

# Endocrinology ROUNDS®

October 2006  
Volume 6, Issue 8

AS PRESENTED IN THE ROUNDS  
OF THE DIVISION OF  
ENDOCRINOLOGY AND METABOLISM,  
ST. MICHAEL'S HOSPITAL

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## Pituitary Apoplexy: Don't Miss the Diagnosis!

BY JEANNETTE GOGUEN, MD

Pituitary apoplexy is a rare and potentially lethal endocrine and neurosurgical emergency. It is often misdiagnosed or diagnosed late in its course.<sup>1</sup> The purpose of this issue of *Endocrinology Rounds* is to review the pathophysiology of pituitary apoplexy and discuss how to confirm the diagnosis in a timely manner.

### A case presentation

Ms GL is a 45-year-old woman with a past history of hypertension and obesity. One day, she abruptly develops the worst headache of her life and is rushed to the hospital by her family. She has a significantly decreased level of consciousness (Glasgow Coma Scale 7) and is febrile at 40°C. A computed tomography (CT) scan of her head reveals a large pituitary adenoma, but no signs of hemorrhage. Because she is very obese, a lumbar puncture and magnetic resonance imaging (MRI) scan cannot be performed. She is treated empirically for sepsis/meningitis with antibiotics. All cultures ultimately come back negative. A cortrosyn adrenocorticotrophic hormone (ACTH) stimulation test is done and, at 60 minutes, her cortisol level is 530 µmol/L (the time "0" sample was lost). A morning cortisol several days later is only 19 µmol/L and stimulates to only 117 µmol/L, with an ACTH of 4. She is treated with intravenous glucocorticoids and her hypotension resolves. When she regains consciousness, it is noticed that she has a right cranial third nerve palsy. Visual field testing is normal, with visual acuity 20/25 OD and 20/50 OS. Ms GL then reveals that she has had amenorrhea for 6 years. Furthermore, pituitary testing reveals the following: sTSH 0.74 mIU/L (0.4-5.5), free T4 pmol/L 6.2 (7.5-20), LH 0.6 IU/L (1.4-7.7), FSH 0 IU/L (1.5-14), estradiol 50 (low), and prolactin 1 µg/L (0.0-18). The correct diagnosis – pituitary apoplexy – is finally made.

Pituitary apoplexy is a clinical, not a pathological, diagnosis. It can be considered an acute symptomatic "stroke" of the pituitary, and almost always occurs in the setting of a pituitary macroadenoma. The event is usually hemorrhagic, but there may also be an infarct with edema that may or may not become hemorrhagic later.<sup>2</sup> This process results in any of the following: tumour expansion; extravasation of blood beyond the dura surrounding the tumour; partial or complete destruction of the normal pituitary gland.

The patient typically presents with the triad of acute headache, visual complaints, and hypopituitarism. Subclinical, small, pituitary tumour hemorrhages are identified by pathology or MRI in 14% to 25% of patients with adenomas; however, these asymptomatic events are not considered to be cases of pituitary apoplexy.<sup>2</sup>

### Pathophysiology

There are case reports of pituitary apoplexy occurring in the normal pituitary gland (especially after postpartum hypotension [Sheehan's syndrome]) and rarely in other sellar lesions (eg, craniopharyngioma,<sup>3</sup> tuberculosis,<sup>4</sup> lymphocytic hypophysitis<sup>5</sup>), but it is most commonly associated with pituitary adenomas. This may be because these tumours are more prone to bleeding (see below).

Three main theories have been advanced to explain apoplexy.<sup>2</sup> First, if the adenoma outgrows its blood supply, tumour infarction and then hemorrhage can result. Second, the infundibular and superior hypophysial vessels may become compressed by the tumour



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against the diaphragma sella, which in turn, may result in ischemia, infarction, and hemorrhage. As the tumour arterial supply usually comes from the inferior hypophyseal arteries (on angiographic studies), this suggests that it may be the normal pituitary and not the tumour that is hemorrhagic. Finally, pituitary adenomas may have an intrinsic vasculopathy since they are associated with aneurysms and are 5 times more likely to bleed than other intracranial tumours.

Three general mechanisms have been proposed for hypopituitarism.<sup>6</sup> These include decreased release or secretion of hypothalamic hormones or decreased delivery of hypothalamic hormones due to stalk disease, transection, or compression. Both mechanisms result in mild-to-moderate elevations in prolactin levels (due to loss of tonic suppression by dopamine) and low pituitary hormone levels that increase with stimulation by hypothalamic hormones in triple bolus testing. The third mechanism involves destruction of the hormone-producing cells of the pituitary. In this case, all pituitary hormones are decreased, including prolactin, and pituitary hormones exhibit decreased or no response to stimulatory hypothalamic releasing hormones. Theoretically, the hypopituitarism of apoplexy may be caused when any of the above mechanisms are precipitated by compression or destruction of the gland, interruptions in its blood supply, or stalk damage. Prolactin levels can be used to differentiate destruction of the pituitary from decreased hypothalamic signals, the latter being potentially reversible.

