# 42 M who presents with elevated cortisol level

Rajesh Jain

Endorama 5/25/2017

# HPI

- 42 M who was referred to endocrinology for a second opinion
- He developed a blood clot 8 months prior to visit. Since that time, he developed worsening fatigue, weight gain of 50 LB, easy bruising, pink stretch marks, weakness, and depression
- Feels weight gain is mostly in his face and abdomen
- Fatigue is making it difficult for him to work as a trauma RN
- Saw an endocrinologist in Indiana where evaluation was started

# Full history

**PMH**: Obesity, type 2 diabetes

**PSH**: None

**Family history**: No history of endocrinopathies or pituitary tumors. Factor V Leiden mutation.

**Social history**: married, non-smoker, no alcohol. Trauma RN.

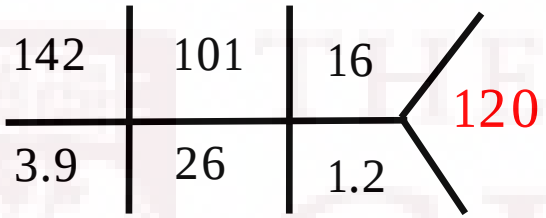
**Allergies**: Latex, PCN

**Medications**: Alprazolam, amlodipine, benicar, furosemide, glimepiride, Lovaza, Metformin, olmesartan, pantoprazole, tramadol, rivaroxaban

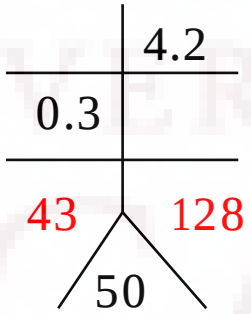
# Physical Exam

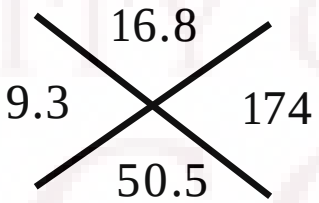
**Vitals**: BP 134/97, P 93, Ht 6', Wt 309 LB, BMI 41.9
**Gen**: Male in NAD
**Eye**: non-injected anicteric sclera
**ENT**: Clear oropharynx, normal hearing
**Neck**: Thyroid difficult to palpate
**Resp**: CTAB
**CV**: RRR, no m/g/r. 1+ LE edema, L>R
**Abd**: central obesity, soft, non-tender
**Skin**: 1 cm reddish striae over abdominal flanks and bilateral axillae
**MSK**: Normal gait and station
**Lymphatics**: No lymphadenopathy in the neck
**Psych**: A&O x 3. Appropriate mood and affect

# Outside Labs







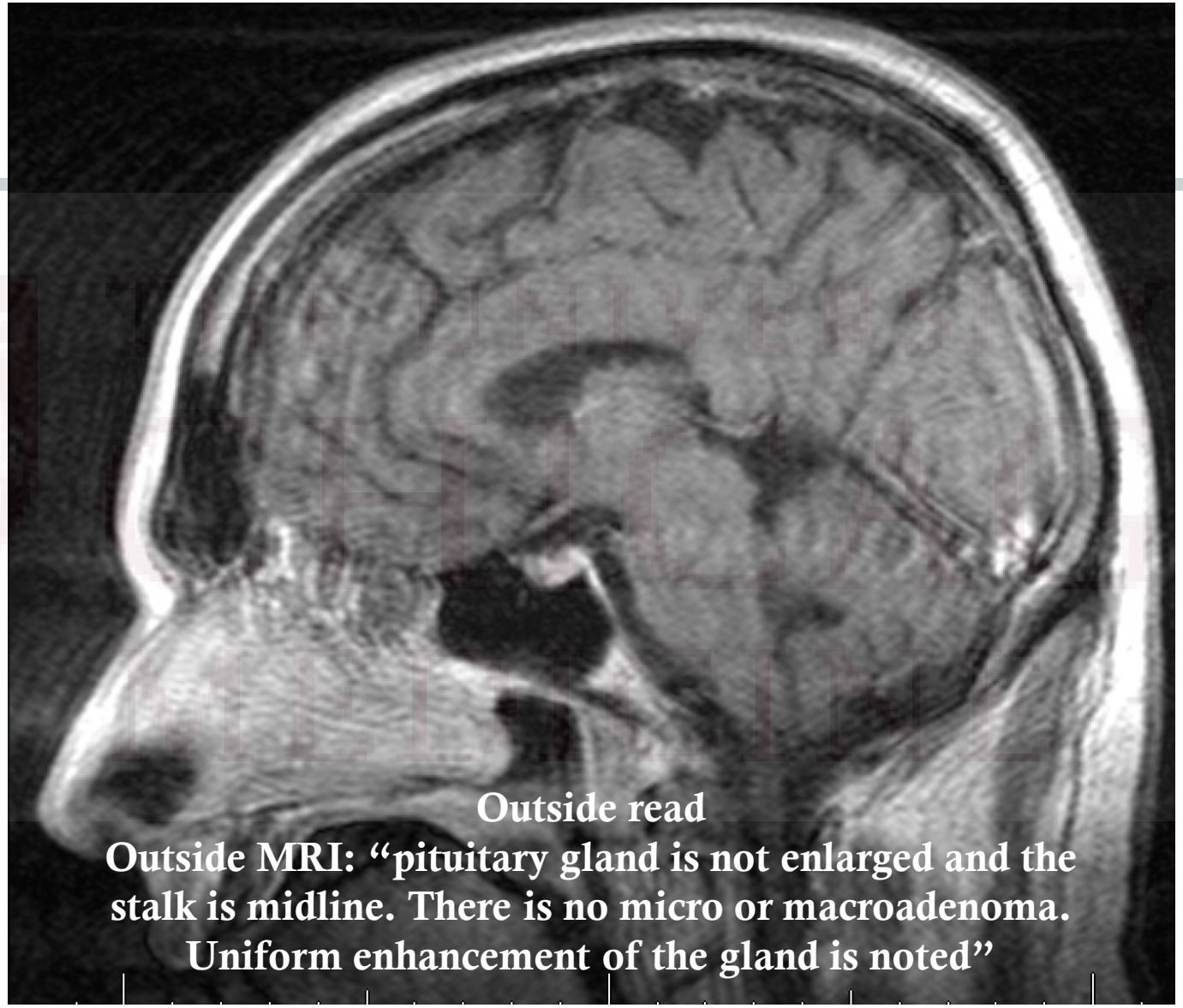

A1c 7.5, Total testosterone 134 (RR 193-836)

TSH 1.69

ACTH 52.5

24 hour Urine cortisol 364 ug/24 hour (RR 0-50), Volume 1625 mL

1 year prior: LH 6 (1.2-8.6), FSH 12.1 (1.27-19.26), Total Testosterone 103.8 (193-950), ACTH 60.8, Cortisol 28.4



**Outside read**

**Outside MRI: "pituitary gland is not enlarged and the stalk is midline. There is no micro or macroadenoma. Uniform enhancement of the gland is noted"**

# Hypercoagulability in Cushing's Syndrome?

- Not specifically addressed in Cushing's treatment guidelines
- JCEM review suggests incidence of 2.0-2.5% in those not undergoing surgery
- Reported risk of postoperative VTE was <6% in 7 studies but reported to be 20% in one study
- Unanswered question - Is routine prophylaxis needed?

