

## Foreword



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Pituitary tumors cause a number of varied endocrine disorders, sometimes developing rapidly, such as hyperprolactinemic amenorrhea, and sometimes developing gradually over years, such as acromegaly and Cushing's disease. Clinical features, diagnostic testing, and therapy are of importance to the clinical endocrinologist, and Dr. Ariel Barkan has developed an outstanding issue on this topic that is designed to update the endocrinologist on different aspects of these interesting clinical problems.

The normal physiology of hypothalamic pituitary hormonal regulation is presented by Drs. Sam and Frohman. The well-studied regulatory control of pituitary hormone production and release involves hypothalamic-produced releasing (or suppressing) hormones/factors, and peripheral feedback control mechanisms, both negative and positive, some of which are involved in short-loop, and others in long-loop, feedback regulation. More recently, there is intensive examination of the role of intrapituitary regulation of pituitary hormone release. The total effect of all these regulatory controls is the eventual circadian rhythmicity and pulsatile release that lead to normal growth and development, normal reproduction, and total body homeostasis.

The etiology of pituitary tumors is an area of basic research that has revealed interesting results. Unlike tumors that develop secondary to classic oncogenic transformation, pituitary tumors rarely do so. However, as described by Dr. Levy in his scholarly article, they are associated with genetic causes, such as gain of function mutations in *GNAS1*, for example.

Obviously, further research will reveal the underlying genetic causes that may lead to the development of targeted therapeutics.

Pituitary tumors often require surgical removal both to reduce the level of excessive hormone secretion and to avoid or correct local effects, such as encroachment on the visual system, and thereby to prevent visual loss. Transsphenoidal surgery is the most common method, though transcranial surgery is occasionally necessary. Obviously, surgery is totally dependent on excellent pituitary imaging. Drs. Chandler and Barkan provide a concise guide to the MRI diagnosis of the most frequent pituitary lesions and discuss indications for various functioning and nonfunctioning pituitary tumors, the limitations, side effects and need for re-resection that is not uncommon.

The article by Drs. Brada and Jankowska describes the use of radiation therapy for pituitary tumors, a technique usually reserved for those tumors that are not completely “cured” by surgery or medical therapy. Conventional radiation therapy, while effective, is associated with hypopituitarism in the long term. Radiosurgery and stereotactic conformal radiotherapy is becoming more available as stereotactic “radiosurgery” and fractionated stereotactic conformal radiotherapy. The results of these techniques show distinct effectiveness, though long-term side effects are too early to assess.

Dr. Molitch describes nonfunctioning pituitary tumors and how they are detected as incidentalomas. By definition, they fail to show excess hormonal production and secretion, though they may cause hormonal deficiency, either due to a mass effect within the pituitary or on the hypothalamus. If small and not associated with symptoms or hormonal imbalance, they can be followed with periodic MRIs to assess growth. Usually, when necessary, they are treated by transsphenoidal surgery and dopamine agonists and rarely with radiotherapy to prevent regrowth after surgery.

As described by Drs. Mancini, Casanueva, and Giustina, hyperprolactinemia is a common disorder in clinical endocrine practice and is commonly associated with female and male hypogonadism. After drug-induced and secondary causes of hyperprolactinemia have been excluded, prolactinoma is the most common cause. Both serum prolactin measurements and an MRI are needed for the diagnosis. Treatment is often quite successful with the use of dopamine agonists, and transsphenoidal surgery (or radiation therapy) is usually reserved for the cases not responding to medical therapy or with large adenomas encroaching on critical structures. In their article, the authors also discuss the effect of pregnancy on prolactinomas and the treatment of prolactinomas during pregnancy, an important issue since many prolactinomas appear in women during their fertile years.

Though acromegaly may be caused by an extra-pituitary tumor producing excessive amounts of growth hormone releasing hormone (GHRH), the most common cause is a benign pituitary adenoma. Drs. Ben-Shlomo and Melmed describe the well-known clinical features and the long-term

complications of inadequately treated acromegaly. Transsphenoidal surgery is the treatment of choice for micro-adenomas and the more common macroadenomas; with the latter, there is generally incomplete resection, and medical suppression of the excessive growth hormone and IGF-1 concentrations is commonly used (both somatostatin analogues and pegvisomant). Radiation is reserved for the more unusual cases, because, while it can definitively stop tumor growth, it is usually associated with hypopituitarism and even long-term neurological complications.

Cushing's syndrome, while relatively rare, is commonly a challenge both for diagnosis and for therapy. The most common cause is iatrogenic, due to prolonged steroid therapy for chronic disorders. Pituitary tumors are more common than adrenal adenomas in causing Cushing's syndrome, and ectopic neuroendocrine tumors are relatively rare.

Drs. Pivonello, De Martino, De Leo, Lombardi and Colao describe, in depth, the difficulties in diagnosis that often lead to problems with therapy, how therapy is often not entirely successful, and the factors often resulting in poor prognoses.

A rare cause of hyperfunctioning pituitary tumors is thyrotropinomas. As described in the article by Drs. Beck-Peccoz and Persani, thyrotropinomas may be easily distinguished from other causes of hyperthyroidism such as Graves' disease and a toxic nodule, as the latter have suppressed thyroid stimulating hormone levels. Pituitary resistance to thyroid hormone needs to be excluded, since its treatment is thyroid ablation, whereas thyrotropinomas are surgically removed with or without radiation therapy. Incidentally, somatostatin can suppress TSH secretion when necessary.

Drs. Karavitaki and Wass discuss the rare condition of craniopharyngioma. These tumors may be discovered in children or in adults, and are often treated with surgery and radiation therapy. Long-term morbidity results from endocrine hypofunction and neurologic (visual) morbidities, and cognitive loss stems either from the lesion or as a result of treatment.

Most pituitary tumors are either hormone producing (functional) or non-functional adenomas. There are, however, rare sellar masses that mimic pituitary adenomas, and these should always be considered in the differential diagnosis. They include a large and varied range of neoplastic, inflammatory, infectious, developmental, and vascular lesions. The list, as outlined in the article by Drs. Glezer, Belchior, and Bronstein, is quite long; however, the authors summarize some important features of the more common abnormalities.

Hypopituitarism may present as an isolated hormonal deficiency or as pan-hypopituitarism. The etiology ranges from primary deficiencies to secondary causes such as pituitary or suprasellar tumors, infiltrative lesions or destructive lesions seen following brain injury or radiation therapy. Drs. Toogood and Stewart describe the various hormonal deficiencies, the classic tests required to detect each deficiency, and replacement therapies. Their article offers both an academic and practical point of view.

Drs. Loh and Verbalis, in their article, discuss disorders of sodium and water metabolism, as related to pituitary diseases. Although hyponatremia is generally a more common disorder than hypernatremia, in the case of pituitary lesions, diabetes insipidus, and resultant hypernatremia are more common than the syndrome of inappropriate antidiuretic hormone (SIADH) secretion with concomitant hyponatremia. Once again, their article reveals both important information on the pathophysiology, possible complications, diagnostic testing, and therapeutic approaches.

Given the outstanding contributions by the international experts in the field, I believe the readers of this issue certainly owe all the authors and the issue editor, as I do, for the excellent, while predictable outcome!

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