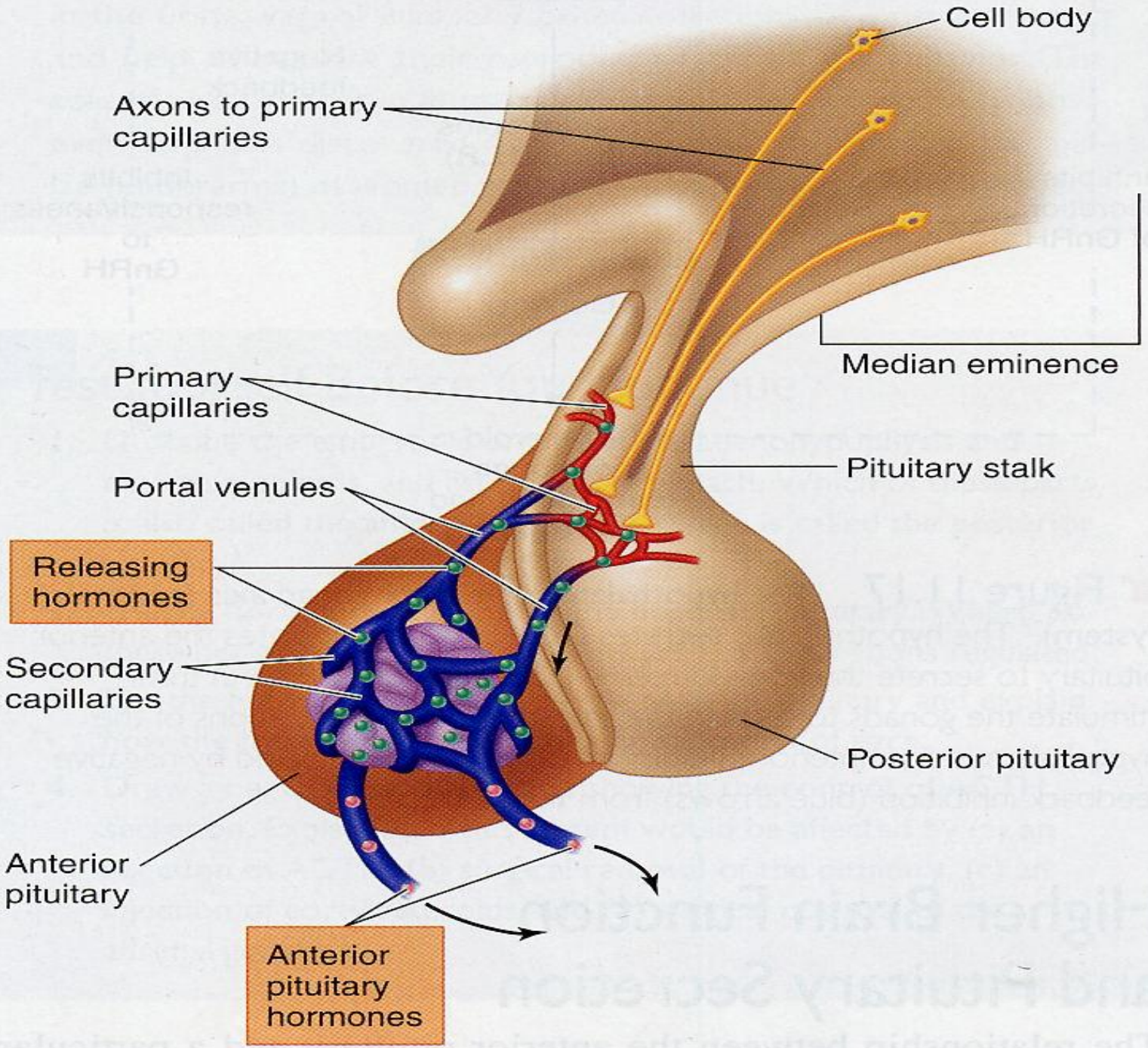
Prolactinoma

Refs.

- *The Journal of Clinical Endocrinology & Metabolism*, 2020, Vol. 105, No. 12, e4558–e4566
- European Journal of Endocrinology, 2020, 182, 177–183
- Pituitary (2020) 23:27–37
- Up to date. updated: Oct 18, 2019
- Front. Endocrinol., 13 November 2018. https://doi.org/10.3389/fendo.2018.00625
- *J Cell Mol Med.* 2018;22:6368–6379.
- Endocrinology, De Groot, Seventh edition, 2016
- Endocrine (2015) 49:242–249


Cell body
Axons to primary capillaries
Median eminence
Primary capillaries
Pituitary stalk
Portal venules
Releasing hormones
Secondary capillaries
Posterior pituitary
Anterior pituitary
Anterior pituitary hormones

Prolactin release

Stimulation

- TRH
- VIP
- Estrogen
- AVP
- Oxytocin
- Epidermal growth factor
- REM sleep (Unknown mechanism)

Neuroendocrine Reflex:

- Suckling in lactating women
- Stress
- Sexual orgasm

Inhibition

- Dopamin

Endocrinology, De Groot, Seventh edition, 2016

Normal prolactin concentration

Women

Up to 20ng/ml

Men

Up to 15ng/ml

Food has only a small effect on serum prolactin concentrations.

Fasting is usually not necessary when having serum prolactin measured. If an initial value is mildly elevated (21 to 40 ng/mL), the measurement should be repeated on a fasting specimen.

Hyperprolactinemia

Physiologic causes:

- Pregnancy
- Postpartum
- Nipple stimulation
- Stress

Hyperprolactinemia

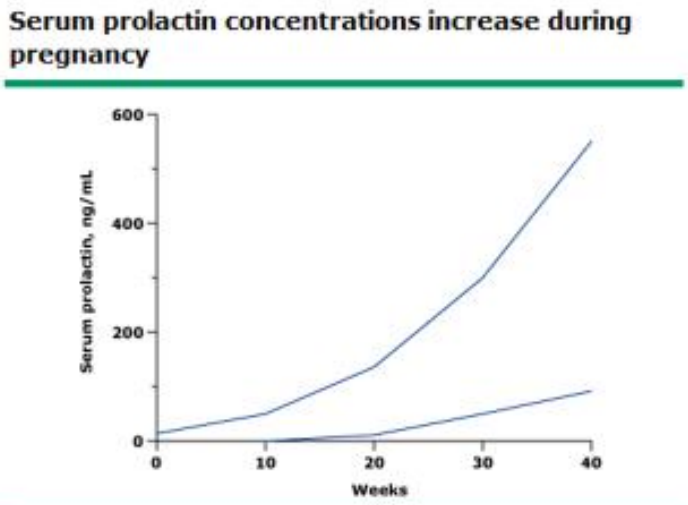
Pathologic causes

- Medications: Phenothiazines, methyldopa, cimetidine, metoclopramide, risperidone
- Hypothyroidism
- CRF (resistance of lactotrophs to dopamine, decreased clearance)
- Estrogen (The amount of estrogen in hormonal contraceptives generally does not cause hyperprolactinemia)
- Chest wall lesions
- Macroprolactin
- Prolactinoma (microprolactinoma or macroprolactinoma)
- Idiopathic hyperprolactinemia

