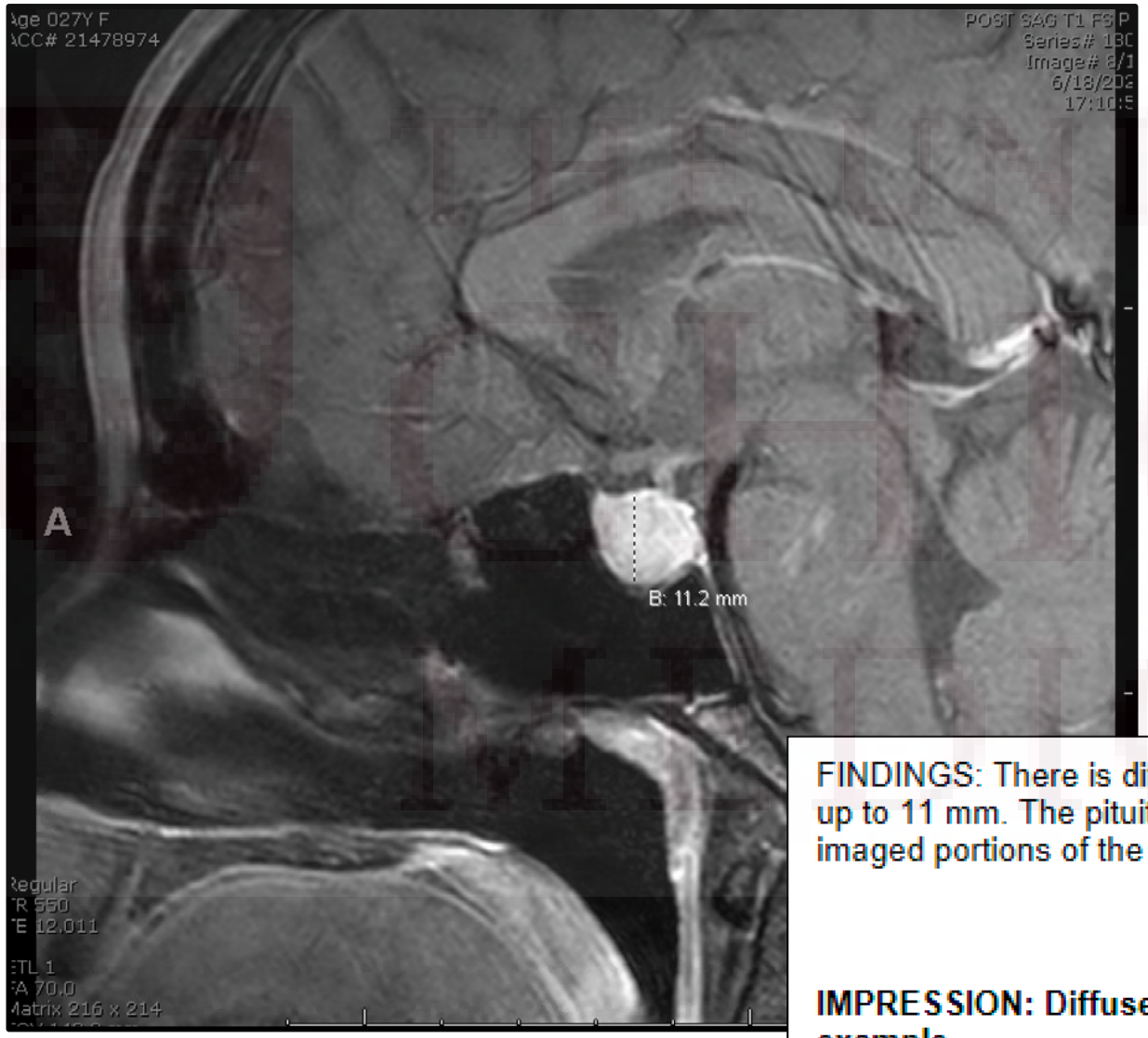
47 ng/mL (66 – 303 ng/mL)

