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Functioning Pituitary Adenoma

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1. Introduction

Pituitary adenomas are typically benign, slow-growing tumors that arise from cells in the pituitary gland. Those are classified based on secretory products (1). The functioning (endocrine-active) tumors include almost 70% of pituitary tumors which produce 1 or 2 hormones that are measurable in the serum and cause definite clinical syndromes that are classified based on their secretory product(s). Non-functioning adenomas are endocrine-inactive tumors (2). Because of the physiologic effects of excess hormones, functioning tumors usually present earlier than non-functioning adenomas (3). On the other hand, mass effect from large pituitary adenomas (often due to endocrine-inactive tumors) may lead to pressure symptoms such as headaches, visual field defects (typically loss of peripheral vision), cranial nerve deficits, hypopituitarism (compression of normal pituitary gland), pituitary apoplexy (sudden bleeding or infarction from outgrowing tumor blood supply), or stalk dysfunction (4). Compression of pituitary stalk is termed "stalk effect" which can cause a mild elevation in prolactin, and must be differentiated from a prolactinoma (5).

The purpose of this chapter is to review all types of functioning pituitary adenoma (prolactin, ACTH, GH, TSH, LH and FSH secreting) from studies indexed in PubMed. We describe the symptoms, epidemiology, diagnosis, management, outcome and complications of each.

2. Prolactinoma

This type of pituitary adenoma arises from neoplastic transformation of anterior pituitary lactotrophs and produces an excessive amount of hormone prolactin. A prolactinoma is the most common cause of chronic hyperprolactinemia once pregnancy, primary hypothyroidism, and drugs that elevate serum prolactin levels have been excluded (6).

2.1 Symptoms

In female patients, even small prolactinomas can cause irregular menstrual periods or complete loss of menses. Higher prolactin levels lead to galactorrhea in women, whereas men may experience gynecomastia. In male patients, altered spermatogenesis with oligospermia and infertility may be found; galactorrhea and gynaecomastia are much less frequent. Hypogonadism, reduced libido and infertility are the most frequent symptoms in both genders. Patients can also present with osteopenia and osteoporosis (due to estrogen and testosterone deficiency, not due to the elevated prolactin itself). Large prolactinomas, more commonly found in men, may cause mass effect from the tumor (5-9).

2.2 Epidemiology

The estimated prevalence of prolactinoma is 100 per million adults (10). Prolactinomas are the most common hormone-secreting pituitary tumors, representing approximately 40% of all pituitary tumors (8, 11, 12). Recent data show a high prevalence of prolactinoma in the general population, 3-5 times more than the previously reported ones (13). The incidence of prolactinomas varies with age and sex; these tumors occur with the highest frequency in women aged 20–50 years, at which point the ratio between the sexes is estimated to be 10:1. In adults aged >60 years, prolactinomas occur with a similar frequency in both sexes (12). Men generally have macroadenomas (≥10mm diameter) whereas women generally have microadenomas (<10mm) (6, 13, 14). The mean age at diagnosis is 10 years greater in men. This delay possibly accounts for their greater incidence of macroprolactinomas with visual field defects and hypopituitarism at first presentation (15).

2.3 Diagnosis

A serum prolactin level is acquired in response to a specific presentation, including symptoms of hyperprolactinemia (such as amenorrhea and galactorrhea) it may also be an integral part of an infertility assessment. An initial level above the normal range should be followed by a repeat level from a blood sample drawn in the morning with the patient in a fasting state. When hyperprolactinemia is confirmed, a cause for the disorder needs to be sought. This involves a careful history and examination, followed by laboratory tests and diagnostic imaging of the sella turcica. If serum prolactin levels are above 200 μg/L, a prolactinoma is almost certainly the underlying cause, but if levels are lower, the differential diagnoses include pregnancy, treatment with drugs (such as neuroleptics) that reduce dopaminergic effects on the pituitary, compression of the pituitary stalk by other pathology, primary hypothyroidism, renal failure, cirrhosis, chest wall lesions, or idiopathic hyperprolactinemia. In the absence of such causes, radiologic imaging of the sella turcica is necessary to establish whether a prolactinoma or other lesions are present (4, 6, 16).