Van Zaane et al. Hypercoagulable state in Cushing's syndrome: A systematic review. JCEM 2009.

# Now what?

- Patient also underwent heme evaluation (outside of University of Chicago) and found to have Factor V Leiden mutation
- Next steps?

# More tests

24-hour urine cortisol: 27 ug/24 hour (RR 0-50)

Midnight salivary cortisol 0.123 (RR<0.010-0.09)

1 mg dexamethasone suppression test: Cortisol 2.3, ACTH 52

# Clinical Course

- Time course is a little unclear but had CT abdomen/pelvis for abdominal symptoms, no relevant findings
- Also had CT chest at some point (unclear reason) – no tumor
  - Necessary in the Cushing's evaluation?

## The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline

Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, John Newell-Price, Martin O. Savage, Paul M. Stewart, and Victor M. Montori

"Because UFC levels in a patient with Cushing's syndrome are variable, at least two collections should be performed"

# What can cause a false positive elevated urine free cortisol?

- Physiological hypercortisolism (e.g. severe depression)
- High fluid intake (>5 L / 24 hours)

# Further workup

24-hour urine cortisol: 80 ug/24 hour (RR 0-50)

Midnight salivary cortisol 0.241 (RR<0.010-0.09)

# Cyclic Cushing's?

- Controversial entity!
- Has been defined by some as having three peaks and two troughs of cortisol production, sometimes weeks to years apart
- "Irrespective of permanent or variable clinical expression, the cycle length of hypercortisolism is remarkably constant within one subject but can vary from days to months between individuals."
- The Endo Society guidelines recommend urinary free cortisol or salivary cortisol rather than dex-suppression tests in patients with suspected cyclic Cushing's and/or repeat testing over time

Meinardi et al. Cyclic Cushing's syndrome: a clinical challenge. Eur J Endo 2007.

# Review of 65 reported cases

**Table 2** Clinical characteristics of patients with cyclic Cushing's syndrome. Data retrieved from 65 case reports.

| | Overall[a] (*n*=65) | Pituitary (*n*=35) | Ectopic ACTH (*n*=17) | Adrenal (*n*=7) |
|---|---|---|---|---|
| Female sex, *n* (%) | 47 (72) | 25 (71) | 13 (76) | 4 (57) |
| Age at diagnosis, median (range), years | 41 (0–72) | 41 (4–71) | 43 (12–72) | 21 (0–46) |
| Cushing features[b], *n* (%) | 61 (94) | 32 (91) | 17 (100) | 6 (86) |
| Additional disorders, *n* (%) | | | | |
| Diabetes mellitus or glucose intolerance | 25 (38) | 12 (34) | 8 (47) | 1 (14) |
| Mood disorders | 15 (23) | 6 (17) | 3 (18) | 2 (29) |
| Acne | 7 (11) | 3 (9) | 2 (12) | 0 (0) |
| Hirsutism | 15 (23) | 9 (26) | 4 (24) | 0 (0) |
| Amenorrhoea (% of women) | 6 (13) | 6 (17) | 0 (0) | 0 (0) |
| Cycle length, median (range), days | 21 (3–510) | 18 (0.5–510) | 30 (4–180) | 35 (14–60) |
| Intercyclic phase, median (range), days | 30 (1–2160) | 20 (1–1642) | 35 (1–2160) | 120 (60–720) |
| Survival, % of reported (*n*/*n*) | 94 (58/62) | 97 (33/34) | 80 (12/15) | 100 (7/7) |
| Follow-up, years, median (range) | 2.7 (0.08–26) | 3 (0.08–13) | 2.25 (0.8–11) | 7 (1–26) |

[a]Including cases with an uncertain origin of cyclic hypercortisolism.
[b]Two or more of the following signs: hypertension, truncal obesity, buffalo hump, moon face, oedema, muscle weakness, striae.

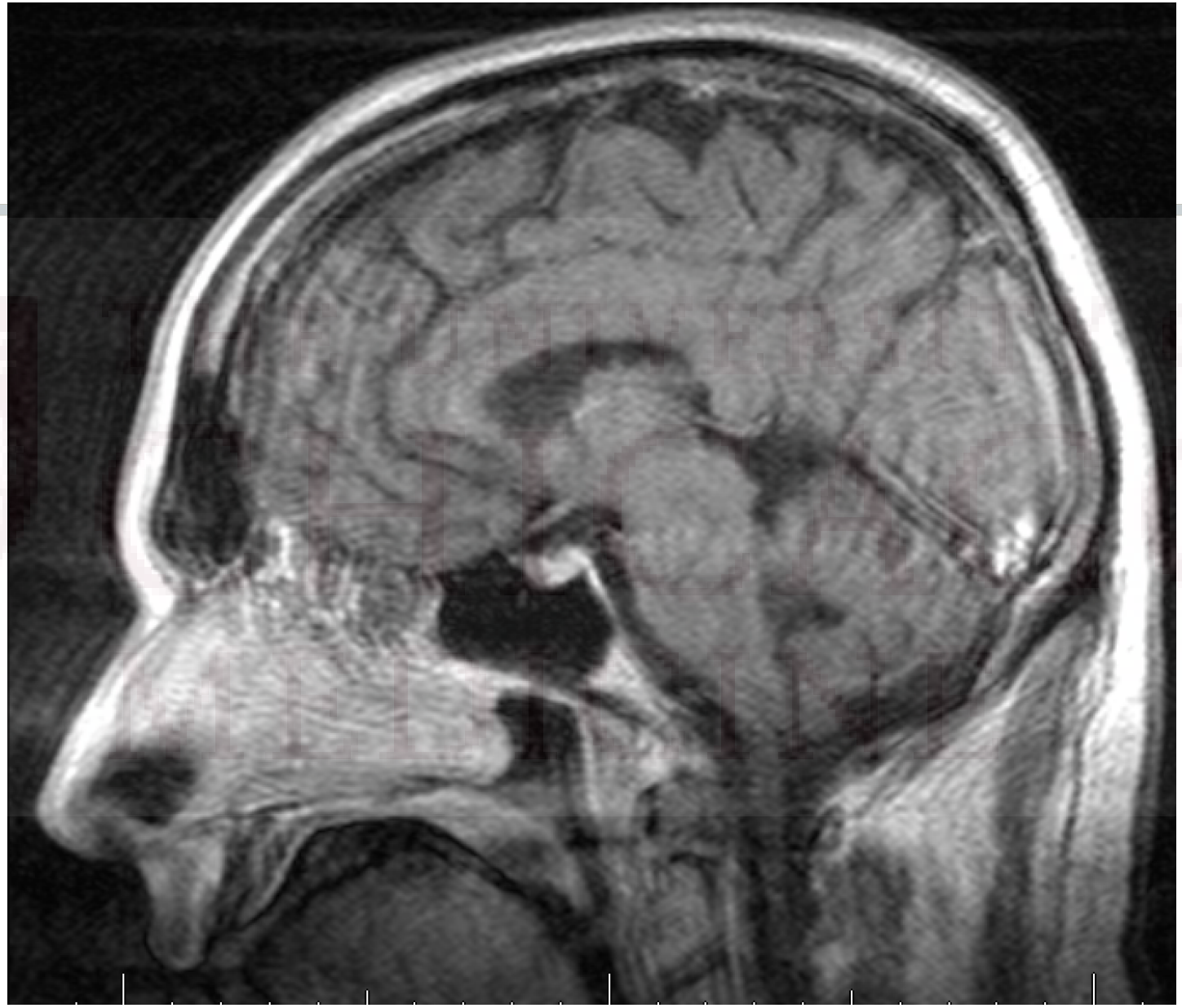
Meinardi et al. Cyclic Cushing's syndrome: a clinical challenge. Eur J Endo 2007.

