A 72 Year-Old Female with Slurred Speech

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Presenting Symptoms

Patient presented to Emergency Department with son with acute onset of slurred speech in the setting of prior history of multiple strokes

History of the Present Illness

- Sudden onset of slurred speech noted by son at 11:45 am
- Prior to this, had been at her baseline except that she was getting progressively weaker over the last few months – difficulty even using her walker
- Denies recent headaches, dizziness, syncope. Did have blurriness of vision and diplopia x 1 day a few days prior to admission
- Endocrine service is consulted for pituitary incidentaloma

Past Medical History

- **Diabetes Mellitus – Type 2**
  Diet-controlled
- **Prior Cerebrovascular Accident x 2**
  Residual left-sided weakness
- **Stage V Chronic Kidney Disease** – GFR 5
  Has refused dialysis for 10 years
- **Congestive Heart Failure**
  Systolic (EF 47%)
- **Hypertension**
- **Hyperlipidemia**
- **Obstructive Lung Disease**
- **Mild Cognitive Impairment**
- **Surgical Hx: None**

Family & Social History

- Multiple family members with ESRD
  Sisters died on HD in their 50s
- Divorced, lives with son
- No tobacco, etoh, illicit drug use
- Denies sexual activity

Prior to Admission Medications

- Albuterol inhaler prn
- Aspirin 81 mg daily
- Calcitriol 0.5 mcg daily
- Donepezil 5 mg qhs
- Famotidine 30 mg bid
- Furosemide 40 mg daily
- Hydralazine 50 mg tid
- Isosorbide mononitrate 30 mg daily
- Simvastatin 40 mg qhs
- Spironolactone 25 mg daily

Review of Systems

Constitutional: Denies fevers, chills, night sweats, hot or cold intolerance, fatigue.
Decreased appetite and weight loss.

HEENT: Denies headaches. Denies neck mass.
Patient reports that she had double vision and blurriness a few days PTA which have since resolved.

CV: Patient denies chest pain, light-headedness, palpitations, syncope. **+Dyspnea**

Pulm: Denies cough, wheezing.

GI: Denies abdominal pain, vomiting, diarrhea, constipation. **+Nausea**

GU: Negative for urinary frequency, hematuria. Denies change in libido.

MSK: Denies myalgias, arthralgias, swelling. Denies change in shoe size, ring finger.

Neuro: Denies numbness, tingling, or tremor. Denies syncope or dizziness.
Slurred speech, left-sided weakness. ? New proxmial m. weakness.

Skin: Denies diaphoresis. Denies new or violaceous striae.
Left heel pressure ulcer.

Psych: Denies agitation or change in mood.

Physical Examination

BP 134/62 **P** 84 **T** 36.8 **R** 18 **O2** 100% RA
HT 173 cm **WT** 116 kg **BMI** 38.9

General: Well-developed, well-nourished. Appearing in NAD.
HEENT: EOMI. Poor dentition. Oropharynx clear. **Mild macroglossia. Visual fields with no defect on confrontation.**
Neck: Supple. Thyroid is symmetric and does not feel enlarged. No palpable nodules are appreciated.
CV: Regular rate and rhythm. **2/6 radiating SEM heard best at RUSB.**
Chest: Clear to auscultation bilaterally. No wheezes or rales appreciated. No galactorrhea.
Abd: Soft, non-tender. **Mildly distended abdomen**. No abd striae.
MSK: Moving all extremities. No significant edema. 2+ peripheral pulses.
Neuro: **Strength 4/5 LU and LLE.** No right-sided proxmial m. weakness. Sensation to light touch intact.
Skin: Warm, dry, non-diaphoretic. **Stage II pressure ulcer on left heel.**
Psychiatric: Pleasant and smiling. Not agitated.

Diagnostic Evaluation

Glucose	120
Sodium	144
Potassium	5.1
Chloride	108
CO2	21
Anion Gap	15
BUN	78
Creatinine	7.4
GFR	5
Calcium	9.1