2.4 Management

The main purpose of treating prolactinomas, both micro- and macroprolactinomas, are to suppress excess hormone secretion and its clinical effects, to remove the tumor mass, and to prevent disease return or progression (16, 17). If there is no indication for therapy (such as amenorrhea, infertility or bothersome galactorrhea), microadenomas may be followed conservatively, and regular follow-up with serial prolactin measurements and pituitary

imaging should be organized (6, 16). Most prolactinomas can be effectively treated with dopaminergic drugs as primary management. For most patients, medical therapy produces normalization of prolactin secretion, gonadal function, and considerable tumor shrinkage in the majority (16). The most commonly used dopamine agonists are bromocriptine, cabergoline (ergot derivatives) as well as quinagolide (a non-ergot derivative) (4, 18). Bromocriptine (D_2 receptor agonist and D_1 receptor antagonist) is the oldest drug for medical treatment of prolactinomas, and normalizes prolactin levels in 80-90% of microprolactinomas and 70% of macroprolactinomas. Tumor-mass shrinkage and improvement of visual-field deficits are commonly achieved in macroprolactinomas. Bromocriptine frequently can cause several side effects such as nausea, vomiting, postural hypotension, headache and dizziness (12). Cabergoline (a selective D_2 receptor agonist) is very effective and well tolerated in more than 90% of the patients with either microprolactinomas or macroprolactinomas. Cabergoline treatment also induces tumor shrinkage in most macroprolactinomas. If patients have not previously been treated with other dopamine agonists, tumor shrinkage is more evident (17). When comparing the plasma half-life, efficacy and tolerability of these drugs, cabergoline seems to have the most favorable profile, followed by quinagolide (16). As a well tolerated and effective therapy and a simple dosing regimen, quinagolide (selective D2 receptor agonist) can also be considered a first-line therapy in the treatment of hyperprolactinaemia (19). Pergolide (a D1 and D2 agonist) normalizes prolactin excess and reduces tumor size in recently diagnosed patients with macroprolactinomas with a potency of about 100-fold that of bromocriptine (20). However pergolide as approved treatment for prolactinomas was withdrawn in 2007 because of adverse effects on cardiac valves (12).

If prolactin levels are well controlled with dopamine agonist therapy, gradual tapering of the dose to the lowest effective amount is recommended, and in some cases medication can be stopped after several years. Evidence to date suggests that cabergoline and quinagolide appear to have a good safety profile for women who wish to conceive, but hard evidence proving that dopamine agonists do not provoke congenital malformations when taken during early pregnancy is currently only available for bromocriptine. Once pregnant, dopamine agonist therapy should be immediately stopped, unless the growth of a macroprolactinoma or pressure symptoms is likely to occur (4, 16). Hyperprolactinemia may recur after dopamine agonist withdrawal in a considerable proportion of patients. The probability of successful treatment was highest when cabergoline was used for at least two years (21).

Surgery is generally used as second-line treatment in prolactinomas (22). Transsphenoidal surgery is an alternative for patients who are intolerant of or resistant to dopamine agonists or when hyperprolactinemia is caused by non-prolactin-secreting tumors compressing the pituitary stalk (4).

Because pituitary adenomas respond well to radiation, radiotherapy has been a part of their management for the past three decades (23). Radiotherapy is given if both pharmacologic therapy and surgery fail (4, 16). However, Sasaki et al. reported that the local control rate for secreting adenomas by radiotherapy is unsatisfactory (23).

Gamma knife radiosurgery can be offered as a safe and effective treatment option especially for those patients with recurrent or residual pituitary adenoma after surgical removal. The

tumor control rate after gamma knife radiosurgery for pituitary adenomas is equivalent to fractionated radiation therapy (24).

Some experimental treatments have been attempted, such as somatostatin analogues, hybrid molecules (both somatostatin and a dopamine agonist in a single molecule), selective estrogen receptor modulators, prolactin-receptor antagonists, and temozolomide are utilized in selected case reports or in trial settings. These have not yet been included in standard medical practice (12).

2.5 Outcome

The ultimate goal of therapy for prolactinomas is restoration or achievement of eugonadism through the normalization of hyperprolactinemia and control of tumor mass (11). Medical and surgical therapies generally have excellent results, and most prolactinomas are well controlled or even cured in some cases (19). Dopamine agonists are the preferred therapy for prolactinomas because of the risk of recurrent hyperprolactinemia that accompanies transsphenoidal surgery (25, 26). Dopamine agonists are the first line of therapy for macroprolactinomas, resulting in normalizing prolactin levels in 85%, inducing tumor shrinkage in 57%, and long-term remission rates in 22% of the patients (11, 27).

