SEE YOUR ENDOCRINOLOGIST FOR PITUITARY TUMOUR; YOU MAY NOT NEED SURGERY

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Abstract
This brief review emphasizes the importance of proper diagnosis prior to management of patients with pituitary lesions. Surgery remains the treatment of choice for many pituitary adenomas but not all of them require surgery. Lactotroph adenomas secreting excessive amount of prolactin (often termed as Prolactinomas) are usually responsive to pharmacological treatment with dopamine receptor (D2) agonists and should not be treated surgically except in a selected group of patients. Surgery is no longer the first line treatment for prolactinomas. All those patients of prolactinomas who may be considered for surgery must be discussed in an MDT (multi-disciplinary team) meeting prior to surgical intervention. In clinical practice in Pakistan one comes across a noticeable number of patients of lactotroph adenomas referred after surgical resection performed as a primary treatment for their pituitary adenomas. Most of these patients were referred to Endocrinology department following recurrence of prolactinomas and further surgical resection could not be performed. There is no local data of those prolactinomas which may have been cured after surgery. The comparison between surgical and pharmacological treatment is not possible in local population but worldwide data available in literature clearly suggests that surgery should no longer be the first line treatment in majority of patients with prolactinomas. Pharmacological treatment is convenient, more effective and longer lasting compared to surgical treatment.

Keywords Pituitary adenoma, Lactotroph adenoma, Prolactinoma, Dopamine agonists, Cabergoline, Hyperprolactinemia

Introduction:
This brief review is aimed at reviewing basic aspects of management of Prolactinomas for healthcare professionals of all specialties and grades. There seems to be lack of awareness about prolactinomas not only among patients but also among some of the healthcare professionals in Pakistan. Most patients present late to a doctor but even after presentation they are not referred to an appropriate centre immediately. Lack of availability of appropriate laboratory facilities in most of the hospitals further emphasizes the importance of timely referral to appropriate centres for investigation and management of these patients. Also, many of these patients may not present to general practitioners but may present to Gynaecologists (with amenorrhea) and Ophthalmologists (visual field defects). In essence a multidisciplinary approach is required for the best management of such patients.

Prolactin is a single chain polypeptide hormone of 198 amino acids and approximately 24200 D (1). It is produced and secreted by the acidophilic cells of anterior pituitary gland. Most of the anterior pituitary gland hormones’ secretion is regulated by stimulatory and inhibitory effects of hypothalamic hormones. Prolactin production and secretion by lactotroph cells is inhibited by dopamine produced in hypothalamus and released in hypophysial-hypothalamic circulation. All the stimulating factors for Prolactin are not fully understood but Thyrotropin releasing hormone (TRH) produced in hypothalamus is one of the prolactin stimulatory agents. This explains the reason of high prolactin level in some patients of...
primary hypothyroidism. Lactation has almost always been considered as its main function and the hormone has been named accordingly (2) but this is not the only functions it performs in mammary glands. It has trophic effect on the secretory epithelial tissue of the mammary glands. This trophic effect results in growth and prepares the tissue for initiation of lactation. Prolactin not only helps in initiation of lactation but then maintains it as well. Since almost all the vertebrates produce prolactin, most of the functions of prolactin have been studied in animal models. In addition to its function in reproduction and lactation it has also been associated with a role in metabolism, behaviour, thermoregulation and osmoregulation. Up to 300 different biological actions of prolactin have been described in vertebrates (3). It is important to manage abnormalities of such an important hormone properly.

Presentation

Prolactinoma is one of many causes of hyperprolactinemia (4). Hyper-prolactinemia could be physiological (during lactation and pregnancy) or pathological which should be investigated and treated. Hyper-prolactinemia can also be transient due to a number of reasons but clinical symptoms of hyper-prolactinemia develop if it remains persistently high. Most patients with prolactinomas usually present with symptoms and signs of hyper-prolactinemia or compression of pituitary tumour on the surrounding intracranial structures. Hyper-prolactinemia reduces gonadotropin levels and patients often present with clinical and biochemical features of hypo-gonadotrophic hypogonadism. In a retrospective study conducted by Peng et al. found that most adult men experience growth hormone deficiency and hypogonadism with prolactinomas (5). Most of these patients are young however, older patients may also present with prolactinomas. Fernandez et al conducted a study in 81,449 inhabitants of Banbury, Oxfordshire, in the United Kingdom and determined the incidence of pituitary adenomas there to be 77.6 cases per 100,000 population, with the majority of cases (57%, or 44.4 persons per 100,000 population) being prolactinomas. In this particular population the incidence of prolactinomas was 75% of all pituitary adenomas occurring in individuals up to the age of 20 years and 61% of all the pituitary adenomas in individuals between the ages of 20 and 60 years.

