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Hyperprolactinemia

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Abstract

Hyperprolactinemia is frequently diagnosed endocrine problem in routine clinical practice. Once hyperprolactinemia is suspected, repeat test for s prolactin can be done with appropriate precondition for sampling like rest, single prick, adequate light etc. to exclude macroprolactinemia specially in asymptomatic or unrelated symptoms. Once diagnosed as Hyper prolactinemia, secondary causes should be ruled out by history, specially drugs. Pregnancy should be excluded by history and if indicated, by test. Mild elevation of s prolactin can be also due to Polycystic Ovary Syndrome (PCOS), hypothyroidisom, CKD, CLD etc. Of course Hook Effect should be kept in mind.

Contrast MRI should be done to see if there is any prolactinoma or hyperplasia. Sometimes Growth Hormone (GH) secreting tumors may be associated. Rarely extra pituitary tumors or disconnection of hypothalamus-pituitary may be seen. In symptomatic patient (hypogonadism, infertility, menstrual disturbances, sexual weakness, unexplained low bone mass and sometimes galactorrhoea etc) and specially if s prolactin is more than 2-3 times of upper limit of reference range, MRI with contrast should be done.

Medical therapy with dopamine agonist is the treatment of choice for symptomatic any level of s prolactin and with prolactinoma. Cabergoline may be tried as a first line of treatment because it is more effective and better tolerated than bromocryptine. Though cabergoline is coming up with safety issues, bromocriptine has the largest safety database in pregnancy till date. All patient should be tried with medical treatment, specially cabergoline irrespective of symptoms and size of the tumor. Transsphenoidal microsurgery remains second option when medical treatment is ineffective. Radiotherapy may be the last adjuvant in the management . Rarely malignant prolactinoma may be found and have poor response to medical treatment.

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Introduction:

Prolactin (PRL) is a protein hormone secreted by the lactotroph cells of the pituitary.[1,2] The gene encoding PRL is unique and it is located in Chromosome 6.[3] Though from the time of Hippocrates (Aforisms, Section 5 # 39) it is said that" If a woman is neither pregnant nor has given birth, and produces milk, her menstruation has stopped" , until 1970 the identification of PRL in human was elusive and it was not clearly distinct from GH, because human GH is highly lactogenic and active in bioassays used to isolate and measure PRL and also because GH is present in human pituitary gland in much higher concentration than Prolactin (PRL 100 mcg Vs hGH 5 to 10 mg).[4] Afterwards the association of Hyperprolactinemia with menstrual irregularities, galactorrhoea and infertility and decreased libido were described in 1930s.

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Epidemiology: The prevalence of hyperprolactinemia in women with secondary amenorrhea or oligomenorrhorea is estimated to be 10-25%. Hyperprolactinemia is noted in 30 % of women with galactorrhoea and infertility and in 75% of those with both amenorrhea and galactorrhoea.[5]

The Lactotroph Cells: The lactotroph cells comprise 15 to 25% of functioning anterior pituitary cells. Somatomammotroph cells expressing both PRL and GH arise from the acidophilic stem cells. Somatotrophs are located predominantly in the lateral wings of the gland and comprise 35% to 45% of pititary cells.[6]

Prolactin Structure: The Prolactin is a 199 amino acid polypeptide containing three intermolecular bonds. It circulates in the blood in various forms including the 23 kd monomeric PRL (Little Prolactin) 48 - to 56 - kd dimeric PRL (bog Prolactin and polymeric form of larger than 100-kd (big, big PRL). Monomeric form is the most bioactive Prolactin.[7]

Regulation: The hormone Prolactin is under the inhibitory control of dopamine which is largely secreted

by infundibular cells and hypothalamic dopaminergic system. Lacking of insensitivity to D2 receptor will develop hyperprolactinemia and lactotroph adenoma [8]. Several substances acts as PRL releasing factor like FGF(fibroblast Growth Factor), EGF (epidermal GF). VIP, Oxytocin, TRH, Estrogen, Opiates, GnRH etc also stimulates PRL secretion. The production range of PRL from 200 to 536 mcg/day per Square meter, clears from the blood rapidly, half life ranging from 26-47 minutes. It is secreted episodically 4 to 14 pulses in 24 hours. The highest level is achieved during sleep and lowest during daytime from 10 AM to noon.[9]