# Further work up

24-hour urine cortisol: 66 ug/24 hour (RR 0-50)

Next steps?


S



# Determining source of ACTH

8 mg overnight dexamethasone suppression test:

Cortisol 1.2 ug/dL

Next step(s)?

# Next Steps

- Patient declines inferior petrosal sinus sampling
- Alternative?

# Alternatives to IPSS

- In an NIH retrospective review of ectopic ACTH, 43 of 48 (90%) did not suppress plasma cortisol after 8 mg overnight dexamethasone suppression & 68 of 75 (91%) had no response of ACTH and cortisol
- 54 of 68 (79%) had no response to either dexamethasone or CRH, 1/68 responded to both
- 66 of 67 patients had no petrosal-to-peripheral ACTH gradient on IPSS

Ilias et al. Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. JCEM 2005.

# CRH testing

- To differentiate between pituitary source of ACTH (i.e. Cushing's disease) vs. Ectopic ACTH secretion
- Administering CRH should cause an increase in ACTH/Cortisol if it is a pituitary source
- However, the best cutoffs have been debated (30-105% increase in ACTH and 14-20% increase in cortisol)

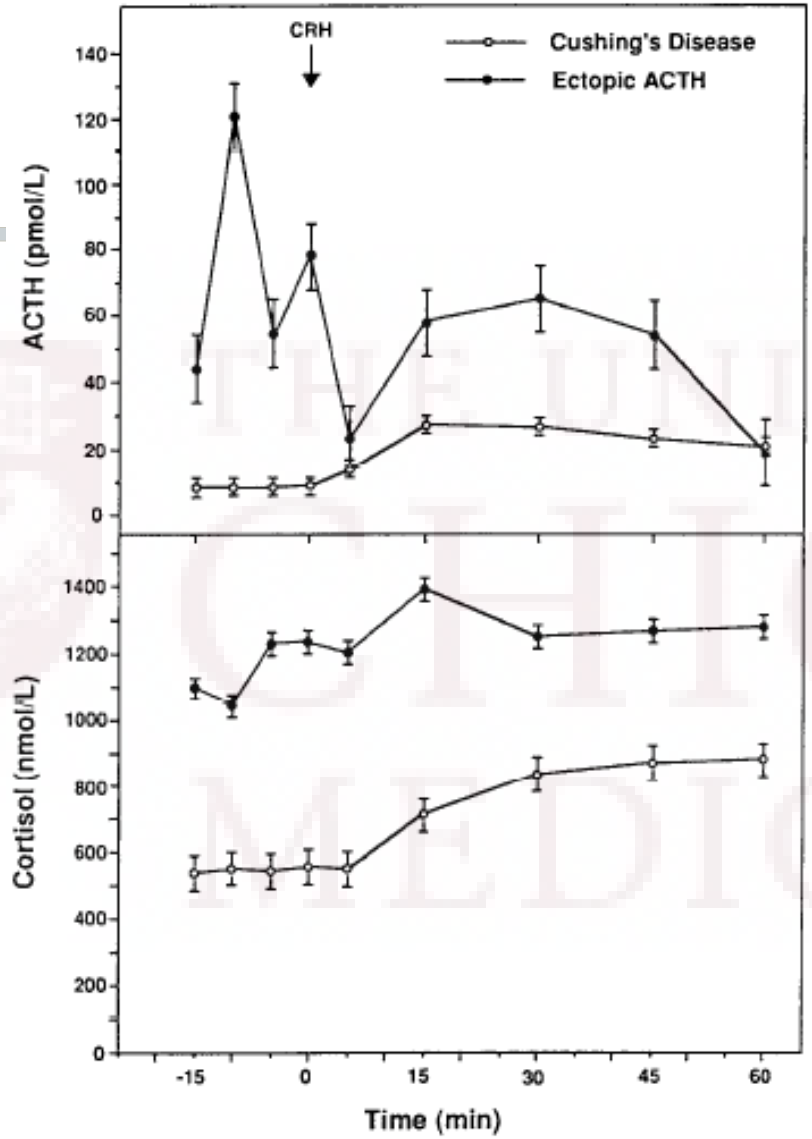



FIG. 1. Responses of plasma ACTH and cortisol to CRH (mean ± SE) in 101 untreated patients with Cushing's disease and 17 untreated patients with Cushing's syndrome due to ectopic ACTH secretion.

118 patients evaluated prospectively
101 patients ended up having Cushing's disease based on hypocortisolism after microadenectomy or hemihypophysectomy and/or pathology
17 with Ectopic ACTH based on ACTH staining of non-pituitary tumor

Nieman et al. A simplified morning ovine corticotropin-release hormone stimulation test for the differential diagnosis of ACTH-dependent Cushing's syndrome. JCEM 1993;77:1308-12.

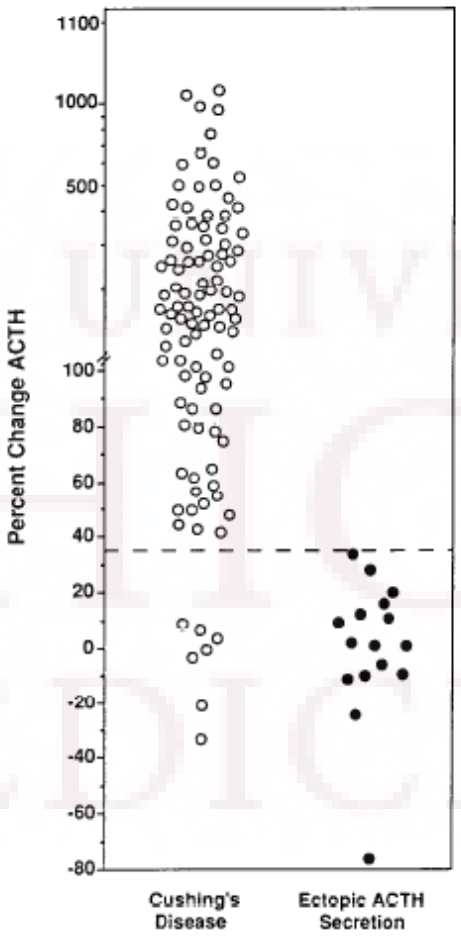



FIG. 2. Responses of plasma ACTH to CRH in 100 patients with Cushing's disease and 16 patients with ectopic ACTH secretion. Responses are expressed as the percent change in mean ACTH concentration 15 and 30 min after ovine CRH administration from the mean basal value 1 and 5 min before the injection. The *dashed line* indicates a response of 35%.