Incidence of prolactinomas was higher among women compared to men as prolactinomas made 76% of all the pituitary adenomas in women while in men 57% were non-functioning adenomas (6). Carter et al. found that 60% of men present with macro-prolactinomas and 90% of women present with micro-prolactinomas (7). Women present early with menstrual irregularities. It can present with oligomenorrhea, amenorrhea or irregular menstrual bleeding (8). Patients can sometimes present with secondary amenorrhea or primary amenorrhea. Hyper-prolactinemia is often detected during work up in infertility clinics (8). Women may also experience vaginal dryness, dyspareunia and bone mineral density (BMD) loss secondary to hypoestrogenemia secondary to hypogonadotrophic hypogonadism (4). Men with prolactinomas usually present late. They present with either compression effects on surrounding structures or deficiency of other pituitary hormones. Since hypogonadotrophic hypogonadism develop gradually over time most patients may not notice this until the symptoms are fairly advanced. Many such patients present for the first time with visual field defects due to compression of tumour on optic chiasm.

Large tumours may affect other surrounding structures in the vicinity including III, IV and VI cranial nerves. Many patients present with headache with large tumours stretching onto to pain sensitive surrounding structures. Men could present with erectile dysfunction, low libido, loss of BMD and infertility (7). Galactorrhea remains the other most commonly experienced symptom among such patients. Approximately 30 to 60% patients experience this symptom with hyper-prolactinemia. Gynaecomastia is not a typical sign in such patients although; it has been reported to be associated with some patients of hyper-prolactinemia. Pre-pubertal hyper-prolactinemia can result in female body habitus in male patients due to hypogonadotrophic
hypogonadism. Incidental detection of pituitary adenomas has increased in recent years with increased number of CT and MRI scans. Prolactinomas constitute a reasonable proportion of these incidentally detected pituitary adenomas. Larger adenomas can cause deficiency of other pituitary hormones in addition to gonadotropins. Cortisol and thyroxin must be replaced once their deficiency is confirmed. Cortisol has to be replaced prior to thyroxin replacement to avoid adrenal crisis. Prolactinomas can also present along with other endocrine neoplasias termed as multiple endocrine neoplasia (MEN). Prolactinomas associated with parathyroid and pancreatic tumours are termed as MEN type 1. Such patients usually present early in their lives with symptoms of one or more hormones’ excess; Parathyroid in 90%, Prolactin in 66% and Gut hormones excess in 50% patients. In younger patients, it is advisable to assess other hormones (pituitary, gut hormones and parathyroid) once an adenoma is detected in pancreas, pituitary or parathyroid glands.

Laboratory Assessment

Most laboratories use immunoassay as the first line investigation for prolactin level assessment. Prolactin immunoassay is more like antigen antibody reaction. Prolactin molecule in sample acts as antigen while anti-prolactin antibodies in assay attach to prolactin. One prolactin molecule is sandwiched between two antibodies. This suggests that laboratory assay should have more antibodies than antigen to reliably detect prolactin concentration in a given blood sample. If the antigen concentration increases significantly the laboratory assay antibodies may not be able to sandwich prolactin molecules properly (9,10). In this situation a significant proportion of prolactin is attached to only one antibody and is not detected. This leaves fewer antibodies in the assay to be attached on two antigen sites (sandwich prolactin molecule) of prolactin and be detected. This will result in a falsely low detectable prolactin level in a given blood sample. This is called “hook effect” when very high levels of prolactin in a blood sample result in a falsely low detectable prolactin and hook the result in wrong direction. One could overcome this phenomenon by either reducing concentration of antigen or increasing concentration of antibody. One way of reducing antigen concentration would be to dilute the blood sample. Normally with dilution you would expect the detectable prolactin levels to drop however; with hook effect sample the prolactin levels will be higher in diluted sample. The dilution of blood sample is continued to be increased in a stepwise manner as long as prolactin level continues to rise with increasing sample dilution. Once the prolactin level starts to drop with increasing dilution further dilutions are not necessary. The corrected level of prolactin is then documented by multiplying it with the number of times the blood sample was diluted. The immunoradiometric PRL assay must be performed with serum dilution in order to overcome the high-dose PRL hook effect in all new patients with pituitary macroadenomas who may have a prolactinoma (11). Dilution of sample is especially recommended when there is discrepancy between pituitary tumour size and prolactin levels. The hook effect was first described in 1992 (12) and Comtois et al (13) reported the first patient in whom the hook effect lead to misdiagnosis of a large macroprolactinoma. Subsequently a good number of cases were reported in literature with hook effect. It is important to recognize this phenomenon for correct diagnosis and treatment of pituitary tumours.

