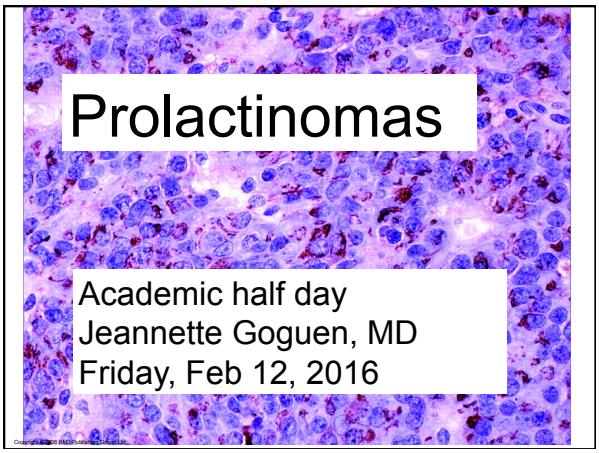


Prolactinomas

Academic half day
Jeannette Goguen, MD
Friday, Feb 12, 2016

Objectives

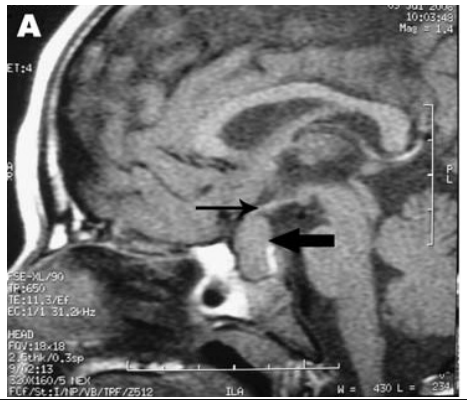
1. Review some pitfalls in making the diagnosis of prolactinoma.
2. Discuss therapeutic challenges.
   - When do you use dopamine agonists?
   - What are the risks? Do you need to do serial ECHOs?
   - When is it safe to stop the DA?
   - Treating the patient with schizophrenia

Case 1 - A child with hyperprolactinemia

Alves Child's Nervous System(2008) 24:1505–1508

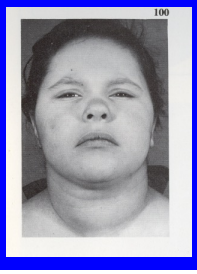
- 10 year old girl, investigated for ovarian cysts
- 10%ile wt, <5%ile ht, no sexual development

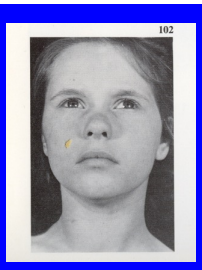
- Prolactin 347
- Rest of pituitary panel:
- free T4 3 (low), cortisol 180, FSH 5, LH 2



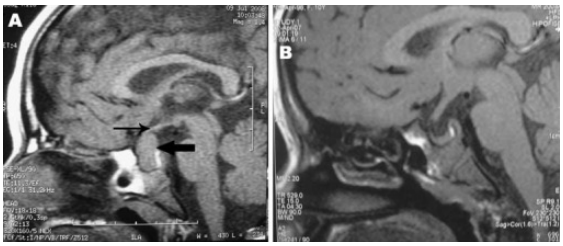
What's the diagnosis?

Before treatment: After treatment:





Case 1: MRI before and after treatment

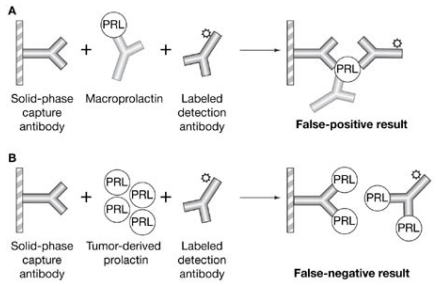


What is in the differential of macroadenoma and modestly elevated prolactin?

What is in the differential of macroadenoma and modestly elevated prolactin?