# CRH testing

| Time (min) | -15 | 0 | 15 | 20 | 30 | 45 | 60 |
|---|---|---|---|---|---|---|---|
| ACTH | 24.5 | 25.7 | 69.3 | 68.6 | 72.2 | 68.4 | 51.4 |
| Cortisol | 9.7 | 7.8 | 15.3 | 19.0 | 21.8 | 23.4 | 22.0 |

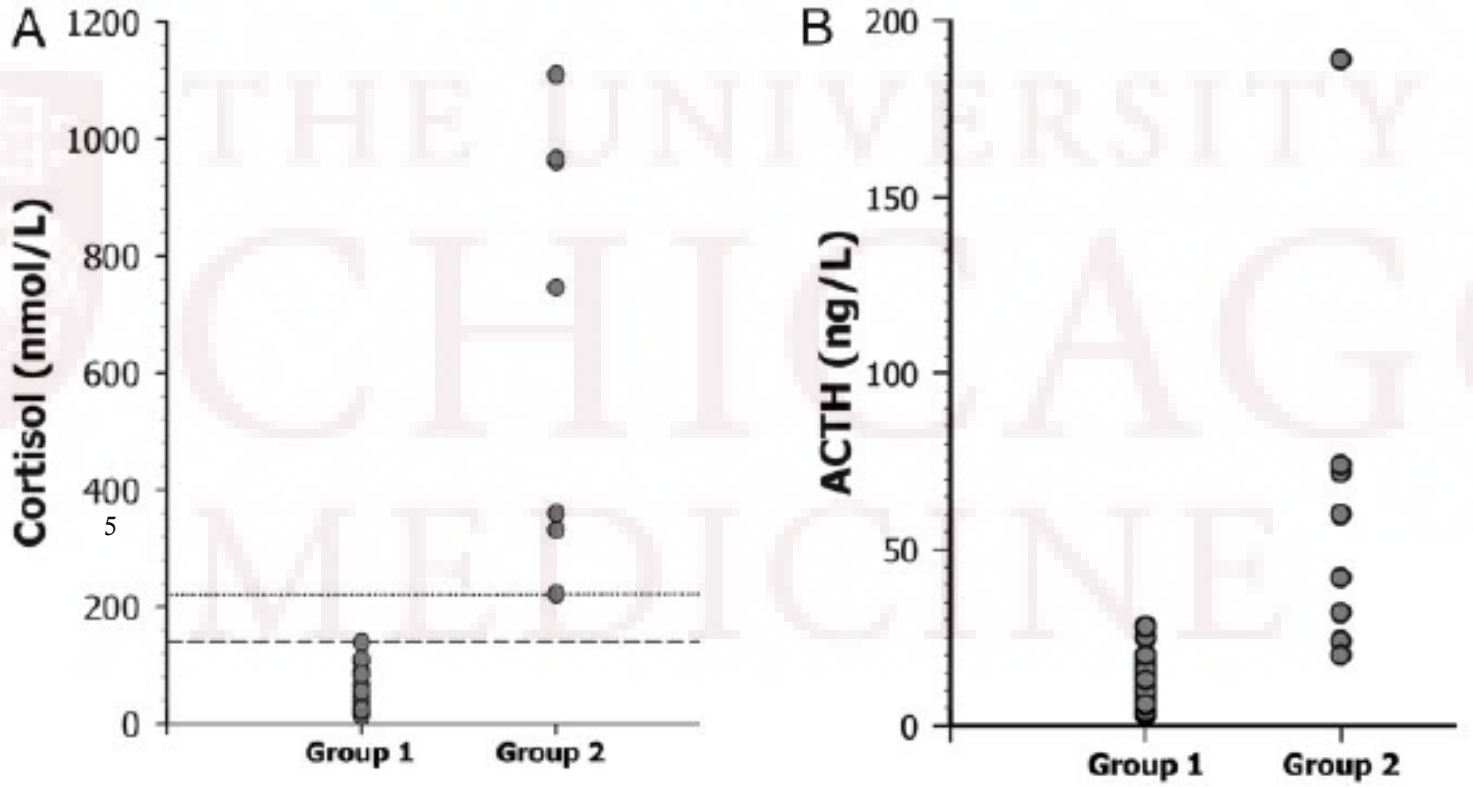
# Patient course

- Patient diagnosed with Cushing's disease and referred for surgery

# Post-operative management

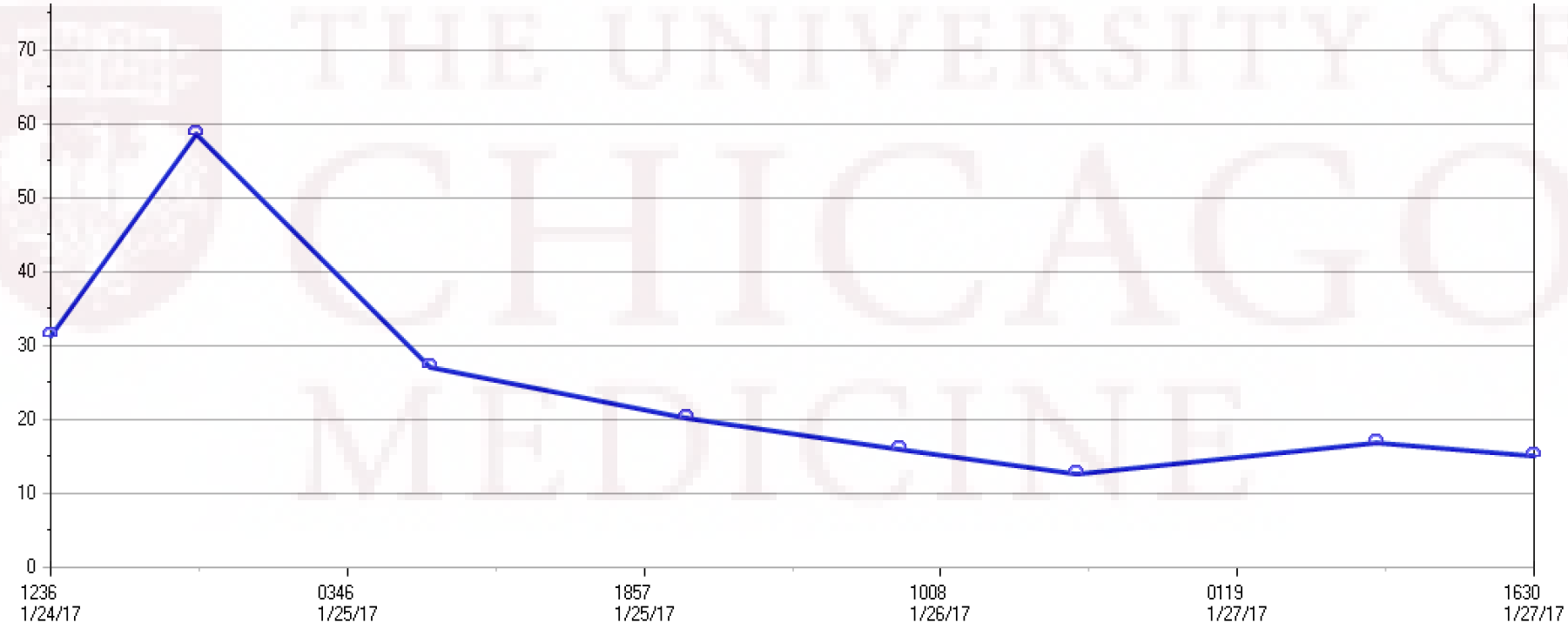
You are called post-operatively. The 4 mm adenoma was removed in its entirety. Patient was not given any steroids peri-operatively.