Surgery should be reserved for patients with dopamine agonist resistance or intolerance. Success rates after surgical treatment of microadenomas range from 73–90% and 30–50% for macroadenomas, with little morbidity and near zero mortality (28). However, subsequent relapse is possible in up to 20% of the cases (22). Surgical outcomes are highly dependent upon the expertise and experience of the neurosurgeon (11, 22).

Following radiotherapy the prevalence of subsequent hypopituitarism is high; therefore, this therapy should be carefully considered, and rather be indicated for mass control than for hyperprolactinemia (27).

Overall, patients with pituitary adenoma treated with surgery and radiotherapy have an increased risk of cerebrovascular motrtality compared to the general population, which mirrors the increased incidence of stroke (29).

2.6 Complications

As mentioned in the symptoms section, prolactinomas left untreated may lead to various complications. In both women and men, prolactinoma can cause reduced libido, infertility and osteoporosis. Women with prolactinoma may experience complications during pregnancy. A woman who has a large prolactinoma and becomes pregnant may experience additional pituitary growth and associated mass effect. Prolactinoma may also lead to impaired glucose tolerance and diabetes. If tumor grows large enough, prolactinoma may cause visual loss, headache and hypopituitarism. Disturbances of the haemostatic system and dyslipidemia may lead to excess mortality in patients with prolactinoma (5-9, 30, 31).

3. ACTH secreting PA

Approximately 80% of the cases of Cushing's syndrome are due to the excessive secretion of adrenocorticotropic hormone (ACTH). This is usually (60-80%) due to a pituitary corticotroph adenoma and is defined as Cushing's disease (2, 32).

3.1 Symptoms

Cushing's syndrome refers to clinical manifestations induced by chronic exposure to excess glucocorticoids. The most common symptom of glucocorticoid excess is centripetal fat deposition which is frequently the initial symptom of the patient.

Fat accumulates in the face as well as supraclavicular and dorsocervical fat pads, resulting in a typical moon face and buffalo hump, which is most often accompanied by facial plethora. Fat also accumulates over the thorax and the abdomen, which becomes protuberant (33).

Other symptoms and signs include obesity; protein-wasting features such as skin thinning, large and purple abdominal striae, multiple ecchymotic lesions or purpura generated by minimal trauma, lower limb edema, spontaneous ruptures of tendons, slow healing of minor wounds, muscle atrophy, particularly in the lower limbs; bone wasting such as osteoporosis, pathological fractures, kyphosis and loss of height (34, 35); impaired protection mechanism against infections (36); high blood pressure and cardiovascular complications (37, 38); hirsutism; gonadal dysfunction (39); psychic disturbances such as anxiety, irritability, sleep disorders, depression, maniac disorders, delusions and/or hallucinations (40); and decreased short-term memory and cognition (41).

3.2 Epidemiology

The prevalence of Cushing's disease is approximately 40 per million. ACTH-producing adenomas comprise 10-20% of pituitary adenomas (42). Cushing's disease is nine times more common in women than men(2).

3.3 Diagnosis

The clinical history is important to assess the general impact of hypercortisolism on organs and systems as well as to guide suspicion toward more aggressive entities such as the ectopic ACTH syndrome or to detect an iatrogenic etiology of Cushing's syndrome (43). Initial diagnosis is performed using tests such as urinary free cortisol, nocturnal salivary cortisol and 1 mg dexamethasone suppression that are sensitive but not specific, and still require established assessment criteria(44). A dexamethasone- corticotrophin releasing hormone (CRH) test can discriminate between Cushing's syndrome and pseudo-Cushing's syndrome. If ACTH is elevated, combinations of high-dose dexamethasone tests, CRH/desmopressin tests, and pituitary magnetic resonance imaging can indicate a pituitary source. Discrimination from an ectopic ACTH tumor often requires inferior petrosal sinus sampling to confirm the source of ACTH. If ACTH is low, adrenal computed tomography will identify the adrenal lesion(s) implicated. Some cortisol-producing adrenal tumors or, more frequently, bilateral macronodular hyperplasia, are under the control of aberrant membrane hormone receptors, or the altered activity of ectopic receptors (43-46). Sophisticated imaging and isotopic techniques play a significant role in locating the source of ACTH in ectopic syndromes but are not always effective. In general, biochemical and imaging tests should be combined in order to assess different mechanisms and perspectives of the syndrome. Rigorous methodology is essential to obtain accurate results, allowing a correct diagnosis and in improving therapeutic performance in this devastating disease (43).