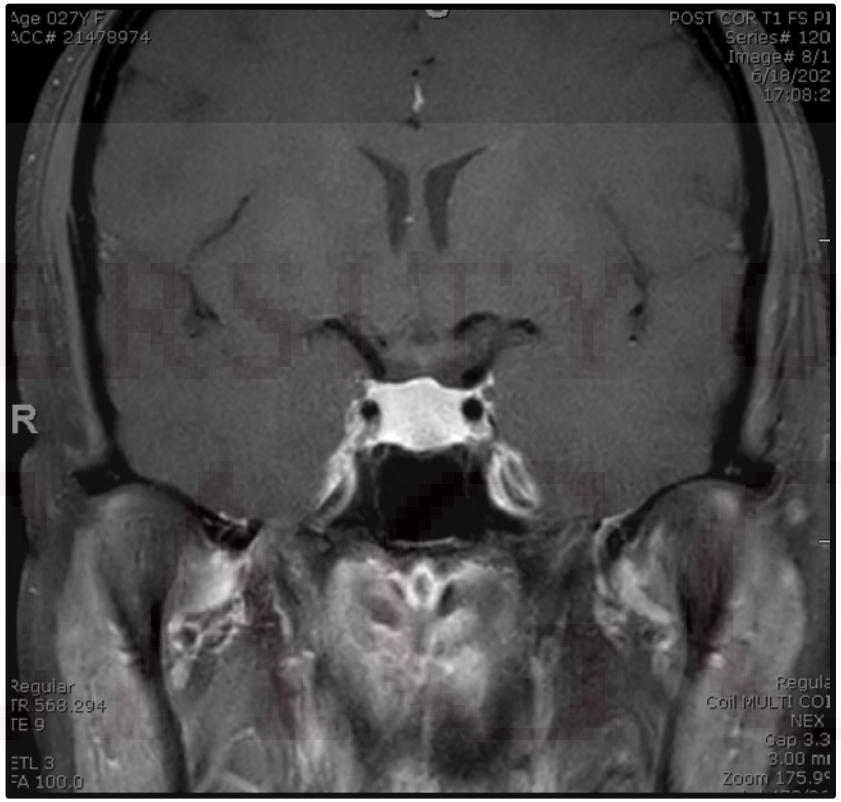
Major causes of hypopituitarism

Hypothalamic diseases
Mass lesions – Benign (craniopharyngiomas) and malignant tumors (metastatic from lung, breast, etc)
Radiation – For CNS and nasopharyngeal malignancies
Infiltrative lesions – Sarcoidosis, Langerhans cell histiocytosis
Infections – Tuberculous meningitis
Other – Traumatic brain injury, stroke
Pituitary diseases
Mass lesions – Pituitary adenomas, other benign tumors, cysts
Pituitary surgery
Pituitary radiation
Infiltrative lesions – Hypophysitis, hemochromatosis
Infection/abscess
Infarction – Sheehan syndrome
Apoplexy
Genetic mutations
Empty sella

CNS: central nervous system.

pituitary dysfunction





FINDINGS: There is diffuse enlargement and enhancement of the pituitary gland, measuring up to 11 mm. The pituitary stalk, cavernous sinuses, and optic chiasm are intact. The imaged portions of the brain are unremarkable, without evidence of acute infarction.

IMPRESSION: Diffuse enlargement of the pituitary gland could represent hyperplasia, for example.

pituitary dysfunction

Hypophysitis fundamentals

There are now five recognized primary forms of hypophysitis:

1. lymphocytic
   - dense infiltration by lymphocytes, disruption of anterior pituitary architecture, fibrosis
   - Associated with pregnancy
2. granulomatous
   - characterized by giant cell granulomas, presents as a mass lesion, affects both men and women equally
3. xanthomatous
   - extremely rare, foamy histiocyte infiltration
4. plasmacytic
   - associated with IgG4 disease, infiltration by plasma cells
5. Immunotherapy-related
   - Seen with ipilimumab and combination therapy
   - Usually permanent

Horm Res 2007;68(suppl 5):145-150
Endocr Rev. 2019 Feb 1:40(1):17-65

pituitary dysfunction

Clinical symptoms and MRI findings of lymphocytic hypophysitis

Symptoms	Frequency, %
Mass effects	
Headache	60
Visual disturbance	40
Bitemporal hemianopsia	32
Impaired visual acuity	
Diplopia	<5
Endocrine dysfunction	80
Adrenal insufficiency	65
Hypothyroidism	60
Growth hormone deficiency	54
Hypogonadism	40
Hyperprolactinemia	30
Diabetes insipidus	15