The role of increased intrasellar pressure (ISP), the resulting compression of surrounding structures, and hypopituitarism was investigated by Zayour et al.<sup>7</sup> They studied 13 patients with apoplexy who had surgery within 7 days of their initial presentation. They directly measured ISP and pituitary function: ISP inversely correlated to prolactin levels and those patients who ultimately recovered pituitary function had lower ISP and higher prolactin levels. Therefore, higher prolactin levels may be a marker of viable pituitary cells, while lower prolactin levels may indicate pituitary destruction.

## Incidence

On average, pituitary apoplexy occurs in patients in their fifth and sixth decades, but they can occur in younger and older patients.<sup>8-10</sup> There is a gender predisposition; it occurs 1.5-2 times more frequently in men.<sup>8-10</sup> In case series, from 0.6% to 9% of all pituitary tumours that are surgically treated undergo apoplexy. (The exact percentage depends on referral patterns and indications used for surgery). Most pituitary adenomas are undiagnosed at the time of apoplexy.<sup>8,9,11,12</sup> What is the risk of apoplexy in a known pituitary adenoma that has been followed prospectively? Two recent studies examined the natural history of "incidental" pituitary macroadenomas (ie, tumours that are nonfunctional, with no cranial nerve involvement and normal pituitary function).

Nishzawa et al followed 28 patients with incidentally discovered pituitary macroadenomas (discovered on routine "screening" MRIs of the head) for 6 months to 10 years.<sup>13</sup> The 24 patients who were classified as Hardy's class A (intrasellar) had no increase in size but, of the 4 with Hardy's Class B size (extending suprasellarly), 2 patients had apoplexy (1 patient had refused surgery for a growing tumour, while the other had a traumatic head injury at the time of apoplexy).

In the second study, Arita et al followed 37 patients with incidental macroadenomas (30 with suprasellar extension on initial MRI). In 19 of the 37, there was an increase in height by >10%; of these, 10 were symptomatic and 4 had apoplexy (11% of the total number of macroadenomas).<sup>14</sup> The risk of symptomatic tumour enlargement was greater for tumours that were >15 mm in size (apoplexy occurred in tumours that were initially 18, 20, 20, and 24 mm in size).

These two studies suggest there is an approximate 10% risk of apoplexy in incidentally-discovered, asymptomatic macroadenomas that are followed prospectively. It is important to inform conservatively-treated patients of this potential complication.

## Clinical features

As noted above, the classic triad includes severe headache, loss of vision and/or diplopia, and hypopituitarism. The frequency of each symptom often depends on how apoplexy is defined in the case series.

### Headache

Typically, at the time of presentation, patients complain of a 1-2 day history of severe headache. The classic location of the pain is retro-orbital but, in one study, 7 of 8 patients had frontal headaches, while 1 of the 8 had occipital pain.<sup>11</sup> In 7 recent retrospective studies,<sup>8-12,15,16</sup> 84%-100% of patients had headache (in most studies >95%) that was typically accompanied by nausea and vomiting (in 43%-80%). Less common complaints included meningismus or photophobia (25%-33%), fever (24%), and a decreased level of consciousness (11%-22%).

### Loss of vision and diplopia

Expansion of the hemorrhagic tumour in a superior suprasellar direction can lead to stretching of the optic chiasm with resultant decreased vision and classic bitemporal hemianopsia. Decreased visual acuity is seen in 46%-82% of patients.<sup>8-12,15,16</sup> The defect ranges from mild blurred vision to frank blindness. Loss of vision can also be demonstrated on visual field testing, which is abnormal in 36%-71% of patients at presentation.<sup>8-12,15</sup> Expansion of tumour and/or blood laterally into the cavernous sinus can compromise the cranial nerves within the cavernous sinus, including cranial nerves III, IV, V1, V2, and VI. An ocular paresis occurs in 40%-69% of patients, with the most commonly affected nerve being the oculomotor nerve (cranial nerve III), resulting in

**Table 1: Initial endocrine dysfunction on presentation.**

Percentage of patients with hormonal deficiencies (or excess prolactin) at the time of presentation.							
Study	N	Any dysfunction	↓ Cortisol	↓ T4	2° hypogonadism	↓ Prolactin	↑ Prolactin
Randeva <sup>15</sup>	35		76%	50%	80%		6%
Lubina <sup>9</sup>	40		65%	50%			32%
Imboden <sup>11</sup>	8		50%	12%	100%	38%	50% (1 prolactinoma)
Semple <sup>12</sup>	62	73%					
Ayuk <sup>10</sup>	33		50%	38%	65%	24%	38%

diplopia, ptosis, plus or minus pupil dilation on the affected side.<sup>8,10,15</sup> Next in frequency is the abducens nerve (cranial nerve VI), followed by cranial nerve IV (trochlear nerve); paresis in either also causes diplopia.<sup>8,10,15</sup> Up to 40% of patients with ocular paresis will have a mixed defect, with cranial nerves III and VI being the most commonly involved.<sup>8,10,15</sup> Less commonly reported symptoms from mass expansion include rhinorrhea from inferior expansion and seizures or hemiparesis from carotid artery involvement.<sup>2,17</sup> The frequency of involvement of the trigeminal nerve branches V1 and V2 has not been reported in the literature, possibly because this nerve is difficult to examine in the comatose patient.

