



# Prolactinoma

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# Agenda

- Epidemiology
- Diagnosis
- Clinical consequences of hyperprolactinemia
- Biochemical diagnosis
- Imaging
- Medical treatment
- Surgical treatment
- Prolactinoma and pregnancy

# Epidemiology

- ▶ A **prolactinoma** is the most common cause of chronic hyperprolactinemia once **pregnancy**, primary **hypothyroidism**, and **drugs** that raise serum prolactin (PRL) levels have been ruled out.
- ▶ Between the age of **20 and 50** years, the ratio between **women** and men is estimated to be **10:1**, whereas after the **fifth decade** of life, both genders are **equally** affected .
- ▶ Although prolactinomas are **rare** at the **pediatric** and adolescent ages, they account for approximately **half of all pituitary** adenomas in that population .
- ▶ PRL-secreting **carcinomas** are extremely **rare**.

# Epidemiology

- **Prevalence**: 50 per 100,000
- **incidence** 3-5 new cases/100,000/year.
- microadenomas are 4-5 fold more frequent than macroadenomas
- The **ratio between macro- and microprolactinomas** is approximately 1:8 in women, whereas it is inverted in men (macroadenomas in 80% of cases)
- **Peak age** of occurrence in women occurs at approximately 30 years, while most men are diagnosed after age 50.

- ▶ The most **characteristic signs** and symptoms found in patients with hyperprolactinemia are those related to hypogonadotropic **hypogonadism** and **galactorrhea**.  
Increased PRL levels **decrease gonadotropin** pulsatile secretion through **inhibition** of hypothalamic **GnRH** release

## Diagnosis(Clinical consequences of hyperprolactinemia)

### ■ Women (Classic symptoms of prolactinomas)

- oligo- or amenorrhea :almost all patients (85-90%)
- Galactorrhea:84% of patients
- infertility
- prevalence of mild HPL in an unselected, asymptomatic population with infertility is approximately 5%

## Diagnosis( Clinical consequences of hyperprolactinemia)

### ■ Postmenopausal women

- They present with mass effects related to large tumors
- Although prolactinomas may also be discovered incidentally or because of a history of “premature” menopause

### ■ Men

- Approximately 80% are diagnosed with a macroprolactinoma
- Half of men typically present with symptoms caused by the tumor mass
- Other half with symptoms of hypogonadism, including a loss of libido, ED, gynecomastia, infertility, and/or osteopenia
- Testosterone concentrations are often decreased, these levels may be normal in men with prolactinomas



## Diagnosis( Clinical consequences of hyperprolactinemia)

### ▪ **Mass effects**

- **Visual field defects** (chiasmal compression depend on the extent of suprasellar extension)
- **Headaches** are a frequent symptom which is often associated with the lateralization of the tumor, and cluster-like headache may also occur as a major manifestation
- **Hypopituitarism** (from direct pituitary compression or more commonly from hypothalamic/stalk dysfunction)
- **cavernous sinus syndrome** is rare and is generally observed in the context of pituitary apoplexy, which is characterized by headache with a sudden and severe onset that is generally associated with visual disturbances or ocular palsy.
- **cerebrospinal fluid (CSF) rhinorrhea**, **hydrocephalus** and **seizures**, can also occur

- ▶ **Some** women present with non-puerperal **galactorrhea** in the presence of **regular** menstrual cycles and **normal PRL** levels This so-called “**idiopathic galactorrhea**” is estimated to be present in up to **40-50%** of all women with non-puerperal galactorrhea
- ▶ In contrast, the finding of **galactorrhea** in **men** is highly suggestive of a **prolactinoma**

