Handbook of Inpatient Endocrinology

Rajesh K. Garg
James V. Hennessey
Alan Ona Malabanan
Jeffrey R. Garber
Editors

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Dedicated to our fellows.

– Rajesh K. Garg,
James V. Hennessey,
Alan Ona Malabanan,
and Jeffrey R. Garber

Preface

During the last two decades, there has been increasing emphasis on physicians seeing more patients in ambulatory settings. As a result, hospital-based physicians are providing more inpatient care, and fewer endocrinologists, after fellowship training, are caring for their hospitalized patients. Yet managing endocrine diseases in the inpatient setting has become more complex, while transitioning that care back to the ambulatory setting is as critical as ever. Examples of complex care and challenges regularly encountered in hospitalized patients abound and include managing diabetes emergencies, those with diabetes mellitus on total parenteral nutrition, insulin treatment protocols for pregnancy in diabetes, and thyroid crises. Additionally, the diagnosis and management of adrenal insufficiency; perioperative care of patients undergoing pituitary, parathyroid, adrenal, and thyroid surgery; and patients with thyroid dysfunction who have heart disease as well as those who cannot take oral medications frequently are encountered. The editors of this handbook, attending endocrinologists in Boston's Longwood Medical Area at either the Brigham and Women's Hospital or Beth Israel Medical Center, decided to produce this volume after agreeing that even the most experienced endocrinologist working on a busy inpatient consult service would benefit from an easy-to-navigate and concise text for guidance.

Many authors were in their fellowship training when they contributed to this book. The book is designed to highlight salient clinical points with more detailed information available on each point. The well-established clinical approaches are emphasized

with suggestions for further reading. In addition to serving as a practical, easy-to-navigate reference guide for those taking care of inpatients with endocrine disorders, each section provides guidance about bridging their care from the inpatient to the outpatient setting.

The audience for this book includes physicians who provide most inpatient consultative care, for example, endocrinology fellows, their attending physicians, surgical and obstetrical specialists, primary care physicians, and hospitalists. We look forward to receiving your feedback so that future editions can remain up-to-date and we can address issues that we have not sufficiently emphasized in this, our first edition.

Coral Gables, FL, USA
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Pituitary Apoplexy

1

Ana Paula Abreu and Ursula B. Kaiser

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Definition

Apoplexy means "sudden attack" in Greek. Classical pituitary apoplexy (PA) is a clinical syndrome characterized by abrupt hemorrhage and/or infarction of the pituitary gland. Severe headache of sudden onset is the main symptom, sometimes associated with visual disturbances or ocular palsy. Apoplexy usually occurs in patients with preexisting pituitary adenomas and evolves within hours or days.

Subclinical PA is defined as asymptomatic or unrecognized pituitary hemorrhage and/or infarction. It may be detected on routine imaging or during histopathological examination. The frequency of subclinical hemorrhagic infarction in pituitary tumors is around 25%.

Precipitating Factors/Patients at Risk

The precise pathophysiology of PA is not completely understood. Since most cases occur in preexisting pituitary adenomas, it has been hypothesized that a reduction in blood flow or abnormal vascularity of the tumor could be mechanisms contributing to PA. The underlying process can be simple infarction, hemorrhagic infarction, or mixed hemorrhagic infarction.

The pituitary gland is enlarged in pregnancy and prone to infarction from hypovolemic shock. Pituitary necrosis that occurs in the setting of large-volume obstetric hemorrhage postpartum is referred to as Sheehan syndrome. It is a rare but potentially life-threatening complication that can result in postpartum hypopituitarism.