Phosphate, I	5.9
Magnesium	1.9

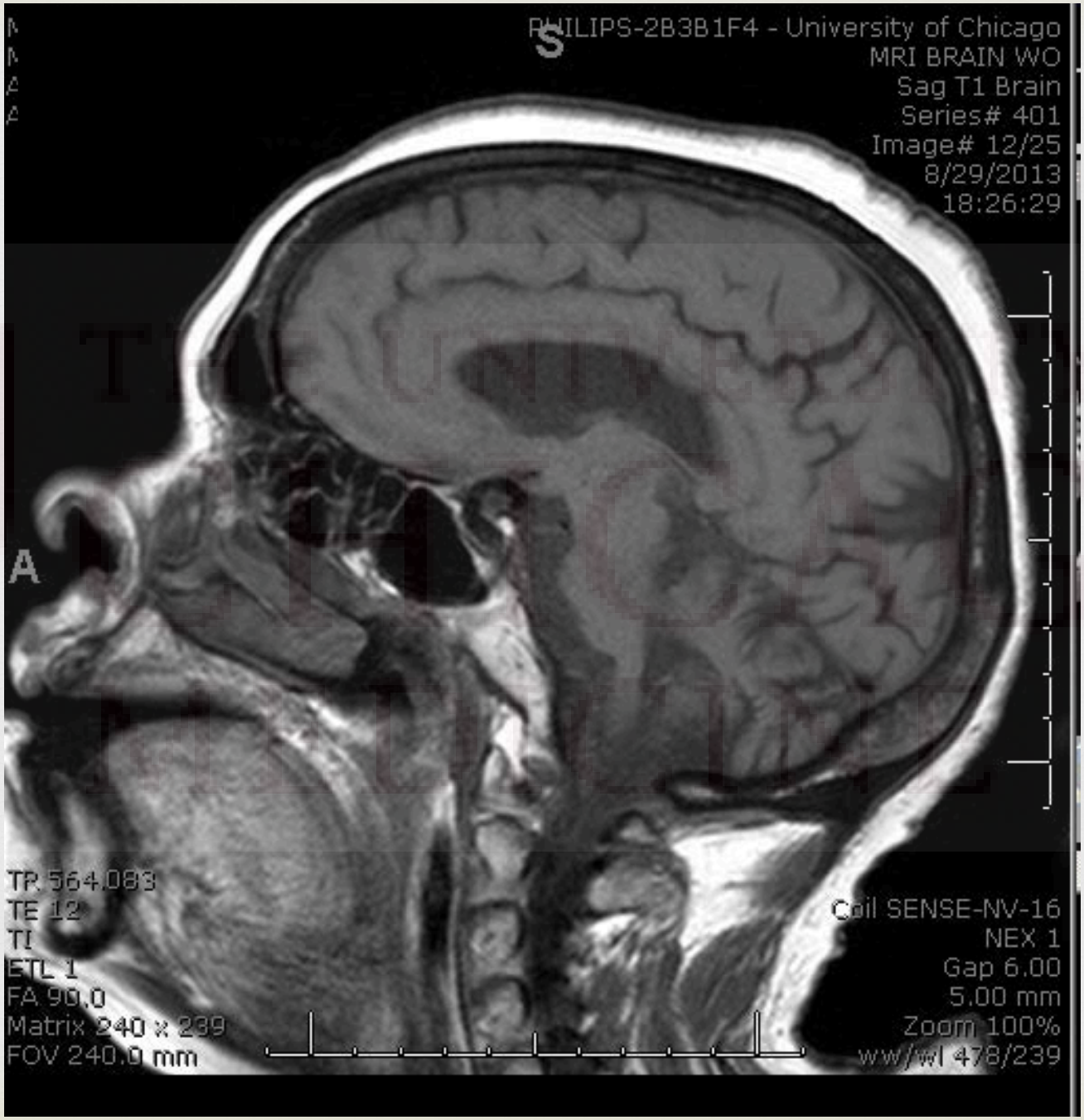
PTH	735
1,25-OH Vitamin D	< 8

%HgB A1C	4.7

WBC	11.7
HGB	10.7 Iron 78 TIBC 141 Ferritin 233
HCT	34.3
PLT	165

MRI Brain W/o

1. Left vertebral artery occlusion
2. High grade stenosis along the distal right vertebral artery and distal basilar artery
3. Findings are compatible with prior lacunar infarcts in the brainstem, thalami, and posterior limb of the right internal capsule
4. Hypertensive foci of microhemorrhages in the brainstem
5. There is a pituitary region mass extending into the right cavernous sinus measuring 11 x 18 mm.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Biochemical Evaluation of a Macro-adenoma

Prolactin	125.1
Prolactin (by dilution)	125.6

IGF-1	103
Growth Hormone	1.9

Cortisol (14:09)	24.1
Cortisol (08:49)	11.8
ACTH (08:49)	23.9

LH	< 0.1
FSH	1.7
Estradiol	54

TSH	1.14
Free T4	1.30

24-Hour Urine Cortisol (ref range 3.5 to 45)	3.3 (700 ml/24 h)