MRI characteristic	Hypophysitis	Macroadenoma
Signal intensity on T_1	Relatively low	Isointense
Signal intensity on T_2	High	Usually isointense
Contrast enhancement	Marked	Moderate
Pattern of enhancement	Homogeneous	Focal
Shape	Symmetric	Dumbbell
Dural enhancement	Common	Rare

Horm Res 2007;68(suppl 5):145-150

pituitary dysfunction

Histopathological appearance of lymphocytic hypophysitis

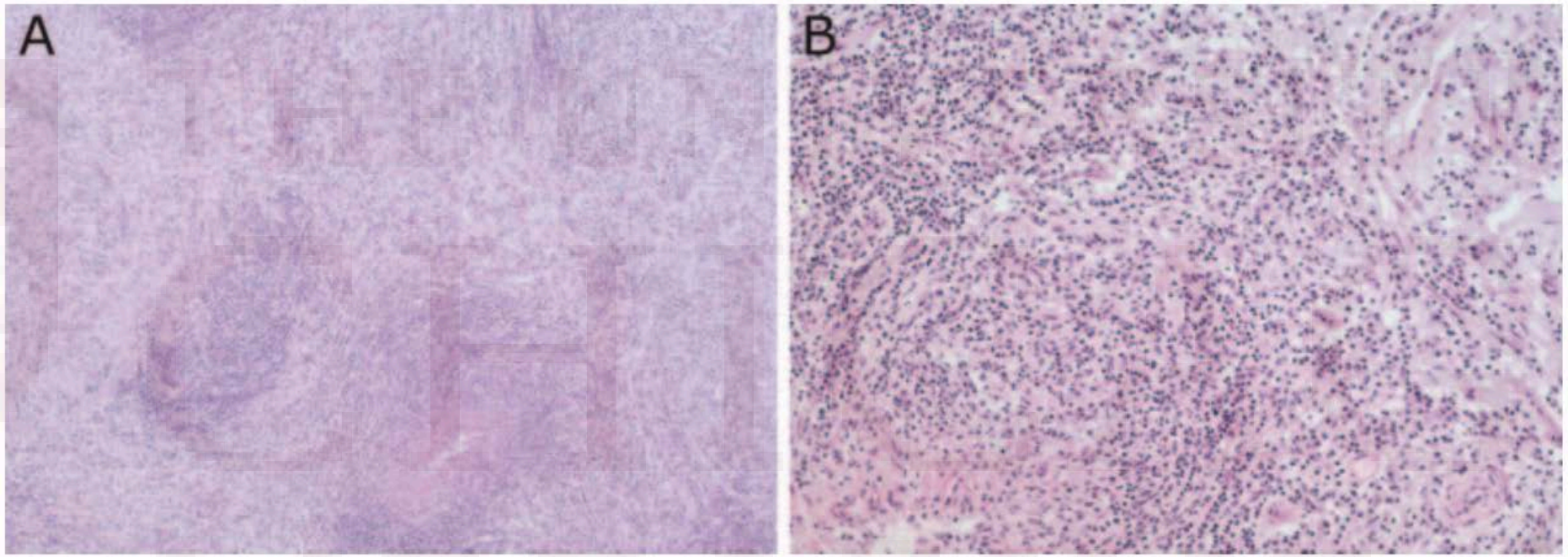


FIG. 3. Histological appearance of the pituitary in AH. The infiltrate disrupts the normal acinar architecture and damages the hormone-secreting cells (A). The infiltrate is mainly mononuclear and composed of lymphocytes and scattered plasma cells (B).

