HYPERPROLACTINEMIA

Hyperprolactinemia is the most common pituitary disorder. It can occur in both genders, however it is more prevalent in women. About 5% of all women attending a family planning clinic were shown to have hyperprolactinemia. Women who have symptoms related to hyperprolactinemia have a much higher prevalence of the disorder, including approximately 25% of patients with galactorrhea and up to 70% of women who have both amenorrhea and galactorrhea. This disorder should be suspected in any patient with reproductive problems. The evaluation of patients with hyperprolactinemia is particularly important, in order to exclude serious cranial pathology, as well as to offer treatment for any associated symptoms.

CLINICAL FEATURES

The clinical features of hyperprolactinemia are shown in Table 1.

<table>
<thead>
<tr>
<th>TABLE 1. HYPERPROLACTINEMIA – CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypogonadism</td>
</tr>
<tr>
<td>- Amenorrhea</td>
</tr>
<tr>
<td>- Oligomenorrhea</td>
</tr>
<tr>
<td>- Infertility</td>
</tr>
<tr>
<td>- Decreased libido</td>
</tr>
<tr>
<td>- Impotence</td>
</tr>
<tr>
<td>• Galactorrhea</td>
</tr>
<tr>
<td>• Hirsutism, acne</td>
</tr>
<tr>
<td>• Mass Effect Symptoms (if macroadenoma)</td>
</tr>
<tr>
<td>- Headaches</td>
</tr>
<tr>
<td>- Visual loss (visual field deficits)</td>
</tr>
<tr>
<td>- Cranial neuropathies</td>
</tr>
<tr>
<td>- Hypopituitarism</td>
</tr>
<tr>
<td>- Temporal lobe seizures</td>
</tr>
<tr>
<td>- CSF rhinorrhea</td>
</tr>
<tr>
<td>- Hydrocephalus</td>
</tr>
<tr>
<td>- Hypothalamic Syndromes</td>
</tr>
</tbody>
</table>

DIAGNOSIS

In patients with clinical features of hyperprolactinemia, a prolactin should be measured. If high on two occasions, it is essential to determine whether the source of hyperprolactinemia is physiologic (Table 2) or pathologic (Table 3). If the disorder is pathologic, the next question is the source. This includes determining whether the patient has a prolactinoma versus whether the patient has a pseudoprolactinoma. This distinction is critical, because prolactinomas can be treated with medical therapy, (if there is an indication for treatment), whereas pseudoprolactinomas usually require surgical therapy. Additional questions to be addressed during the diagnostic evaluation are whether there is any evidence of hormone excess or deficiency, and whether there are mass effect symptoms.
TABLE 2. PHYSIOLOGIC CAUSES OF HYPERPROLACTINEMIA

- Pregnancy
- Post partum
- Nursing
- Nipple stimulation, intercourse
- Physical stress, exercise
- Food

TABLE 3. PATHOLOGIC CAUSES OF HYPERPROLACTINEMIA

- **SELLAR MASSES**
  - PITUITARY ADENOMAS
    - Prolactin-secreting
    - Corticotropin-secreting
    - Growth hormone-secreting
    - Gonadotropin-secreting
    - Thyrotropin-secreting
  - NONSECRETING
  - MALFORMATIONS AND HAMARTOMAS
    - Ectopic anterior pituitary
    - Hypothalamic hamartoma
    - Gangliocytoma
    - Mucocele
  - OTHER TUMORS
    - Craniopharyngioma
    - Meningioma
    - Chordoma
    - Schwannoma
    - Myoblastoma
    - Germ cell tumors
    - Vascular tumor
    - Metastases
    - Granular cell tumor
  - GRANULOMATOUS, INFECTIONS, INFLAMMATORY
    - Abscess (bacterial and fungal)
    - Sarcoidosis
    - Tuberculosis
    - Giant cell granuloma
    - Histiocytosis X
    - Lymphocytic hypophysitis
    - Echinococcal cyst
  - MISCELLANEOUS
    - Hemochromatosis
    - Empty sella syndrome
    - Arachnoiditis
    - Aneurysms