Macroprolactinemia

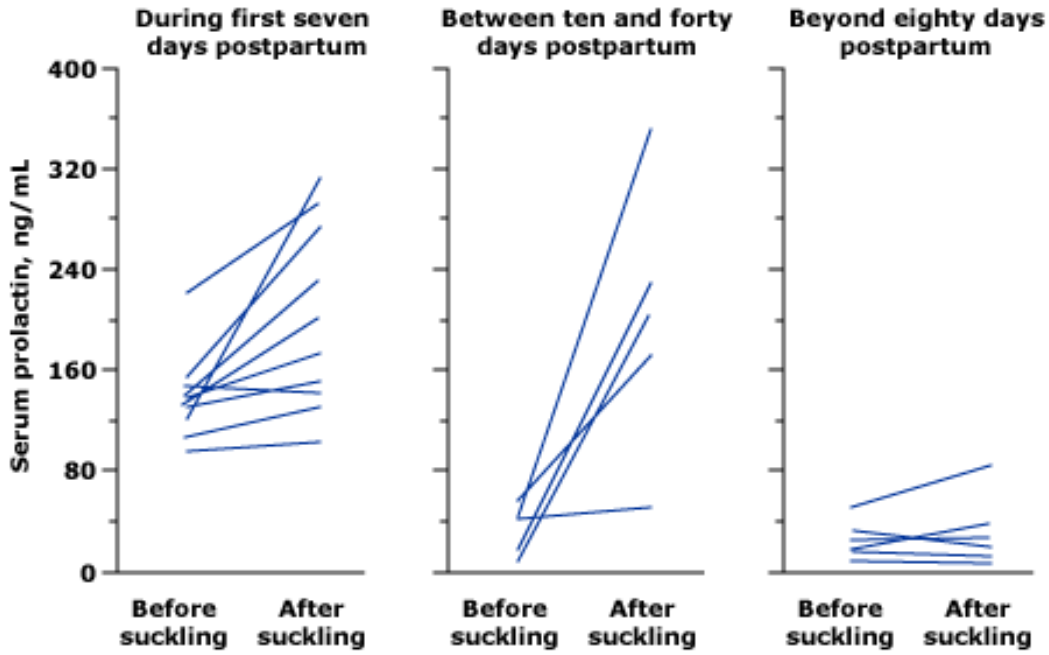
- Aggregates of prolactin and antibodies (in particular, antiprolactin autoantibodies)
- Immunologically detectable but not biologically active
- No clinical abnormality
- A benign clinical condition
- Misdiagnosis of prolactin hypersecretion can be avoided by asking the laboratory to pretreat the serum with polyethylene glycol to precipitate the macroprolactin before the immunoassay for prolactin

Pregnancy (increasing E2 level)



- Peak at delivery
- 35 to 600 ng/mL
- By six weeks after delivery, estradiol secretion has decreased, and the basal serum prolactin concentration is usually normal, even when the mother is breastfeeding

Serum prolactin and suckling



Serum prolactin concentrations basally and in response to suckling as a function of time after delivery. Within the first week after delivery, the basal value is high relative to the nonpregnant state, and there may be a further increase in response to suckling. Several weeks after delivery, the basal value is close to that of the nonpregnant state, but there is still a pronounced increase in response to suckling. Three months after delivery, the basal value is similar to that of the nonpregnant state, and there is a minimal response to suckling, if any.

Data from Tyson JE, Ito P, Guyda H, et al. Studies of prolactin secretion in human pregnancy. Am J Obstet Gynecol 1972; 113:14.

Nipple stimulation and breast exams

- In men, nonlactating women, nipple stimulation, breast imaging (mammography, ultrasound), or breast examination does **not** increase prolactin secretion

- Prolactin may be measured after a breast exam.

Stress

- Stress of any kind increase in the serum prolactin concentration
- Women have greater increase than men
  due their higher serum estradiol
- The magnitude of increase in prolactin is small.
- Rarely exceed 40 ng/mL