Function of Prolactin: Most important function in human is milk production and secretion during pregnancy and lactation. It has got also some action in mammary development, reproduction and few metabolic effects. It also acts on immune system, menstruation regulation etc. In male subjects with hyperprolactinemia LH and FSH pulsatility is attenuated, testosterone level is suppressed and libido is decreased and sometimes sperm count and motility is low.

Prolactin Assays: The Radio Immuno Assay (RIA) of Prolactin clearly distinguishes prolactin from GH. Other recommended methods are IRMA (Immunoradiometric assay) and ICMA (Chemiluminescent). As these assays are usually done by single dilution, extremely high level may show "Hook Effect" and misdiagnose MacroProlactinoma by showing "Normal" Prolactin level which is reported in 5 % of the patients. Therefore, patients having Macroprolactinoma and features of Hyperprolactinemia, serum saples should be diluted 1:100 before assay.

Causes of Hyperprolactinemia:

Physiological

Pregnancy and puerperium
Neonates
Physical activity, Sleep
Nipple stimulation, Coitus
Stress

Drugs

Haloperidol, Risperidone, Metoclopramide, Domperidone, TCA, Verapamil etc

Pathological

Prolactinoma
Acromegaly, Cushings, Lymphocytic Hypophysitis, "Empty Sella" syndrome
Hypothalamic disorders or "Disconnection" etc
Nonfunctional tumours of Pituitary, Craniopharyngioma, Dysgerminoma, Meningioma
Histocytosis, Sarcoidosis
Pituitary Stalk lesion, Vascular
Chest wall Injury, Spinal cord Lesion

Others

Hypothyroidism
Adrenal Insufficiency
CKD
CLD
Paraneoplastic
Idiopathic

Clinical Features

- The clinical feature of Hyperprolactinemia is usually straight forward in case of premenopausal woman and in adult men but not in post menopausal women. In premenopausal women it produces hypogonadism, infertility, menstrual disturbances and sometimes galactorrhoea.[10] The symptoms of hypogonadism due to hyperprolactinemia in premenopausal women correlate with the magnitude of the hyperprolactinemia. In most laboratories, a serum prolactin concentration above 15 to 20 ng/mL (15 to 20 mcg/L SI units) is considered abnormally high in women of reproductive age.[11] Higher the prolactin value more is the chance of hypogonadism.[12] A serum prolactin concentration greater than 100 ng/mL (100 mcg/L SI units) is typically associated with overt hypogonadism, subnormal estradiol secretion and its consequences, including amenorrhea, hot flashes, and vaginal dryness etc. Moderate degrees of hyperprolactinemia, eg, serum prolactin values of 50 to 100 ng/mL (50 to 100 mcg/L SI units), cause either amenorrhea or oligomenorrhea. Women with classic amenorrhea –galactorrhea syndrome where as men frequently ignore the symptoms of decreased libido, impotence, gynecomastia associated with hyperprolactinemia and the diagnosis is often made with signs of SOL in the brain or compression syndrome. Hyperprolactinemia sometimes associated with oligospermia.[13] Neurological symptoms (headache, visual impairment) are more common with Macroprolactinoma (>10 mm). Malignant tumours are rare but may produce diplopia, cranial nerve palsy.[14]

Another well known feature of presentation is unexplained osteopenia or osteoporosis.[15] The relative contributions of hyperprolactinemia-induced hypogonadism and the PRL excess per se, to bone damage have still not been completely clarified, even if in vitro and in vivo studies suggest a predominant role for estrogen deficiency.[16] Other possible clinical feature may be insulin resistance with or without PCOS. Some of the autoimmune disease like SLE show relation with serum prolactin level. That's are the concept to treat some of the diabetics and SLE subjects with bromocriptine having good results.

