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Review Article

Hyperprolactinemia: A Major Challenge in Clinical Practice

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ABSTRACT

Hyperprolactinemia is not a distinct disease but a condition and laboratory sign related to several pathologies. It has been associated with a large number of etiologies. The challenge is in identifying the cause of the hormone hypersecretion. Patients can present with hypogonadism, infertility, galactorrhea, osteopenia, and mass effects of the tumour. It should be stressed that finding of elevated prolactin serum levels constitute the beginning of diagnostic procedure. When hyperprolactinemia is confirmed, a cause for the disorder needs to be sought followed by detailed diagnosis including MRI. The goals of treatment are to normalize prolactin levels, restore gonadal function, and reduce the effects of chronic hyperprolactinemia. Dopamine agonists are strong and reliable treatment for patients with hyperprolactinemia, but surgery or radiotherapy should be considered for patients with suboptimal results following medical treatment. Cabergoline has been shown to be more effective and better tolerated than bromocriptine. However, bromocriptine remains the treatment of choice in hyperprolactinemic women wishing to conceive.

Keyword: Hyperprolactinemia, dopamine agonists, bromocriptine, cabergoline.

INTRODUCTION

Hyperprolactinemia (HPL) is the most common hypothalamo-pituitary disorder encountered in clinical endocrinology and prolactinomas the most frequent pituitary tumour. The elevation of serum prolactin levels can occur due to physiological, pharmacological or pathological causes. A majority of the patients are women in reproductive age seeking health care for menstrual disorders or infertility. The prevalence is lower in men who typically present with symptoms that are due to hypogonadism and tumour expansion. Management of this condition depends heavily on the cause and on the effects it has on the patient.

PREVALENCE: The occurrence of clinically apparent HPL depends on the study population. It occurs more commonly in women. The prevalence of HPL has been reported from 0.4% in an unselected adult population to as high as 9-17% in women with reproductive diseases. Its prevalence was found to be 5% in a family planning clinic, 9% in women with adult-onset amenorrhea, and 17% among women with polycystic ovary syndrome. [1]

PROLACTIN:

Structure: Human Prolactin (PRL) is a polypeptide hormone composed of 199 amino acids (23 kDa) synthesized in the lactotroph cells of the anterior pituitary gland. It is secreted in a pulsatile manner,

and increases with sleep, stress, pregnancy, chest wall stimulation or trauma.

Macroprolactin: Although 85% of circulating PRL is monomeric (23.5 kDa), there are variants of PRL because of post-translational modifications. These include 50kDa dimer, known as 'big prolactin' and 150kDa polymeric form (PRL-IgG complex), known as 'big big prolactin'. Macroprolactinemia denotes the situation in which the circulating prolactin consists of these larger molecules. These variants are less bioactive and macroprolactinemia should be suspected when typical symptoms of HPL are absent.

Biological Action: The most important role of PRL is assisting in the development and maturation of the breast during pregnancy and the subsequent production of milk during lactation. Another effect is to provide the body with sexual gratification after sexual acts. High amounts are suspected to be responsible for impotence and loss of libido. PRL has been found to stimulate proliferation of oligodendrocyte precursor cells which differentiate into oligodendrocytes, the cells responsible for the formation of myelin coating on axons in the CNS. [2] PRL possibly contributes to surfactant synthesis of the fetal lungs at the end of pregnancy and immune tolerance of the fetus by the mother during pregnancy. [3] It decreases normal levels of sex hormones (estrogen in women and testosterone in men). From animal studies, PRL is now recognized to have over 300 identifiable bioactivities owing to the wide distribution of PRL receptors, including osmoregulation, reproduction, behavior modification and immune modulation. Many of these functions are difficult to discern in man, however, where the reproductive roles of PRL are the most evident in terms of clinical disease.