Differential Diagnosis

TABLE 1. Etiology of hyperprolactinemia

- Physiological
  - Coitus
  - Exercise
  - Lactation
  - Pregnancy
  - Sleep
  - Stress
- Pathological
  - Hypothalamic-pituitary stalk damage
    - Granulomas
    - Infiltrations
    - Irradiation
    - Rathke's cyst
    - Trauma: pituitary stalk section, suprasellar surgery
    - Tumors: craniopharyngioma, germinoma, hypothalamic metastases, meningioma, suprasellar pituitary mass extension
  - Pituitary
    - Acromegaly
    - Idiopathic
    - Lymphocytic hypophysitis or parasellar mass
    - Macroadenoma (compressive)
    - Macroprolactinemia
    - Plurihormonal adenoma
    - Prolactinoma
    - Surgery
    - Trauma
  - Systemic disorders
    - Chest—neurogenic chest wall trauma, surgery, herpes zoster
    - Chronic renal failure
    - Cirrhosis
    - Cranial radiation
    - Epileptic seizures
    - Polycystic ovarian disease
    - Pseudocyesis
- Pharmacological
  - Anesthetics
  - Anticonvulsant
  - Antidepressants
  - Antihistamines (H_2)
  - Antihypertensives
  - Cholinergic agonist
  - Drug-induced hypersecretion
  - Catecholamine depletor
  - Dopamine receptor blockers
  - Dopamine synthesis inhibitor
  - Estrogens: oral contraceptives; oral contraceptive withdrawal
  - Neuroleptics/antipsychotics
  - Neuropeptides
  - Opiates and opiate antagonists

Melmed S, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Endorcinol Metab 2011;96(2):273-88.

Clinical Questions

1. **Is there a limit to the prolactin level one can attribute to chronic kidney disease? Stalk effect?**

Elevated Prolactin Levels In…

Chronic Kidney Disease

1. Increased prolactin secretion
2. Mildly reduced clearance
3. Reduced responsiveness to dopaminergic inhibition

In absence of other causes of ↑prolactin, hyperprolactinemia associated with renal failure is mild (< 100 ng/mL)

Stalk Effect

Elevations in prolactin from stalk compression rarely exceed 150 ng/mL

Hou SH, et al. Hyperprolactinemia in patients with renal insufficiency and chronic renal failure requiring hemodialysis or chronic ambulatory peritoneal dialysis. Am J Kidney Dis 1985;6(4):245-9.

Klibanski A. Prolactinomas. N Engl J Med 2004;362(13):1219-25.

Prolactin Levels in Chronic Renal Failure

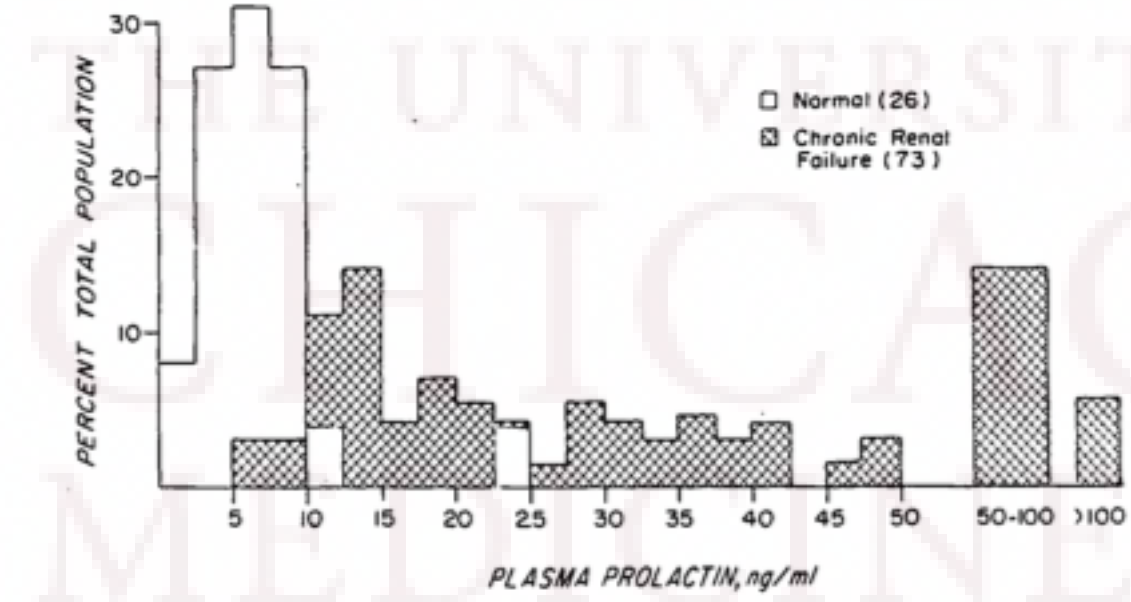


FIG. 1. Distribution of basal PRL levels in normal subjects and patients with CRF on maintenance hemodialysis. All values are represented as a percentage of the total population, and the number of subjects in each group is shown in parentheses.

Silverstein GD. Metabolic clearance and secretion rates of human prolactin in normal subjects and in patients with chronic renal failure. J Clin Endocrinol Metab 1980;50(5):846-852.

Clinical Questions

1. Is there a limit to the prolactin level one can attribute to chronic kidney disease? Stalk effect?

1. **Is the level of prolactin elevation always proportional to the size of the macroadenoma?**

Does Size Matter?

- In most instances:
  - Prolactin level > 250 mcg/L is usually due to prolactinoma and the size will usually be greater than > 1 cm

- This association is not always absolute, and tumor mass and prolactin levels can be dissociated

Melmed S, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Endorcinol Metab 2011;96(2):273-88.