What would you like to do?




Esposito et al. Clinical review: early morning cortisol is predictor of remission after transsphenoidal surgery for Cushing's disease. JCEM 2006;91:7-13.

# Cortisol trend



# Clinical Course

- Developed recurrent DVT of LLE in setting of holding Xarelto. Seen by heme in house – started on Lovenox x 10 days, then Xarelto
- Given AM cortisols of 15-20, no glucocorticoids were recommended at discharge
- Patient was to get a repeat cortisol in 1 week and was counseled about symptoms of adrenal insufficiency
- Cortisol came back at 12.0 and no GC was started

# Pathology

Pituitary adenoma with expression of ACTH

**Comment**: histologic sections show a proliferation of anterior pituitary type cells with features of pituitary adenoma. These label for synaptophysin and are negative for GH, FSH, LH, TSH, and prolactin. ACTH staining is not as robust as that observed in the positive control but based on repeat staining ACTH expression is nevertheless seen.

# How do you test for cure of CD?

- There are no consensus guidelines
- Some suggest not using dexamethasone suppression
  - Argument is that it relies on incomplete suppression of ACTH/cortisol but after some (but not all) of the tumor is removed, the circulating ACTH/cortisol levels are lower and apparent suppression can occur

McCance et al. Review: Assessment of cure after transsphenoidal surgery for Cushing's disease. Clinical Endocrinology 1996;44:1-6.

# Long-Term Predictive Value of Postsurgical Cortisol

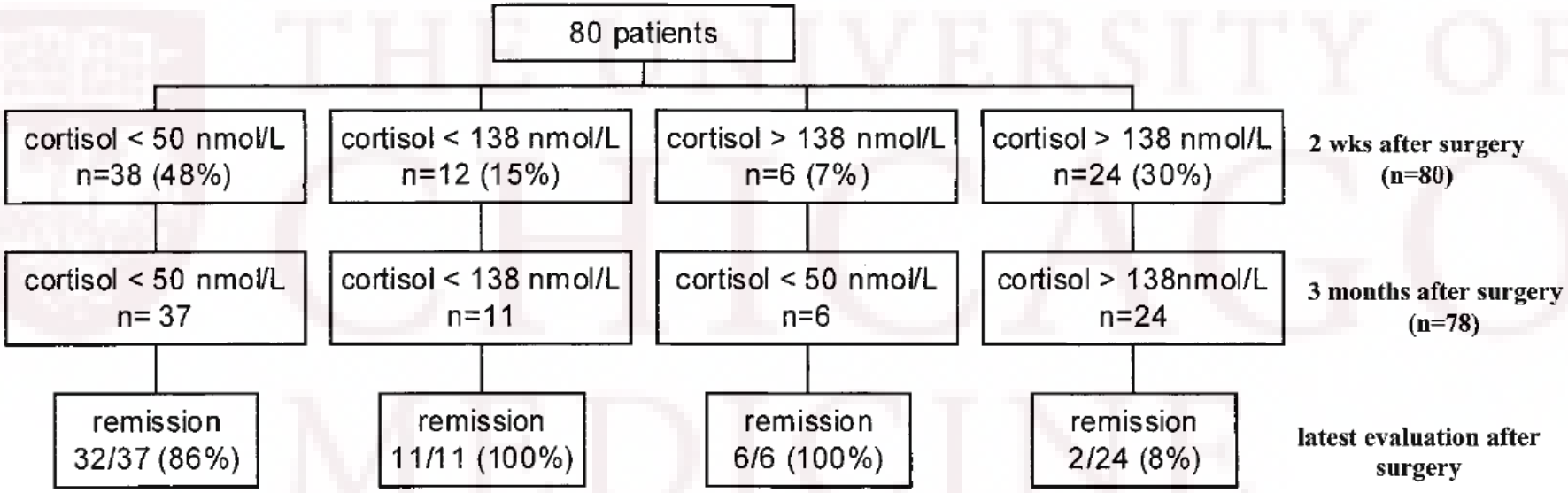



FIG. 1. Biochemical and clinical outcome of TS

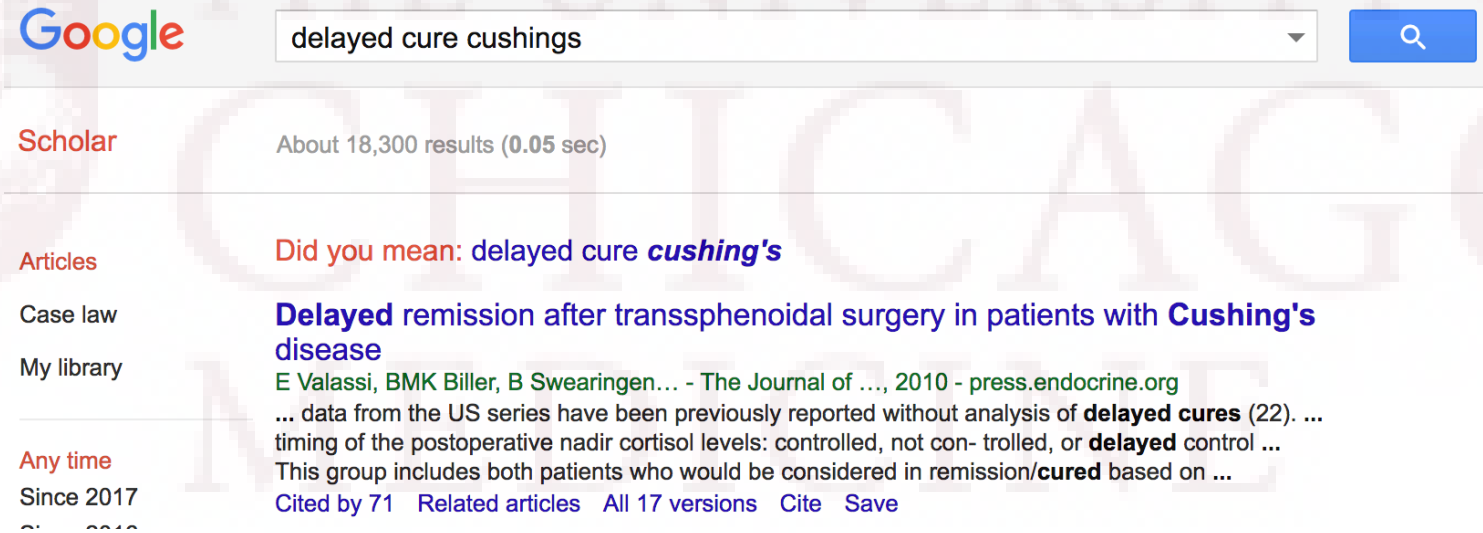
Pereira et al. Long-term predictive value of postsurgical cortisol concentrations for cure and risk of recurrence in Cushing's disease. JCEM 2003.