The clinical symptoms of PA mimic other common neurological disorders such as subarachnoid hemorrhage, migraine, bacterial meningitis, or stroke, which can lead to delayed or even missed diagnosis. A high degree of clinical suspicion is needed to diagnose pituitary apoplexy, as most patients do not have a previous history of known pituitary adenoma. Precipitating risk factors have been identified in 10–40% of cases of PA, and it is important to recognize them. Hypertension has been considered a precipitating factor for PA, although recent studies question this association. Surgery, particularly coronary artery surgery, and angiographic procedures have been reported to be associated with PA. Dynamic testing of pituitary function, using growth hormone-releasing hormone, gonadotropin-releasing hormone, thyrotropin-releasing hormone, and corticotrophin-releasing hormone (less commonly), or an insulin tolerance test, is also associated with PA. Initiation or withdrawal of dopamine receptor agonists, estrogen therapy, radiation therapy, pregnancy, head trauma, and coagulopathy are some other factors known to induce pituitary apoplexy. A diagnosis of PA should be considered in all patients with these risk factors who present with acute severe headache, with or without neuro-ophthalmologic signs.

Diagnosis

Obtain Detailed Clinical History

The clinical presentation can be acute or subacute and is highly variable, determined by the extent of hemorrhage, necrosis, and edema. Headache is present in more than 80% of patients. It is usually retro-orbital but can be bifrontal or diffuse. Nausea and vomiting can be associated. As most patients have an underlying macroadenoma, signs and symptoms of hypopituitarism may have been present prior to the episode of PA. As discussed earlier, most patients do not have a history of a known prior pituitary adenoma and therefore do not carry a diagnosis of hypopituitarism.

Sheehan syndrome usually presents with a combination of failure to lactate postdelivery and amenorrhea or oligomenorrhea, but any of the manifestations of hypopituitarism (e.g., hypotension, hyponatremia, hypothyroidism) can occur at any time from the immediate postpartum period to years after delivery.

Perform Detailed Physical Exam Including Cranial Nerves and Visual Fields

More than half of patients with PA have some degree of visual field impairment, with bitemporal hemianopsia being the most common. About half of patients have oculomotor palsies due to functional impairment of cranial nerves III, IV, and/or VI. Cranial nerve III is most commonly affected, resulting in ptosis, limited eye adduction, and mydriasis due to nerve compression. Extravasation of blood or necrotic tissue into the subarachnoid space can result in meningismus and an altered level of consciousness.

Evaluation of Endocrine Dysfunction/Laboratory Assessment

Most patients will have dysfunction of one or more pituitary hormones at the time of initial presentation. The most clinically important hormone deficiency is adrenocorticotrophic hormone (ACTH), which can be life-threatening. It is present in 50–80% of patients and can cause hemodynamic instability and hyponatremia. Of note, hyponatremia is a consequence of cortisol deficiency, with loss of feedback inhibition of arginine vasopressin/antidiuretic hormone (ADH) release despite hypoosmolality and a direct water excretion defect. Additionally, hypothalamic irritation in the setting of PA can result in the syndrome of inappropriate antidiuretic hormone. Nausea/vomiting and hypoglycemia (secondary to GH and/or ACTH deficiency) are also stimuli for ADH secretion. Secondary hypothyroidism can also contribute to hyponatremia.

Patients with suspected PA should have electrolytes, renal function, kidney function, coagulation, and CBC checked to assess for risk factors and for the general condition of the patient.

Pituitary endocrine evaluation is necessary to diagnose secretory pituitary adenomas as well as hypopituitarism. An initial random cortisol, ACTH, LH, FSH, testosterone or estradiol, FT4, TSH, IGF-1, and prolactin should be measured immediately upon the diagnosis of PA to screen for a hyperfunctioning pituitary adenoma. Low serum prolactin at presentation is seen in patients with the highest intrasellar pressure, who are less likely to recover pituitary function. It is important to emphasize that blood samples for ACTH and cortisol measurements should be obtained prior to the administration of steroids. The hypothalamic-pituitary-adrenal axis usually responds to critical illness with an increase in serum cortisol levels, and it is expected that a random cortisol level will similarly be elevated during the acute phase of PA without hypopituitarism. There is no clearly agreed-upon cutoff for random cortisol levels for the diagnosis of adrenal insufficiency during the acute phase of PA, but studies have shown that in patients with PA and proven central adrenal insufficiency, cortisol levels are very low.