Medication Effects?

DONEPEZIL

Acetylcholinesterase Inhibitor

Increased acetylcholine →
TIDA stimulation →
Increased dopamine →
Decreased prolactin secretion.

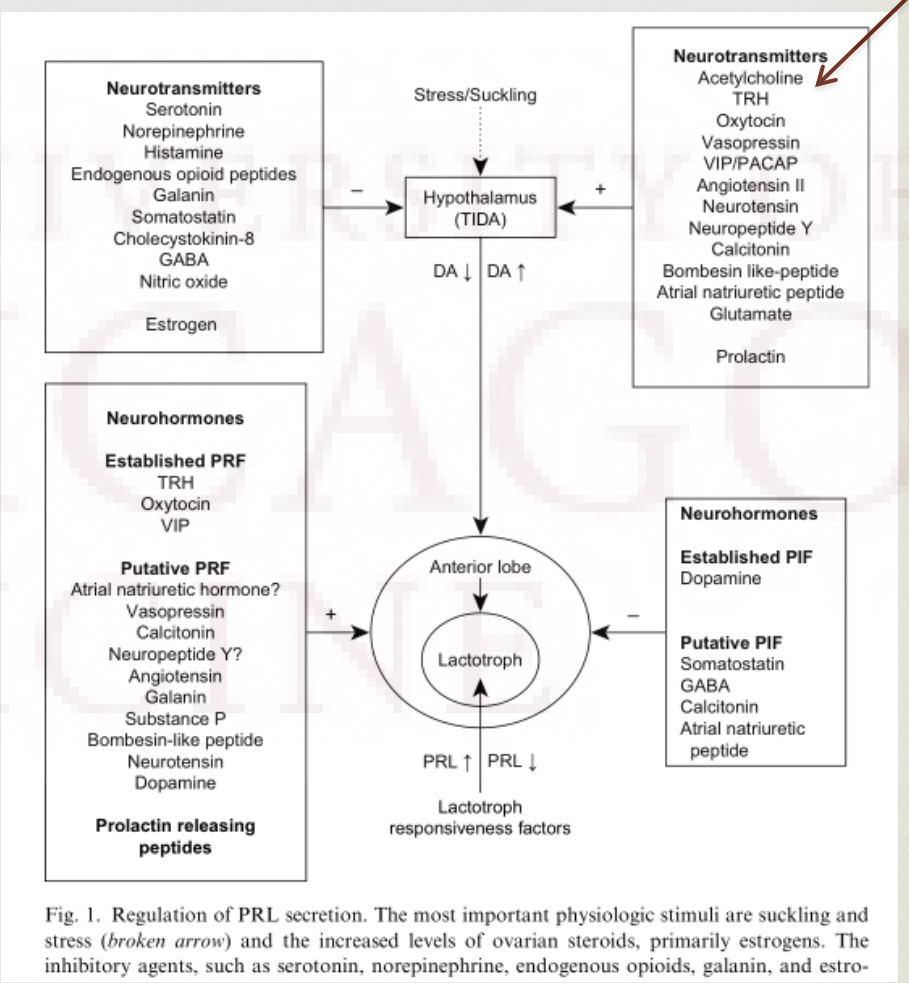


Fig. 1. Regulation of PRL secretion. The most important physiologic stimuli are suckling and stress (*broken arrow*) and the increased levels of ovarian steroids, primarily estrogens. The inhibitory agents, such as serotonin, norepinephrine, endogenous opioids, galanin, and estro-

Mancini T, et al. Hyperprolactinemia and prolactinomas. Endocrinol Metab Clinic N Am 2008;37:67-99.