Diagnosis:

Once Hyperprolactinemia is established by repeat samples specially milid to moderate hyperprolactinemia cases, secondary causes should be ruled out. In such History, physical examination including breast, drug history, pregnancy test if necessary, kidney and liver function test if suspect, and TSH should be tested[15]. Magnetic resonance imaging (MRI) of the head should be performed in a patient with any degree of hyperprolactinemia to look for a mass lesion in the hypothalamic-pituitary region, except if the patient is taking a medication known to cause hyperpro-lactinemia.[19] The degree of elevation that can be attributed to a drug depends on the drug. Most drugs do not cause an elevation to over 100 ng/mL from upper limit, but the antipsychotic drug risperidone can cause an elevation up to 300 or even 400 ng/mL.[20] Therefore, usual recommendation of ordering an MRI, if the serum prolactin concentration is greater than 100 ng/mL from upper limit in patients taking a drug known to elevate the prolactin concentration but greater than 300 ng/mL in those taking risperidone. Those who are having large adenoma or sign and symptoms of SOL in the brain or visual field defects VFA(Visual Field Analysis) should be checked initially and in follow up. More important during pregnancy to diagnose any enlargement and pressure effect in optic chiasma.

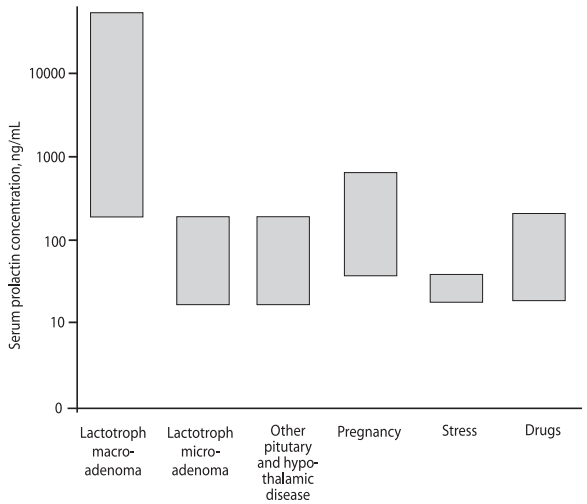
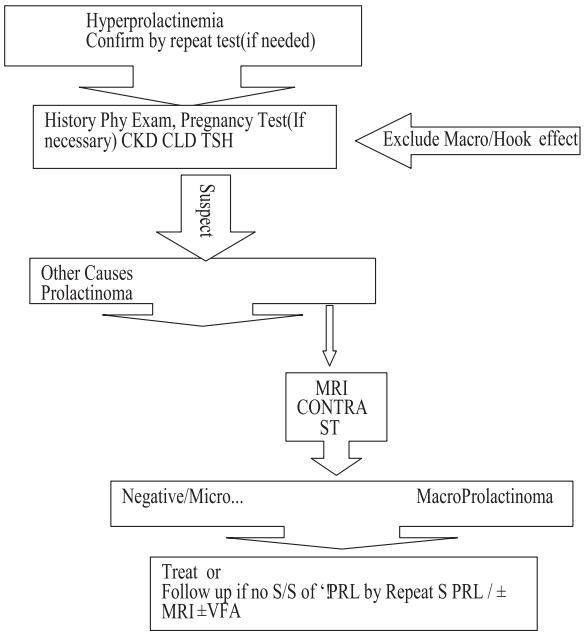


Fig-1: *Ranges of serum prolactin concentrations in several causes of hyperprolactinemia*

Macroprolactinemia : Other than Hook Effect another potential pitfall in the biochemical diagnosis of hyperprolactinemia is the presence of Macro-prolactinemia. Macroprolactin is a complex of PRL with an IgG antibody. Transient hyperprolactinemia results from a reduced clearence of this complex and produces false positive results.[17] Macroprolactinemia presents reduced bioactivity and is not detected by all prolactin assay. This condition is more suspected when there is moderately elevated PRL but less symptomatic such as regular cycle, fertile, no headache, no sexual weakness etc.[18] The imaging studies are always normal. This is just opposite clinical feature of "Hook Effect". That's why with less C/F with hyperprolactinemia s. prolactin level it should be repeated before imaging or treatment.