- Stalk effect
- Prior pituitary apoplexy
- Hook effect
- Primary hypothyroidism
- Two conditions (nonsecretory adenoma + other cause for elevated prolactin)

Macroprolactin (F+) and Hook effect (F-)



Case 2

- 32 yo woman with 12 year history of prolactinoma (8 mm on last MRI 8 years ago)
- Prolactin went from 180 to 15 (normal) on bromocriptine 2.5 mg daily
- Never felt well...

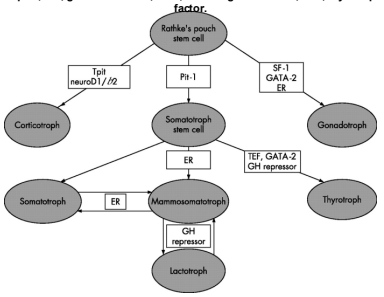
Lab results

- sTSH 1.2, free T4 12
- 8 AM cortisol 342
- LH 4, FSH 1, estradiol 146
- Prolactin 12

- What's the diagnosis?

Mammosomatotroph tumor

Figure 5 Pathways of cell differentiation in adenohypophysis. The three main pathways of cell differentiation are determined by transcription factors that can serve as diagnostic markers. ER, oestrogen receptor; GH, growth hormone; SF-1, steroidogenic factor 1; TEF, thyrotroph embryonic factor.



Al-Brahim, N Y Y et al. J Clin Pathol 2006;59:1245-1253

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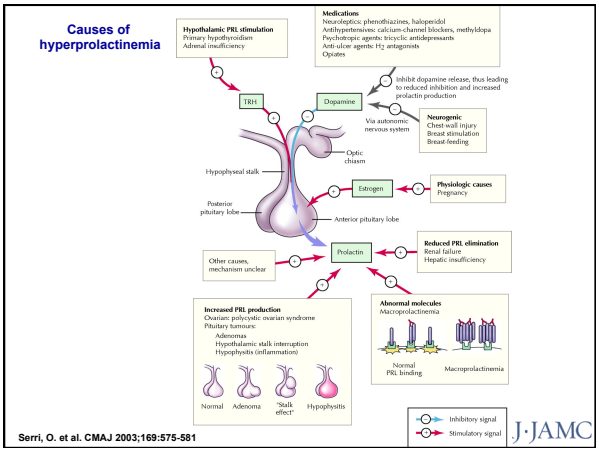

Serri, O. et al. CMAJ 2003;169:575-581

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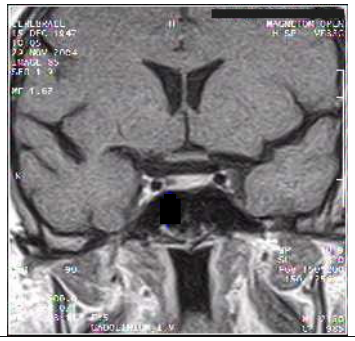
Case 3

- 32 yo woman c/o amenorrhea for 6 months following initiation of a new medication
- Galactorrhea also for 3 months
- no h/a, no visual complaints
- Normal exam, except galactorrhea
- Prolactin 150, LH 1, FSH 1, estradiol 22
- (rest normal)
- MRI ...



T1: focal, 80% hypointense, esp with gadolinium

T2: most are isointense, 1/3 hyperintense

Hyperprolactinemia
in association with dopamine antagonists

1. How high do prolactin levels get?
2. When do you image?
3. How do you treat?
   What if they also have a microadenoma?

Hyperprolactinemia
in association with dopamine antagonists

1. How high do prolactin levels get on antipsychotics?
   - 100-350 (10X elevated!)
2. When do you image?
   - h/a, visual symptoms
   - Symptoms are not correlated to timing of drug therapy
   - ↑ Prolactin (what level?)
   - Stop drug for 4 days and check prolactin level

Hyperprolactinemia
in association with dopamine antagonists

3. How can you treat the hyperprolactinemia?
   - Monitor for side-effects including bone loss
   - Estrogen and progesterone/androgens
   - Change antipsychotic or reduce its dose (aripiprazole best)
   - Prescribe a dopamine agonist cautiously

What if they also have a microadenoma?
- could be incidentaloma
- if prolactinoma, consider surgery