- **NEUROGENIC**
  - Chest wall lesions
  - Spinal cord lesions

- **MEDICATIONS**
  - Psychiatric medications (Phenothiazines, MAOIs, Fluoxetine, Butyrophenones, Tricyclics, Amoxapine etc)
  - Anti-hypertensives (Methyldopa, calcium channel blockers, Reserpine)
  - Miscellaneous (cocaine, metoclopramide, IV cimetidine)

- **MISCELLANEOUS**
  - Primary hypothyroidism
  - Seizures
  - Renal failure
  - Hepatic disease

Evaluation should include a TSH, a pregnancy test in amenorrheic women, a careful history for medications which elevate prolactin, and for other miscellaneous causes of hyperprolactinemia. A summary of the steps to be taken in the evaluation of hyperprolactinemia is shown in Table 4.
TABLE 4. EVALUATION OF HYPERPROLACTINEMIA

- Measure serum prolactin, repeat to confirm (perform in dilution if a large lesion to exclude “hook effect”)
- Exclude other causes of high prolactin
  - Pregnancy
  - Primary hypothyroidism
  - Medications
  - Miscellaneous
- Obtain head MRI scan
- If macroadenoma, evaluate for hypopituitarism and GH cosecretion

In every hyperprolactinemic patient who is not pregnant, does not have primary hypothyroidism, has no neurogenic or other miscellaneous cause and is taking no medication which would raise prolactin, head imaging is essential. This is true even in patients who have mild prolactin elevations. The preferred test is head MRI, with CT as a second choice; skull films should not be used. The primary purpose of head imaging is to exclude the possibility of a large mass causing “stalk hyperprolactinemia”. Any mass compressing the hypothalamus or stalk may interrupt the tonic inhibition of prolactin by hypothalamic dopamine, resulting in elevated prolactin. Prolactin levels correlate with tumor size in true prolactinomas. As in all pituitary tumors, prolactinomas are classified as microadenomas if they are <1 cm and as macroadenomas if they are larger than 1 cm. A patient with a large mass but only a mild prolactin elevation is unlikely to have a prolactinoma (or could have a poorly functioning/cystic prolactinoma that may not respond to medical treatment) and may need surgery.

TREATMENT

Indications for therapy of prolactinomas are shown in Table 5. A lesion of >1 cm is an indication for therapy, in order to prevent further tumor enlargement which might compromise the optic chiasm located just above the pituitary gland. Hypogonadism is an indication for therapy because of its association with osteoporosis in both men and women. Hyperprolactinemia diagnosed in the evaluation of infertility should be treated as well. Relative indications for therapy include acne, hirsutism and headaches (which are usually unrelated if the lesion is small; a circumscribed therapeutic trial can make this distinction). For patients without these treatment indications, natural history studies show that most patients with small microprolactinomas will remain stable. However, a small percent of patients may experience tumor enlargement, therefore all patients require long-term follow-up, including those being managed with observation alone.

TABLE 5. HYPERPROLACTINEMIA - TREATMENT INDICATIONS

- Macroadenoma
- Hypogonadism
- Infertility
- Significant galactorrhea
- Acne, hirsutism
- Possibly headaches (often not related)

Treatment options for hyperprolactinemia are shown in Table 6. The primary therapy for prolactinomas is medical, using either bromocriptine or cabergoline. These dopamine agonists are successful in normalizing prolactin, restoring gonadal function, and shrinking tumor mass in most patients with prolactinomas.
TABLE 6. TREATMENT OF HYPERPROLACTINEMIA

- Medical therapy - dopamine agonists
  - Bromocriptine
  - Cabergoline
- Surgery (needed infrequently)
- Radiation (rarely used)

Bromocriptine

This medication, which has been available for several decades, is initiated at a very low dose (1/4 of a 2.5 mg tablet) for patients with microprolactinomas and gradually increased over a period of a month. Patients with macroadenomas may need to be treated with more rapid dose escalations, particularly if they have visual field defects. All patients being treated for prolactinomas require periodic clinical, hormonal and radiologic evaluations.

The major difficulty with bromocriptine is that some patients experience side effects, including gastrointestinal symptoms and orthostatic hypotension. Dosing at bed time and with a snack may help minimize side effects. Intolerance to oral bromocriptine sometimes precludes its use. If the patient desires contraception, OCPs reverse the amenorrhea, but does not treat the tumor. While increased bone mass has been found in patients who had reversal of hyperprolactinemia, it is not known whether this effect is seen with OCP use alone. Alternative medical therapies directed at the hyperprolactinemia include intravaginal bromocriptine and cabergoline. In other countries, long acting IM bromocriptine and quinagolide may also be options.