# Diagnosis:

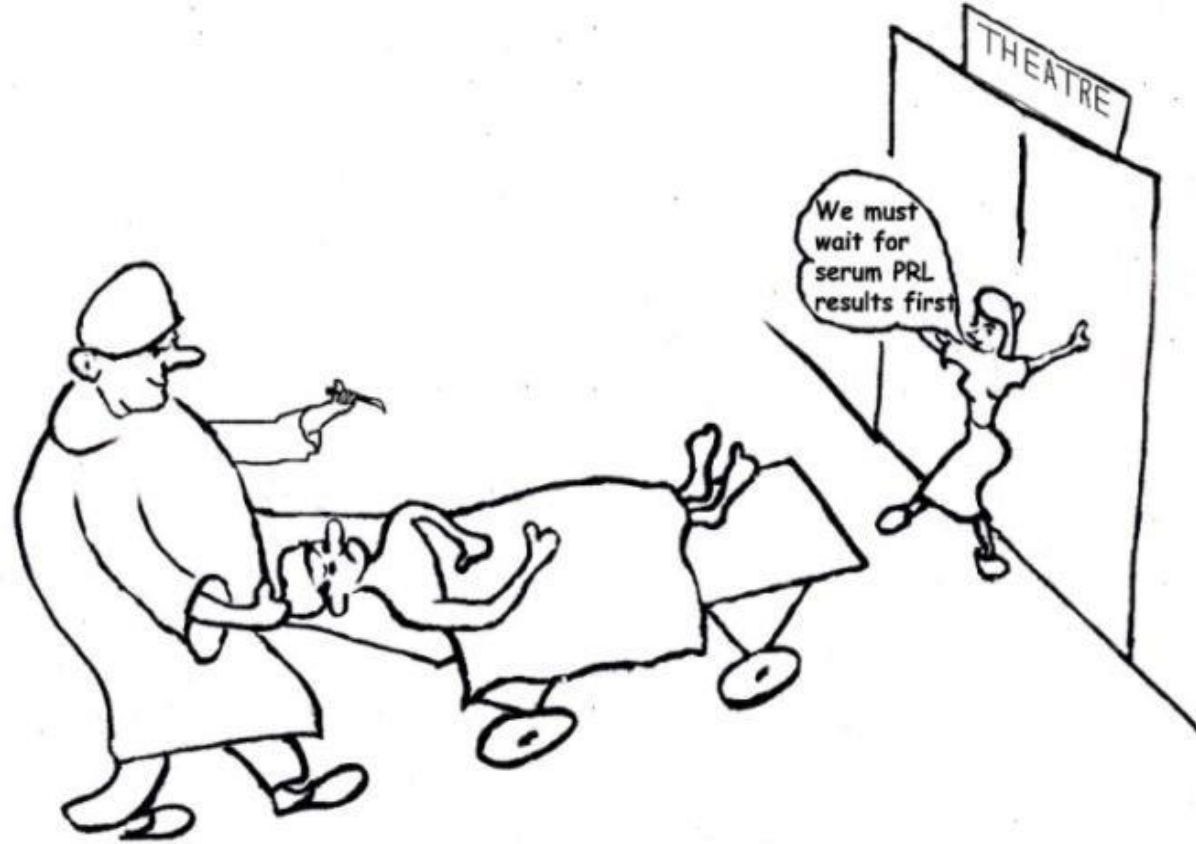
- PRL > 250 ng/ml: Usually prolactinoma
- PRL > 200 ng/ml: Prolactinoma, some drugs
- 25 ng/ml < PRL < 200 ng/ml & pituitary macroadenoma: R/O hook effect
  - (macroprolactinoma, non-prolactin secreting tumor)
- Pituitary MRI

# Diagnosis:

- ▶ circulating PRL levels usually **parallel** the **tumor size**
- ▶ **microprolactinomas** (MIC) (diameter < 10 mm) usually result in PRL levels of **100-200 ng/mL**, but not infrequently, they may be **< 100 ng/mL**, and occasionally reach **500 ng/mL** or more
- ▶ **Macroprolactinomas** (MACs) (diameter  $\geq$  10 mm) are typically associated with PRL values **> 250 ng/mL** (4-7).
- ▶ In the vast majority of patients with **giant** prolactinomas (maximum diameter  $\geq$  4 cm), PRL levels will be **> 1000 ng/mL**

- ▶ **Artificially** low PRL levels may result from the so-called “**hook effect**”, which should be considered in all cases of large ( $\geq 3$  cm) pituitary macroadenomas associated with normal or mildly elevated PRL levels (< 200 ng/mL)
- ▶ Patients harboring **cystic MACs** may also present with **mild PRL** elevation

# Patient with macroadenoma



**Figure 1.**

Serum prolactin measurement is required in all patients presenting with hypothalamic-pituitary lesions before surgery is accomplished (Figure courtesy of D. Korbonits)

# Treatment of microprolactinoma

- **Dopamin Agonists**

- Dopamine agonists reduce the size of prolactinomas and the concentration of prolactin through binding to the dopamine **D2 receptor** in the tumor cells.
- **DAs** are the **gold standard** treatment for prolactinomas, as their use **controls** hormonal secretion and tumor **growth** in approximately **80%** of cases .
- DA is initiated at a low dose (typically 0.25-0.5 mg of CAB 1-2/W), dose is escalated at 1-3 monthly intervals according to PRL levels and the reduction in tumor size.