Box 1: Clinical presentations of hyperprolactinemia

Premenopausal women

- Marked prolactin excess (> 100 μg/L [normally < 25 μg/L]) is commonly associated with hypogonadism,* galactorrhea and amenorrhea
- Moderate prolactin excess (51–75 μg/L) is associated with oligomenorrhea
- Mild prolactin excess (31–50 μg/L) is associated with short luteal phase, decreased libido and infertility
- Increased body weight may be associated with prolactin-secreting pituitary tumour[2]
- Osteopenia is present mainly in people with associated hypogonadism
- Degree of bone loss is related to duration and severity of hypogonadism*[6]

Men

- Hyperprolactinemia presents with decreased libido, impotence, decreased sperm production, infertility, gynecomastia and, rarely, galactorrhea
- Impotence is unresponsive to testosterone treatment and is associated with decreased muscle mass, body hair and osteoporosis[7]

*The degree of hypogonadism is generally proportionate to the degree of prolactin elevation

Serri, O. et al. CMAJ 2003;169:575-581

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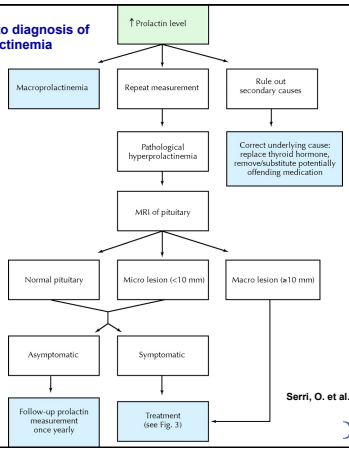
Approach to diagnosis of hyperprolactinemia



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What are your treatment objectives?

Box 2: Objectives of treatment of hyperprolactinemia

- Restoration and maintenance of normal gonadal function
- Restoration of normal fertility
- Prevention of osteoporosis

If a pituitary tumour is present:

- Correction of visual or neurological abnormalities
- Reduction or removal of tumour mass
- Preservation of normal pituitary function
- Prevention of progression of pituitary or hypothalamic disease

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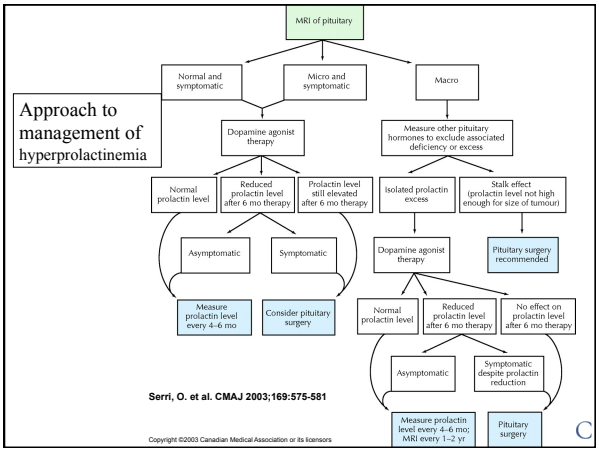

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Important points...

- 90% of patients have microadenomas
- It is very rare for microadenomas to progress to macroadenomas (6.5% of intrasellar tumors expanded beyond sella when followed 8 yrs)
- Prolactin level correlates with tumor size/ progression, as long as not co-secreting GH

Box 3: Medical therapeutic options for the managment of hyperprolactinemia

- Dopamine agonists are currently the first therapeutic option (Table 1)
- Dopamine agonists have proven efficacy in reducing prolactin levels, restoring ovulation in premenopausal women and restoring gonadal function in men[7,9]
- Prolactin levels may remain above normal in about 20% of cases of macroprolactinoma and about 10% of cases of microprolactinoma despite dopamine agonist therapy[9]
- Bromocriptine has been used the longest.
- Cabergoline has greater affinity and selectivity for pituitary dopamine D_2 receptors and longer duration of action.[9–11] It is indicated in cases of bromocriptine resistance or intolerance
- Quinagolide is an alternative dopamine agonist[10] but with limited access

Serri, O. et al. CMAJ 2003;169:575-581

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What about the issue of valvular heart disease and DA?

