Prolactin-secreting pituitary adenoma, or prolactinoma, is the most common type of secretory pituitary tumor. Neither etiology nor pathology of the development or progression of prolactinomas is known with certainty. They appear to arise independently out of the pituitary gland itself and are not related in growth to any degree of hypothalamic dysfunction.

The majority of prolactinomas appear to develop slowly, over the course of years in most cases. Autopsy studies show that up to 25 percent of individuals have growths consistent with prolactinoma; most however had no evidence of any endocrinologic dysfunction and serum prolactin levels are only slightly, if at all elevated.

The clinical presentation to a physician of hyperprolactinemia varies according to age, sex and degree of prolactin elevation. Obviously degree of tumor size correlates as well, but increases in prolactin don't always mirror size of the lesion itself. Men who have prolactinoma usually present with signs such as visual disturbance, headache, or cranial nerve involvement. Women are more likely to present with more age related symptoms. Those with prolactinoma in the teen years may present with delayed or absent menarche, those in reproductive age with either a disturbed pattern of menses or galactorrhea. Galactorrhea presents in some 30 to 70 percent of those with prolactinoma and is usually related to the duration of gonadal dysfunction; women with long-standing menarche are less likely to have galactorrhea postulated on the fact that it more reflects prolonged estrogen deficiency.

There are other significant presentations to be aware of. Men may complain of decreased sexual function, impotence or infertility in the course of a work-up for same. Visual field cuts may be a presentation when the tumor involves the optic chiasm; beachcomber hemianopsia appears to be the most common finding. In addition, those who have skull X-rays, CT scans, or MRI imaging for completely unrelated reasons (e.g. trauma) may have this as the first presenting sign of a potential problem.

During evaluation of a patient with suspected or documented pituitary tumor or just hyperprolactinemia with no initial localizing signs, pituitary function testing is a key. Certain conditions unrelated to pituitary tumor can be ruled out clinically; these include Cushing's syndrome, acromegaly and hypothyroidism (the degree of hypothyroidism usually must be quite significant to elevate prolactin levels.

Medications can significantly increase prolactin levels. Dopamine receptor antagonists such as chlorpromazine (Thorazine), Fluphenazine (Stelazine), Haloperidol (Haldol), and Metoclopramide (Reglan) are among some of the more common ones, which also include perphenazine, promazine, domperidone and sulpiride. Antihypertensives, such as methyldopa, reserpine and verapamil also cause elevations in prolactin in many people taking them. Other common drugs that must be first ruled out as a cause for the elevation in prolactin include estrogen containing medication (both oral contraceptives and estrogen replacement therapy), opiates, and cimetidine (Tagamet).

Isolated elevations in prolactin levels can be obtained, so that more than one elevated value is needed to confirm the diagnosis. measures of serum prolactin, thyroxine (T-4) and thyroid stimulating hormone (TSH) are made in all cases. Leutinizing hormone (LH), Follicle stimulating hormone (FSH), estradiol, and a pregnancy test (beta-hCG) are obtained in women; testosterone is substituted for these in men. A morning cortisol concentration is used as a screen for adrenal function; more sophisticated testing may be used if this is in a questionable range such as insulin-induced hypoglycemia, or metyrapone testing to determine if the hypothalamic-pituitary-adrenal axis is intact.

Imaging with CT or MRI scanning is the next logical step when hyperprolactinemia is real, sustained, and/or associated with other signs of neurologic compromise that may indicate a brain lesion. Mild or moderate hyperprolactinemia (levels anywhere from 15 to 50 ug/l) are most likely due to microprolactinoma (a growth generally less than 10 mm in size). A serum prolactin concentration of greater than 200 ug/l in the presence of a macroadenoma (size greater than 10 mm) is most likely due to a prolactinoma. A serum prolactin between these ranges in the sitting of a pituitary tumor demonstrated on radiographic imaging most likely represents secondary hyperprolactinemia resulting from the mechanical effects of a non-prolactin secreting tumor that compresses the pituitary stalk or interferes with the transport of dopamine from the hypothalamus to the anterior pituitary. This distinction is particularly important in selecting

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appropriate therapy; agonists that will work on prolactinomas as a cause of increased prolactin are much less effective when a different primary growth is involved.