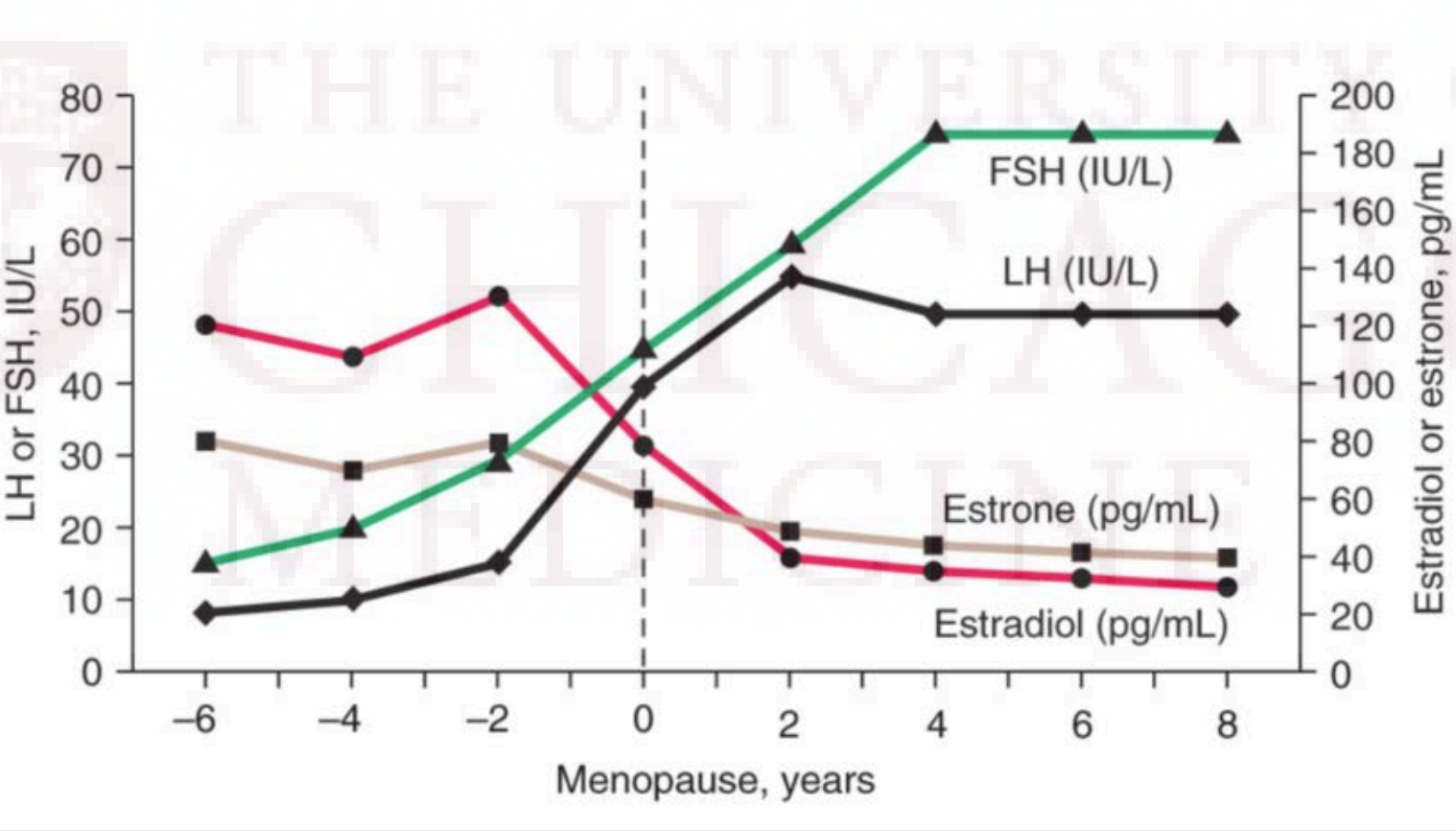
Clinical Questions

1. Is there a limit to the prolactin level one can attribute to chronic kidney disease? Stalk effect?

1. Is the level of prolactin elevation always proportional to the size of the macroadenoma?

1. **How does chronic kidney disease (CKD)/end-stage renal disease (ESRD) affect the hypothalamic-pituitary-gonadal axis?**

Hormone Levels During Menopausal Transition



Source: Fauci AS, et al. *Harrison's Priciples of Internal Medicine*. 17th edition: http://www.accessmedicine.com.

Estradiol and Kidney Disease

- 186 post-menopausal ESRD patients on HD
- 44% had low estrone levels (<15 pg/mL)
- 30% had low estradiol levels (< 5pg/mL)
- Mean estradiol levels were 8.57 pg/mL