3.4 Management

The best treatment option for Cushing's disease is when the responsible corticotroph adenoma can be entirely removed surgically by the trans-sphenoidal approach, with sufficient skill to preserve normal anterior pituitary function (32, 46). This induces remission in approximately 80% of the patients, but long-term relapse occurs in up to 30% of these cases (45). The choice of second-line therapy remains controversial (46). Repeat surgery can be successful when residual tumor is detectable on magnetic resonance imaging; however, it carries a high risk of hypopituitarism. The histological pseudocapsule of a pituitary adenoma is a layer of compressed normal anterior lobe that surrounds the adenoma and can be used during surgery to identify and guide the removal of the tumor. With this approach, the overall remission rate is high and the rate of complications is low (47). Radiotherapy combined with ketoconazole or radiosurgery was recently found effective, but a longer-term evaluation of hypopituitarism and brain function is required. As soon as residual tumor progresses, surgery and radiotherapy should be initiated. Various drugs which inhibit steroid synthesis (ketoconazole, metyrapone, aminoglutethimide, mitotane) are sometimes temporarily effective for rapidly controlling hypercortisolism either in preparation for surgery, after the unsuccessful removal of the etiologic tumor, or while awaiting the full effect of radiotherapy or more definitive therapy (45). Other modes of radiotherapy (heavy particles, stereotactic radiosurgery with gamma knife) are limited to specialized centers. Despite initial enthusiasm for gamma knife (48), a relapse rate of up to 20% has been reported following treatment. It may, however, be more rapid than conventional radiotherapy in onset of lowering cortisol levels (49).

3.5 Outcome

The long-term follow-up of patients treated for Cushing's disease should include the adequate replacement of glucocorticoids and other hormones, treatment of osteoporosis, and detection of long-term relapse of Cushing's disease (45). Following pituitary surgery, careful ongoing expert endocrine assessment is mandatory, as the incidence of relapse increases with time and also with the increasing rigor of the endocrine evaluation. (50).

3.6 Complications

Today, cardiovascular and psychiatric co-morbidities still remain the major life-threatening complication. The final prognostic criterion for Cushing's syndrome lies in the severity of the hypercortisolism and the aggressiveness of the responsible tumor (37, 46). Bone wasting results in generalized osteoporosis. The prevalence of bone demineralisation assessed by bone mineral density using dual energy X-ray absorptiometry is about 40% (51). Compression fractures of the spine are evident on plain radiographs in about 20% - 80% of the patients, depending on the studies, and almost half the patients complain about backache. Kyphosis and loss of height, sometimes dramatic, are frequent. Pathological fractures can occur elsewhere, particularly in the ribs, feet and pelvis (36). Transient features of brain atrophy can disappear after cure (52). Impaired quality of life may persist years after controlling hypercortisolism (53).

4. GH secreting PA

Excessive secretion of growth hormone (GH) is responsible for acromegaly (54). This disease is almost always due to a GH-secreting pituitary adenoma. It is distinguished by a gradual

progressively acquired somatic disfigurement (primarily involving the face and extremities) and leads to acromegaly: a disorder of disproportionate tissue, skeletal, and organ growth (55, 56).

4.1 Symptoms

Because of the insidious onset and slow progression, acromegaly is frequently diagnosed from four to more than ten years after its onset (57). Patients usually display coarsened facial appearance, acral enlargement, increased skin thickness and soft tissue hyperplasia. Other manifestations include increased sweating, goiter, joint involvement, carpal tunnel syndrome, visual abnormalities, headache, colon polyps, sleep apnea, reproductive disorders, metabolic disturbances (hypertriglyceridemia, reduced insulin sensitivity), and cardiovascular disease (cardiac hypertrophy, hypertension, arrhythmias, and cardiomyopathy) (57-59).

4.2 Epidemiology

The prevalence is estimated to be 40-130 per million inhabitants, with 3-4 new cases per million populations per year (55, 58). It is most often diagnosed in middle-aged adults (average age 40 years). Men and women are equally affected (57).