Regulation: Like most anterior pituitary hormones, PRL is under dual regulation by hypothalamic hormones delivered through the hypothalamic–pituitary portal circulation. Under most conditions the predominant signal is inhibitory control of hypothalamic dopamine, which traverse the portal venous system to impinge on lactotroph D2 receptors. Any factor disrupting the delivery of dopamine to the anterior pituitary or disturbing signal transduction may result in HPL. Other PRL inhibiting factors include gamma amino butyric acid (GABA), somatostatin, acetylcholine, and norepinephrine. The stimulatory signal is mediated by hypothalamic peptides, thyrotropin releasing hormone (TRH), vasoactive intestinal peptide (VIP), epidermal growth factor (EGF), estrogen, oxytocin and dopamine receptor antagonists. The balance between the two signals determines the amount of PRL released from the anterior pituitary gland.

Serotonin physiologically mediates nocturnal surges and suckling‐induced prolactin rises and is a potent modulator of prolactin secretion. Histamine has a predominantly stimulatory effect due to the inhibition of the dopaminergic system.

Estrogen stimulates the proliferation of pituitary lactotroph cells especially during pregnancy. However, lactation is inhibited during pregnancy due to high levels of estrogen and progesterone. Lactation is commenced in the postpartum period due to the rapid decline of estrogen and progesterone.

ETIOLOGY: Causes of HPL fall into three main categories: physiological, pharmacological and pathological. Furthermore, HPL can arise when macroprolactin is the predominant isoform. (Table 1 and 2)

PHYSIOLOGICAL CAUSES: The most important physiologic causes of HPL are pregnancy and breast-feeding. During normal pregnancy, serum PRL progressively

rises to around 200 to 500 ng/mL due to rising estrogen concentrations.

PRL is a stress hormone that increases in response to a number of stressful conditions like physical discomfort, exercise, hypoglycemia, myocardial infarction, surgery, fear of venipuncture, food ingestion, coitus, postictal state and sleep.

PHARMACOLOGICAL CAUSES: Any drug that affects the hypothalamic dopamine system and/or pituitary dopamine receptors can potentially induce HPL. Antipsychotic agents are the ones most commonly causing HPL.

Various drugs act through different mechanisms: increased transcription of PRL gene (estrogens), antagonism of dopamine receptor (risperidone, haloperidol, metoclopramide, domperidone, sulpiride, etc.), dopamine depletion (reserpine, methyldopa), inhibition of hypothalamic dopamine production (verapamil, heroin, morphine, enkephalin analogs, etc.), inhibition of dopamine reuptake (tricyclic antidepressants, cocaine, amphetamine, monoamine oxidase inhibitors), inhibition of serotonin reuptake (opiates, fenfluramine, fluoxetine, sibutramine), etc.

PATHOLOGICAL CAUSES:

Pituitary and hypothalamic disorders: Prolactinomas account for 25-30% of functioning pituitary tumors and are the most frequent cause of chronic HPL.Based on size, they are classified as microprolactinoma (<10 mm), which are more common in premenopausal women and macroprolactinoma (≥10 mm) which are more common in men and postmenopausal women. Other tumors of the hypothalamic-pituitary region may also present HPL, either by increased production of PRL (mixed pituitary adenomas producing GH and PRL, TSH and PRL, or ACTH and PRL) or by compression of the pituitary stalk (non-functioning pituitary adenomas and craniopharyngiomas). The latter tumors are called pseudoprolactinomas since they do not secrete PRL, but rather interfere with the supply of dopamine from the hypothalamus to the pituitary. Infiltrating lesions, hypophysitis, aneurisms, empty sella, and radiotherapy can also result in HPL due to inadequate hypothalamic production of dopamine or to pituitary stalk disruption.

Systemic diseases: Pathological HPL can be also caused by other endocrine and non-endocrine systemic diseases.

Hypothyroidism: In response to the hypothyroid state, a compensatory increase of hypothalamic TRH results in increased stimulation of PRL secretion. Other mechanisms likely to be involved are reduced PRL clearance, decreased sensitivity to the suppressant effect of dopamine on PRL synthesis, and decreased circulating thyroid hormone levels. Upto 40% percent of patients with overt primary hypothyroidism, and up to 22% of those with subclinical hypothyroidism could have mild elevation of PRL levels that can be normalized by thyroid hormone replacement. [4]

Adrenal insufficiency: Glucocorticoids have a suppressible effect on PRL gene expression and PRL release. Thus, HPL may occasionally be observed in patients with adrenal insufficiency in whom PRL levels return to normal with glucocorticoid replacement. [5]