Endocr Rev 26(5):599-614

pituitary dysfunction

Prevalence of affected pituitary hormone axes

TABLE 6. Endocrine assessment of pituitary function at presentation in patients with LAH, LINH, or LPH

	LAH (n = 245)	LINH (n = 38)	LPH (n = 95)
Adrenal axis			
Pituitary defect	136 (56)	0	44 (46)
Adrenal defect	8 (3)	0	0
Normal	56 (23)	33 (84)	34 (36)
Not recorded	45 (18)	6 (16)	17 (18)
Thyroidal axis			
Pituitary defect	107 (44)	0	37 (39)
Thyroid defect	27 (11)	0	8 (9)
Normal	62 (25)	34 (87)	35 (37)
Increased	6 (2)	0	0
Not recorded	43 (18)	5 (13)	15 (16)
Gonadal axis			
Pituitary defect	104 (42)	3 (8)	45 (47)
Gonadal defect	2 (1)	0	0
Normal	72 (29)	30 (77)	33 (35)
Not recorded	67 (27)	6 (15)	17 (18)
GH			
Decreased	63 (26)	0	48 (51)
Normal	76 (32)	31 (79)	25 (26)
Increased	4 (1)	8 (21)	0
Not recorded	100 (41)	0	22 (24)
PRL			
Decreased	62 (25)	0	15 (16)
Normal	75 (31)	28 (72)	29 (30)
Increased	57 (23)	5 (13)	38 (40)
Not recorded	51 (21)	6 (15)	13 (14)
ADH			
Decreased	0	38 (98)	90 (95)
Normal	47 (19.2)	0	5 (5)
Increased	1 (0.4)	0	0
Not recorded	197 (80.4)	1 (2)	0

Data represent number of patients, with percentages in *parentheses*.

Loss of ACTH production is the most common defect, followed by TSH and LH, FSH

Posterior pituitary dysfunction can be seen, but usually with preserved anterior function