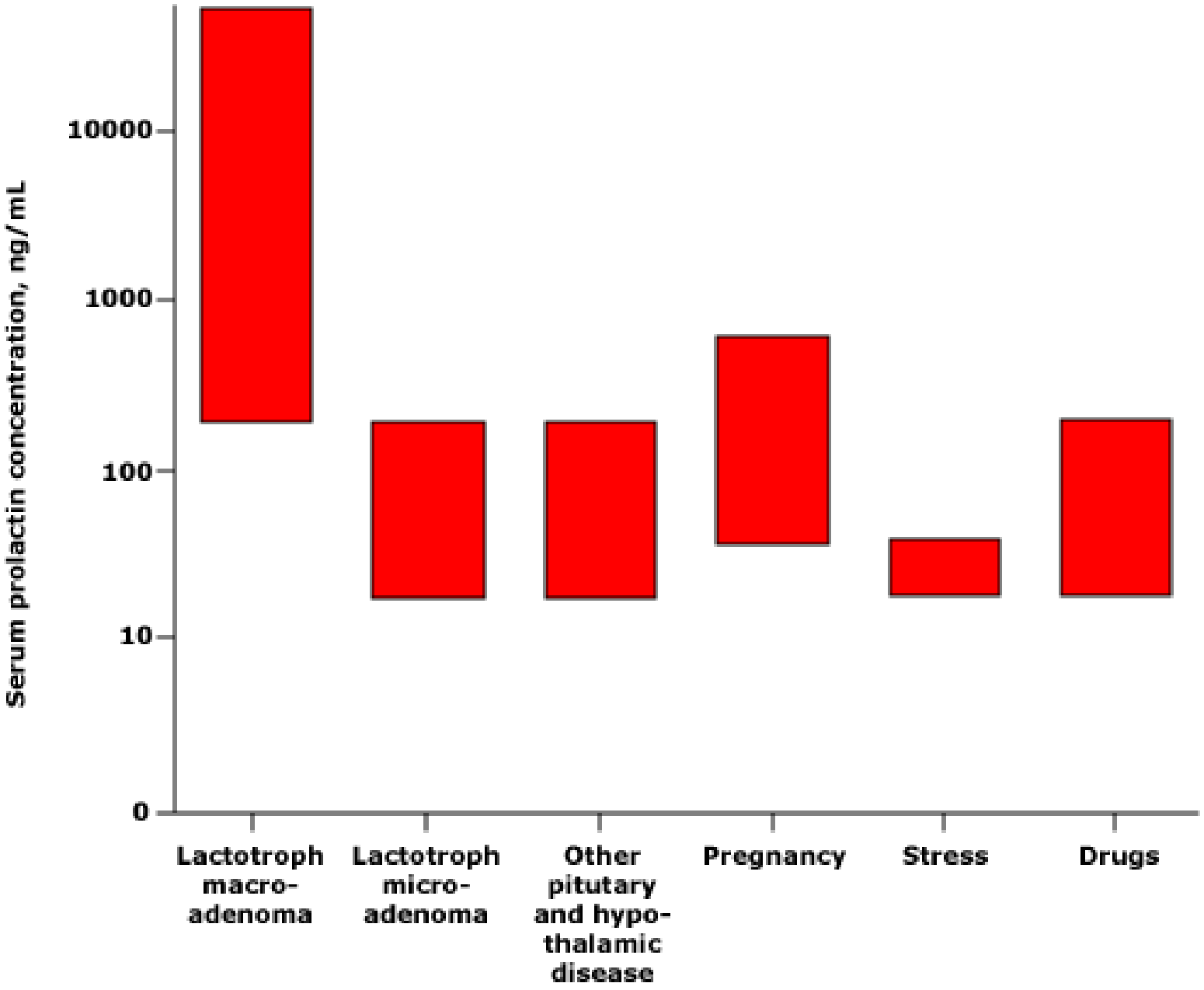
Hypothalamic-pituitary disease

- Lactotroph adenomas (prolactinomas)
- Decreased dopaminergic inhibition of prolactin secretion
- Disease in or near the hypothalamus or pituitary that interferes with the secretion of dopamine or its delivery to the hypophysis

Lactotroph adenomas (prolactinomas)

- Benign tumors of the lactotroph cell
- Serum prolactin range from minimally elevated to 50,000 ng/mL

- Hyperprolactinemia due to other causes, rarely exceed 200 ng/mL


Serum prolactin concentration, ng/mL
10000
1000
100
10
0
Lactotroph macro-adenoma
Lactotroph micro-adenoma
Other pitutary and hypo-thalamic disease
Pregnancy
Stress
Drugs

DRUG INDUCED

- Drugs do not cause lactotroph adenomas
- Serum prolactin concentrations: 25 to 100 ng/mL
- one exception: risperidone, as high as 200 ng/mL

Antipsychotics:

mostly (*dopamine D2 receptor antagonists*): Most common

Serum prolactin concentrations increase within hours after acute administration of these drugs and return to normal within two to four days after cessation of chronic therapy

SSRIs:

Selective serotonin reuptake inhibitors: little, if any, increase in serum prolactin concentration

Others: Metoclopramide and domperidone (*dopamine D2 receptor antagonists*), methyl dopa (*inhibits dopamine synthesis*), Verapamil but not other calcium blockers (unknown mechanism)

Clinical Presentations

- Premenopausal women:

  -Hypogonadism (infertility, oligomenorrhea, or amenorrhea)

  -Galactorrhea
- Postmenopausal women:

  Headaches, impair vision, rarely galactorrhea

- Men:

  -Hypogonadism (decreased energy and libido, decreased muscle mass, body hair, impotence, infertility and osteoporosis)

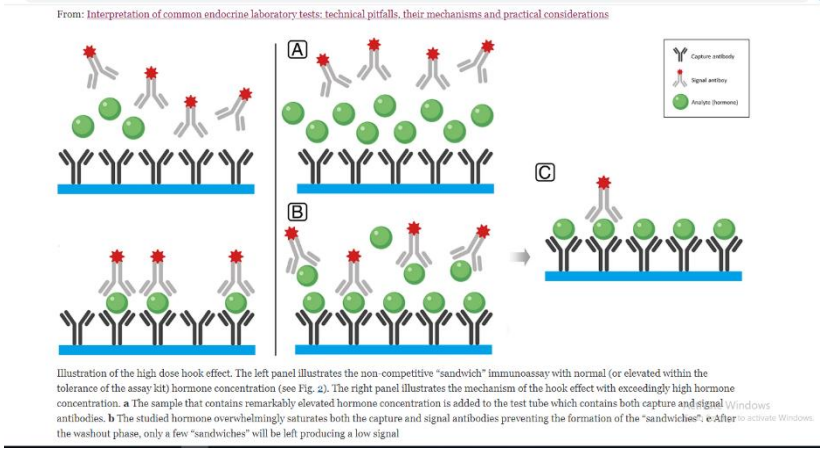
  - Galactorrhea, gynecomastia

  -Headaches, impair vision

Diagnosis

- R/O secondary causes of hyperprolactinemia
- 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



Hook Effect

From: Interpretation of common endocrine laboratory tests: technical pitfalls, their mechanisms and practical considerations

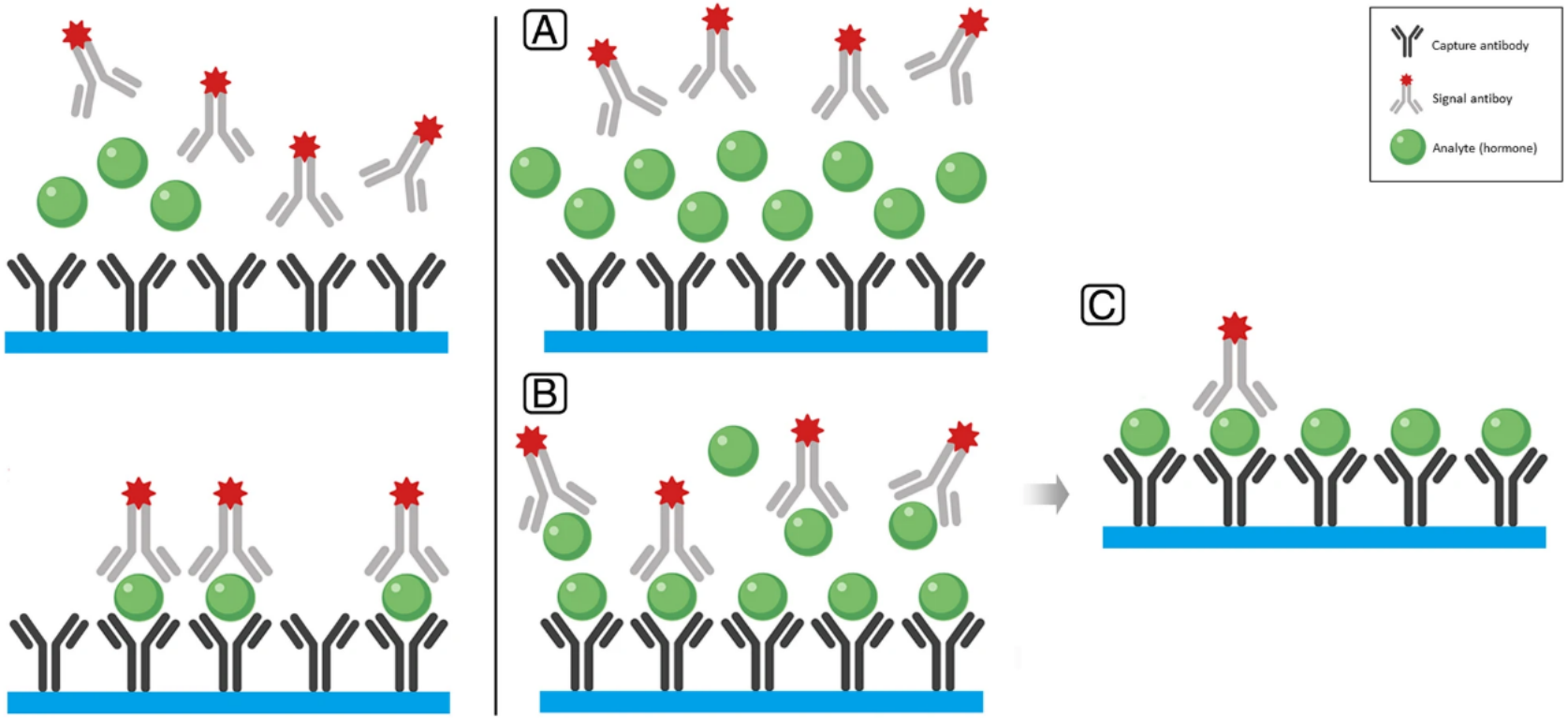


Illustration of the high dose hook effect. The left panel illustrates the non-competitive "sandwich" immunoassay with normal (or elevated within the tolerance of the assay kit) hormone concentration (see Fig. 2). The right panel illustrates the mechanism of the hook effect with exceedingly high hormone concentration. **a** The sample that contains remarkably elevated hormone concentration is added to the test tube which contains both capture and signal antibodies. **b** The studied hormone overwhelmingly saturates both the capture and signal antibodies preventing the formation of the "sandwiches". **c** After the washout phase, only a few "sandwiches" will be left producing a low signal

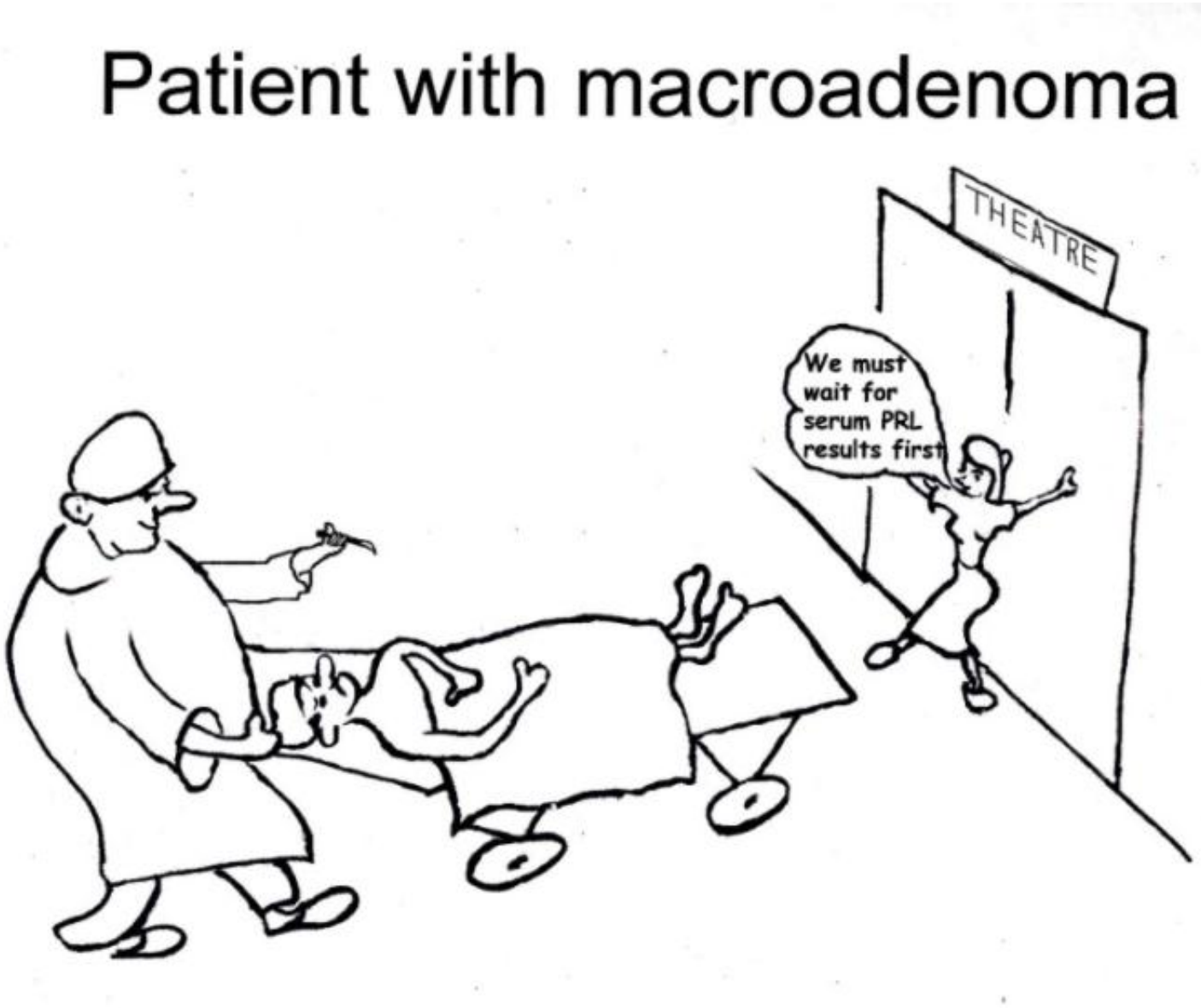
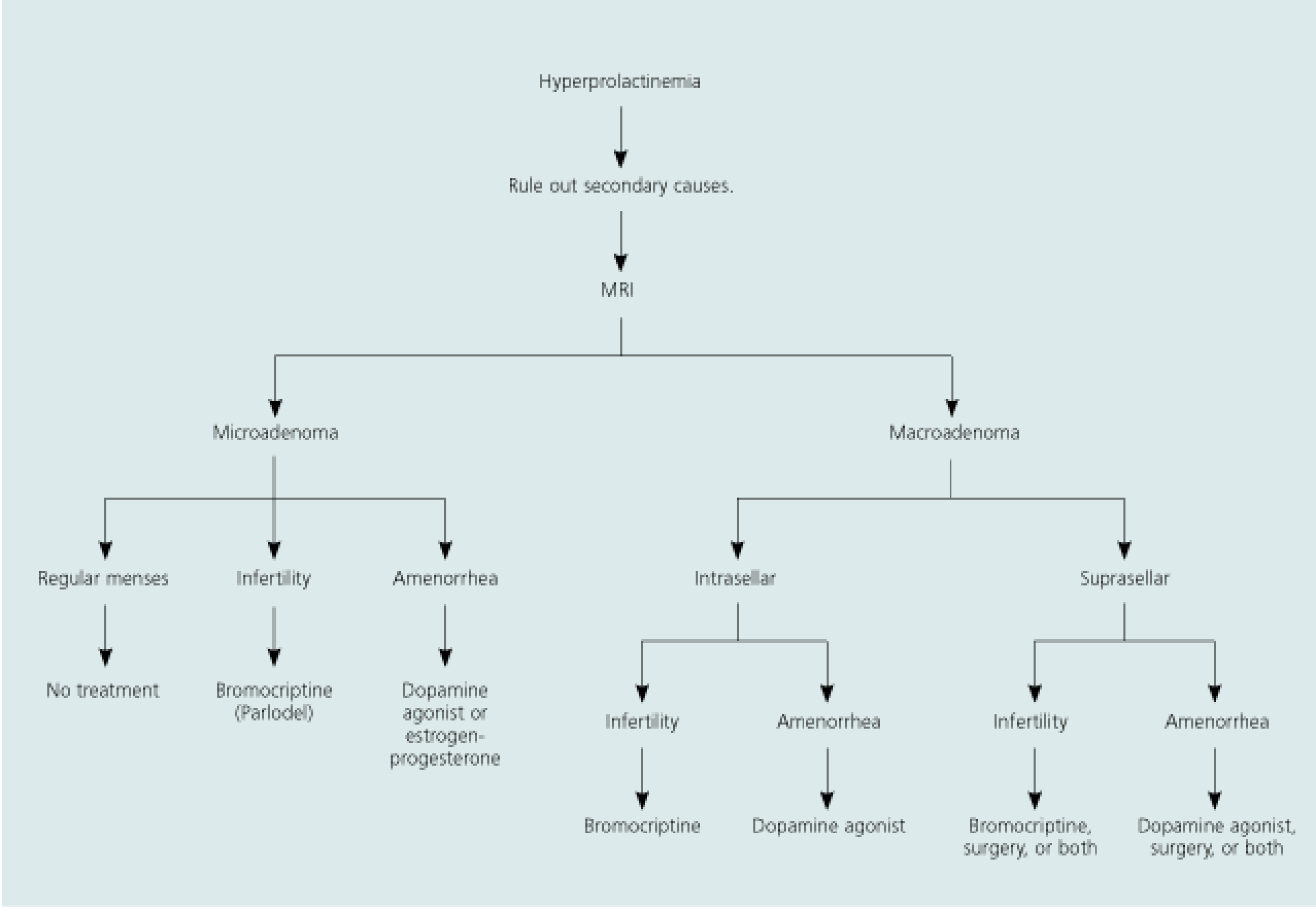


Figure 1.

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


Hyperprolactinemia
Rule out secondary causes.
MRI
Microadenoma
Macroadenoma
Regular menses
Infertility
Amenorrhea
Intrasellar
Suprasellar
No treatment
Bromocriptine (Parlodel)
Dopamine agonist or estrogen-progesterone
Infertility
Amenorrhea
Infertility
Amenorrhea
Bromocriptine
Dopamine agonist
Bromocriptine, surgery, or both
Dopamine agonist, surgery, or both

Treatment of microprolactinoma

Dopamin Agonists

Mechanism of dopamine action

Dopamine agonists reduce the size of prolactinomas and the concentration of prolactin through binding to the dopamine D2 receptor in the tumor cells.

This causes inhibition of cyclic adenosine monophosphate (cAMP) production due to coupling to the Gαi inhibitory protein leading to a decrease in the size of the cells as a result of the reduction of nuclear, nucleolar, and cytoplasmic areas with involutions of the endoplasmic reticulum and Golgi complex. Furthermore, it leads to cell death

Oh MC, Aghi MK. Dopamine agonist–resistant prolactinomas. A review. J Neurosurg. (2011) 114:1369–79. doi: 10.3171/2010.11.JNS101369

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

Postmenopause

- Discountine medication and measure PRL for follow up

- PRL>200 ng/ml: Do MRI

  Clinically important size: resume drug therapy

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

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 untolerable 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

Steroid replacement

- Hypogonadism in premenopausal women with microprolactinoma who can not tolerate or do not respond to dopamine agonists

- Hypogonadism in hyperprolacinemia due to antipsychotic agents

Prolactinoma during pregnancy

Microadenoma

- 5.5% develop neurologic symptoms

Macroadenoma

36% develop neurologic symptoms

Prolactinoma during pregnancy

- Resume dopamin agonist if increased adenoma size impairs vision

- Cabergolin is safe in pregnancy, data is limited

Prolactinoma and pregnancy

Microadenoma

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

Prolactinoma and pregnancy

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 minimum dose of 3.5mg per week of cabergoline for 3 months
- Or
- bromocriptine for 6 months with highest dose tolerated

Tumor volume was calculated using the formula:
(cranio-caudal diameters x laterolateral x antero-posterior) / 2

Front. Endocrinol., 13 November 2018.
https://doi.org/10.3389/fendo.2018.00625

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

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 13 November 2018
doi: 10.3389/fendo.2018.00625

Prolactinomas Resistant to Treatment With Dopamine Agonists: Long-Term Follow-Up of Six Cases

Maria de Fátima de Magalhães Gonzaga[1,2], *Lucas Faria de Castro*[3], *Luciana Ansaneli Naves*[1,3], *José Luiz Mendonça*[4], *Benicio Oton de Lima*[5], *Iruena Kessler*[3,6,7] *and Luiz Augusto Casulari*[1,2]*

Results: Six patients were selected. Three patients were initially treated with bromocriptine prior to treatment with cabergoline. Four patients were men, and two were women. At the time of diagnosis, ages ranged from 9 to 62 years. Initial prolactin concentrations ranged from 430 to 14,992 ng/mL and in the last assessment ranged from 29.6 to 2,169 ng/mL. The tumor volume ranged from 0.77 to 24.0 mm^3. Tumor regression occurred in all patients, ranging from 20 to 100%, but total disappearance of the adenoma with an empty sella occurred in one patient. The maximum weekly doses of cabergoline ranged from 3.0 to 4.5 mg. Follow-up time ranged from seven to 17 years. Normalization of prolactin concentrations occurred only in one woman after 17 years of treatment. Three patients also underwent surgery, but only one woman was cured of the disease.

Conclusion: This study confirms that tumors resistant to dopamine agonists are more aggressive, since we did not have any microadenoma; treatment with high dose of cabergoline may reduce the size of the tumor without its disappearance, and that normalization of prolactin concentration rarely occurs. To our knowledge, this is the longest follow-up of a series of cases with resistance to dopamine agonists.

TABLE 1 | Clinical and laboratory characteristics of the six patients with resistance to dopamine agonists.

Cases	**1**	**2**	**3*†**	**4*†**	**5†**	**6***
Gender	M	M	M	M	F	F
Age (years)	54	62	9	50	22	22
Prolactin (ng/mL)						
Initial	1,947	14,992	2,400	2,600	659	430
Final	353	2,169	44.5	765	367	29.6
Tumor (mm^3)						
Initial	3.75	12.5	24.0	giant‡	0.77	12.6
Final (%)§	95.0	90.0	90.0	90.0	20.0	100.0
Cabergoline (mg/week)						
Initial	1.5	1.0	1.0	1.5	2.0	1.0
Maximum	3.5	3.5	4.5	3.5	3.5	3.0
Final	2.0	2.0	4.5	3.5	–	1.5
Time (months)	180	162	179	180	88	201

**patients initially used bromocriptine; †underwent surgery; ‡measures not available; §percentage reduction of tumor.*

Front. Endocrinol., 13 November 2018.
https://doi.org/10.3389/fendo.2018.00625

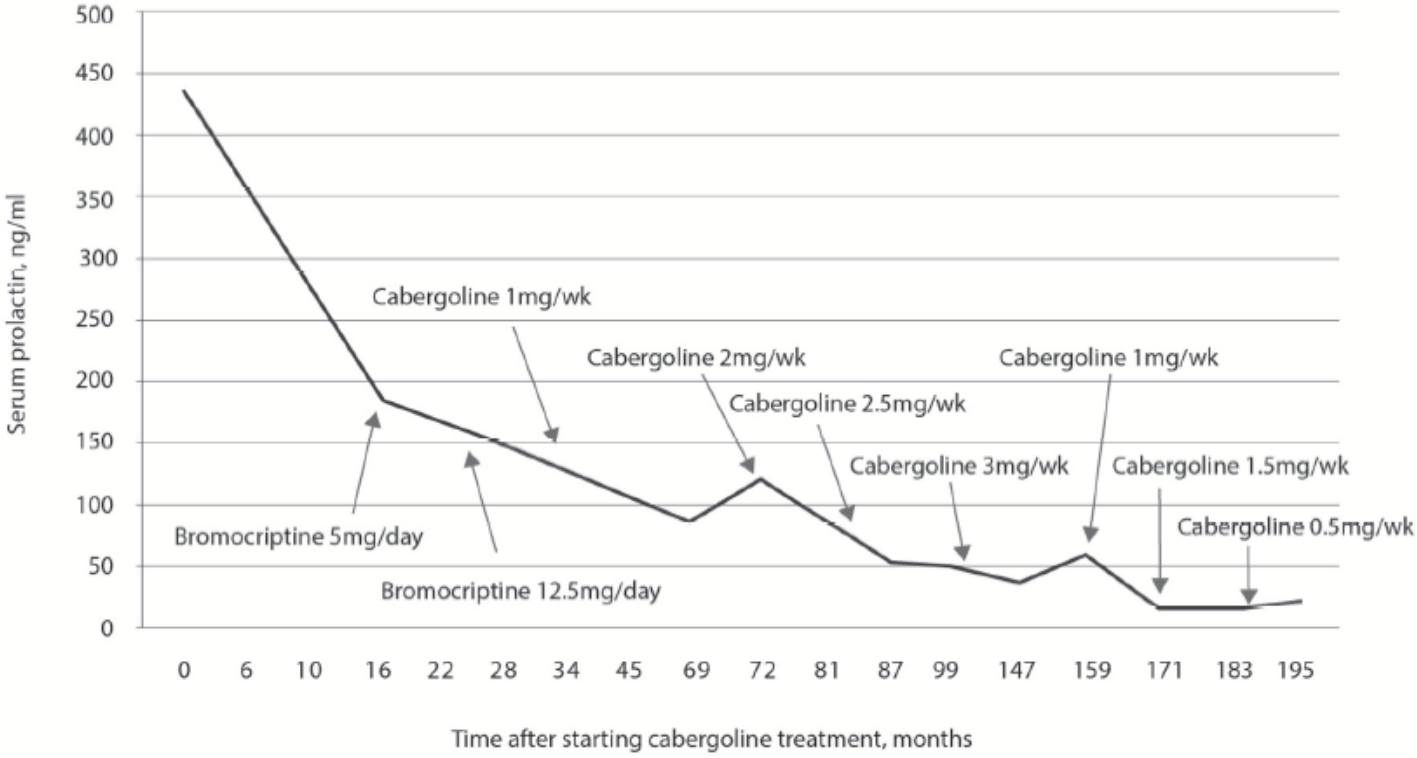


FIGURE 11 | Plasma prolactin concentrations during treatment with dopamine agonists. It was observed that even with a dose of 12.5 mg of bromocriptine over 28 months, prolactin concentrations were not normalized; replacement with cabergoline only normalized prolactin concentrations 14 years after starting the treatment with this drug.

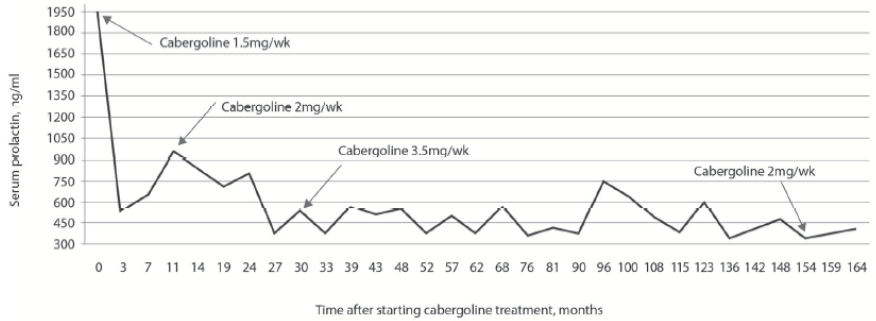


FIGURE 1 | Prolactin concentration in response to treatment with cabergoline over 14 years and 6 months. Prolactin concentrations were never normalized, even while using a dose of 3.5 mg per week of cabergoline for 10 years; after 13 years of treatment, decreasing the weekly dose to 2 mg maintained prolactin concentrations at values similar to those observed for a dose of 3.5 mg.

Front. Endocrinol., 13 November 2018.
https://doi.org/10.3389/fendo.2018.00625

ELSEVIER

World Neurosurgery

Volume 115, July 2018, Pages 94-98

Case Report

Combination Treatment with Bromocriptine and Metformin in Patients with Bromocriptine-Resistant Prolactinomas: Pilot Study

Xiaohai Liu [1], Yang Liu [1, 2], Jun Gao [1], Ming Feng [1], Xinjie Bao [1], Kan Deng [1], Yong Yao [1], Renzhi Wang [1]

Metformin: 1.5 g/day

Case Description

This study is a retrospective review of 2 cases including 1 patient with prolactinoma who was resistant to bromocriptine, diagnosed with impaired glucose tolerance, and administered metformin. Surprisingly, combining the patient's treatment with metformin decreased prolactin (PRL) levels to 12 ng/mL and significantly decreased the size of the tumor after 1 year of combination therapy. As menstruation resumed and galactorrhea resolved, the patient became pregnant and stopped using metformin but continued taking bromocriptine. She gave birth to a healthy boy in August 2016. After delivery, she decided to breastfeed the baby and only took bromocriptine. After 14 months of using bromocriptine alone, her PRL level increased to 208 ng/mL and the tumor reappeared (7 mm × 8 mm × 9 mm). Interestingly, the patient's PRL level decreased from 208 ng/mL to 150 ng/mL 2 months after using combination treatment with bromocriptine and metformin. On the basis of these findings, a second bromocriptine-resistant patient was recruited. After 3 months of combined treatment with bromocriptine and metformin, the patient's PRL level decreased to 2.08 ng/mL, testosterone levels increased significantly, and the tumor size decreased.

Highlights

- We reported 2 patients with bromocriptine-resistant prolactinomas who were administrated bromocriptine combined with metformin and subsequently exhibited improved prolactin levels and remarkable tumor shrinkage.
- Metformin might be a novel therapeutic target for prolactinomas and is not associated with any apparent complications.
- The mechanism for this effect remains unidentified and needs more investigation.

Endocrine (2015) 49:242–249
DOI 10.1007/s12020-014-0428-2

ORIGINAL ARTICLE

The effect of short-term metformin treatment on plasma prolactin levels in bromocriptine-treated patients with hyperprolactinaemia and impaired glucose tolerance: a pilot study

Robert Krysiak · Joanna Okrzesik · Boguslaw Okopien

4 months of metformin treatment
(2.55–3 g daily)

In patients with hyperprolactinaemia, but not in the other groups of patients, metformin slightly reduced plasma levels of prolactin, and this effect correlated weakly with the metabolic effects of this drug

Table 1 Baseline characteristics of patients

Variable	Bromocriptine-treated patients with hyperprolactinaemia (Group A)	Bromocriptine-treated patients with normal prolactin levels (Group B)	Control group (Group C)
Number of patients	12	14	15
Age [years; mean (SD)]	32 (3)	31 (4)	32 (4)
Women [%]	75	71	80
Smokers [%]	25	29	27
Duration of bromocriptine treatment [months; mean (SD)]	11 (2)***	12 (3)***	0 (0)
Bromocriptine dose [mg; mean (SD)]	6.4 (1.3)***	6.2 (1.2)***	0 (0)
Body mass index [kg/m^2; mean (SD)][a]	28.3 (2.4)	28.9 (2.2)	27.9 (2.0)
Waist-hip ratio [mean (SD)][b]	0.92 (0.08)	0.94 (0.07)	0.91 (0.06)
Systolic blood pressure [mmHg; mean (SD)][c]	129 (10)	127 (11)	125 (9)
Diastolic blood pressure [mmHg; mean (SD)][c]	84 (4)	81 (3)	82 (3)
Hypertension [%][d]	25	21	20
Prolactin-secreting tumours [%]	67***	57***	0
Fasting glucose [mmol/L; mean (SD)]	4.81 (0.25)	4.72 (0.23)	4.77 (0.21)
2-h postchallenge plasma glucose [mmol/L; mean (SD)]	9.72 (0.63)	9.17 (0.80)	9.32 (0.70)
HOMA-IR [mean (SD)]	5.0 (0.5)	4.7 (0.4)	4.6 (0.5)
Glycated haemoglobin [%; mean (SD)]	6.1 (0.2)	6.0 (0.2)	6.0 (0.2)
Total cholesterol [mmol/L; mean (SD)]	5.56 (0.61)	5.62 (0.52)	5.51 (0.58)
LDL-cholesterol [mmol/L; mean (SD)]	3.31 (0.42)	3.25 (0.32)	3.19 (0.28)
HDL-cholesterol [mmol/L; mean (SD)]	1.12 (0.18)	1.25 (0.15)	1.19 (0.16)
Triglycerides [mmol/L; mean (SD)]	2.56 (0.38)	2.43 (0.35)	2.40 (0.31)
Prolactin [ng/mL; mean (SD)]	46 (10)***###	12 (4)	14 (3)
IGF-1 [ng/mL; mean (SD)]	235 (61)	195 (43)	189 (41)
Thyrotropin [mIU/L; mean (SD)]	2.0 (0.7)	1.5 (0.4)	1.4 (0.5)

Only data of individuals who completed the study were included in the final analyses

[a] Weight in kilograms divided by the square of the height in meters [25]

[b] The ratio of the circumference of the waist (the midpoint between the lower margin of the last palpable rib and the top of the iliac crest) to that of the hips (the widest portion of the buttocks) [25]

[c] Average of two blood pressure measurements taken in the sitting position, spaced 2 min apart,after at least 5 min of rest [26]

[d] Blood pressure greater than 140/90 on two or more blood pressure readings taken at each of two or more visits after initial screening [26]

*** $p < 0.001$ versus control subjects (group C)

$p < 0.001$ versus bromocriptine-treated patients with normal prolactin levels (group B)

Table 2 The effect of metformin on glucose homeostasis markers, plasma lipids and the investigated pituitary hormones in bromocriptine-treated patients and the control group

Variable	Bromocriptine-treated patients with hyperprolactinaemia (Group A)	Bromocriptine-treated patients with normal prolactin levels (Group B)	Control group (Group C)
	Mean (SD) [Δ %]	Mean (SD) [Δ %]	Mean (SD) [Δ %]
Fasting glucose [mmol/L]			
Baseline	4.81 (0.25)	4.72 (0.23)	4.77 (0.21)
After 4 months	4.56 (0.30) [−5]	4.51 (0.24) [−4]	4.58 (0.26) [−4]
2-h postchallenge plasma glucose [mmol/L]			
Baseline	9.72 (0.63)	9.17 (0.80)	9.32 (0.70)
After 4 months	7.94 (0.56) [−18]***	7.78 (0.52) [−15]***	7.72 (0.76) [−17]***
HOMA-IR			
Baseline	5.0 (0.5)	4.7 (0.4)	4.6 (0.5)
After 4 months	3.4 (0.4) [−32]***	3.1 (0.4) [−34]***	3.2 (0.4) [−30]***
Glycated haemoglobin [%]			
Baseline	6.1 (0.2)	6.0 (0.2)	6.0 (0.2)
After 4 months	5.5 (0.2) [−10]***	5.6 (0.2) [−7]**	5.5 (0.3) [−8]**
Total cholesterol [mmol/L]			
Baseline	5.56 (0.61)	5.62 (0.52)	5.51 (0.58)
After 4 months	5.38 (0.58) [−3]	5.34 (0.48) [−5]	5.28 (0.51) [−4]
LDL-cholesterol [mmol/L]			
Baseline	3.31 (0.42)	3.25 (0.32)	3.19 (0.28)
After 4 months	3.16 (0.38) [−5]	3.08 (0.29) [−5]	3.01 (0.26) [−6]
HDL-cholesterol [mmol/L]			
Baseline	1.12 (0.18)	1.25 (0.15)	1.19 (0.16)
After 4 months	1.24 (0.16) [11]	1.35 (0.18) [8]	1.30 (0.14) [9]
Triglycerides [mmol/L]			
Baseline	2.56 (0.38)	2.43 (0.35)	2.40 (0.31)
After 4 months	2.16 (0.28) [−16]*	2.06 (0.32) [−15]*	2.08 (0.34) [−13]*
Prolactin [ng/mL]			
Baseline	46 (10)***###	12 (4)	14 (3)
After 4 months	34 (8) [−26]***###	11 (4) [−8]	12 (3) [−14]
IGF-1 [ng/mL]			
Baseline	235 (61)	195 (43)	189 (41)
After 4 months	220 (62) [−6]	185 (40) [−5]	176 (29) [−7]
Thyrotropin [mIU/L]			
Baseline	2.0 (0.7)	1.5 (0.4)	1.4 (0.5)
After 4 months	1.6 (0.6) [−20]	1.3 [−13]	1.2 [−14]

Only data of individuals who completed the study were included in the final analyses

*** $p < 0.001$ versus control subjects (group C)

$p < 0.001$ versus bromocriptine-treated patients with normal prolactin levels (group B)

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$ versus baseline value

Received: 21 April 2018 | Revised: 2 September 2018 | Accepted: 20 September 2018

DOI: 10.1111/jcmm.13963

ORIGINAL ARTICLE

WILEY

Metformin inhibits growth and prolactin secretion of pituitary prolactinoma cells and xenografts

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Abstract

Metformin (MET) is a diabetes drug that activates AMP-activated protein kinase (AMPK), and is suggested to have anticancer efficacy. Here, we investigated the role of AMPK signalling in prolactinoma (PRLoma), with particular respect to MET and bromocriptine (BC) as a PRLoma treatment. We analysed AMPK phosphorylation, dopamine D2 receptor (D2R), and oestrogen receptor (ER) expression in both BC-sensitive and -resistant PRLoma samples; effects of the AMPK agonist MET (alone or with BC) on in vitro proliferation and apoptosis, xenograft growth and prolactin (PRL) secretion of BC-sensitive and -resistant cells, and ER expression in xenografts. Some BC-resistant PRLomas showed high D2R expression but extremely low AMPK activation. MET significantly inhibited proliferation of cultured PRLoma cells; MET + BC notably restrained their PRL secretion. MET + BC further decreased tumour growth and serum PRL levels in xenografts than BC treatment alone. ER was down-regulated after AMPK activation in both cultured cells and xenografts. Together, we propose that the AMPK signalling pathway down-regulates ERα and ERβ, and suppresses PRLoma growth as well as PRL secretion. Combined MET + BC is a potential treatment for PRLomas.

KEYWORDS

AMPK, bromocriptine, drug-resistant prolactinomas, metformin, oestrogen receptor

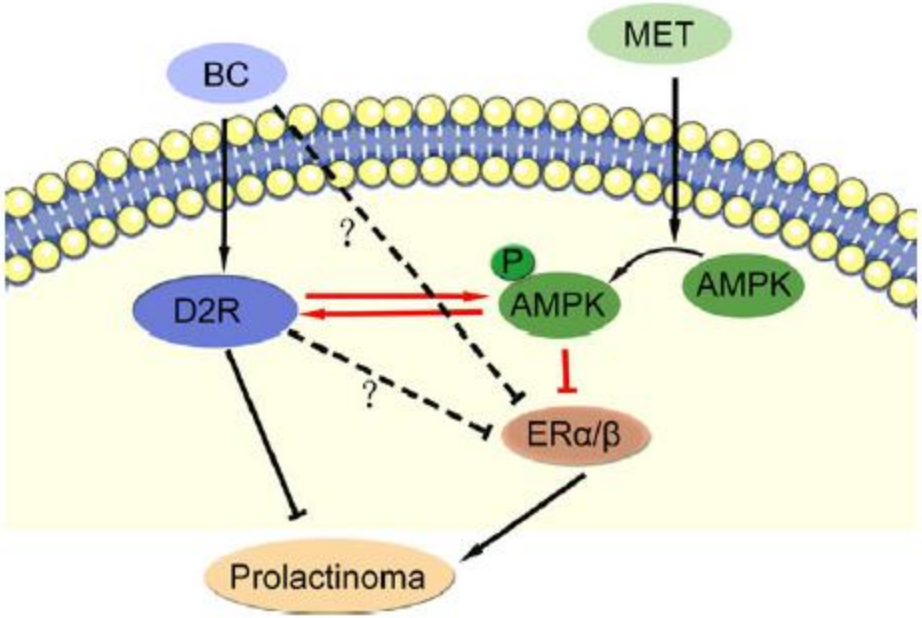

FIGURE 8 Schematic representation of metformin/AMPK/ER signalling pathway and its potential crosstalk with bromocriptine/D2R pathway in prolactinoma treatment. Red arrow/line refers to regulatory relationship proposed in this study. Dashed line with question mark refers to potential AMPK-independent pathway for BC/D2R to regulate ER expression

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Dopamine agonist resistant prolactinomas: any alternative medical treatment?

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Abstract

Consensus guidelines recommend dopamine agonists (DAs) as the mainstay treatment for prolactinomas. In most patients, DAs achieve tumor shrinkage and normoprolactinemia at well tolerated doses. However, primary or, less often, secondary resistance to DAs may be also encountered representing challenging clinical scenarios. This is particularly true for aggressive prolactinomas in which surgery and radiotherapy may not achieve tumor control. In these cases, alternative medical treatments have been considered but data on their efficacy should be interpreted within the constraints of publication bias and of lack of relevant clinical trials. The limited reports on somatostatin analogues have shown conflicting results, but cases with optimal outcomes have been documented. Data on estrogen modulators and metformin are scarce and their usefulness remains to be evaluated. In many aggressive lactotroph tumors, temozolomide has demonstrated optimal outcomes, whereas for other cytotoxic agents, tyrosine kinase inhibitors and for inhibitors of mammalian target of rapamycin (mTOR), higher quality evidence is needed. Finally, promising preliminary results from in vitro and animal reports need to be further assessed and, if appropriate, translated in human studies.

Treatment of dopamin agonists resistance prolactinoma

- Switching to another dopamine agonist
- Increasing the dose of the agonist above the dose recommended by themanufacturer, i.e., a dose of 3.5mg per week was used, which is above the recommended dose of 2.0mg
- Surgical resection of the tumor
- Adjuant radiotherapy (after surgery)
- Alternative medical treatment:
- - Metformin?
- - Estrogen modulators?
- - Somatostatin analogues (not useful)
- - Temozolomide, *other cytotoxic agents, tyrosine kinase inhibitors and for inhibitors of mammalian target of rapamycin (mTOR)* (for aggressive lactotroph tumors)

Conclusion:

- Treatment prolactinoma:
- Dopamine agonists
- Surgical resection of the tumor
- Adjuant radiotherapy (after surgery)
- Alternative medical treatment:
- - Alternative medical treatment:
- - Metformin?
- - Estrogen modulators?
- - Temozolomide, *other cytotoxic agents, tyrosine kinase inhibitors and for inhibitors of mammalian target of rapamycin (mTOR)* (for aggressive lactotroph tumors)