Lactotrope adenomas are the most common pituitary adenoma in surgical series, compromising between 25 and 50 percent of primary surgical pathology. Other causes of primary tumor causing prolactin elevations include metastasis from other primary growths (e.g., colon and lung), craniopharyngioma, germinoma, glioma or simple cyst. Infiltrative disease, such as sarcoidosis, tuberculosis, histiocytosis X and nonspecific granulomas are not uncommon. Pseudotumor cerebri, non-secretory tumors, meningioma and intracellular germinomas are also implicated in ultimate findings.

Sometimes non-pathologic findings may be a cause of hyperprolactinemia and/or galactorrhea. Neurogenic causes, such as breast manipulation, chest wall lesions, and both physical and psychological stress are recognized causes of increased prolactin, although not into the 200 range, for example. Advanced disease on the other hand, such as chronic renal failure and cirrhosis, may also cause increased prolactin found incidentally in a workup for sexual dysfunction but do not result in other primary brain pathology being found.

The choice of therapy must meet certain defined therapeutic objectives. These include correction of the presenting abnormality (when symptomatic), reduction or removal of tumor mass, preservation of anterior and pituitary function, restoration and maintenance of normal gonadal function for both men and women and prevention of progression of disease. All depend on the prompt recognition of the cause of the hyperprolactinemia and specific therapy directed to it.

Surgical therapy for prolactinomas has been the mainstay until effective medical therapy was developed. Transsphenoidal resection of the demonstrated adenoma is most frequently employed and is associated with better results and less morbidity than other surgical procedures. People with microadenomas (less than 10 mm in size) treated in centers with large experience have 60 to 80 percent full success rates of bringing prolactin levels to normal; these percentages drop to less than 40 percent with macroadenomas. Transsphenoidal surgery is a recommended option in prolactinomas unresponsive to medical therapy, those with prolactin levels less than 200 ug/l and in those affected who refuse long-term medical therapy.

Medical therapy has increased as a primary mode of treatment. The drug of choice is bromocryptine (Parlodol), which is effective in reducing plasma prolactin levels, inducing ovulation in females and restoring proper gonadal function in males. Prolactinoma size may be substantially reduced in a matter of weeks, and even neurological findings such as visual abnormalities may be promptly reversed. However, there are two significant considerations. First, the degree of prolactin suppression is variable and may not always be enough to relieve significant symptoms. Second, withdrawal of therapy is often followed by prompt recurrence of prolactinemia and a reappearance of the offending symptoms. Medical therapy is still, however, a mainstay in prolactinomas of small to moderate size and in symptomatic hyperprolactinemia.

Observation only has also become an accepted modality in many cases. Those with asymptomatic hyperprolactinemia of moderate degree and those who have suspected microprolactinomas that cannot be adequately demonstrated for localization on radiographic imaging are often followed without definitive treatment for long periods of time without untoward effect.

Those with other specific causes are treated specifically with those affections in mind. Larger tumors causing compression and other symptoms may be summarily resected. Pituitary disease such as acromegaly and Cushing's is treated more specifically. Correction of hypothyroidism, specific treatment for infiltrative disease (tuberculosis, sarcoid, etc.) are treated and underwritten with the primary disease process in mind.

Underwriting prolactinoma successfully involves recognizing not only the cause but the possible complications of treatment. Most cases of microadenoma with no suprasellar extension and those where prolactin is found to be incidentally elevated with no primary cause found can be taken standard. Sometimes, however, those who opt to undergo transsphenoidal or transfrontal surgery have, as a possible complication, the possibility of developing either anterior or posterior pituitary insufficiency as a result of the operation. These are not major mortality implications given optimal medical treatment, but must be considered in the overall picture if and when they do occur.

Macroadenomas, both with and without suprasellar extension, should probably be mildly rated in the 50 to 100 percent extra mortality range. Although surgery is effective in debulking larger tumors and may be curative for smaller tumors, the potential for recurrent hyperprolactinemia and presumptive tumor re-growth must be taken into consideration. Recurrence rates in up to five years of follow-up range from 10 to 50 percent in those with microadenoma and up to 80 percent in those with macroadenoma.

Those who must take replacement hormone, such as cortisone, may be initially rated but degree of compliance and pituitary compromise should be taken into account. The conditions where other tumors are the cause of the increased prolactin or other medical conditions are the cause of the elevated prolactin should be underwritten with the primary disease in mind.

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