4.3 Diagnosis

The measurement of fasting or random GH and of Insulin-like Growth Factor 1 (IGF-1) are baseline biochemical criteria for the diagnosis of acromegaly. A random GH level lower than 0.4 µg/l and an IGF-1 value in the age- and sex-matched normal range exclude the diagnosis of acromegaly. When these two parameters are dissonant, a 75 gram oral glucose tolerance test (OGTT) should be performed: a fall of serum GH to 1 µg/l or less within two hours will exclude acromegaly (60, 61).

Measurement of circulating GH-releasing hormone (GHRH) is the preferred test for the differential diagnosis between GH-secreting pituitary adenoma and ectopic GHRH secretion. Stimulatory tests (thyroid releasing hormone (TRH) stimulation test or gonadotropin releasing hormone (GnRH) stimulation test) provide no advantage over OGTT, and their use is not recommended for diagnosis (58).

Acromegaly is caused by an adenoma of the pituitary gland in more than 98% of all patients. The size of the tumor and its expansion should be documented by MRI. If the tumor expands into the suprasellar space and/or laterally beyond the cavernous sinus, an ophthalmological assessment is suggested to determine the possible impairment of the visual field and function of oculomotor nerves (58).

4.4 Management

The goal of treatment is to relieve symptoms, to obtain control of local tumor mass, and to reduce morbidity and mortality. Treatment options include surgery, medical therapy and radiotherapy. Transsphenoidal surgery is the first choice of treatment when a definitive cure can be achieved, mainly in the cases of microadenomas and when decompression of surrounding structures (optic chiasm, ophthalmic motor nerves) is indicated. This treatment

is the first-line therapy except when the macroadenoma is giant or if surgery is contra-indicated. Primary medical therapy should be conducted in patients bearing macroadenomas with significant lateral extension. In addition, preoperative primary medical therapy may result in tumor shrinkage, facilitating tumor resection, and may reduce preoperative complications due to GH excess. Within the spectrum of medical therapy, long-acting somatostatin analogues (somatostatins) are considered as primary therapy. Treatment with somatostatins results in GH control in about 60% of the cases. Somatostatins also induce tumor contraction in 30-50% of the patients, most effectively when applied as first-line treatment. Prolonged treatment with somatostatins is safe and well tolerated. Octreotide and lanreotide (two currently available somatostatins) appear to have equal effectiveness. In patients with suboptimal clinical and biochemical response to somatostatins, combination therapy with dopamine receptor agonists or pegvisomant (a new GH-receptor antagonist) typically leads to effective disease control. New developments in the medical therapy of acromegaly include the universal somatostatin receptor agonist pasireotide, and chimerical compounds that interact with both somatostatin and dopamine receptors with synergizing effects on GH secretion (54, 58, 62, 63).

If surgery fails, medical therapy should be started or reinstated. Dopaminergic drugs might be considered for a small group of patients with mildly elevated GH/IGF-1 levels or harboring GH-prolactin co-secreting adenomas (64, 65). The use of radiotherapy (fractionated, or by gamma-knife) appears to be justified as a treatment of last resort in patients with tumors progressively growing and unresponsive to somatostatins, and in a small group of patients who bear aggressive pituitary adenomas invasive of local structures including the cavernous sinus and even the temporal lobes. These tumors occur more frequently in younger patients, for whom the concerns about radiation-dependent hypopituitarism and second tumor formation are higher. Therefore several considerations must be taken into account when choosing an individualized treatment program for each patient (63, 66).

4.5 Outcome

Rheumatologic, cardiovascular, respiratory and metabolic consequences are major factors that determine the prognosis (55). The control of GH and IGF-1 secretion is the main goal of treatment, since normalization of these two parameters is the most significant determinant of reversing the increased mortality rate of the patients. The outcome of transsphenoidal surgery is far better for microadenomas (80-90%) than for macroadenomas (less than 50%), which unfortunately represent more than 70% of all GH-secreting pituitary tumors. Therefore, pituitary surgery is the first line treatment for microadenomas (58). Indeed, survival in acromegaly is restored to that observed in the general population after correction of GH/IGF-1 hypersecretion, while morbidity (obstructive sleep apnea, carpal tunnel syndrome, cardiac dysfunction, and diabetes mellitus) is markedly improved by lowering IGF-1 levels(67).