# Patient calls in

- One month later, patient calls in, complaining that he feels very fatigued, “can’t get out of bed”
- Muscle and joint pains, currently being treated for a sinus infection
- PCP measured cortisol of 5.7 at 8:45 AM

What is going on?

# What is going on?



ORIGINAL ARTICLE

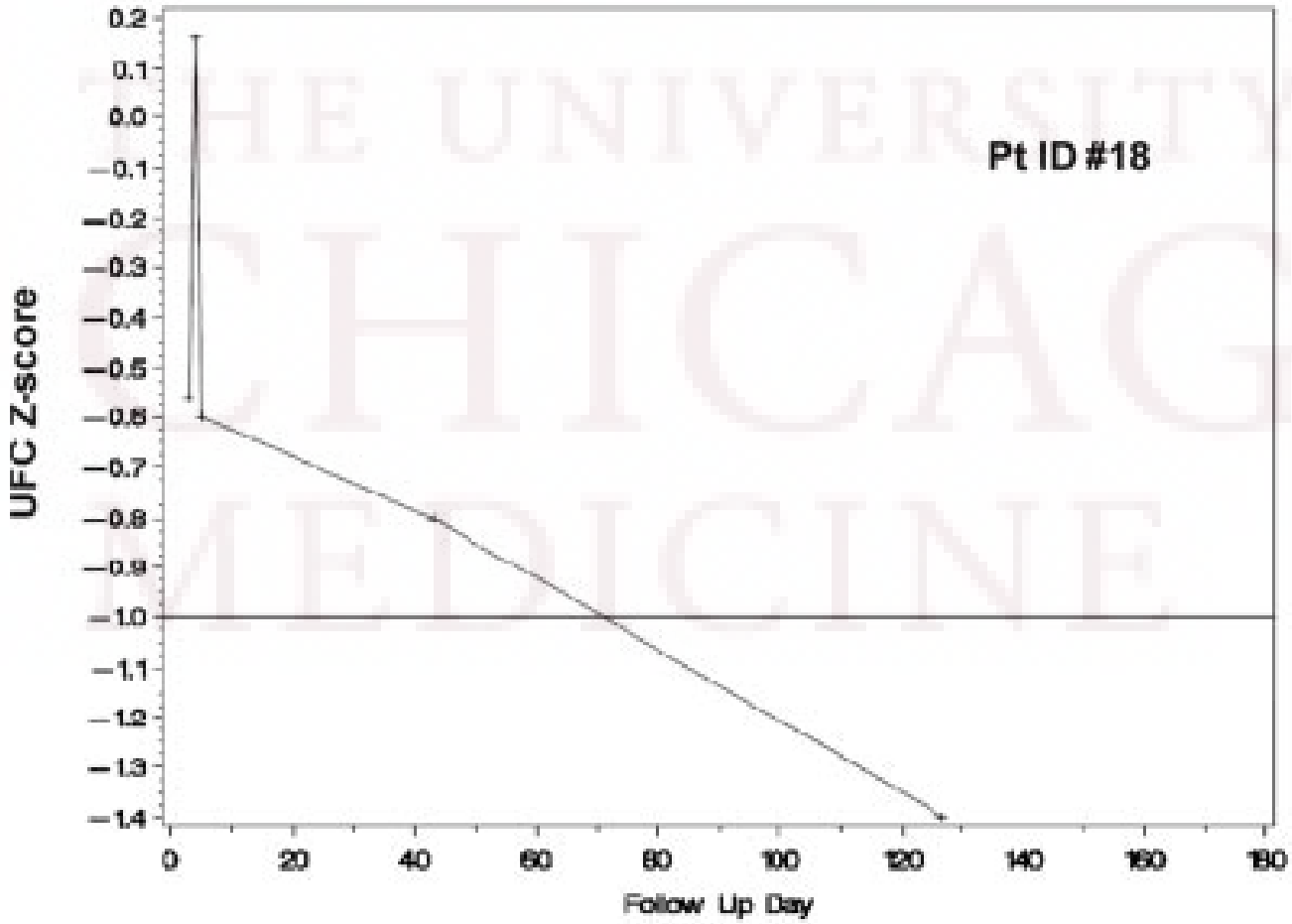
Endocrine Care

# Delayed Remission after Transsphenoidal Surgery in Patients with Cushing's Disease

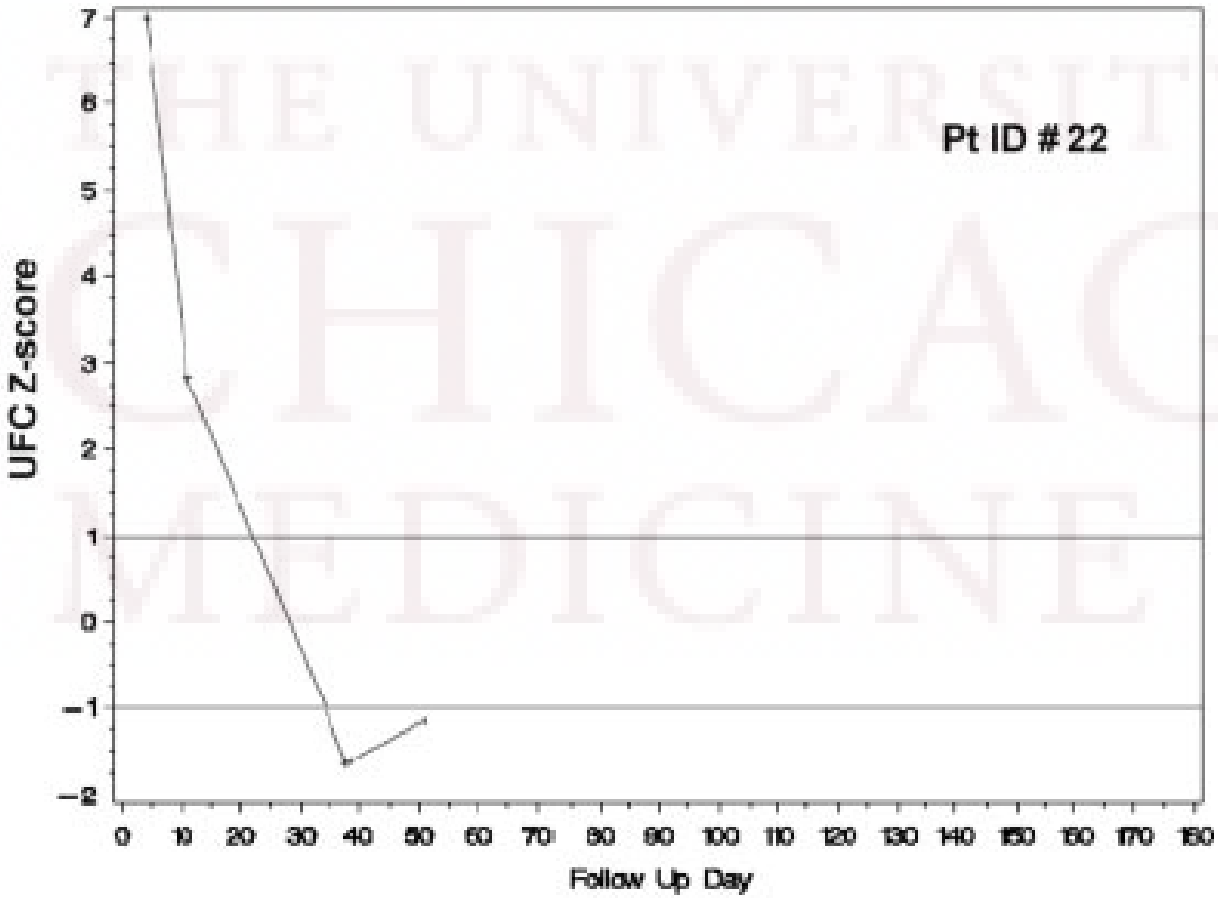
Elena Valassi, Beverly M. K. Biller, Brooke Swearingen, Francesca Pecori Giraldi, Marco Losa, Pietro Mortini, Douglas Hayden, Francesco Cavagnini, and Anne Klibanski