Treatment:

The primary goal of treatment is:

Relief of sign symptoms, normalization of s prolactin, reduction of tumor size, fertility and complete normalization of sexual and gonadal function. Most of the microprolactinomas donot increase in size over 4-6 years.[21, 22,23] So all macroadenoma should be treated always. In cases of microadenomas(<10 mm) treatment should be started if there is galactorrhoea, infertility, hypogonadism, delayed puberty and osteoporosis.[15,24,25] All other asymptomatic and normal pituitary can be followed up without starting dopa agonist(DA) at once. Hypogonadal women with microprolactinoma may be treated with oral contraceptive.[26,27] In fact no substantial risk for tumor growth was observed with estrogen containing oral contraceptive for idiopathic hyperprolactinemia or microprolactinoma. Treatment should be started with a view to normalize s prolactin level but many investigator suggested to reach as low as much of S prolactin level with DA with a view to maximally reduce the tumor size. After achieving shrinkage of tumor DA dose can be reduced to keep s prolactin with normal reference range.

The mainstay of medical treatment till date is bromocriptine and cabergoline. Though other antiparkinsons drugs like quinagolide (nonergot) and pergolide (Ergot) are also available. Newer drugs like metergoline is studied in women but not in men nor macroprolactinoma. A dopamine agonist drug should usually be the first treatment for patients with hyperprolactinemia of any cause, including lactotroph adenomas of all sizes, because these drugs decrease hyperprolactinemia due to any cause and decrease the size and secretion of most lactotroph adenomas.[28] Other approaches must be considered for the minority of patients whose adenomas are resistant to dopamine agonists or who cannot tolerate these drugs and for those who are taking a medication, such as an antipsychotic drug, that cannot be discontinued.

Bromocriptine: Bromocriptine is an ergot derivative that has been used for approximately three decades for treatment of hyperprolactinemia. It should be given twice a day to have optimal therapeutic effect. Start with low dose 1.25-2.5 mg usualy at bedtime and gradually increase the dose. Maximum daily dose 20 mg/day in 2-3 divided doses. Effectively starts from 2.5 mg once daily. Better choice in young girls and women expected to become pregnant at near future.

Cabergoline: Cabergoline is an ergot dopamine agonist that is administered once or twice a week and has much less tendency to cause nausea than bromocriptine.[29] It may be effective in patients resistant to bromocriptine.[30] Cabergoline may be superior to bromocriptine in decreasing the serum prolactin concentration.[29] Start at 0.25 mg once or twice a week. If the serum prolactin concentration is not normal after one to two months, the dose can be increased gradually up to 0.5 mg twice a week. Sometimes even much higher doses are needed. At the high doses used for the treatment of Parkinson disease, cabergoline is associated with an increased risk of valvular heart disease[31] but at the lower doses generally used for the treatment of hyperprolactinemia, cabergoline is not clearly associated with this risk.

The fall in serum prolactin typically occurs within the first two to three weeks of therapy with a dopamine agonist. In patients with macroadenomas it always precedes any decrease in adenoma size. The decrease in adenoma size can, in many patients, be detected by imaging within six weeks after initiation of treatment; in some patients, however, a decrease is not apparent for six months.[32]

Others: Pergolide is also an ergot derivative and had been used primarily for the treatment of Parkinson disease. However, when used for hyperprolactinemia, typical doses range from 0.05 to 1.0 mg/day. At the high dose used for Parkinson disease (>3 mg/day), pergolide is associated with an increased risk of valvular heart disease.