Approximately 40–70% of patients with PA have thyrotropin or gonadotropin deficiency. Hormone replacement of these deficiencies can begin when the patient has recovered from the acute illness. GH deficiency is seen in almost all patients but is not always tested or treated.

Diabetes insipidus is present in less than 5% of patients with PA and may be further masked by the development of secondary adrenal failure and/or hypothyroidism.

Imaging

CT is usually the initial imaging modality performed for patients with sudden onset of headache. CT is useful to rule out subarachnoid hemorrhage and can detect a sellar mass in up to 80% of cases. In 20–30% of cases, the CT scan will detect hemorrhage into the pituitary mass, confirming the diagnosis of PA. Magnetic resonance imaging (MRI) is the imaging procedure of choice and has been found to identify an underlying tumor, if present, in over 90% of the cases. Therefore, MRI is more sensitive for the diagnosis of PA and should be done in all patients with suspected

PA. MRI can detect hemorrhagic and necrotic areas and can show the relationship between a tumor and adjacent structures such as the optic chiasm, cavernous sinus, and hypothalamus (Fig. 1.1). However, conventional MRI sequences may not detect an infarct

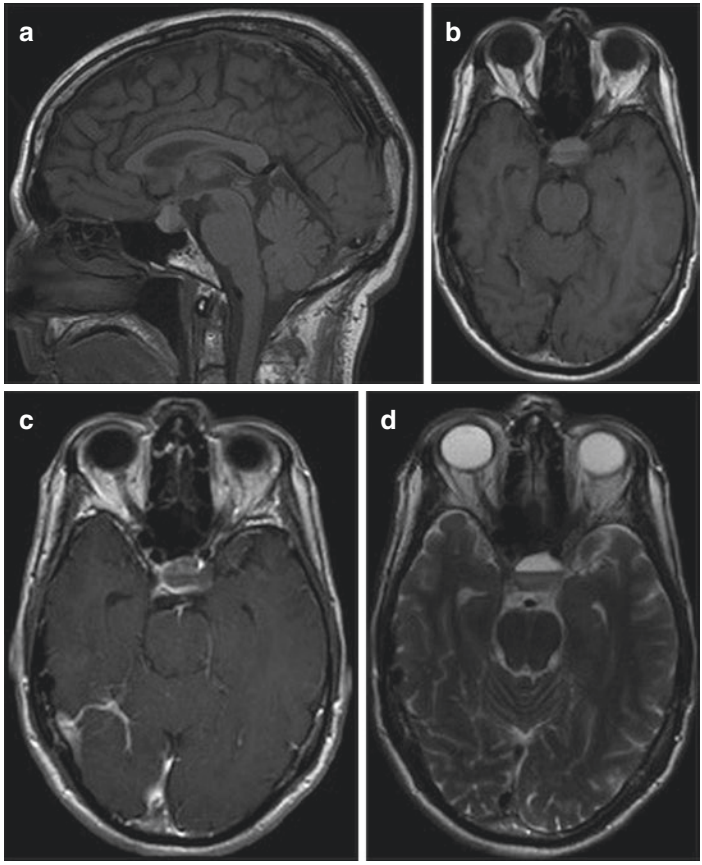

Fig. 1.1 MRI of a patient with pituitary apoplexy. Images were obtained approximately 24 hours after onset of symptoms (sudden headache, nausea, vomiting, and fatigue). Images show enlargement of the pituitary gland, which contains a fluid hematocrit level. (**a**) T1 sagittal, the upper margin of the pituitary gland is contacting and slightly displacing the optic chiasm superiorly. (**b**) Axial pre-contrast. (**c**) T1 axial post gadolinium. (**d**) T2 axial

for up to 6 hours after the acute event. Diffusion-weighted imaging (DWI) is a commonly performed MRI sequence for the detection of small infarcts and initial hemorrhage and can be very helpful in the early phases of PA.

Thickening of the sphenoid mucosa in the sphenoid sinus beneath the sella turcica has been reported during the acute phase of PA and corresponds with marked mucosal swelling from increased pressure in the venous sinuses draining the sinus area. Such mucosal thickening has been shown to correlate with worse neurological and endocrinological outcomes.

Management

Patients with PA should be managed by neurosurgeons and endocrinologists in a hospital with an acute care neurosurgical unit available and with access to ophthalmological evaluation.

Consider Initiation of Corticosteroid Treatment

PA can be a true medical emergency. The course of PA is variable and management will depend on a patient's clinical condition. The first intervention is hemodynamic stabilization and correction of electrolyte disturbances. As corticotropin deficiency is present in the vast majority of patients and may be life-threatening, corticosteroids should be administered intravenously as soon as the diagnosis is confirmed and blood is collected for cortisol and ACTH measurement. A bolus of 100 mg (some studies recommend 200 mg) of hydrocortisone followed by 50–100 mg IV every 6–8 hours is given; alternatively, 2–4 mg/h by continuous administration should be given. There are no randomized trials comparing different doses, so the ideal dose of hydrocortisone administration is not known. Dexamethasone may be used instead of hydrocortisone to reduce edema as a part of a conservative approach for treatment of PA. Although the majority of the literature recommends empiric corticosteroid treatment for all patients with diagnosis of PA, the UK guidelines for the management of

pituitary apoplexy recommend steroid therapy in patients with hemodynamic instability, altered level of consciousness, reduced visual acuity, and severe visual field defects, or if a 9:00 am cortisol is less than 18 mcg/dL.

Acute Intervention: Surgery vs. Conservative Treatment

Most cases of PA improve with either surgical or expectant management, but the most appropriate approach in the acute phase is controversial. Studies comparing the two modalities are retrospective and suffer from selection bias. The ideal surgical treatment is via the transsphenoidal approach. One important factor to consider is the risk of surgery, and in the acute setting, the operation may be performed by the on-call neurosurgeon rather than by skilled pituitary surgeons; this may increase the risk of complications. Studies suggest that the posttreatment prevalence of pituitary deficiency is similar after either treatment modality. The endocrine prognosis is poorer in patients with pituitary adenoma and PA than in uncomplicated pituitary adenoma, as pituitary damage more commonly occurs during the acute apoplectic event. Studies suggest that visual field defects improve or normalize in most patients regardless of the treatment modality. However, it is the general consensus – and is the recommendation by the UK guidelines for the management of PA – to consider surgical treatment in patients with severe neuro-ophthalmologic signs such as severely reduced visual acuity or severe and persistent or deteriorating visual field defects. A deteriorating level of consciousness is also an indication for surgical treatment. Studies suggest, although one should keep selection bias in mind, that patients treated conservatively have better outcomes with regard to ocular palsies. Resolution of ocular paresis resulting from involvement of cranial nerve III, IV, or VI is usually seen within days to weeks, and it is not an indication for surgery. Surgery should be performed within 7 days of the onset of the symptoms. One study showed that the prognosis of visual defects is less favorable when surgery is done more than a week after onset. A Pituitary Apoplexy

Table 1.1 Pituitary Apoplexy Score

Variable	Points
Level of consciousness	
Glasgow Coma Scale 15	0
Glasgow Coma Scale 8–14	2
Glasgow Coma Scale <8	4
Visual acuity	
Normal	0
Reduced unilateral	1
Reduced bilateral	2
Visual field defects	
Normal	0
Unilateral defect	1
Bilateral defect	2
Ocular paresis	
Absent	0
Present unilateral	1
Present bilateral	2

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Score (see Table 1.1) was designed by the UK guidelines for the management of PA to enable more uniform clinical description of PA and enable better comparison between different management options.

It is rare to change from conservative treatment to an operative course, but urgent imaging should be done in the presence of a new or deteriorating visual field deficit or neurological deterioration.

Reduction in tumor size is frequent after apoplexy, and follow-up imaging can show empty sella, partially empty sella, or even normal pituitary. The tumor recurrence rate is similar with both treatment modalities, and it has been shown to be approximately 6%. Therefore, long-term surveillance is recommended. Patients with simple infarction on MRI typically have less severe clinical features and better outcomes than those with hemorrhage or hemorrhagic infarction.

Postoperative Care

Postoperative management of patients following surgery for PA is similar to that of elective pituitary surgery for pituitary tumors. In some cases, patients may not have had a complete evaluation prior to surgery, and the pituitary function status will not be known. An early postoperative CT or sellar MRI should be performed in any patient with a new or worsened neurological deficit such as visual deterioration or diplopia and in anyone with significant rhinorrhea and a suspected CSF leak.

Monitor for Signs and Laboratory Abnormalities Suggestive of Diabetes Insipidus (DI)

Alterations in sodium and fluid balance are relatively common in the early postoperative phase. The classic reported triphasic response, in which patients initially develop DI in the first 24 to 48 hours, followed by transient SIADH developing 4–10 days postoperatively, followed by the return of DI in a matter of weeks, is not the most common pattern seen postpituitary surgery but can occur. More often, patients present with DI within the first days postsurgery and then either recover completely or develop SIADH about 5 days postsurgery or later. Fluid balance, serum electrolytes, urea, creatinine, and plasma and urine osmolality should be monitored closely during the first week postsurgery. During the first 2 days after surgery, fluid balance, electrolytes, and urine and serum osmolality should be checked every 8–12 hours; thereafter, further monitoring will depend on the patient's clinical status.

DI is present in about 5% of the patients after PA but can be seen in up to 25% of patients undergoing transsphenoidal pituitary surgery. In most cases, the patients may develop transient DI but do not require any therapy. They should be allowed to drink to thirst and their serum sodium should be monitored closely. When treatment is needed, desmopressin (DDAVP) should be given sub-

cutaneously or intravenously (0.5–2 mcg every 24 hours as needed), or alternatively, an oral formulation can be given (often starting with 0.1–0.2 mg orally as a single evening dose, with doses up to 0.3 mg orally three times daily sometimes needed). Intranasal DDAVP is not generally used acutely in patients who have undergone transsphenoidal surgery until after the nose has healed and nasal congestion has improved. SIADH, when it occurs, usually presents 4 to 10 days postoperatively and can often be treated with fluid restriction and close monitoring.

Assess Pituitary Reserve

As discussed above, most of the patients will receive corticosteroid treatment during the acute phase of PA. The dose should be tapered to replacement doses when the patient is clinically stable. In patients without a previous diagnosis of adrenal insufficiency, a morning fasting cortisol should be checked on day 2 or 3 after surgery to assess residual postpituitary infarction and post-steroid treatment reserve after the acute event of PA and postoperatively. Hydrocortisone should be held for at least 24 hours prior to measuring cortisol levels. In patients with known and documented cortisol deficiency before surgery, a morning cortisol level should be checked within 4 to 8 weeks to determine if they will need long-term steroid treatment.

TSH and free T4 (FT4) should be checked on day 3 or 4 postoperatively, and thyroid hormone replacement should be considered if deficient. The interpretation of thyroid function tests postsurgically should be careful as "sick euthyroid syndrome" can alter TSH and FT4 hormone levels and affect the interpretation of these tests. Thyroid deficiency may take several weeks to be diagnosed given thyroid gland reserve and the half-life of T4, so thyroid function can be normal in the immediate postoperative period; hence it is important to test it again ~4–8 weeks postoperatively or if symptoms of hypothyroidism develop.

Visual Assessment

Visual fields, eye movements, and visual acuity should be examined at the bedside as soon as the patient can cooperate with the examination, ideally within 48 hours. A formal visual field assessment using a Humphrey analyzer or Goldmann perimetry should be performed within a few weeks after the acute event.

Follow-Up After Discharge

Check Electrolytes After 1 Week

Patients should be seen in follow-up within 1 week of surgery to have sodium, thyroid function, ACTH, morning cortisol, and urine osmolality tested. As discussed earlier, patients may develop SIADH up to 10 days after surgery or after PA and should be monitored closely.

Reassess Pituitary Function After 4 to 8 Weeks

Hypopituitarism (discussed separately) is one of the complications of PA and may not be detected during the acute phase of PA. Thyroid deficiency may take several weeks to be diagnosed given thyroid gland reserve and T4 half-life. All patients should be seen 4–8 weeks after presenting with PA for evaluation of pituitary function. On the other hand, some pituitary hormonal deficiencies may recover postoperatively, and such recovery can also be assessed as part of this evaluation. Studies have shown partial or complete recovery of pituitary function in up to 50% of patients. In most cases, patients will be treated with glucocorticoids during the acute episode of PA; the long-term need for glucocorticoid replacement therapy should be determined at this time. Thyroid, adrenal, gonadal, and GH axes may be assessed at this visit. Patients should also have formal visual field, visual acuity, and eye movement assessment.

Patients treated for apoplexy should have at least annual biochemical assessment of pituitary function, which should usually include FT4, TSH, LH, FSH, testosterone in men, estradiol in women, prolactin, IGF-1, and dynamic tests of cortisol and growth hormone secretion if clinically appropriate.

Suggested Reading

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Panhypopituitarism

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Definition and Significance

Hypopituitarism is the inability of the pituitary gland to provide sufficient hormones for the needs of the individual. It is the result of the failure in either the production or secretion in one or more pituitary hormones. The diagnosis of hypopituitarism is important in the hospital because some hormone deficiencies, such as ACTH, pose significant risk to the patient's life and need to be treated. Also, it is crucial to diagnose and treat diabetes insipidus as it can cause hypernatremia, severe dehydration, coma, and death. The diagnosis of central hypothyroidism is challenging in the hospital, but thyroid hormone should be replaced in patients with secondary hypothyroidism. On the other hand, other pituitary hormone deficiencies do not pose acute risk to patient's life, and replacement may be postponed to the outpatient setting.

Identify Causes of Hypopituitarism

A high diagnostic suspicion is necessary to identify patients not previously diagnosed with hypopituitarism. Therefore, it is important to know what causes hypopituitarism in order to detect it (Table 2.1). Insults in the regulation, production, or secretion of any pituitary hormones can result in pituitary insufficiency. Physiological secretion of pituitary hormones relies on intact function of the hypothalamus.

Mass Lesions

Any structural disruption of the hypothalamic-pituitary region can cause decreased production or secretion of the hormones. Pituitary tumors are the most common cause of hypopituitarism, but any other tumor occupying the region can also cause pituitary dysfunction (Table 2.1). Mechanical compression of portal vessels and the

Table 2.1 Causes of hypopituitarism

Structural causes:	
Mass lesions	Pituitary adenoma Craniopharyngioma Rathke's cleft cyst Metastatic disease Lymphomas, germinomas, and other tumors
Infiltrative diseases	Hypophysitis (lymphocytic and others) Sarcoidosis Hemochromatosis Tuberculosis and other infections Syphilis
Vascular events	Pituitary apoplexy Sheehan's syndrome (infarction of the pituitary gland after postpartum hemorrhage) Intra-sellar carotid artery aneurysm
Traumatic injury	Traumatic brain injury Perinatal trauma Neurosurgery Radiation
Functional causes:	
Medications	Glucocorticoids Megestrol acetate Immunotherapy – CTLA-4 inhibitors/PDL1 antibodies Opioids GnRH agonists
Systemic diseases	Chronic illness Anorexia nervosa
Developmental and inherited genetic causes	Several genetic defects can cause isolated or combined pituitary deficiency

pituitary stalk, with resulting ischemic necrosis, is thought to be the predominant mechanism by which mass lesions cause hypopituitarism. Hyperprolactinemia in non-prolactin producing tumors is common with pituitary macroadenomas, given the disruption of the normal suppressive effects of dopamine from the hypothalamus.