Most laboratories usually assess total prolactin as the initial investigation in all patients. Once the immunoassay detects high prolactin level further work up is required to assess if the prolactin is biologically active. Assessment of bio-active (monomeric) prolactin is the laboratory investigation of choice in patients with clinical features of hyperprolactinemia and/or pituitary tumour. Most of human circulating prolactin exists in a monomeric form of 23 kDa (85-90%). A proportion of prolactin circulates as high molecular mass isoforms including big-PRL, a dimer of 50 kDa and big–big-PRL or macro-prolactin, a variant of 150–170 kDa. (14). It is believed that macro-prolactin is formed when prolactin binds to a protein IgG (immunoglobulin G) in circulation. This IgG – prolactin complex becomes bigger in size and becomes biologically inactive although stays in circulation for longer than
monomeric prolactin. Post-translational modification of pituitary prolactin with varying glycosylation and phosphorylation degrees has also been suggested as a possible cause of macro-prolactin (15, 16). Macro-prolactin usually does not cause clinical symptoms and does not require any treatment. There are only a few case reports suggesting clinical symptoms with high levels of macro-prolactin but an overwhelming majority of patients with macro-prolactin are asymptomatic and do not require treatment. The exact mechanism of inactivity of macro-prolactin is not known but the most widely believed theory is about the size of IgG – prolactin complex. IgG – prolactin complex becomes too big to cross the vessel wall and not released into tissues to produce any biological effects. Prolactin part of Prolactin-IgG complex maintains its immunoreactivity and is detected during laboratory assays. The gold standard test to determine the presence of macro-prolactinemia is gel filtration chromatography, but more available and less expensive alternatives have been described, like precipitation with polyethylene glycol (PEG) (17).

In addition to prolactin other hormones of anterior pituitary gland should be assessed regardless of prolactin level. This should include Lutenizing hormone (LH), Follicle stimulating hormone (FSH), Testosterone (for men), Estradiol (for women), Cortisol with or without Adrenocorticotropic hormone (ACTH), Insulin like growth factor 1 (IGF-1), Thyroid stimulating hormone (TSH) and free thyroxin (FT4). Certain pituitary adenomas can co-secrete hormone, especially growth hormone and prolactin. All patients with high prolactin level should have their IGF-1 level assessed to look for this possibility of co-secretion.

Treatment

Once the diagnosis is confirmed treatment is planned according to biochemical and radiological findings. Prolactinomas are divided into two main sub-types based on their size: Micro-prolactinoma (tumour less than 1 cm in size on radiologic imaging) and Macro-prolactinoma (tumour over 1 cm in size). This size based divide helps in planning treatment of these adenomas. The exact aetiology of micro- and macro-prolactinomas is not known however, micro-prolactinomas generally do not grow in size to become macro-prolactinomas in 95% of cases. Hence, the treatment is tailored according to tumour size and behaviour. One of the following approaches can be used to treat prolactinomas:

1. Monitoring without active intervention
2. Pharmacological and surgical intervention
3. Others e.g. Radiotherapy

Monitoring without intervention:

Asymptomatic micro-prolactinomas with stable prolactin levels and no abnormality of any of the other pituitary hormones do not always require intervention and these prolactinomas can sometimes be monitored with prolactin levels and size on pituitary MRI scans. Pharmacological treatment will be indicated if prolactin level continues to raise, other pituitary hormones are affected and/or prolactinoma increases in size. Also, some infertility centres recommend normalization of prolactin levels in women prior to IVF (in-vitro fertilization) treatment cycle to maximize chances of ovulation. In the absence of any of these conditions radiological and biochemical monitoring is advised on three to six monthly intervals. Many patients of polycystic ovarian syndrome (PCOS) have high prolactin levels with no identifiable adenoma in pituitary gland. The exact mechanism of high prolactin in these patients in not known however, these patients should be monitored for symptoms as above and treatment should be offered using the same criteria as those who have got prolactinomas. Since there is no detectable pituitary adenoma on MRI scan, most centres would not recommend repeating scans if two scans at least six months apart do not show a change in pituitary gland. After initial two scans another scan should be considered if there is a considerable increase in prolactin level or there are clinical signs of pituitary tumour – visual field loss.