# Dopamin Agonists

- **Cabergoline (CAB)**, a specific agonist of the dopamine receptor type 2

(D2R), is the first choice because of its

better tolerability

greater efficacy

in inducing PRL normalization and tumor shrinkage



# Dopamin Agonists

- **Bromocriptine** use leads to normal serum **PRL** levels in **80%** of **micro**prolactinomas and **70%** of **macro**prolactinomas, whereas with **CAB**, this goal is achieved in **85%** of patients

## Short-term side effects

- Nausea and vomiting, GI symptoms
- Postural hypotension, dizziness, headache
- Nasal stuffiness and Raynaud's phenomenon
- short-term side effects are related to a parallel activation of 5-HT<sub>1R</sub> and D<sub>1R</sub> receptors, and are much more common with BMC than with CAB or quinagolide ,likely because less specific D<sub>2R</sub> agonist activity.
- They can be minimized by introducing the drug at a low dose at bedtime, taking it with food, and then escalating the dose very gradually.

## Long-term side effects

- constrictive pericarditis
- pleuropulmonary fibrosis have been reported in patients who are **chronically treated with high doses of bromocriptine or cabergoline for Parkinson's disease** but rather exceptionally in patients treated with lower doses for a prolactinoma
- cardiac valve disease
  - fibrotic thickening and stiffening of the leaflets and chordae and a reduction of the valve tenting area (an index of valve closure ability)
  - involved mainly the tricuspid, mitral and aortic valves
  - Cabergoline, pergolide > bromocriptine > quinagolide (negligible)
  - The risk is mainly related to some DAs for the serotonergic 5-HT<sub>2B</sub> cardiac receptors present in heart valves