4.6 Complications

Acromegaly is a slowly progressive disease characterized by a 30% increase of mortality rate for cardiovascular disease (atherosclerosis, cardiomyopathy), respiratory complications, arthrosis and malignancies. Patients with acromegaly display an enhanced mortality rate,

cardiovascular disease represents the cause of death in 60%, respiratory disease in 25% and malignancies in 15% of the cases. High GH levels, high blood pressure and heart disease represent the major negative survival determinants in acromegaly, whereas symptom duration, diabetes mellitus and cancer play a minor role in determining mortality (54, 58). If the condition is untreated, enhanced mortality due to cardiovascular, cerebrovascular, and pulmonary dysfunction is associated with a 30% decrease in life span (56).

5. TSH secreting PA

Thyroid stimulating hormone (TSH) secreting pituitary adenomas are a rare cause of secondary or central hyperthyroidism (68, 69). The pathogenesis of TSH-secreting-adenomas is indefinite and no definite role for various oncogenes has been demonstrated (70). Based on the Clarke et al. study, these tumors are often delayed in diagnosis, are frequently macroadenomas and plurihormonal in terms of their pathological characteristics, have a heterogeneous clinical picture, and are difficult to treat (71). Sometimes mixed pituitary tumors co-secrete TSH, growth hormone and prolactin (70).

5.1 Symptoms

Because of the long standing duration of the disease, patients present mild or moderate signs of hyperthyroidism and can rarely be asymptomatic (68, 72, 73). In addition, mass effects of the pituitary tumor such as loss of vision and visual field defects may be occurred (70, 73). Moreover, hyperthyroid features can be eclipsed by those of acromegaly in patients with mixed TSH/GH adenomas, thus emphasizing the importance of systematic measurement of TSH and free thyroxin (FT4) in patients with pituitary tumor (74).

5.2 Epidemiology

TSH secreting tumors account for 0.9 to 2.8% percent of all pituitary adenomas. The diagnosis of these tumors has been increasing in the past 20 years (69). Most patients have macroadenomas, and microadenomas are exceptional (75).

5.3 Diagnosis

Hormonal evaluation shows increased free thyroid hormone concentration with detectable, normal or increased serum TSH level, raising the differential diagnosis of pituitary resistance to thyroid hormone (72). Ultrasensitive TSH assays allow a clear distinction between patients with suppressed and those with non-suppressed circulating TSH concentrations, i.e. between patients with primary hyperthyroidism (Graves' disease or toxic nodular goiter) and those with central hyperthyroidism (TSH-secreting adenomas or pituitary resistance to thyroid hormone action) (73). The MRI discloses the pituitary adenoma (72). A (99 m) Tc-octreotide scan can be a useful tool for confirming diagnosis of TSH-secreting adenoma (76).

5.4 Management

Therapy of TSH-secreting adenomas can be accomplished by surgery, radiation therapy, and medical treatment with somatostatin analogs or dopamine agonists (70).

The major aim is to remove the pituitary tumor and restore euthyroidism. Thus, the first therapeutic approach to TSH-secreting pituitary microadenomas should be the transsphenoidal or subfrontal adenomectomy, the choice of the route depending on the tumor volume and its suprasellar extension. This may be complex because of the occasional marked fibrosis of these tumors, possibly related to high expression of basic fibroblast growth factor (68, 77). In patients with macroadenomas or invasive pituitary tumors, long-acting somatostatin analogs may be an effective therapeutic measure to decrease TSH and thyroid hormone secretion (72, 78). Octreotide can control central hyperthyroidism, induce tumor shrinkage, and it can be a satisfactory method of preoperative preparation for TSH-secreting adenoma (73, 76). Aberrant expression of TRβ4 (a novel thyroid hormone receptor β isoform) could possibly contribute to the aberrant secretion of TSH in a TSH-secreting adenoma (79).

5.5 Outcome

In the past, about one third of the patients were diagnosed as having a primary hyperthyroidism (Graves' disease) and thus mistakenly were treated with thyroid ablation (thyroidectomy and/or radioiodine) (73).

The increasing frequency and early diagnosis of TSH secreting pituitary adenoma may be explained by ultrasensitive methods now used for TSH measurement and progress in pituitary imaging, mainly with MRI. This change in the presentation and the state of disease at diagnosis and the excellent response to somatostatins has improved the prognosis for this uncommon disease (70, 80).