Table 1. Estrogen Levels Among Nonusers of Estrogen Replacement Therapy

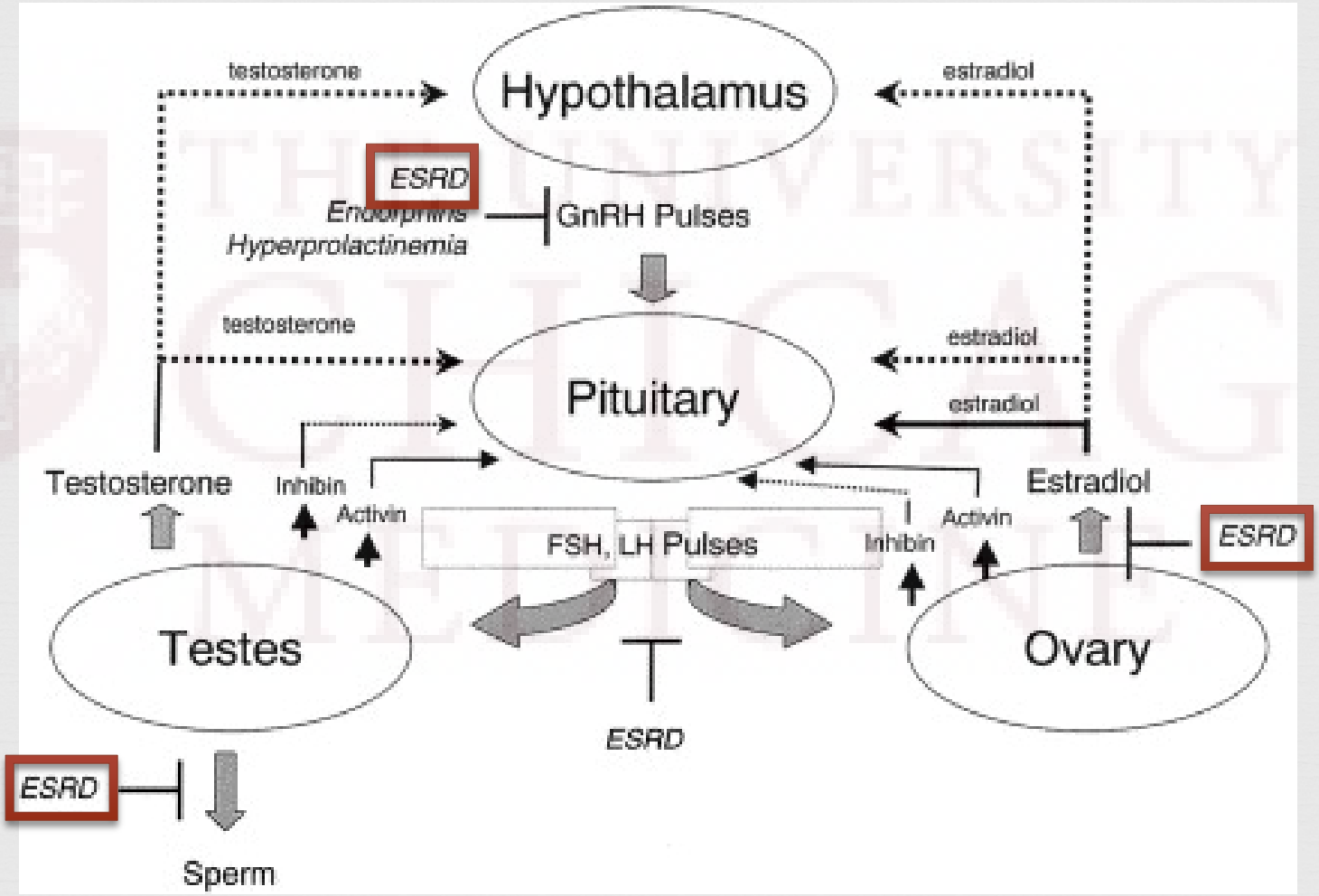
Estrogen	Mean ± SD	Range	No. (%) Below Sensitivity of Assay
E_1 (pg/mL)	21.80 ± 16.16	<10-99.00	45 (24)
Total E_2 (pg/mL)	8.57 ± 6.19	<2-38.00	6 (3)
Free E_2 (pg/mL)	0.18 ± 0.17	<0.04-1.63	18 (10)

N

NOTE. N = 186. Normal values in healthy postmenopausal women: E_1 , 15-80 pg/mL; total E_2 , less than 20 pg/mL; free E_2 , less than 0.23 pg/mL. [19] Conversion factors: E_1 , multiply pg/mL × 3.70 for pmol/L; E_2 , multiply pg/mL × 3.67 for pmol/L; free E_2 , multiply pg/mL × 3.67 for pmol/L.

Kramer HM, et al. Hemodialysis and estrogen levels in postmenopausal (HELP) patients: the multicenter HELP study. Am J Kidney Dis 2003;41(6)1240-46.

HPG Axis in Chronic Kidney Disease



Holley, JL. The hypothalamic-pituitary axis in men and women with chronic kidney disease. Adv Chronic Kidney Dis 2004;11(4):337-341.

Women

Table 2. Effects of CKD/ESRD on Hypothalamic-Pituitary-Ovarian Function

Impaired ovulation in premenopausal women
Anovulatory cycles
Preovulatory estradiol and LH peaks absent (absent cyclicity)
FSH and LH levels high or normal during follicular phase but lack cyclicity
Estrogen levels low or normal for follicular phase
Progesterone levels very low
Dysfunctional uterine bleeding
Menopausal women
Appropriate elevation of FSH, LH
Appropriate low estradiol
Elevated prolactin
Increased production and reduced clearance

Abbreviations: FSH, follicle-stimulating hormone; LH luteinizing hormone.