Polycystic Ovarian Syndrome (PCOS): Mild to moderate HPL is frequently detected in 30 % women with PCOS, and thought to be a consequence of elevated estrogen levels and dopaminergic tonus reduction. [6] More recently, a pathophysiological link between PRL and PCOS was not confirmed, and their relationship was considered a fortuitous association. [7]

Chronic Renal Failure (CRF): About 30% patients with chronic renal failure and upto

80% patients on hemodialysis have raised prolactin levels. This is because of decreased clearance and enhanced production of the hormone. Dialysis does not alter serum levels, but PRL levels normalize after renal transplantation. [8] HPL may contribute to hypogonadal symptoms that accompany chronic kidney disease, and menses may return after bromocriptine therapy.

Cirrhosis: About 60% of cirrhotic patients accuse the presence of mild HPL, [9] without correlation between PRL levels and the severity of liver failure. Etiopathogenesis is unknown.

Idiopathic HPL: Idiopathic HPL with no demonstrable pituitary or central nervous system disease and without any recognized cause of increased PRL secretion is the most common disorder of the hypothalamic-pituitary axis and has been found in up to 25% of patients with secondary amenorrhea. Approximately 10% of these patients are subsequently diagnosed with a microadenoma, while spontaneous normalization of PRL levels occurs in 30%. [10]

Neurogenic HPL: Sexual breast stimulation and breastfeeding lead to reflex release of PRL by afferent neural pathways going through spinal cord. The same mechanism would be involved in elevation of PRL levels following traumatic or irritative lesions, disorders of the chest wall (mastectomy and thoracotomy, herpes zoster, burns, etc.), of the spinal cord (cervical ependymoma, syringomyelia, tabes dorsalis, extrinsic tumours), and nipple rings.

Ectopic prolactin secretion: An unusual and extremely rare cause of HPL is the ectopic production of PRL. Symptomatic HPL due to well-documented PRL production has been reported from renal cell carcinoma, gonadoblastoma, uterine cervical carcinoma, non-Hodgkin lymphoma, colorectal adenocarcinoma.

Macroprolactinemia: Macroprolactinemia is defined by the presence of more than 60% of serum PRL as macroprolactin (or big-big prolactin), an isoform of high molecular weight and low biological activity. Macroprolactin causes HPL as a consequence of low renal PRL clearance and a decreased stimulation of dopaminergic tonus. Macroprolactinemia is responsible for HPL in 10-46% of the cases, [11] and it should be screened in the following situations: individuals with high PRL levels but no indications of clinical symptoms, atypical clinical picture, conflicting PRL results in distinct assays, and delayed decline of serum PRL levels with the usual doses of dopamine agonists.

Table 1. Causes of hyperprolactinemia

Physiological Pregnancy; lactation; stress; sleep; coitus; exercise
Pathological Hypothalamic diseases – tumors (craniopharyngiomas, dysgerminomas, meningiomas, etc); infiltrative disorders (histiocytosis, sarcoidosis, etc); metastasis; cranial radiation; Rathke's cleft cysts; etc Pituitary diseases – Prolactinomas; acromegaly; thyrotropinomas; Cushing's disease; infiltrative disorders; metastasis; lymphocytic hypophysitis; empty sella syndrome; etc Systemic diseases – Primary hypothyroidism; adrenal insufficiency; PCOS; renal insufficiency; cirrhosis; pseudocyesis; epileptic seizures Stalk disorders – Hastitis; seccion; traumatic brain injury Neurogenic – chest wall lesions (burns; breast surgery; thoracotomy; nipple rings; herpes zoster); spinal cord injury (cervical ependymoma; tabes dorsalis; extrinsic tumors); breast stimulation; etc
Idiopathic Ectopic prolactin production – renal cell carcinoma; ovarian teratoma; gonadoblastoma; non-Hodgkin lymphoma; uterine cervical carcinoma; colorectal adenocarcinoma; etc Macroprolactinemia
Drug-induced (Table 2)