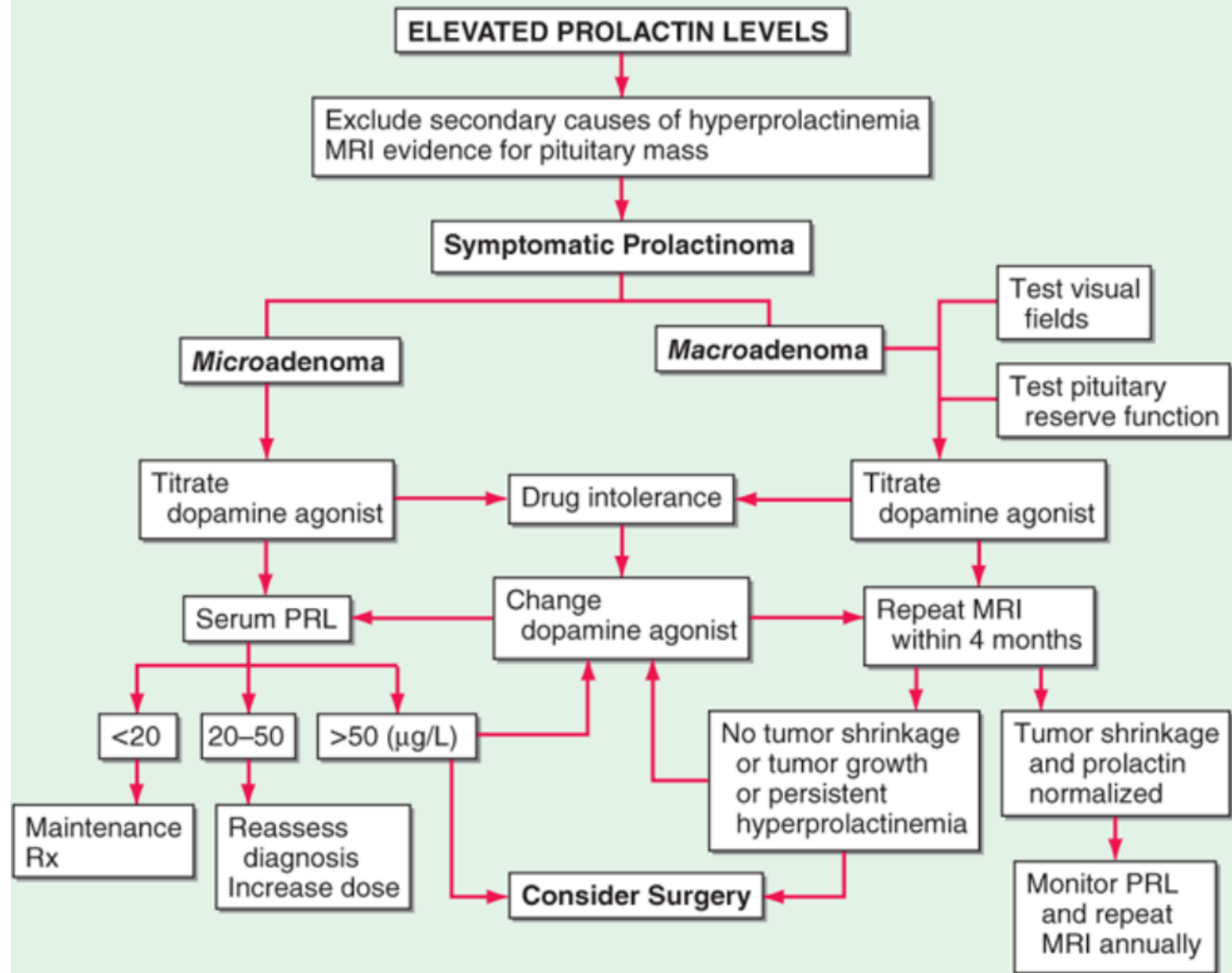
# Monitoring of microadenoma treatment

- Measure **PRL** & evaluate the side effects after **one** month
- Improve **gonadal** function: Within **a few months**
- **Decrease** the dose after **one year**
- **Discontinue** medication: Normal PRL > **2 years and Normal MRI**

# Macroadenoma management

- Medical therapy regardless of size
- Reassess vision within one month if initially abnormal  
.(improvement may be observed within a few days)
- Adenoma size decrease within weeks or months and can continue for years.
- Repeat MRI 4 months later.

# MANAGEMENT OF PROLACTINOMA



# Monitoring of macroadenoma therapy

- Normal PRL > 1 years and markedly decreased size: decrease the dose gradually to keep PRL normal
- Discontinue if initial size was 1-1.5 cm and PRL normal >2 yrs and no mass lesion by MRI
- Monitor PRL and Size indefinitely
- Macroadenoma not met above criteria should be treated even after menopause

# Surgical therapy

- Unsuccessful or intolerable medical therapy
- Adenoma (>3cm) in women wish to become pregnant even if the respond to therapy



# Radiation

- Not indicated in microadenoma
- Not indicated as primary treatment of macroadenoma
- Adjuvant therapy for surgically debulking macroadenomas

# •Prolactinoma during pregnancy

- Microadenoma:

5.5% develop neurologic symptoms

- Macroadenoma:

36% develop neurologic symptoms

- Resume dopamin agonist if increased adenoma size impairs vision
- Cabergolin is **safe** in pregnancy, data is limited

## • **Microadenoma**

- Visit q3 mo, ask about headaches and changes in vision, if no symptom, measure PRL 2 mo after delivery or cessation of nursing.

- ## Macroadenoma

- If adenoma is very large or elevates the optic chiasm: transsphenoidal surgery and perhaps postoperatively by radiation, with dopamine agonist and then pregnancy with normal PRL level
- **Macroadenoma not respond to medical therapy: pregnancy is discourage**
- If adenoma does not elevate optic chiasma and respond well to medication do the same as microadenoma.

# •Breast feeding

- Do if micro (macro)adenomas remained stable in size during pregnancy
- Dopamine agonists should not be taken during breast feeding, because breast feeding fails.
- Contraindicated in women who have neurologic symptoms at the time of delivery, because they should be treated with dopamin agonists

## Dopamin agonists resistance prolactinoma

- Not to achieve **normalized prolactin** concentrations and a reduction of more than **50% of the tumor volume** with the maximum dose of **3.5mg** per week of **cabergoline** for **3 months**
- Or
- **bromocriptine** for **6 months** with highest dose tolerated

## • Dopamin agonists resistance prolactinoma (Cont.)

- Resistance of prolactinomas to bromocriptine is more frequent than resistance to cabergoline
- Cabergoline is effective in normalizing prolactin concentrations in 80% of patients resistant to bromocriptine and causes tumor size reductions in 70% of them

- ▶ It is **not clear why** CAB should be so effective in patients resistant to BCR, but this may be due to **cabergoline's** possessing a **higher affinity** for dopamine binding sites, a **longer time** occupying the receptor, and a **slower elimination** from the pituitary. By contrast, the response to **BCR** in a patient **resistant to CAB** is much more **rare** and has only been reported twice .



THANK YOU