Men

Table 1. Effects of CKD/ESRD on Hypothalamic-Pituitary-Testicular Function

Impaired spermatogenesis
Reduced ejaculate volume
Oligospermia or azospermia
Reduced percentage of motile sperm
Testicular damage
Reduced numbers of mature spermatocytes
Aplasia of germinal elements
Atrophy of Sertoli cells
Interstitial fibrosis and calcifications
Impaired gonadal steroidogenesis
Reduced total and free serum testosterone
Disruption of Gonadotropin release
Reduced amplitude of LH secretory burst
Blunted increase in peak LH
Elevated LH (caused by reduced testosterone feedback)
Variable elevated FSH (caused by reduced testosterone and inhibin)
Elevated prolactin
Increased production and reduced clearance
Abnormal control

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Holley, JL. The hypothalamic-pituitary axis in men and women with chronic kidney disease. Adv Chronic Kidney Dis 2004;11(4):337-341.

Putting It All Together

- Modest prolactin elevations (< 150 ng/mL) can be seen with large non-prolactin secreting tumors due to stalk compression and renal disease
- Her elevated estradiol levels (which are typically not seen with renal failure) may also account for some of the prolactin elevation
- Patient likely has a nonfunctioning "null-cell" adenoma
  - Clinically nonfunctioning macroadenomas account for ~80% of all pituitary macroadenomas

Clinical Questions

1. Is there a limit to the prolactin level one can attribute to chronic kidney disease? Stalk effect?

1. Is the level of prolactin elevation always proportional to the size of the macroadenoma?

1. How does chronic kidney disease (CKD)/end-stage renal disease (ESRD) affect the hypothalamic-pituitary-gonadal axis?

2. **What is the optimal medical management approach for a non-surgical candidate with a nonfunctioning pituitary macroadenoma?**

Management of Nonfunctioning Pituitary Adenomas

- Transphenoidal surgery is recommended for macroadenomas large enough to cause visual field deficits, severe headaches, and neurologic symptoms
- In cases where surgery is not performed, growth will be observed in ~50% of patients w/null-cell adenoma in 5 years
- In one case series, 34/304 (11%) of patients had spontaneous regression of tumor during long-term follow-up

Dekkers OM, Pereira AM, and Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. J Clin Endocrinol Metab 2008;93(10):3717-26.

Management of Nonfunctioning Pituitary Adenomas

- If surgery is not performed:
  - Hormone assessments should be performed 6 months after initial, and then annually if stable
  - Follow-up Pituitary MRI
    - 6 months after initial scan if macroadenoma
    - 12 months after initial scan if microadenoma
    - If stable, frequency decreases
  - Interval for visual field testing depends on how close tumor is to chiasm

Freda PU, et al. Pituitary incidentaloma: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96(4):894-904.

Dekkers OM, Pereira AM, and Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. J Clin Endocrinol Metab 2008;93(10):3717-26.

Role of Dopamine Agonists?

- Prior studies have shown disappointing results with bromocriptine
- Newer data shows increased D_2 receptor expression and function in ~70% of non-functioning adenomas, which may respond better to cabergoline since it has better affinity to D_2 receptor
- Cabergoline 1 mg/wk x 1 year induced tumor shrinkage in 60% of patients.
  - Tumor shrinkage of > 25% was seen in less than 10%
- Cabergoline 3 mg/wk x 1 year in patients with persistent tumor after surgery showed tumor shrinkage in 56% of patients
  - Tumor shrinkage of 50-60%
  - Independent of tumor shrinkage, cabergoline reduced headaches, visual function in 70-80% of patients

Pivonello R, et al. Dopamine receptor expression and function in clinically nonfunctioning pituitary tumors: comparison with the effectiveness of cabergoline treatment. J Clin Endocrinol Metab 2004;89(4):1674-83.