Table 2 Drug-induced hyperprolactinemia

Antipsychotics Typical – Phenothiazines; butirophenones; thyoxanthenes Atypical –Risperidone; molindone; amisulpride; quetiapine; olanzapine
Antidepressants Tricyclics – Amitriptyline; desipramine; clomipramine MAO inhibitors – Pargyline; clorgyline SSRIs – Fluoxetine; citalopram; paroxetine
Antihypertensive drugs Verapamil; α-methyldopa; reserpine; labetolol
Anticonvulsants Phenytoin
Prokinetic agents Metoclopramide; domperidone
Others Estrogens; anesthetics; cimetidine; ranitidine; opiates; methadone; morphine; apomorphine; heroin; cocaine; marijuana; alcohol; sibutramine; etc

CLINICAL PRESENTATION: HPL usually presents in a dimorphic fashion in both females and males. Women may present with irregular menses or amenorrhea, galactorrhea, infertility, decreased libido and decreased bone mass. In men, hypogonadism, infertility, and libido impairment could be found. Additionally, patients with HPL can also exhibit hypopituitarism, visual impairment, and headache due to an expanding mass.

Galactorrhea, which requires adequate estrogenic or progesterone priming of breast, is frequently present in premenopausal women. Isolated galactorrhea with normal PRL levels is due to hypersensitivity of breast to the lactotrophic stimulus. The discharge in HPL is the result of persistent high PRL levels stimulating the mammary gland for milk production. Only one-third of women with high PRL levels have galactorrhea because the low estrogen environment associated with the amenorrhea prevents a normal response to PRL. Another possible explanation is heterogeneity of peptide hormones.

Both women and men with HPL and hypogonadism have an increased risk of reduced bone mineral density, most notably in trabecular bone. Spinal bone density is decreased by approximately 25% in women with HPL [12] and is not necessarily restored with normalization of PRL levels.

Hyperprolactinemic women may present with signs of chronic hyperandrogenism such as hirsutism and acne, possibly due to increased dehydroepiandrosterone sulfate secretion from the adrenals, as well as reduced sex hormone binding globulin leading to high free testosterone levels.

Hypogonadism seen in hyperprolactinemics is due to elevated PRL levels interfering with the action of gonadotrophin on ovaries and impaired gonadal steroid secretion, which in turn alters positive feedback effects at the hypothalamic and pituitary levels. This leads to lack of gonadotrophin cyclicity and to infertility. HPL inhibits the pulsatile secretion of gonadotrophin releasing hormone, which causes decreased pulsatile release of follicle stimulating hormone, luteinizing hormone and testosterone, producing secondary hypogonadism and infertility.

Men with HPL may present with infertility, galactorrhea, gynecomastia and decreased libido or potency. They may also have reduced muscle mass and increased risk of osteopenia.

Both men and women with macroprolactinomas usually present with

neurological symptoms caused by mass effects of the tumor. These include headaches, visual field losses, cranial neuropathies, hypopituitarism, seizures, and cerebrospinal fluid rhinorrhea.

DIAGNOSIS OF HYPERPROLACTINEMIA: To establish the diagnosis of HPL, a single measurement of serum PRL level above the upper normal limit is sufficient to confirm the diagnosis of HPL as long as the serum sample is obtained without excessive venipuncture stress. Doubtful results (mild PRL elevations) or inconsistent with the clinical picture, should be confirmed in additional sampling taken at 15-20 min intervals to minimize the effect of pulsatility. [13] HPL is usually defined as fasting levels of above 20 ng/ml in men and above 25 ng/ml in women [14] at least 2 hours after waking up.

A careful history, including medications, physical examination, screening blood chemistries, liver, kidney and thyroid-function tests and pregnancy test will exclude almost all causes of HPL other than hypothalamic-pituitary disease. Furthermore, the screening for macroprolactinemia should often be considered. Moreover, acromegaly must be investigated by means of IGF-1 measurement in all patients with a macroadenomas even though there are no manifestations of this disease.

Consequently, the next step in the investigation is a radiological examination of the hypothalamic-pituitary region. Although computerized axial tomography (CAT) scan can beused, magnetic resonance imaging (MRI) with gadolinium enhancement provides the best visualization of the sellar area.