- Retrospective review of 620 patients in the U.S. and Italy who underwent transsphenoidal pituitary surgery for Cushing's disease between 1982-2007
- They found that 5.6% of patients had delayed decline in cortisol

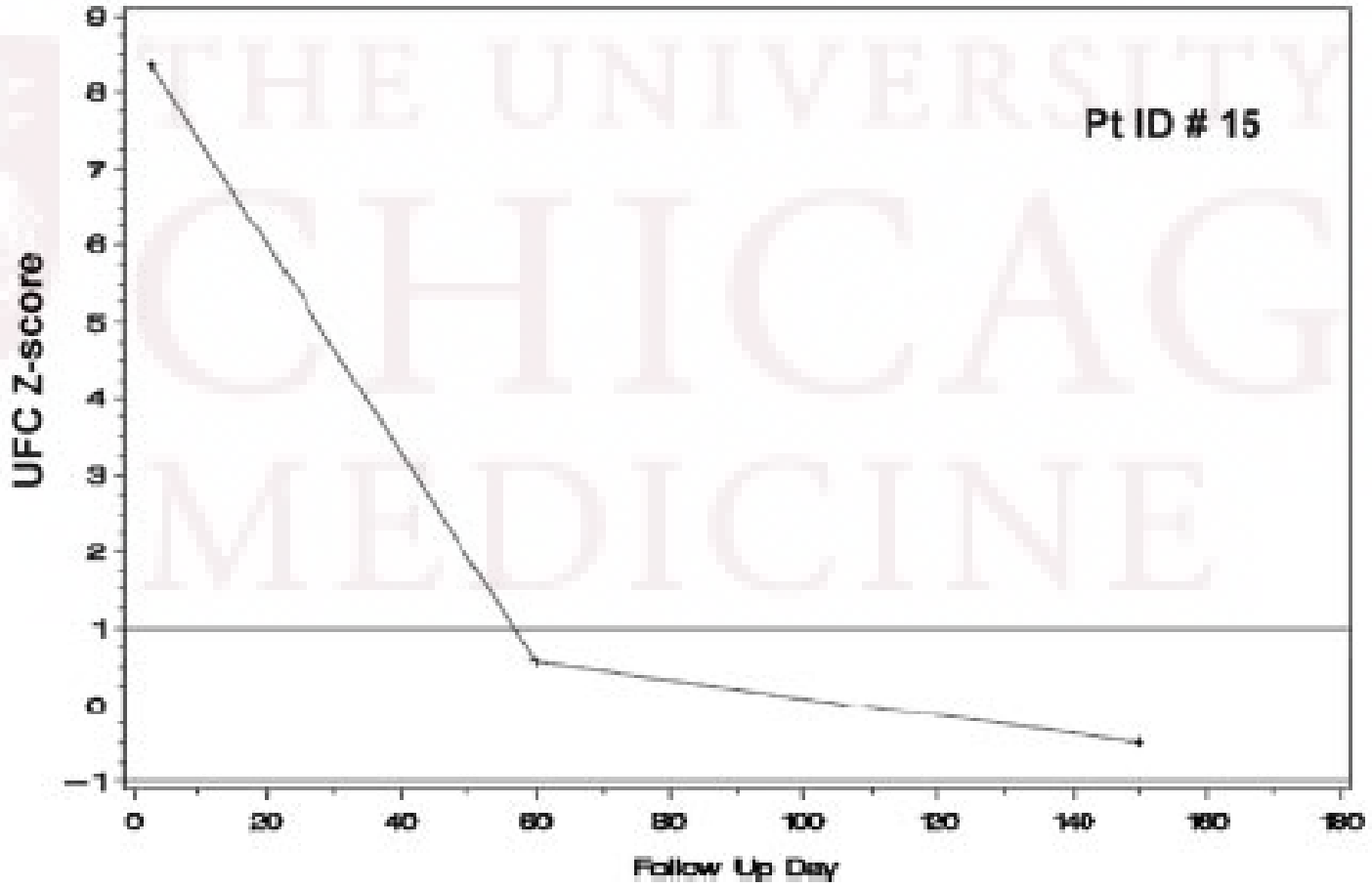
# Individual patient courses



# Individual patient courses



# Individual patient courses



ORIGINAL ARTICLE

Endocrine Care

# Delayed Remission after Transsphenoidal Surgery in Patients with Cushing's Disease

Elena Valassi, Beverly M. K. Biller, Brooke Swearingen, Francesca Pecori Giraldi, Marco Losa, Pietro Mortini, Douglas Hayden, Francesco Cavagnini, and Anne Klibanski

- Delayed decrease to low/normal urinary free cortisol was documented at mean 38 ± 50 days (median 9 days, range 4-180 days)
- These patients were slightly more likely to be female, older, and have a macroadenoma (i.e. not our patient!)
- Authors hypothesized the delay was related to adrenal hyperplasia with partial autonomy from chronic exposure to elevated ACTH vs. late necrosis of residual corticotroph adenoma cells after surgery

# Patient's clinical course

- Started on hydrocortisone 20 mg qAM and 10 mg qPM
- He reports 75% of his symptoms improved within a few days
- However, he continues to have persistent symptoms and has called in seven times in about ~8 weeks due to these symptoms

# Recovery from Cushing's

Dr. Young:

"Cushing's is hard but recovering from Cushing's is *really* hard"

# Recovery from Cushing's

- Patients used to high levels of glucocorticoids may struggle to adjust to "physiological" amounts of glucocorticoids
- Mayo approach is very different than what we use
- Prednisone 10 mg qAM and 5 mg qPM and drop the dose by 2.5 mg each week
  - 7.5 and 5 mg → 5 and 5 mg → 5 and 2.5 mg
- Then substitute Hydrocortisone 20 mg qAM and 10 mg qPM and drop the dose by 5 mg every 2 weeks
  - 15 and 10 mg → 15 and 5 mg →15 mg alone
- Then, no further dosage taper but check 8 AM cortisol before the morning every 6 weeks
  - When morning serum cortisol > 10 mcg/dL, stop hydrocortisone

# Patient course

- He was switched to this type of prednisone regimen but continues to have symptoms
  - Even slower taper?