Management in Our Patient

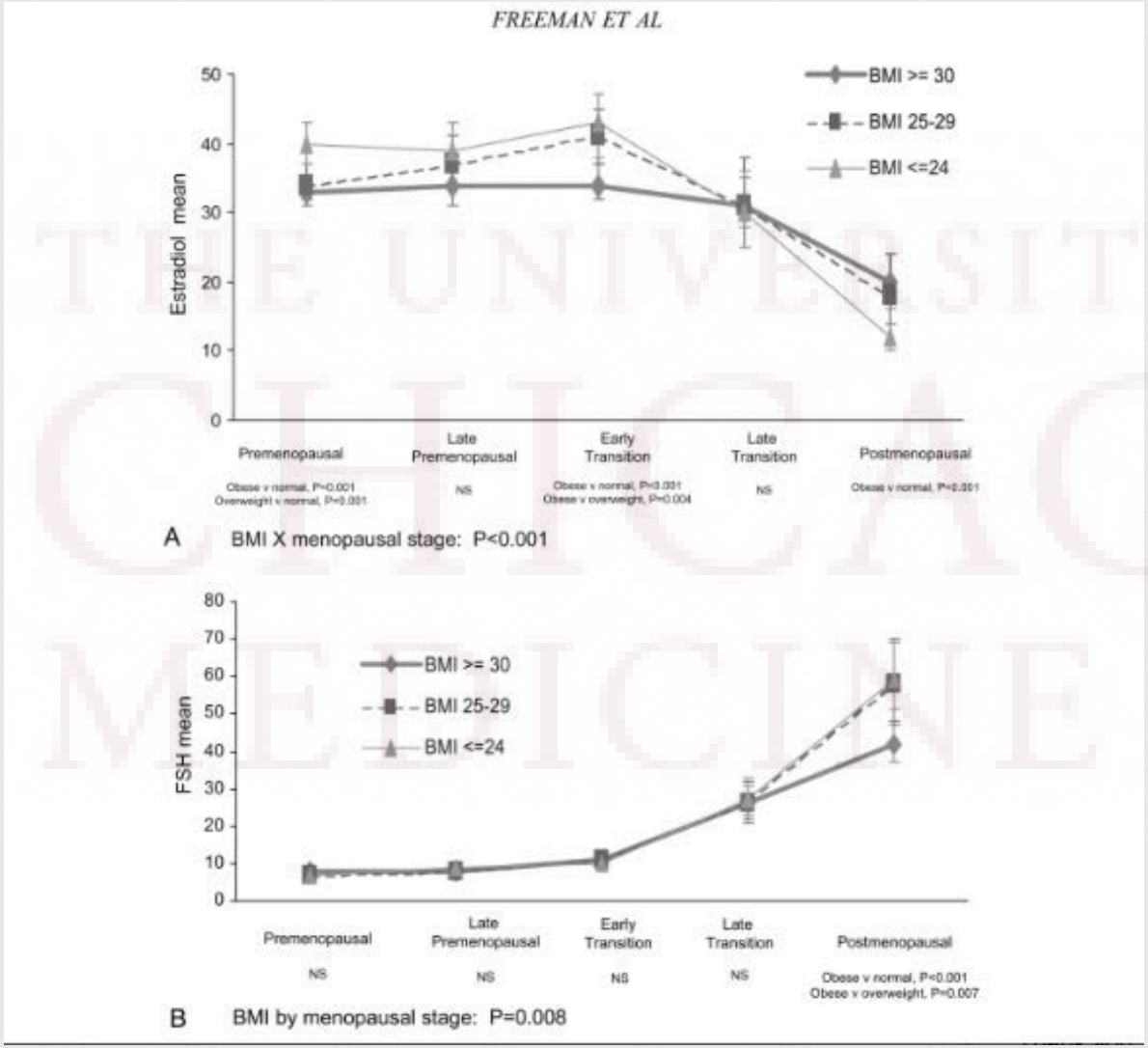
- Neurosurgical consultation was recommended for anatomic evaluation, discussion of stereotactic radiation, and steroid use
- Formal opthalmology consultation and visual field testing advised
- Both recommendations deferred by primary service
- As patient was not a surgical candidate, bromocriptine 1.25 mg x 1 given (cabergoline was not available in-house and use in renal failure not defined); well-tolerated. Started on 1.25 mg bid with decrease of prolactin to 19.2 in 2 days
- Patient will be seen in clinic on 9/27. Follow-up testing should include repeat of serum prolactin, cortisol (8 am), estradiol levels. Will likely switch to cabergoline therapy

Conclusions

- Renal failure and stalk compression can raise prolactin, but rarely to levels > 150
- Degree of prolactin elevation most often (but not always) correlates to size of macroadenoma
- Renal failure disrupts the HPG axis and pulsatile GNRH, FSH, and LH release. Post-menopausal women with kidney disease usually have low estradiol levels but obesity, ethnicity, and treatment of ESRD HD may be confounders
- Treatment of non-functioning macro-adenoma is usually surgical, but there may be a role for cabergoline when surgery is not an option

Comments/Questions?

BMI & Reproductive Hormones



Freeman EW, Sammel MD, Lin H, and Gracia CR. Obesity and reproductive hormone levels in the transition to menopause. Menopause 2010;17(4):718-726.

Estradiol and Kidney Disease

TABLE 1. Mean (±SE) baseline measurements of serum total E_2, free E_2, albumin-bound E_2, SHBG-bound E_2, estrone, albumin, and SHBG in postmenopausal ESRD and control subjects

	ESRD subjects	Control subjects	*P* value
Total E_2 (pg/mL)	25 ± 3	11 ± 1	0.0005
Free E_2	0.6 ± 0.1	0.3 ± 0.03	0.0035
Albumin-bound E_2	12 ± 1	7 ± 1	0.0024
SHBG-bound E_2	12 ± 2	4 ± 1	0.0006
Estrone (pg/mL)	53 ± 4	42 ± 5	<0.05
Albumin (mg/dL)	3667 ± 140	4185 ± 44	0.004
SHBG (nmol/L)	67 ± 7	42 ± 4	0.0069

Ginsburg ES, et al. Estrogen absorption and metabolism in postmenopausal women with end-stage renal disease. J Clin Endocrinol Metab 1996;81(12)4414-17.

Table 1. Estrogen Levels Among Nonusers of Estrogen Replacement Therapy

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