DA + the risk of cardiac valve regurgitation

Schader NEJM 2007

- 11,417 pts on Parkinson drugs in UK database
- Nested case control
- 31 new cardiac valve cases

	Incidence rate ratio
– 6 pergolide	7.1
– 6 cabergoline	4.9
– 19 no exposure	

- Dose carbergoline:
  - – > 3 mg/day 50.3
  - – < 3 mg/day 2.6

Valvular heart disease and the use of DA for Parkinson's

Zanettini NEJM 2007

- 155 pts with Parkinson's disease
- Prevalence of clinically significant valvular disease on 2D ECHO

DRUG	N	PREVALENCE
Pergolide	64	23.4%
Cabergoline	49	28.6%
No ergot	42	0%
Controls	90	5.6%

Summary: Studies with cabergoline in prolactinomas

(and one Parkinson study) Kars Eur J Endocrin 2008

Author	N	Cum dose	Duration Rx (mo)	Relevant valvular regurg	Valv thickening	Mitral tenting area
Yamashiro	153	3000	36	↑AR		
Lancellotti	102	204	79	NS	NS	↑
Bogazzi	100	279	67	NS		
Vallette	70	282	55	NS	NS	
Kars	47	363	62	↑mildTR	↑M & A Ca2+ ↑T thickening	
Wakil	44	311	45	↑mild TR/PR		
Colao	50	414	NA	Mod TR	NS	
Herring	50	443	78	NS	NS	NS

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Safety of long-term treatment with carbergoline on cardiac valve disease

Auriemma Eur J Endocrinol 2013

- 40 pts followed for 60 months
- Prospective ECHOs: 0, 24 and 60 months of Rx for hyperprolactinemia
- Cumulative dose:
  - 12-588 mg at 24 mo
  - 48-1260 mg at 60 mo
- No difference in mild regurgitation, no significant valvular disease

When can you consider withdrawal of therapy?

Recommendations for drug withdrawal

Schlechte JCEM 2007

(After 2-4 years of therapy and normal prolactin):

- Microadenomas
  - Can stop DA abruptly
  - Hx and prolactin q 3 months
- Macroadenomas with negative MRI post Rx
  - Slow taper
  - Can try if > 50% reduction tumor size, stable, esp < 3 mm

Box 4: Indications for pituitary surgery in patients with hyperprolactinemia

- Surgery is indicated in cases of resistance or intolerance to optimal medical therapy
- Surgery should be considered in patients with intrasellar tumour for whom long-term drug treatment is not acceptable
- Surgical decompression may be required for tumours pressing on the optic chiasm
- Surgery should be avoided in cases of extrasellar (without optic chiasm compression) expanding tumours because of the low success rate

Serri, O. et al. CMAJ 2003;169:575-581

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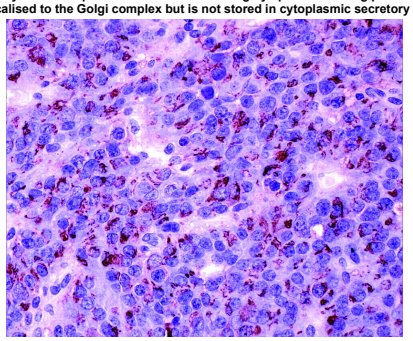
Figure 8 Prolactin staining in sparsely granulated lactotroph adenoma. This tumour represents the vast majority of lactotroph adenomas. It shows a highly specific staining pattern for prolactin that is localised to the Golgi complex but is not stored in cytoplasmic secretory granules.



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Pathology

- Lactotroph adenomas
  - Sparsely and densely granulated variants.
  - Sparsely granulated are responsive to DA
  - Untreated adenomas are:
    - chromophobic
    - have abundant cytoplasm and characteristic juxtanuclear prolactin immunoreactivity
  - Post Rx:
    - small cells in a fibrous stroma, resembling inflammation, plasmacytoma or lymphoma.
    - strong nuclear positivity for Pit-1
    - at least focal prolactin positivity.

Conclusions

1. Remember your pitfalls!
   - Remember to R/O other causes for ↑ prolactin
   - Check TSH, GH, diluted prolactin, R/O macroprolactin
2. Treating hyperprolactinemia
   - use the lowest effective dose of DA
   - withdraw drug when possible