In some cases of hyper-prolactinemia no cause can be found. In the absence of any other cause of hyper-prolactinemia, it is believed that the pituitary adenoma may be too small to be identified as a separate entity in pituitary gland on MRI scans.
Monitoring strategy should remain the same in these patients with initial two scans at least six months apart and subsequent scans if required. Many of the medicines used in treatment of psychiatric conditions can cause hyper-prolactinemia (18). Most of these medicines are dopamine antagonists. Patients need to take these medicines to help with their psychiatric condition. The prolactin released in these conditions causes true hyper-prolactinemia and can cause clinical symptoms of hyper-prolactinemia. I would strongly recommend for every patient to have their prolactin level assessed prior to commencement of these medications. Psychiatrists should get a baseline prolactin level on all these patients and refer to Endocrinologists for assessment of those patients who have high monomeric prolactin level (unpublished; Hanson, P). Most patients will not need diagnostic work up for hyper-prolactinemia if the prolactin level rises after commencement of dopamine antagonists. A sudden significant rise in prolactin level or other signs of pituitary adenoma in such patients may require investigations for hyper-prolactinemia. It is usually not possible to discontinue treatment with psychiatric medications to assess the effect of these medications on prolactin level if baseline prolactin level is not recorded prior to commencement of these medications. One may consider switching to one of the few medications which do not increase prolactin levels however; this is not always possible and may be risky in patients who are symptomatically controlled with a specific medication. It is generally recommended not to treat such patients with dopamine receptor agonists to control prolactin levels but it has been done successfully in some patients to control symptoms of hyper-prolactinemia with good response (19).

Hence, many patients with pituitary micro-prolactinoma will not require any active treatment and monitoring alone may be sufficient. Women who wish to get pregnant during this monitoring can go ahead with pregnancy. Prolactin level rises during pregnancy and cannot be monitored during pregnancy as there are no agreed pregnancy specific values available. Such patients should have visual field assessments once every trimester during pregnancy. Breast feeding is not contraindicated in such patients. Active intervention is indicated if there is deterioration in visual fields during pregnancy. Such patients will require individualized care following discussion with Endocrinologists, Neurosurgeons and Obstetricians. However, the possibility of such a scenario is very low.

**Pharmacological treatment**

Pharmacological treatment is indicated in symptomatic micro-prolactinomas (20), for patients with infertility associated with hyper-prolactinemia and almost all macro-prolactinomas. Dopamine receptor agonists are first line agents. They are very effective not only in controlling growth of tumour but also to reduce tumour size soon after their commencement. The dose is usually gradually increased but treatment with higher doses for immediate response has been reported in literature. Bromocriptine is being used for a long time and is relatively easily available in Pakistan. It is usually started in a dose of 2.5 mg three times a day and can be increased at weekly intervals or according to patient response to 10 to 30 mg in a day in divided doses. Multiple daily dosing regimen and gastrointestinal side effects limit its use in some patients. This is the preferred dopamine receptor agonist to be used in pregnant women or in women planning to get pregnant. Cabergoline is the other dopamine receptor agonist. It is better tolerated of the two, lower treatment failure rate, better dosing regimen and better patient experience. It is usually started at a dose of 250 mcg (half a tablet of 500 mcg) once or twice a week. So far, this is not widely available in Pakistan. If possible, this should be the first line dopamine receptor agonist used in treatment of Prolactinomas. Higher doses of dopamine receptor agonists have been associated with cardiac adverse effects in animal studies. Monitoring of cardiac functions in patients taking low doses of dopamine receptor agonists remains a debatable subject. It is suggested to get a baseline echocardiogram done on patients prior to commencement of therapy and subsequently arrange more scans depending on clinical condition, dose of Cabergoline or at least, once a year. Dopamine receptor agonists are used in much smaller doses in treatment of prolactinoma and
none of the studies have so far conclusively proven adverse cardiac effect in patients treated for prolactinomas with dopamine receptor agonists. Quinagolide is a non-ergot dopamine receptor (D2) agonist which can be used as a second line agent if Bromocriptine or Cabergoline cannot be used. The availability of this agent remains an issue in Pakistan. Response is assessed by reduction in prolactin levels and is confirmed by repeat MRI pituitary scan in three to six months. It is very unlikely that there will be a reduction in tumour size if the prolactin level does not reduce with medications. In some patients prolactin level may not drop to normal range. This is especially found with very high baseline prolactin levels. Most of these patients will become symptoms free with reduction in tumour size despite marginally high prolactin levels. These patients are not considered as treatment failure however, if the prolactin level does not drop at all or it starts to persistently rise again following initial drop, such patients are classed as treatment failure. Cabergoline has the least of the treatment failure rate. It ranges from 10 – 13 % in different studies.

