Question 99

A 60-year-old woman has been on continuous combined hormone replacement therapy since menopause. She complains of mental slowing, weight gain, insomnia, and headaches in the last six months. Her general practitioner has commenced her on nortriptyline one month ago without improvement in symptoms.

The following results are obtained:

- Serum prolactin 1900 mIU/L [30-450]
- Serum luteinizng hormone 0.3 IU/L [premenopausal: 0.4-9.0]
- Serum follicle-stimulating hormone (FSH) 0.5 IU/L [premenopausal: 1.0-9.0]
- Serum thyroid-stimulating hormone (TSH) 2.1 mIU/L [0.4-4.0]
- Free thyroxine (free T4) 8 pmol [10-23]

The best explanation for these results is:

A. nortriptyline therapy
B. depression
C. prolactin-secreting pituitary microadenoma

**D. non-functioning pituitary macroadenoma**

E. hormone replacement therapy

A bit of a tricky one, I probably would have gone straight for C. but the answer is D because of her presentation with symptoms of mass effect.

This lady has prolactineamia

Prolactin secretion
- Prolactin is secreted by the lactotrophs in the anterior pituitary gland.
- Prolactin secretion is regulated by the hypothalamus.
- Hypothalamic influence is predominantly of tonic inhibition via the secretion of a prolactin-release-inhibiting factor (PIF) and a prolactin-releasing factor (PRF).
- PIF is dopamine,
- The nature of the physiological PRF is unclear. Thyrotropin-releasing hormone (TRH) can act as a PRF. Other candidates include vasoactive intestinal peptide (VIP) and PHM-27.

Clinical manifestations of hyperprolactinaemia
- Direct effects of excess prolactin
  - Induction of galactorrhea or hypogonadism.
    - The incidence of galactorrhea in hyperprolactinemic patients is between 30% and 80%.
    - Approximately 50% of women with galactorrhea, however, have normal prolactin
    - Women with hyperprolactinaemia usually present with menstrual abnormalities – amenorrhea or oligomenorrhea – or regular cycles with infertility. Occasionally, patients may present with menorrhagia.
  - The effects of the structural lesion causing the disorder (i.e. the pituitary tumor), leading to, for example, headaches, visual field defects, or external ophthalmoplegia:
    - Men often present late in the course of the disease with symptoms of expansion of their pituitary tumor (i.e. headaches, visual defects, and external ophthalmoplegia)
  - Associated dysfunction of secretion of other anterior pituitary hormones
    - Eg secondary adrenal or thyroid failure.
Physiological Causes

- Pregnancy — The probable cause of the hyperprolactinemia is the increasing serum estradiol concentrations during pregnancy.
- Nipple stimulation — Nipple stimulation increases serum prolactin concentrations, presumably via a neural pathway.
- Stress — Stress of any kind, physical or psychologic, can cause an increase in the serum prolactin concentration.

Pathological Causes

**Hypothalamic Dopamine Deficiency**

Diseases of the hypothalamus such as tumors, arterio-venous malformations, and inflammatory processes such as sarcoidosis result in either diminished synthesis or release of dopamine. Furthermore, certain drugs (e.g. alpha-methyldopa and reserpine) are capable of depleting the central dopamine stores.

**Defective Transport Mechanisms**

Section of the pituitary stalk results in impaired transport of dopamine from the hypothalamus to the lactotrophs. Pituitary or stalk tumors with abnormal blood supplies, or their pressure effects, may interfere with the circulatory pathway from the hypothalamus down the pituitary stalk to the normal lactotrophs or a tumor, producing effective dopamine deficiency due to a functional stalk section.

**Lactotroph Insensitivity to Dopamine**

Dopamine receptors have been found on human pituitary lactotroph adenoma cells. Receptor sensitivity to dopamine may be diminished, which would explain the lack of response to increased endogenous dopamine stimulation; however, an obvious response of the receptors to pharmacologic dopamine agonists makes this possibility less likely. Certain drugs act as dopamine-receptor-blocking agents, including phenothiazines (e.g. chlorpromazine), butyrophenones (haloperidol), and benzamides (metoclopramide, sulpiride, and domperidone). These drugs block the effects of endogenous dopamine and thus release lactotrophs from their hypothalamic inhibition. This sequence of events results in hyperprolactinemia.