The magnitude of PRL elevation can be useful in determining the etiology of HPL, since the highest values are found in patients with prolactinomas. A mildly elevated serum PRL level may be due to a non-functioning pituitary adenoma or craniopharyngioma compressing the pituitary stalk. A PRL level greater than 500ng/ml is diagnostic of a macroprolactinoma. Although a PRL level greater than 250ng/ml usually indicates the presence of a prolactinoma, [15] selected drugs, including risperidone and metoclopramide, may cause PRL elevations above 200ng/ml in patients without evidence of adenoma. [16] In contrast, most patients with pseudoprolactinomas, drug-induced HPL, or systemic diseases present with PRL levels < 100 ng/Ml. [13,15] However, exceptions to these rules are not rare.

The 'hook effect' must be ruled out in large adenomas with only slightly elevated PRL levels, although this is virtually nonexistent with some of the new immunoassays. The possibility that the tumor does not secrete PRL should also be considered.

Visual field should be tested in patients having tumour adjacent to or pressing on optic chiasma, as visualized on MRI.

TREATMENT: The primary goal of treatment in HPL patients is to normalize PRL levels and thereby restore symptoms such as hypogonadism, infertility and galactorrhea, as well as to reduce tumour size. In patients with HPL the treatment varies with the presenting complaint and the etiology of hypersecretion. Prior to any pharmacological intervention, it is essential to exclude potential physiological or pharmacological causes of HPL. The preferred treatment for patients with secondary causes of elevated PRL may be to remove the relevant stimuli. PRL levels can often be corrected by stopping suspected medication or switching to an alternative drug. Correction of hypothyroidism is also effective and specific to reduce PRL levels. Correction of renal failure by transplantation results in normal PRL levels.

Variety of treatment options is available for treating HPL depending on the medical history, condition, overall health and the age of the patients. These include (Figure 1)

1. Expectant management
2. Medical treatment
3. Surgical intervention
4. Radiotherapy

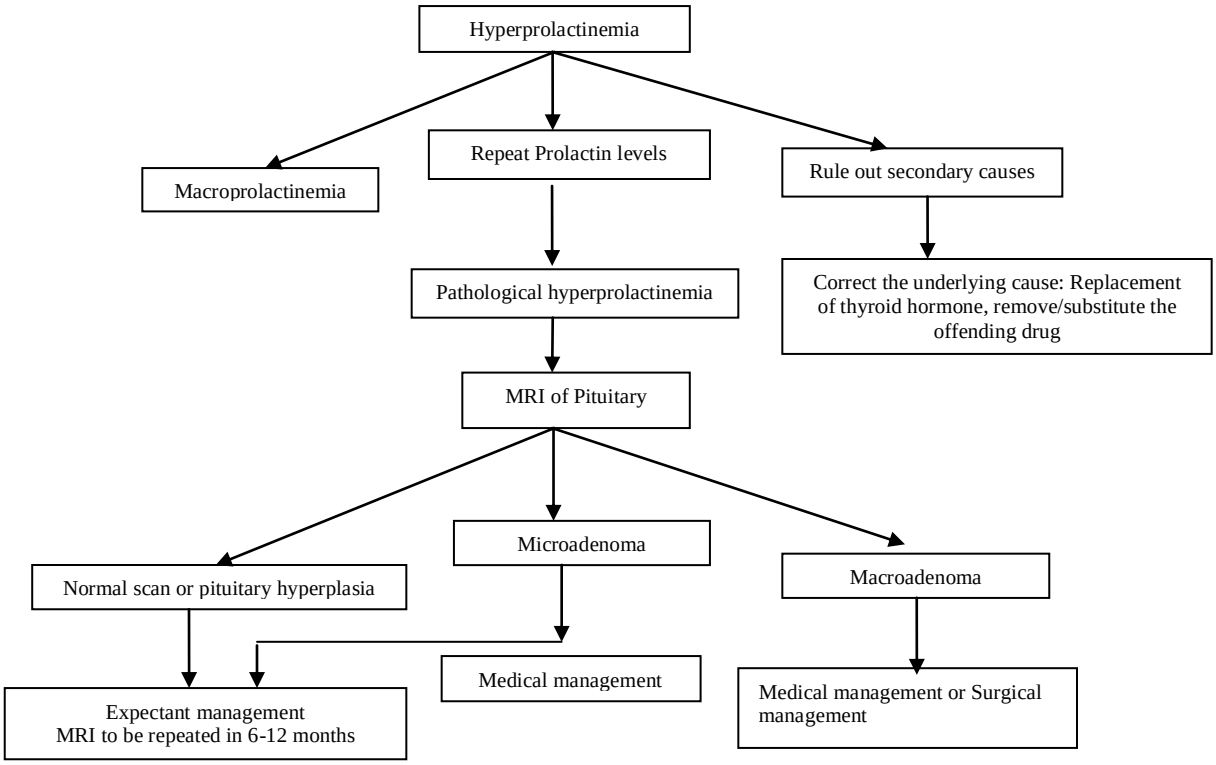

Figure 1 Approach to management of hyperprolactinemia

Expectant treatment: Asymptomatic patients may not require treatment and periodic observation should then suffice. Significant growth of microprolactinomas is uncommon. Women with HP but normal regular menses are not at risk of osteoporosis and periodic observation should suffice.

Medical treatment: It is the treatment of choice in symptomatic patients of HPL. It is considered the primary therapy of choice when some intervention is warranted. It is recommended to initiate ovulation in anovulatory hyperprolactinemic women who desire to conceive. Indications for medical treatment in women who do not wish to conceive include induction of normal menstrual cycles and prevention of potential long-term complications, such as bone loss. Normal conception can occur in some patients and oral contraceptives can be given safely to women with HP. Hormone replacement therapy may be considered in patients with HP-induced amenorrhoea as a means to reduce the risk of bone loss.

Dopamine agonists: Dopamine agonists, characterized by a potent PRL inhibitory effect, a tumor-shrinking effect associated with a satisfactory tolerability, are considered as the main stay of treatment for both idiopathic/non-tumoral and prolactinoma-related PRL excess. These

agents bind to dopamine receptors on the surface of the lactotroph, inhibiting PRL synthesis and release. All (except quinagolide) are ergot alkaloids. Patients who are intolerant or fail to respond to one agent may do well with another. Adverse effects associated with these drugs are nausea, vomiting, headache, constipation, dizziness, faintness, depression, postural hypotension, digital vasospasm, and nasal stuffiness. Neuropsychiatric symptoms present as auditory hallucinations, delusion, and mood changes.

Bromocriptine is a semisynthetic ergot derivative of ergoline, a dopamine D2 receptor agonist with agonist and antagonistic properties on D1 receptors. It is highly effective for normalizing or reducing PRL levels, reduces the size of pituitary adenoma and restores normal gonadal function in approximately 80% of patients with idiopathic HPL or microprolactinoma with a pregnancy rate of 60–80% provided there are no other infertility factors. [17] It is started at an initial low dose (1.25mg daily) that is slowly adjusted upward until therapeutic efficiency is documented. In the remaining women, exogenous gonadotropin stimulation can be added along with dopamine agonist to achieve ovulation. However, the occurrence of side-effects and the need for multiple dosing throughout the day remain important problems in the long-term management of hyperprolactinemic patients. Available alternatives for intolerant patients include vaginal administration and long acting preparations of bromocriptine. PRL returns to elevated levels in 75% of patients after discontinuation of treatment.

Cabergoline, an ergoline derivative, has a high affinity and selectivity for dopamine D1 receptors. It is recommended as the first choice because of its greater efficacy (both in terms of normalization of PRL levels and tumor size decrease and better tolerability. It shares many characteristics and adverse effects of bromocriptine but has a very long half‑life of about 65 hours allowing weekly dosing. It effectively treats HPL, micro and macroadenomas and offers an effective therapy for patients who are resistant or intolerant to bromocriptine. A dose of 0.25 mg twice per week is usually adequate and maximum dose of 1 mg twice a week can be given. Despite some reassuring studies concerning the occurrence of a fibrotic valvular heart disease, an active echocardiographic monitoring is still suggested during the treatment. [18]

Though both drugs have been found to be safe in pregnancy, the number of reports studying bromocriptine in pregnancy far exceeds that of cabergoline.

Response to therapy should be monitored by checking fasting serum PRL levels and evaluation of tumor size with MRI. Therapy should be continued for approximately 12-24 months (depending on the degree of symptoms or tumor size) and then withdrawn if PRL levels have returned to the normal range. After withdrawal, approximately one sixth of patients maintain normal PRL levels.

Kisspeptin, a neuropeptide has been recognized as a potent stimulus of GnRH secretion and of critical importance for regulation of reproductive function. [19] It has the ability to reverse the hypogonadotropic effects of HPL and can also restore pulsatile LH secretion. Treatment with kisspeptin may provide an alternative therapeutic approach to restore the fertility of hyperprolactinemic women who are resistant or intolerant to dopamine agonists. [20]

Future studies are needed to evaluate new treatment modalities. The role of somatostatin analogs, agents directed against estrogen/estrogen receptors, PRL receptor antagonists, nerve growth factor and gene therapy represents a potential future therapy for the treatment of pituitary adenomas,

although it remains at an early stage of investigation.

Surgery: Because of the efficacy of medical treatment, only a minority of patients with prolactinomas require surgery. Transnasal transsphenoidal surgery is helpful in the treatment of patients for debulking a large macroadenoma, the improvement of visual fields, in patients with neurological symptoms, and those intolerant or resistant to medical therapy. Regardless of initial PRL level, preoperative treatment with dopamine agonists may induce tumor regression, enabling resection of a greater percentage of the tumor and leading to better control of the PRL level.

Besides the usual surgical risks, hypopituitarism is a potential long-term effect of surgery.

Radiotherapy: It is not the primary choice of treatment and may be tried if medical management or surgery fails. Radiotherapy is usually limited to patients with a resistant macroadenoma, in conjunction with medical therapy, or in patients with a residual macroadenoma. The response is typically quite modest and delayed. Disadvantage of conventional radiotherapy is the latency of hormonal reduction and the risk of developing pituitary insufficiency. Gamma knife stereotactic radiosurgery has been reported to normalise PRL levels in 18-47% of prolactinoma patients and the risk of pituitary insufficiency was 14-26% in patients followed for at least 4 years. [21]

Management of Resistant and Malignant Prolactinoma: For symptomatic patients who do not achieve normal PRL levels or show significant tumour shrinkage with the standard doses of a dopamine agonist, the dose should be increased rather than referring the patient for surgery. Patients resistant to bromocriptine should be switched to cabergoline. Symptomatic prolactinoma patients intolerant to high doses of cabergoline or unresponsive to dopamine agonist therapy should be subjected to trans-sphenoidal surgery. Patients intolerant of oral bromocriptine may respond to intravaginal administration. Radiation therapy is recommended for patients who fail surgical treatment or having aggressive or malignant prolactinomas. Temozolomide therapy is recommended for patients with malignant prolactinomas.

Management of prolactinoma during pregnancy: Dopamine agonist therapy should be discontinued once pregnancy is diagnosed in women with prolactinomas, except for selected patients with invasive macroadenomas or adenomas abutting the optic chiasma.

Serum PRL measurements should not be performed during pregnancy. Unless there is clinical evidence for tumour growth, routine use of pituitary MRI during pregnancy is not recommended in patients with microadenomas or intrasellar macroadenomas. Visual field assessment followed by MRI without gadolinium should be done in pregnant women with prolactinomas with severe headaches and/or visual field changes.

Women intolerant to dopamine agonists or women with resistant macroprolactinomas should be counselled regarding the potential benefits of surgical resection before attempting pregnancy.

Bromocriptine therapy is recommended in patients who experience symptomatic growth of a prolactinoma during pregnancy.

CONCLUSIONS

Hyperprolactinemia is a real challenge of endocrinology practice. Documenting the presence of hyper-prolactinemia is not difficult. Consequently, a major problem is to establish the pathological relevance of hyper-prolactinemia before commencing treatment

for this endocrinological disorder. Dopamine agonist therapy is the treatment of first choice in treating hyperprolactinemia and reducing associated morbidity. Cabergoline is found to be more effective than bromocriptine in achieving normo-prolactinemia and resolving amenorrhea/ oligomenorrhea and galactorrhea. Radiotherapy and surgery are efficacious in patients with resistance or intolerance to dopamine agonists. Future studies are needed to develop therapies targeting underlying molecular defects involved in the pathogenesis of hyperprolactinemia to treat this disorder.

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