Endocr Rev 26(5):599-614

pituitary dysfunction

Two case reports of lymphocytic hypophysitis

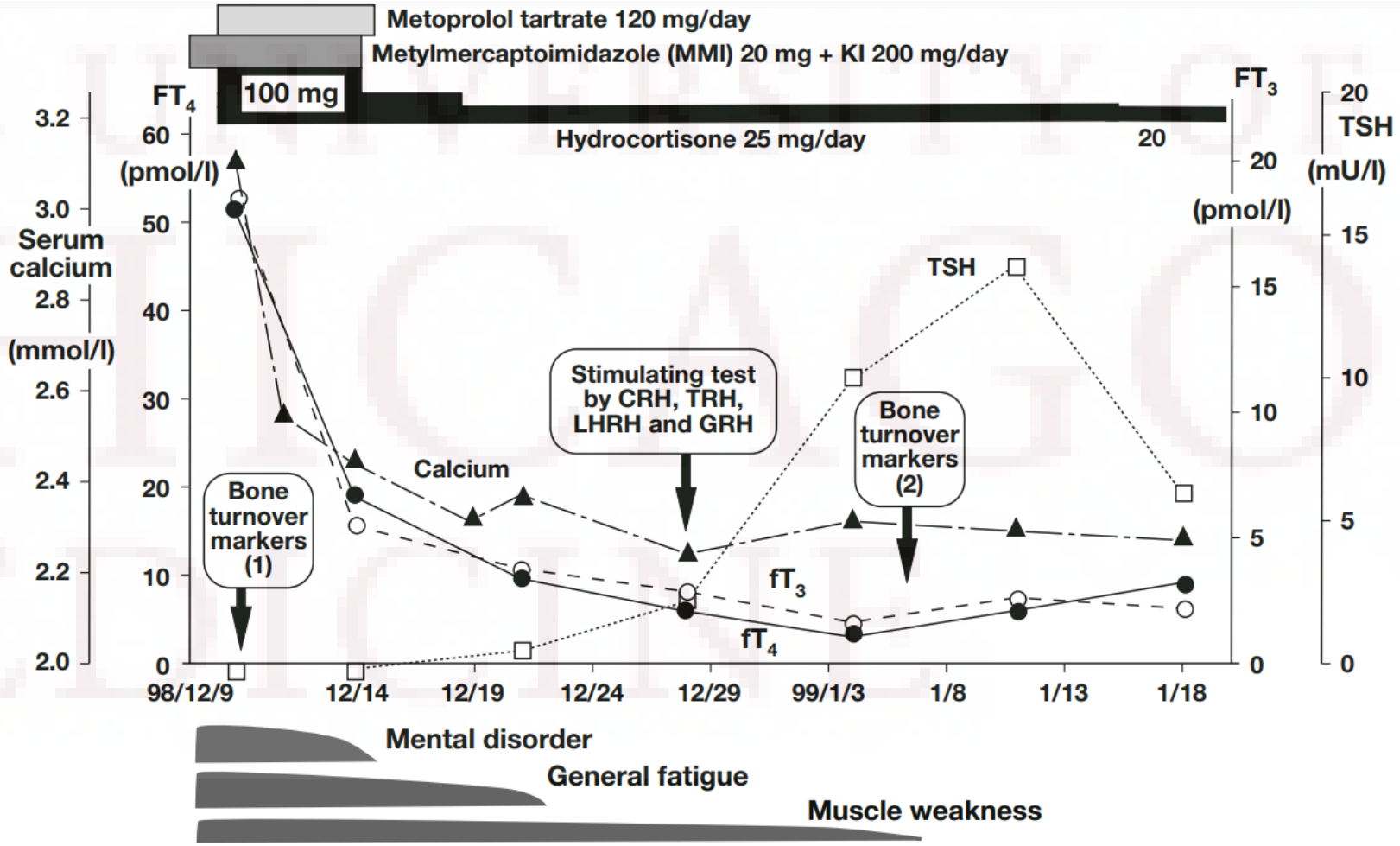
Case report 1

A 36 year old woman presented with fever, tachycardia and failure to lactate 8 weeks after delivery.

She was found to be thyrotoxic, hypercalcemic, and adrenally insufficient.

MRI pituitary showed mild swelling of the pituitary with an irregular region.

She recovered over several months of glucocorticoid therapy.



J. Endocrinol. Invest. (2004). 27: 782-787

pituitary dysfunction

Two case reports of lymphocytic hypophysitis

Case report 2

A 27 year old presented with secondary amenorrhea for 8 months.

Found to have mild hyperprolactinemia with 3.3 cm mass.

Also mildly hypothyroid with positive TPO antibodies (TSH 8.2 mU/L).

Trans-sphenoidal decompression surgery attempted but aborted due to fibrous tissue in sella, path dx c/w hypophysitis.

MRI improved after 2 months of 40 mg of prednisone daily.

J. Endocrine Society, Vol 4, Supp 1, MON-240 (abstract)

Other case notes

NCV/EMG

Conclusion:
This is an abnormal study that demonstrates a moderately-severe axonal sensorimotor polyneuropathy, which can be consistent with an axonal variant of Guillain-Barre Syndrome (e.g. AMSAN) or other inflammatory neuropathies/polyradiculoneuropathies. There is no evidence for myopathy in this study.

Nerve/muscle biopsy

FINAL PATHOLOGIC DIAGNOSIS

Skeletal muscle and periphera

A. Left sural nerve:
EXTENSIVE ONGOING AXONAL DEGE

B. Left gastrocnemius:
CHRONIC ATROPHIC CHANGES, see

Comment
There is some discrepancy between the findings in the nerve and the muscle biopsy: The peripheral nerve biopsy shows fairly diffuse features of axonal degeneration with unraveling myelin sheaths. This goes along with increase staining for CD68 within fascicles. Overall, there are no additional change that would clearly establish the underlying etiology of these changes. No significant inflammatory infiltrates or blood vessel abnormalities are seen. The findings could certainly go along with the time course of the summarized presentation.

The skeletal muscle biopsy shows somewhat chronic atrophic changes with nuclear bags, subtle fatty changes and rare atrophic fibers. The more chronic appearance does not seem to fit the time course described in the history below or that suggested by the changes in the nerve biopsy. To what extent these changes are reflective of the same disease process is difficult to determine. No inflammatory infiltrates or blood vessel abnormalities are present within the muscle biopsy.

Patient follow up

Patient admitted to rehab (Shirley Ryan) for intensive physical therapy for axonal polyneuropathy (variant of Guillain-Barre syndrome). Strength is improved but not yet walking without assistance.

Regarding management of lymphocytic hypophysitis/hypopituitarism:

For secondary adrenal insufficiency:

- Following the diagnosis, patient was started on 40 mg of prednisone to treat hypophysitis, but also served as corticosteroid replacement

- Transitioned to **hydrocortisone** 20 mg in AM, 10 mg in PM. Continues on this dose.

For secondary hypothyroidism:

- Started on 50 mcg **levothyroxine**, has been increased to 125 mcg daily (adherence to medical therapy has been an issue in the past)

Considering **estrogen replacement** if menses do not resume.