# Even years later, patients with cured Cushing's Syndrome have impaired QOL

Lindsay et al. Long term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission. JCEM 2005.

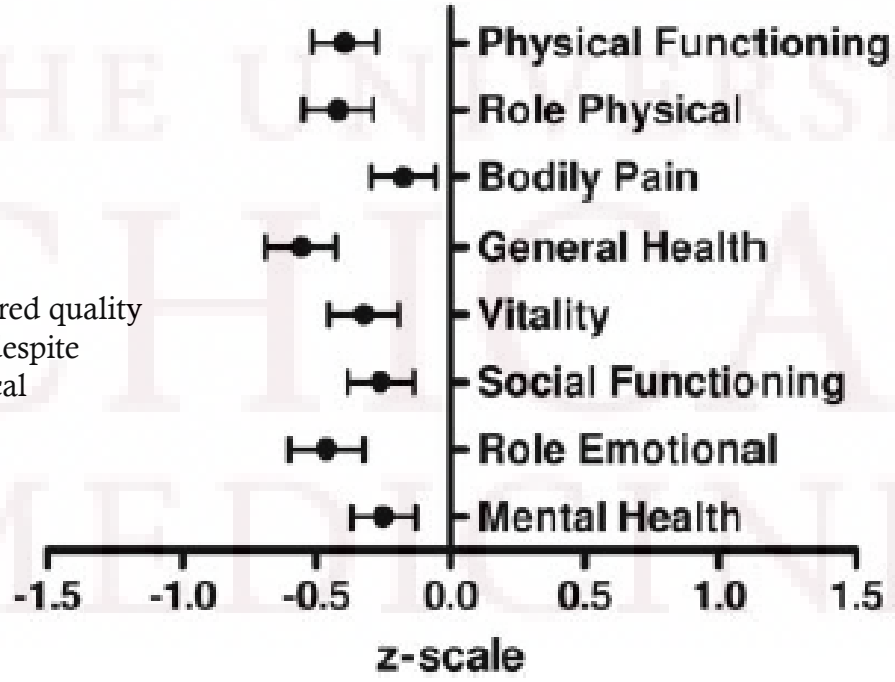
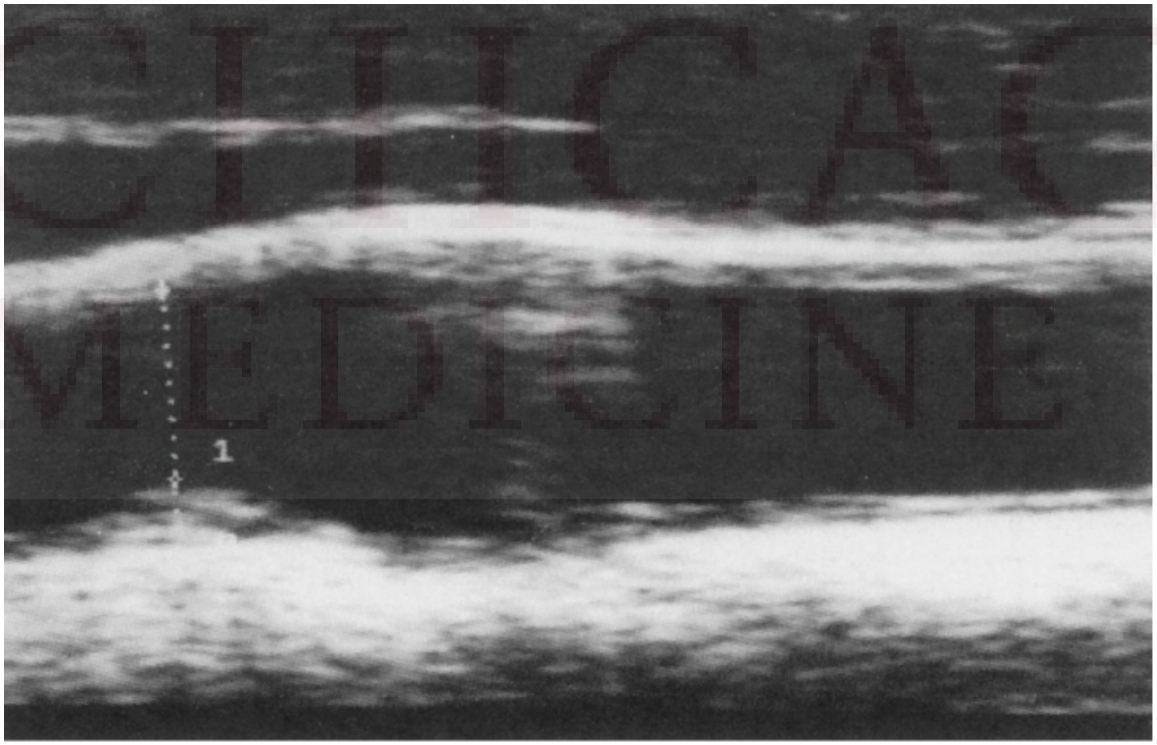



FIG. 2. Individual domains of SF-36 in 343 patients in long-term apparent remission after treatment for CS. Data are presented as the mean ± 95% CIs. All data crossing the zero line (U.S. population age- and sex-matched control values; n = 6742) are not significant.

# …and increased CV risk

**Persistence of Increased Cardiovascular Risk in Patients with Cushing's Disease after Five Years of Successful Cure**



# Patient course

- Also on levothyroxine and testosterone (cleared with hematology given his DVT history)
- Followed up with neurosurgery with no further action needed
- Continues to follow up with us (last visit 2 weeks ago)
  - Has lost 25 LB
  - Still complaining of fatigue and muscle aches but back at work
  - Remains on hydrocortisone 20 mg in the morning and 10 mg in the afternoon
    - Plan to taper to 15 mg and 10 mg next week
  - Continues to have anxiety symptoms, cut his levothyroxine dose in half on his own
    - Re-start previous dose, recommended he discuss anxiety therapies with his PCP

# References


Nieman et al. The diagnosis of Cushing's disease: An Endocrine Society Clinical Practice Guideline. JCEM 2008; 93:1526-40.

Van Zaane et al. Hypercoagulable state in Cushing's syndrome: A systematic review. JCEM 2015.

Ilias et al. Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. JCEM 2005.

Nieman et al. A simplified morning ovine corticotropin-release hormone stimulation test for the differential diagnosis of ACTH-dependent Cushing's syndrome. JCEM 1993;77:1308-12.

Meinardi et al. Cyclic Cushing's syndrome: a clinical challenge. Eur J Endo 2007.

Peira et al. Long-term predictive value of postsurgical cortisol concentrations for cure and risk of recurrence in Cushing's disease. JCEM 2003.

Esposito et al. Clinical review: early morning cortisol is predictor of remission after transsphenoidal surgery for Cushing's disease. JCEM 2006;91:7-13.

McCance et al. Review: Assessment of cure after transsphenoidal surgery for Cushing's disease. Clinical Endocrinology 1996;44:1-6.

Valassi et al. Delayed remission after transsphenoidal surgery in patients with Cushing's Disease. JCEM 2010.

Lindsay et al. Long term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission. JCEM 2005.