Resistant cases with Dopamine agonist: Failure to normalize PRL level in patients who have microprolactinomas occur in approximately 20% of patients treated with bromocriptine and in approximately 10% of patient treated with cabergoline. In macroprolactinoma this percentage may be higher.[33] Resistance is sometimes observed with somatoma-mmotrophic tumours. Resistant to one drug may respond to other Dopa agonist. Sometimes partial resistance is also noted.Cabergoline is the most effective dopamine agonist and tumours resistant to bromocriptine frequently respond to cabergoline.[34]

New prospects: Resistance may be biochemical (Hyperprolactinemia) and or mass (Prolactinoma) with dopamine agonist. Benefits from newer drugs have been proposed for clinical use based on interesting

experimental evidence. Somatostatin analogues and chimeric compounds shown in vitro to reduce PRL by 46% to 74%[35]. Prolactin receptor antagonist is also having promising result.[36]

Indication of Surgery in Prolactinoma : A group of patient may be resistant to dopamine agonist and may have or develop visual field defects. About 10% patients may require surgical treatment. Patients having neurologic symptoms due to suprasellar extension of prolactinoma, apoplexy, cystic prolactinoma(may not shrink with medical treatment),intolerant to all dopamine agonists and occasionally macroprolactinoma for women who desire pregnancy. Symptomatic tumor enlargment during pregnancy if medical treatment fails may need standard transsphenoidal microsurgery.[37]

Radiotherapy (RT): The RT is usually not recommended due to available mostly medical and occasionally surgical treatment. Stereotactic conformal radiotherapy or single dose radiotherapy(Gamma Knife and linear accelerator) may be considered as second line therapy for prolactinomas who donot respond or malignant.[38]

Prolactinoma in Pregnancy: Estrogen causes lactotroph cell hyperplasia and stimulates prolactin synthesis during pregnancy. Pituitary size also increases during pregnancy and becomes normal rapidly after delivery. Reduction or regression sometimes ended with empty sella[39]. Studies showed,the risk of enlarging micro- prolactinoma during pregnancy is usually low(2.6%) and also lower in macro-prolactinoma surgically resected before conception (5%).But the risk is much higher (31%) for macro-prolactinomas that has not been treated with dopamine agonists before pregnancy.[40,41]

Safety of Dopamine agonists during pregnancy: There are considerable experience with bromocriptine during pregnancy specially for first few weeks. The incidence of maternal or foetal complications is not higher than in general population.[42] Experience with cabergoline during pregnancy is accumulating. In one study with 350 pregnant mother cabergoline is shown safe for at least first several weeks.[43] The babies born were also have short term follow up (N=100) having normal physical and mental development. Considering long-term data of bromocriptine vs cabergoline(6000 vs700) current guideline suggest that bromocriptine is still the treatment of choice. But cabergoline can be given to those who are intollertent to bromocryptine or larger tumour size. When a dopamine agonist is needed to lower the serum prolactin concentration to permit ovulation, it is suggested either bromocriptine or cabergoline. Bromocriptine has the advantage of the greater certainty that it does not cause birth defects, but cabergoline has the advantage that it is more likely to be tolerated and more likely to be effective in lowering the prolactin.[19]

There is no data that breast feeding may cause enlagement of prolactinoma tumor size and dopamine agonist should not be given at that time because it impairs lactation.[15,26] During pregnancy if there is signs of tumour growth must be assased carefully, in that case breast feeding must be interrupted dopamine agosist reinstated.[43]

Treatment during Pregnancy: During pregnancy, women with either a micro- or macroadenoma should be seen every three months and asked about headaches and changes in vision. Macroadenoma should have planned pregnancy, so that tumour shrinkage can be acheived by pretreatment. A perceived change in vision should be assessed by a neuron-ophthalmologist. A woman who has an adenoma that extends above the sella should have visual fields every three months, even if she does not notice a change in vision. An MRI should be performed if a visual field abnormality consistent with a pituitary adenoma is confirmed.

If the MRI shows that the adenoma has enlarged to a degree that could account for the visual abnormality, we suggest treatment with bromocriptine or cabergoline throughout the remainder of the pregnancy. This treatment will usually decrease the size of the adenoma and alleviate the visual defect. If bromocriptine is used first, but the adenoma does not respond, a trial of cabergoline can be given. If cabergoline is not successful and vision is severely compromised, transsphenoidal surgery is indicated in the second trimester. If in the third trimester, surgery for persistent visual symptoms should be deferred until delivery if possible.[19]

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