Intravaginal Bromocriptine

The tablet is inserted vaginally. There is not an applicator available and this method of dosing does not have high patient acceptance. Because it is the same tablet as used orally, the cost is the same as oral bromocriptine. It has been shown that the GI side effects experienced with oral bromocriptine are significantly reduced when the medication is used vaginally.

Cabergoline

This is the longest-acting dopamine agonist, and is specific for the D2 receptor. It can be administered as infrequently as once a week in most microadenoma patients (although the approval by the FDA in the United States was for twice weekly). It is more expensive than bromocriptine. The tablets are 0.5 mg strength, with most microadenoma patients controlled on a dose of approximately ≤1 mg per week.

The largest study comparing bromocriptine and cabergoline was a European multi-center trial published by Webster et al. A total of 459 women, the majority of whom had a microprolactinoma and amenorrhea, were treated with either cabergoline or bromocriptine in a study with an initial double-blind phase. The main findings of the study included that cabergoline was more effective at normalizing prolactin (52% taking bromocriptine versus 92% taking cabergoline) and at restoring menstrual function (68% taking bromocriptine versus 82% taking cabergoline). Additionally, cabergoline was
better tolerated, with 27% of patients discontinuing oral bromocriptine due to intolerance, compared with only 3% of patients discontinuing cabergoline.

It has also been shown by Colao et al. that many patients who are resistant to bromocriptine or other dopamine agonists may respond well to cabergoline. Therefore, in addition to patients who are intolerant of bromocriptine, those who are nonresponders to bromocriptine may also do well with cabergoline. A 2003 NEJM study and several subsequent reports showed that in a carefully selected subset of patients, when cabergoline is withdrawn, some patients do not experience recurrent hyperprolactinemia in the short term (some recurred later). Regular follow up is essential when this is done clinically; further study is needed.

Two NEJM papers in 2007 showed a slightly increased risk of cardiac valve abnormalities in Parkinson’s patients treated with high dose cabergoline. In all but one study in Parkinson’s patients (Tan), bromocriptine has not been shown to have any effect on heart valves. The implications for patients with hyperprolactinemia, most of whom are treated with much lower doses, are not yet clear. There have been over 10 publications evaluating cardiac valve function in patients with hyperprolactinemia taking cabergoline since then; all but one (Colao) show no attributable moderate or severe abnormalities (including Lancellotti, Bogazzi, Kars, Vallette, Wakil, Devin, Herring, Nachtigall). Six of the studies show no difference in valve function between hyperprolactinemic patients taking caberoline and controls. However a few show mild TR, valve thickening, tenting, and calcifications (Wakil, Kars, Lannelotti). Some endocrinologists now prescribe bromocriptine rather than cabergoline as the first line dopamine agonist and/or obtain cardiac echos. Further study of this topic is ongoing.

**Pregnancy**

Although there are no dopamine agonists approved for use during pregnancy in the United States, there are substantial published data supporting the safety of bromocriptine when used for women with infertility due to hyperprolactinemia. In contrast, there are limited data regarding pregnancies in which cabergoline was administered at the time fertility was achieved. While there is no evidence to date that cabergoline is teratogenic, the number of subjects is not large enough to be confident about this. Therefore, bromocriptine use is suggested when fertility is desired. When pregnancy is achieved, the dopamine agonist is discontinued, and if the lesion was a macroadenoma, the patient is followed with regular visual field examinations during the pregnancy.

**Surgery**

While most patients can be managed medically, the indications for surgery in hyperprolactinemia are shown in Table 7.

<table>
<thead>
<tr>
<th>TABLE 7. HYPERPROLACTINEMIA – INDICATIONS FOR SURGERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Intolerance to dopamine agonists</td>
</tr>
<tr>
<td>• Resistance to dopamine agonists (persistent visual loss, tumor growth, etc.)</td>
</tr>
<tr>
<td>• Pituitary apoplexy</td>
</tr>
<tr>
<td>• Psychiatric medications</td>
</tr>
<tr>
<td>• Large lesion with a major cystic component</td>
</tr>
</tbody>
</table>
REFERENCES