**Surgical treatment**

Surgery is neither the first line treatment nor the treatment of choice for almost all prolactinomas. The success rate for micro-prolactinomas is 70-75% but there always remains a possibility of affecting other pituitary hormones during surgery in addition to other possible complications potentially associated with a major neurosurgical procedure. In Pakistan, a significant proportion of patients with macro-prolactinomas undergo surgery as the primary treatment. The cure rate falls to only 30-35% in cases of Macro-prolactinomas. Assessment of prolactin level for all pituitary lesions remains key to diagnosis of prolactinomas and all such cases must be referred to appropriate centres with Endocrinology and Neuro-surgical expertise.

Healthcare professionals in Pakistan need to be mindful of the fact that post-surgical deficiency of other pituitary hormones on lifelong basis significantly affects lives of these patients. Neurosurgeons need to give it a serious thought before attempting any kind of pituitary surgery. We may be able to cure one condition but could potentially leave them with a lifelong complication of hypopituitarism. Each hormone secreted by pituitary gland is essential for normal functioning of an individual. Cortisol deficiency is not only associated with significant morbidity but also carries mortality if not managed properly. Availability of hydrocortisone also remains an issue especially outside big cities of the country. Same is true for thyroxin in cases of secondary hypothyroidism. Not only that growth hormone cost is out of reach for most patients in Pakistan the laboratory assessment of the hormone is also only available in a limited number of laboratories in the country. Since majority of patients with prolactinomas are young surgery is indicated in a selected group of patients with:

1. Prolactinoma is not responsive to pharmacological treatment or those who show progression of disease following initial response to pharmacological treatment.
2. Patient cannot or would not take medications (21,22)

Prolactin level may also be raised in non-functioning pituitary tumours compressing the pituitary stalk. Hypothalamus is believed to produce inhibitory effects on prolactin producing cells in pituitary gland through pituitary stalk. Suprasellar tumours or tumours with supra-sellar extension compress the stalk and can block this inhibitory effect, often termed as “stalk effect”. Treatment of primary tumour will help control prolactin levels in these patients. Prolactin level in these cases is usually not very high. Some studies have used prolactin level to differentiate between different causes of hyperprolactinemia but none of those have been conclusive enough to be used reliably in clinical practice. A prolactin level above 5.25 IU/L (250 μg/L) usually indicates the presence of a prolactinoma and a prolactin level greater than 10.5 IU/L (500 μg/L) is considered very suggestive of a macroadenoma. In some cases of macroadenomas prolactin levels are even far above 21.2 IU/L (1000 μg/L). In contrast, marginally elevated prolactin levels (usually below 2.1 IU/L (100 μg/L) are very suggestive of these large tumours as non-secreting tumours (23).
Other options

Radiotherapy is a last resort for treatment of prolactinomas. This should only be considered a treatment option in patients who cannot undergo surgery and cannot or would not take oral medications for prolactinomas. Success rates remain very low with radiotherapy and due to this not many well designed studies have been performed to accurately assess the success rate of this treatment option.

Treatment during Pregnancy

Many women attend Endocrinology clinic with high prolactin levels and menstrual irregularities due to effect of prolactin on their gonadotropins. This could affect ovulation and hence fertility. With medical treatment the prolactin usually settles in normal range with normalization of gonadotropin functions. Women with micro-prolactinoma are advised to discontinue their medications once pregnancy is confirmed. Medications are generally advised to be continued during pregnancy in patients with macro-prolactinoma. Many clinicians would discontinue medications even in patients of macro-prolactinoma if the tumour is away from optic chiasm and other vital structures. Formal visual field assessments should be carried out at least once, during each trimester. Women can breast feed after delivery and they are assessed after completion of breast feeding for starting pharmacological therapy again.

References:


