Chapter 1
Pituitary Apoplexy

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Objectives

To understand the clinical presentation, the evaluation, the acute medical and surgical management, the long-term management, and the complications of pituitary apoplexy.

Case Presentation

A 36-year-old woman presented to her primary care physician on an urgent basis with "the worst headache of my life." The headache started suddenly. She took an over-the-counter analgesic but vomited soon after swallowing it. She also noticed blurry and double vision while searching for her doctor's phone number. In the doctor's office her heart rate was 115 beats per minute and blood pressure was 90/50 mm Hg. Left eye ptosis was noted as well as a dilated left pupil that did not react to light. The left eye was deviated downward and outward. The patient felt light-headed but had a normal gait, and strength and sensation were grossly intact for all extremities. She was transported promptly to the nearby hospital emergency room.

In the emergency room she denied any significant medical history. Her only medication was oral contraceptive pills. A brain computed tomography (CT) scan without contrast was obtained emergently. There was no evidence of subarachnoid hemorrhage or hemorrhage into the brain parenchyma, but a heterogeneous mass of about 4 × 4 cm was seen extending superiorly from the sella turcica.

Neurosurgical and endocrine consults were obtained. Dexamethasone 6 mg was administered intravenously. An urgent magnetic resonance imaging (MRI) scan of the pituitary was performed, which revealed a mass arising from the sella turcica that was 3.6 cm wide, 4.1 cm high, and 3.6 cm in the anteroposterior dimension

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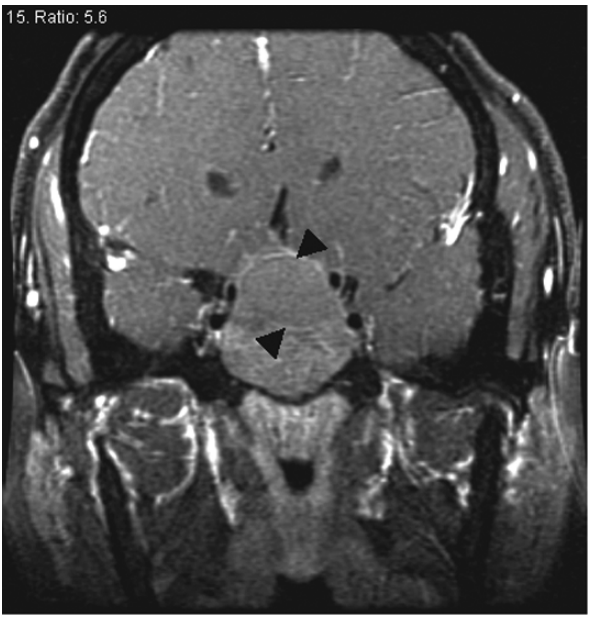

Fig. 1.1 Magnetic resonance imaging of a coronal section through a pituitary macroadenoma with hemorrhage (arrows)

(Fig. 1.1). The mass extended beyond the sella on both sides, displacing the internal carotid arteries laterally. An area in the superior portion of the mass, extending inferiorly on the left, was T1 hyperintense, T2 hypointese, and hypoenhancing compared to the remainder of the mass, consistent with hemorrhage. The optic chiasm was displaced dramatically upward. The decision was made to proceed to transsphenoidal surgery on an urgent basis to decompress the optic chiasm.

During presurgical evaluation the following additional information was obtained by the endocrine fellow: There was no history of unusually severe or frequent headaches, and the patient had not noticed any visual problems prior to the day of presentation. She started oral contraceptive pills for birth control after weaning her second child 12 years earlier, and had taken them continuously since that time. She had complained of fatigue and irritability for several years, and had gradually gained 20 pounds over the last 10 years. In the last 3 months, however, she had lost weight due to poor appetite. Her hair had become brittle, and she complained of increasing scalp hair loss. Her primary care physician had measured the thyroid-stimulating hormone (TSH) level several times at her request, and it had always been normal. There was no history of easy bruising or weakness, hirsutism, or change in ring or foot size. She had experienced some mild galactorrhea ever since weaning her last child. Comparison with a photo from 10 years earlier revealed no obvious changes in the shape of her face. There was no family history of endocrine abnormalities. She reported her height as 5’4”, and her weight was 152 pounds. On exam, vision

was limited to counting fingers bilaterally. Visual fields were difficult to define given her diffusely blurry vision and ophthalmoplegia, but she did have loss of peripheral vision bilaterally. There were no skin lesions. The thyroid was small. There was expressible galactorrhea. Reflexes were normal, and strength was 5/5 proximally in all four extremities. The endocrine fellow ordered a cortisol, free thyroxine (T_4), prolactin, and insulin-like growth factor I (IGF-I).

Late in the afternoon the patient underwent transsphenoidal surgery. Upon entering the sella, the surgeon found soft tumor, followed by dark, hemorrhagic fluid and clot as she worked upward through the mass. The mass was debulked as much as possible, but tumor adjacent to and invading the cavernous sinus bilaterally could not be safely resected. The sella was packed with fat harvested from the subcutaneous tissue of the abdomen. In the recovery room the patient noticed an improvement in vision, with acuity estimated at 20/80.

The following morning the patient's vision had subjectively recovered to that of her baseline and was measured at 20/30. The left ophthalmoplegia had resolved. Her glucocorticoid dose was reduced to 5 mg of prednisone each morning. Laboratory studies done prior to surgery were as follows: cortisol, 2.5 μg/dL; free T_4, 0.7 ng/dL (normal 0.9–1.8); prolactin, 112 ng/mL (normal <15, no dilution effect); and IGF-I, 94 ng/mL (normal 87–230). Morning cortisol on days 2 and 3 after surgery were 4 and 5 μg/dL, respectively. She developed transient diabetes insipidus postoperatively that resolved within 3 days. She was discharged from the hospital on the fourth hospital day in good condition, with instructions to stop taking the oral contraceptive pill (and use an alternative contraceptive method) and take 4 mg of prednisone daily until her follow-up appointment with the fellow in 6 weeks.

At her follow-up appointment the following information was reviewed: The tumor pathology showed mostly necrotic tissue and blood, with the few intact tumor cells staining for follicle-stimulating hormone (FSH), luteinizing hormone (LH), and α-subunit. There was no staining for adrenocorticotropin (ACTH), TSH, prolactin, or growth hormone (GH). The postoperative MRI showed residual tumor in the cavernous sinus partially encasing the internal carotid arteries, and a small amount of enhancing tissue above the fat packing. There was mild bitemporal hemianopsia by formal visual field testing. There had been no menstrual bleeding since discharge. Her only complaints were continued fatigue and irritability. She had been instructed not to take prednisone on the morning of the visit, and an ACTH stimulation test was performed.

At baseline, cortisol was 3 μg/dL, free T_4 0.7 ng/dL, TSH 1.8 μU/mL, IGF-I 90 ng/mL, estradiol <20 pg/mL, FSH 2.6 U/L, LH 3.8 U/L, and prolactin 12 ng/mL. The peak cortisol after stimulation was 10 μg/dL. The prednisone was continued and levothyroxine 112 μg daily was started. Her oral contraceptive pill was restarted.

At a return visit 6 weeks later she reported greater energy. Free T_4 was 1.3 ng/dL, TSH was <0.01 μU/mL, and IGF-I was 102 ng/mL. Peak growth hormone after growth hormone–releasing hormone (GHRH)/arginine stimulation testing was 3.2 ng/mL. Bone mineral density testing revealed hip and spine T scores of −1.7

and −2.3, respectively. Recombinant human growth hormone was started and titrated to a mid-normal IGF-I.

One year after presentation, the patient's fatigue and irritability had resolved, and she had experienced a decrease in waist circumference, although her weight was stable. An MRI revealed no change, with no growth of the residual tumor. The hip and spine T scores were −1.5 and −2.0, respectively.

How the Diagnosis Was Made

In this case, the clinical diagnosis preoperatively was pituitary apoplexy in a likely clinically nonfunctioning macroadenoma. The diagnosis of apoplexy was made based on the history of sudden headache, new visual symptoms, ophthalmoplegia, and a large sellar mass with evidence of hemorrhage. The new onset of severe headache, blurry vision, and ophthalmoplegia implied that the mass had acutely expanded. Note that hemorrhage is not always evident on imaging obtained at the time of presentation. An MRI is generally more sensitive for hemorrhage in this context. Even in the absence of radiographically documented hemorrhage, a pituitary mass in the setting of a clinical syndrome consistent with apoplexy should be treated as apoplexy until proven otherwise.

The patient had no history or clinical signs to strongly suggest an endocrine hypersecretion syndrome. Preoperative laboratory measurements revealed no evidence of elevated IGF-I or thyroid hormone. The prolactin was too low for a prolactinoma of this size, suggesting the elevation was likely due to pituitary stalk compression. The pathology showing necrosis and a population of cells staining for FSH, LH, and α-subunit confirmed the clinical diagnosis of apoplexy in a clinically nonfunctioning pituitary adenoma.

Lessons Learned

Pituitary apoplexy (apoplexy meaning "sudden attack", or "to be struck down") is a clinical syndrome in which the abrupt onset of typical signs and symptoms (see below) result from hemorrhage or infarction within the pituitary or a pituitary tumor. Although almost all cases of pituitary apoplexy occur in the setting of a preexisting tumor, in most cases the tumor has not been diagnosed previously. In retrospect, many patients have a history consistent with endocrine deficiency or hyperfunction. In this case, the preoperative history and laboratory studies were consistent with adrenal insufficiency, hypothyroidism, and growth hormone deficiency. The normal TSH measurements obtained by the patient's primary care physician could not rule out central hypothyroidism, as TSH levels are normal in the majority of patients with central hypothyroidism. The patient's continuous use of oral contraceptive pills may have masked hypogonadism.

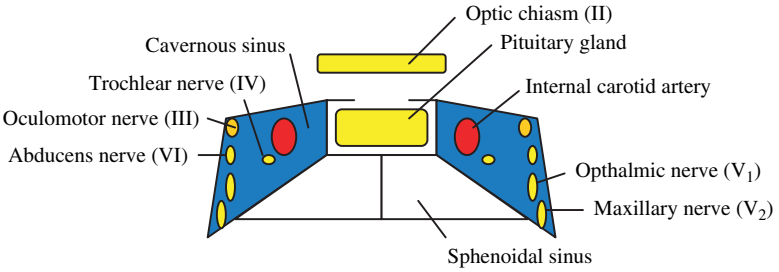

Fig. 1.2 Schematic of a coronal section through the normal pituitary gland and adjacent structures

The presenting symptoms and signs of apoplexy are headache (70–100%), ocular paresis (40–85%), visual disturbance (50–70%), vomiting (20–70%), and less commonly photophobia, meningismus, facial pain or numbness, or decreased level of consciousness. The most common visual symptoms are diplopia, blurred vision, and decreased peripheral vision (bitemporal hemianopsia), but the visual symptoms can vary from subtle ophthalmoplegia to the acute onset of binocular blindness [1, 2]. The most commonly involved cranial nerve in patients with ocular paresis is III, followed by VI, presumably due to their proximity to the sella in the cavernous sinus (Fig. 1.2) and apposition to the relatively unyielding lateral wall of the cavernous sinus. Cranial nerve (CN) III (oculomotor) paralysis may lead to ptosis, meiosis, lack of pupillary light or accommodation reflex, and deviation of the affected eye down and laterally. Cranial nerve VI (abducens) paralysis leads to inward gaze of the affected eye. Less commonly, CN IV (trochlear) paralysis results in outward and downward gaze, and CN V_1 (ophthalmic division of the trigeminal) involvement can lead to facial pain or numbness. Cranial nerves VI and IV abnormalities may not be obvious without specifically testing the extraocular movements, as the patient may move the head to align the two eyes.

It is important to note that, based on surgical series, pituitary tumor hemorrhage may also occur without symptoms or signs in up to 25% of patients, but this does not satisfy the criteria for apoplexy. A history consistent with apoplexy and evidence of pituitary hemorrhage or infarction are present in only 2% to 10% of patients at pituitary tumor surgery. The true incidence of apoplexy in all patients with pituitary tumors, including those that are undetected, is necessarily lower.

Most cases of apoplexy do not present to an endocrinologist. In the modern era, sudden severe headache associated with vomiting often leads to urgent CT imaging of the brain to rule out subarachnoid hemorrhage. If a mass arising from the sella is identified, a pituitary protocol MRI should be obtained and an endocrinologist should become involved. Hemorrhage is not reliably identified within the pituitary by CT; MRI is a more sensitive technique for detection of hemorrhage into pituitary tumors. In less severe cases, consideration of apoplexy by the clinician along with more common etiologies for headache, nausea, and visual disturbance, such as migraine, is essential. In many cases, there is a history suggestive of pituitary pathology that, if obtained by the clinician, may arouse the clinical suspicion of apoplexy.

Apoplexy associated with visual disturbance is considered a neurosurgical emergency because decompression of the optic chiasm is essential to conserve vision. There is evidence that some cases of apoplexy can be managed medically, although what fraction of patients may be managed this way, and the criteria for their selection, are controversial. One prospective study treated apoplexy patients initially with high-dose glucocorticoids, and then crossed over to surgery if glucocorticoid therapy failed to improve ophthalmoplegia, visual loss, or impaired consciousness [3]. Fewer patients in the medically managed group had residual tumor, but patients managed surgically had fewer residual pituitary hormone deficiencies, perhaps due to more complete necrosis of the sellar contents without surgical decompression ("autohypophysectomy"). More patients managed surgically had residual ophthalmoplegia or visual loss, but this may be because patients were selected for crossover to surgery as a result of more severe visual compromise. A later observational study in which 18 of 45 patients were managed medically reported similar findings and supported the idea that a subset of apoplexy patients can be managed medically [4].

Standard of care for apoplexy remains surgical decompression. Based on the available evidence, would candidates for medical management of apoplexy might be patients with mild or nonprogressive visual loss. The availability of a neurosurgeon with significant experience in pituitary surgery is also a critical factor in the management decision.

Apoplexy often is associated with adrenal insufficiency acutely. In this case, the random cortisol was too low (2.5 μg/dL) in the setting of the significant physiologic stress of an intracranial hemorrhage. Early morning values less than 3 μg/dL are strongly suggestive of adrenal insufficiency, but in the absence of significant physical stress, low cortisol values at other times of the day are not diagnostic of adrenal insufficiency. Immediate, empiric, intravenous high-dose glucocorticoid treatment is essential because the physiologic stress associated with apoplexy could prove fatal in the presence of glucocorticoid deficiency.

It is important to assess pituitary function preoperatively to the extent possible in the setting of a surgical emergency. This is especially true because surgical specimens from apoplexy cases may include mostly noninformative necrotic material and blood. Evidence of hypersecretion prior to surgery will guide postoperative monitoring. The identification of a prolactinoma might provide additional support for a trial of a dopamine agonist, as this may rapidly shrink any uninfarcted tumor. Absence of endocrine hypersecretion prior to surgery, even in the presence of tumor staining for a single hormone, might suggest clinically nonfunctioning status. In this case only prolactin was elevated, at levels most consistent with stalk compression rather than a prolactinoma.

Many patients are left with permanent endocrine deficits requiring long-term management [5]; up to 90% of patients require replacement of at least one hormone. If the tumor in which apoplexy arose is not completely removed or entirely necrotic, endocrine hypersecretion may persist. A complete evaluation of anterior pituitary hormone function should be performed approximately 6 weeks after surgical decompression of the sella. In this case, apoplexy was complicated by permanent panhypopituitarism, requiring comprehensive replacement of pituitary hormones.

It is useful to approach the management of hypopituitarism in a staged fashion. The first priority is the replacement of glucocorticoid, if necessary. Because profound adrenal insufficiency is incompatible with life, under conditions of severe physical stress patients are assumed to have adrenal insufficiency until proven otherwise. A replacement dose of glucocorticoids (e.g. 5 mg of prednisone each morning) is given postoperatively until a cortisol value of 18 μg/dL is documented, either on a morning sample or after ACTH (Cortrosyn) stimulation test. Since the ACTH stimulation test actually measures adrenal capacity for glucocorticoid release, an indirect measure of pituitary ACTH release, the test must be performed at least 6 weeks after the apoplexy event. An ACTH test performed before the adrenal zona fasciculata has atrophied, (due to lack of ACTH stimulation), may falsely indicate adequate glucocorticoid production. It is also important to know that oral estrogen (such as from an oral contraceptive pill [OCP]) increases cortisol-binding globulin and elevates cortisol levels, although not the physiologically relevant free cortisol fraction. Therefore, a value of 18 μg/dL is not adequate in the presence of oral estrogen. Because the level of cortisol that is indicative of adequate adrenal reserve is not well defined in patients taking oral estrogen, the best approach is to discontinue oral estrogen (assuming another form of contraception) for 6 weeks before determining adrenal sufficiency. If adequate cortisol production cannot be documented, glucocorticoid treatment will have to be continued indefinitely. The glucocorticoid dose should be titrated down to the lowest dose at which the patient feels well to avoid iatrogenic Cushing's syndrome, usually between 3 and 5 mg of prednisone each morning.

The second priority is to treat hypothyroidism, if present. Because the TSH (usually normal in untreated central hypothyroidism) is not useful in the setting of pituitary pathology, the diagnosis of hypothyroidism and adjustment of levothyroxine dose are based on the free T_4 and clinical signs and symptoms. Patients with a frankly low free T_4, or those with a value in the lower half of the normal range with hypothyroid signs and symptoms, may be treated with thyroid hormone initially dosed on a weight basis. The dose should be adjusted to maintain the free T_4 in the normal range and to avoid symptoms of hypo- and hyperthyroidism. The TSH usually becomes suppressed after appropriate treatment of central hypothyroidism. Misunderstanding of this principle often leads to inappropriate levothyroxine dose reductions. Treatment of hypothyroidism should only be initiated if the patient is taking adequate glucocorticoid therapy, or has been shown to be adrenally sufficient, because increased cortisol metabolism could otherwise precipitate adrenal crisis.

The third priority is replacement of sex steroids. In males, testosterone replacement (usually by patch or topical gel) is indicated when the total testosterone level in the morning (before 9 a.m.) is below the normal range unless fertility is desired, in which case gonadotropin therapy is often necessary. The testosterone dose should be titrated so that the testosterone is in the middle half of the normal range, usually 5 to 10 g of topical gel preparations. In women of premenopausal age, treatment with estrogen and progestogen (or estrogen only in women without a uterus) should be considered if amenorrhea persists for more than 3 to 6 months after apoplexy.

Low-dose oral contraceptive pills or an estradiol patch combined with 10 days a month of oral medroxyprogesterone are both appropriate options.

If the patient is a candidate for GH therapy (e.g., no history of malignancy willing and able to comply with therapy) GH deficiency can be ruled out with GHRH/arginine stimulation testing or an IGF-I that is frankly low in the presence of three additional pituitary hormone deficiencies. If GH deficiency is documented, GH may be initiated at a low dose and titrated upward to a mid-normal IGF-I value. Higher doses of GH are required in women taking estrogen.

Throughout the process of sequentially addressing hormone deficiencies, it is important to reassess dosing of each component of the replacement regimen. For example, treatment of hypothyroidism and GH deficiency may increase the prednisone requirement. Growth hormone increases deiodination of T_4 to triiodothyronine (T_3), so it is important to follow both free T_4 (to monitor for decreases) & T_3 (to monitor for increases) as well as symptoms of thyroid dysfunction it is also important to note that safety monitoring of all hormone replacement regiments over time is critical, but the specifics of such management is outside the scope of this article.

Patients with a history of apoplexy may also develop temporary syndrome of inappropriate antidiuretic hormone (SIADH) after the event (usually within the first 2 weeks) or diabetes insipidus (DI) that may become permanent; DI may be diagnosed in the setting of polyuria and polydipsia with an elevated or high normal serum sodium, or with the use of a water deprivation test when the diagnosis is in question. The DI can be simply treated with nasal deamino-8-D-arginine vasopressin (DDAVP) starting with one puff at night to avoid nocturia. If polyuria is a problem during the day, an additional dose may be added in the morning. Monitoring of the serum sodium is essential to avoid iatrogenic hyponatremia.

References

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Multiple-Choice Questions

1. The cranial nerve injury most commonly associated with pituitary apoplexy is:

   A. Causing headache CN V (trigeminal) nerve involvement
   B. Causing visual symptoms optic chiasm (CN II) compression

C. Causing ophthalmoplegia CN III or VI involvement
D. Causing diplopia cranial nerve IV involvement

Answer: C. Headache is the most common and nearly universal symptom in apoplexy, but in most cases it is not thought be associated with involvement of CN V. Ophthalmoplegia in general is more common than visual impairment, and cranial nerves III and VI are most commonly affected. CN VI and IV impairment may not be obvious with casual observation, so formal examination of extraocular movements is important.

2. Factors reported to be associated with apoplexy include:

A. Anticoagulants
B. Dopamine agonist treatment of prolactinomas.
C. Endocrine stimulation testing
D. All of the above

Answer: D. Many factors have been reported to be associated with the onset of apoplexy. However, it is difficult to establish that a similar number of apoplectic events would not have occurred without the specific factor at issue.

3. What is the percentage of patients with adrenal insufficiency after pituitary apoplexy?

A. ~25%
B. ~65%
C. ~90%
D. ~100%

Answer: B. Studies vary, but a review of 66 cases revealed a 66% rate of adrenal insufficiency [5]. GH deficiency and male hypogonadism were more common, and hypothyroidism was less common.

4. What is the most common tumor type in which apoplexy occurs?

A. Clinically nonfunctioning tumors
B. GH secreting adenomas
C. Prolactinomas
D. There is no clear preference for one tumor type

Answer: D. Although individual case series have reported a predominance of certain tumor types, the findings are not consistent. When taken together, the case series reports do not reveal a clear predominance for one tumor type, but the three tumor types listed are significantly more common than corticotroph adenomas and TSH secreting adenomas.