5.6 Complications

Failure to recognize the presence of a TSH-secreting adenoma may result in dramatic consequences, such as improper thyroid ablation that may cause the pituitary tumor volume to further expand (73).

6. LH and FSH secreting PA

Recent studies have found that a high proportion of clinically non-functioning pituitary adenomas are largely gonadotrope-derived, i.e. produce and secrete low levels of intact follicle-stimulating hormone (FSH), luteinizing hormone (LH) or only biologically inert alpha- or beta-subunits of these hormones (81, 82).

6.1 Symptoms

Gonadotroph adenomas are not typically associated with a clinical syndrome (2). They are almost always discovered in patients presenting with mass effect, including visual field loss and headache, hypogonadism, and hypopituitarism (81). Anterior pituitary insufficiency is much more frequent than gonadal hyperstimulation such as ovarian hyperstimulation (83), testicular enlargement (82), and precocious puberty (81, 84).

6.2 Epidemiology

Advances in immunocytochemistry, electron microscopy, cell culture, and molecular techniques have demonstrated that 80 to 90% of the clinically nonfunctioning pituitary

adenomas are gonadotrope-derived and recently recognized as gonadotropinomas, which account for as many as 40 to 50% of all pituitary macroadenomas (81, 84). Gonadotropinomas have been reported with increasing frequency in middle-aged men, but they are less frequently recognized in women. This could be the result of greater difficulty in diagnosis due to the normal increase in serum gonadotropins in postmenopausal women (85).

6.3 Diagnosis

Both clinical and hormonal characteristics of gonadotropinomas usually make them readily distinguishable from pituitary enlargement due to long-standing primary hypogonadism (86). A careful analysis of hormone assay results show that baseline concentrations of gonadotrophin or their free sub-units are elevated in 30 to 50% of the cases. The GnRH test is positive in 75 to 100% of the cases (84). The majority of the cases can be recognized, even in postmenopausal women, by the serum LH beta responses to TRH, and some can be recognized by the responses of serum FSH and LH (87, 88).

6.4 Management

Most gonadotropinomas are now first treated by transsphenoidal surgery, to make an attempt to restore vision as quickly as possible, and then by radiation therapy to prevent the regrowth of any remaining adenomatous tissue. Radiosurgery using gamma knife, the linear accelerator, or proton beam therapy showed promising results, especially for controlling residual or recurrent tumors (63, 81). Medical therapy for a gonadotrope adenoma with a somatostatin analogs, dopamine agonists, or GnRH agonists and antagonists has limited utility but is employed in patients who are unable to undergo surgery. They may delay or prevent additional tumor growth (64, 84, 89, 90). Experimental therapy with intraoperative local chemotherapy or potential gene therapy requires further investigation (81).

6.5 Outcome & Complications

Long-term outcomes and complications of gonadotropinomas are similar to those of non-functioning pituitary adenomas.

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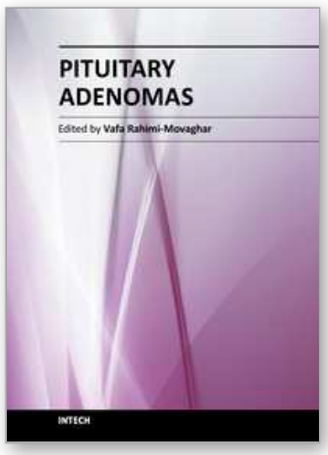
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Pituitary Adenomas is a comprehensive book about the most common pathology of the pituitary gland in the sellar region. The book chapters include epidemiology, symptoms and signs, clinical, imaging, immunohistochemical and ultrastructural pathological diagnosis, therapeutic approaches and outcome of the functional and non-functional pituitary tumors. Therapies include medications, endoscopic transphenoidal and open surgeries; radiotherapy includes gamma knife radiosurgery. Visual symptoms has important and characteristic patterns which has discussed in one specific chapter. Endocrine secretion is another characteristic in 40% of pituitary adenomas. Therefore, another chapter presents it. Stereotactic radiosurgery and endoscopic surgery both have special role in recent decades. Thus, they have considered specifically, too. Authors expect to give excellent insight in pituitary adenoma to the book readers.

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