**Stimulation of Lactotrophs**

Hypothyroidism may be associated with hyperprolactinemia. If hypothyroidism results in increased TRH production, then TRH (which can act as a PRF) could lead to hyperprolactinemia. Estrogens act directly at the pituitary level, causing stimulation of lactotrophs, and thus enhance prolactin secretion. Furthermore, estrogens increase the mitotic activity of lactotrophs, increasing cell numbers. Injury to the chest wall can also lead to hyperprolactinemia; this results from abnormal stimulation of the reflex associated with the rise in prolactin that is seen normally in lactating women during suckling.

- Lactotroph adenomas (prolactinomas)
  - benign tumors of the lactotroph cell.
  - Most adenomas that secrete prolactin and cause hyperprolactinemia are comprised solely of lactotroph cells; however, about 10 percent are comprised of both lactotroph and either somatotroph or somatomammothroph cells and therefore secrete growth hormone as well as prolactin
  - relatively common, accounting for approximately 30 to 40 percent of all clinically recognized pituitary adenomas.
  - Women more than men
  - Age 20 - 40
  - rarely occur as part of the multiple endocrine neoplasia type 1 syndrome

- Decreased dopaminergic inhibition of prolactin secretion.
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- damage to the dopaminergic neurons of the hypothalamus, pituitary stalk section
  - Tumors of the hypothalamus, both benign (eg, craniopharyngiomas) and malignant (eg, metastatic breast carcinoma)
  - Infiltrative diseases of the hypothalamus (eg, sarcoidosis)
  - Section of the hypothalamic-pituitary stalk (eg, due to head trauma or surgery)
  - Adenomas of the pituitary other than lactotroph adenomas
- drugs that block dopamine receptors on lactotroph cells.
  - Dopamine D2 receptor antagonists: risperidone; phenothiazines; haloperidol; butyrophenones; metoclopramide; sulpiride and domperidone
  - Antihypertensive drugs: methldopa and reserpine
  - Verapamil
  - SSRIs cause little if any increase in the serum prolactin concentration

- Other conditions, including decreased clearance of prolactin
  - Estrogen — Estrogen increases prolactin secretion proportionate to the degree of estrogenization. Greater amounts of estrogen, such as occur in pregnancy, increase basal serum prolactin concentrations. The amount of estrogen in hormonal contraceptives generally does not cause hyperprolactinemia.
  - Hypothyroidism — Hypothyroidism predisposes to hyperprolactinemia. However, basal serum prolactin concentrations are normal in most hypothyroid patients and only the serum prolactin response to stimuli, such as TRH (thyrotropin-releasing hormone), is increased. In the few hypothyroid patients who have elevated basal serum prolactin concentrations, the values return to normal when the hypothyroidism is corrected. It is important to recognize hypothyroidism as a potential cause of an enlarged pituitary gland (due to thyrotroph hyperplasia, lactotroph hyperplasia, or both) and hyperprolactinemia, and not to confuse this entity with a lactotroph adenoma. The mechanism of hyperprolactinemia in hypothyroidism is not known. Both enhanced hypothalamic synthesis of TRH and increased pituitary responsiveness to TRH have been described.
  - Chest wall injury — Chest wall injuries, such as severe burns, increase prolactin secretion, presumably due to a neural mechanism similar to that of suckling
  - Chronic renal failure — The serum prolactin concentration is high in patients who have chronic renal failure and returns to normal after renal transplantation [35].
  - Idiopathic hyperprolactinemia — In a substantial number of patients whose serum prolactin concentration is between 20 and 100 ng/mL (100 mcg/L SI units), no cause can be found.
  - Macroprolactinemia — large molecules of prolactin rare

Answers:

Note they did not list hypothyroidism as an option which they could have. The reason it would have been incorrect in this situation is the TSH would have had to be very high to mimic the effects of prolactin releasing factor

A. nortriptyline therapy
A TCA – not specifically known for its dopamine receptor blocker although mims suggests galactorea is a possible side effect. Not the best explanation

B. depression
Depression is not an independent risk factor for prolactinaemia although I’m sure many people with hyperprolactinaemia have depression. Not the best explanation

C. prolactin-secreting pituitary microadenoma

D. non-functioning pituitary macroadenoma
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Either C or D are possible. D is more likely as the presentation describes issues of mass effect ie headache and associated dysfunction of secretion of other anterior pituitary hormones - eg TSH

E. hormone replacement therapy
Estrogen increases prolactin secretion proportionate to the degree of estrogenization. Given her FSH and LH are low it would seem that this is not the best explanation