In the setting of sudden-onset diplopia with cranial nerve III, IV, or VI defect, it is imperative to rule-out pituitary apoplexy in the patient with a pituitary adenoma since the cranial nerves are fairly resistant to chronic pressure. Therefore, symptoms should suggest more than just a slow-growing pituitary adenoma.<sup>18</sup> An aneurysm, a parasellar meningioma, and other tumours should also be considered in the differential diagnosis.

### *Hypopituitarism*

The third component of the symptom complex is hypopituitarism. In addition to the usual symptoms of hypopituitarism, patients may present with hypotension, hyponatremia (12%-44%),<sup>9,12,15</sup> and hypoglycemia, attributed to acute secondary hypoadrenalism or growth hormone deficiency. Patients who collapse with hypotension with or without decreased level of consciousness respond to glucocorticoid replacement and fluid resuscitation, if the collapse was caused by hypopituitarism. However, if it was caused by pressure on the hypothalamus, prompt neurosurgical intervention is necessary.

Pituitary apoplexy usually occurs within the setting of a pituitary macroadenoma. Patients often describe a history of hypopituitary symptoms predating the severe headaches of apoplexy. Not unexpectedly, symptoms reflect the frequency that the different axes are affected in hypopituitarism in general. In 3 studies, decreased libido and sexual dysfunction were the most common complaints (in 25%-33% of patients with apoplexy),<sup>9,10,15</sup> while cold intolerance (in 20%) and lethargy (in 14%)

were less common, and galactorrhea was rarely reported (6%).<sup>9,10,15</sup>

When hormone levels were measured at presentation in 5 retrospective studies, there was at least 1 hormone deficiency in 65%-100% of patients (Table 1). Hormone deficiencies were usually defined as being "low baseline." Triple bolus testing was not reported in respective studies at acute presentation because it is typically done after stabilization (medical or surgical). The most frequent pituitary hormone deficiency is secondary hypogonadism; low LH, low FSH, and low testosterone or estrogen levels are found in 65%-100% of patients.<sup>10,11,15</sup> Secondary hypothyroidism occurs in 12%-50% of patients.<sup>9-11,15</sup> The most clinically significant deficiency is secondary hypoadrenalism. When defined as morning levels that are <170-200 µmol/L, 50%-76% of patients were cortisol deficient.<sup>9-11,15</sup> Given that the diagnosis is often missed or delayed, the ramifications of not detecting (and therefore not treating) hypoadrenalism can have significant implications for patient survival. Low prolactin levels are found in 24%-38% of affected people.<sup>10,11</sup> While only clinically important in lactating woman, low prolactin levels may have important prognostic value in predicting the ability of pituitary function to recover. Dysfunction of the posterior pituitary resulting in diabetes insipidus is much rarer, occurring at presentation in only 0%-8% of cases.<sup>11,15</sup>

Pituitary adenomas can be functional or nonfunctional. The distribution of functional tumours (including prolactinomas, acromegaly, and Cushing's disease) in pathological specimens appears to be similar to that seen in nonapoplectic pituitary adenomas. In 5 studies, 16/190 patients had a prolactinoma, 2/190 had acromegaly, and 4/190 had Cushing's disease.<sup>8-12,15</sup>

**Differential diagnoses:** The differential diagnosis of pituitary apoplexy is broad and includes: ruptured berry aneurysm with subarachnoid hemorrhage, bacterial meningitis, midbrain infarct, cavernous sinus thrombosis, septic shock, encephalitis, intracranial aneurysm, arteriovenous malformation, migraine, and optic neuritis. The diagnosis is often missed; for example, subarachnoid hemorrhage and meningitis are common misdiagnoses.<sup>12</sup> One reason for missing the diagnosis is that the symp-

toms of apoplexy can be atypical if blood beyond the dura results in meningismus, with complaints such as nausea, vomiting, fever, and decreased level of consciousness.<sup>17</sup> Increased pressure and blood in the hypothalamus has also been postulated to cause the fever. Second, the underlying diagnosis of pituitary adenoma is often unknown before the event. It has been reported that between 75% to 90% of patients with apoplexy had previously undiagnosed macroadenomas<sup>9,11,12</sup> and, in 1 study, 43% had symptoms of hypopituitarism prior to apoplexy, but their pituitary adenoma had not been diagnosed.<sup>9</sup>

### Aggravating or precipitating factors

Apoplexy is usually spontaneous; however, in a small case series, the following factors have been noted to be associated with the development of pituitary apoplexy: drugs (eg, GnRH, TRH, bromocriptine, leuprolide, anticoagulation, estrogen), head injury, radiation, hypertension, and diabetes mellitus.<sup>9,11,12,15</sup> Treatment of prolactinomas with dopamine agonists has also been associated with apoplexy,<sup>11,19</sup> and triple bolus testing<sup>20</sup> (or use of GnRH for other reasons, such as prostate cancer) has been reported in the literature to temporally correlate with pituitary apoplexy.

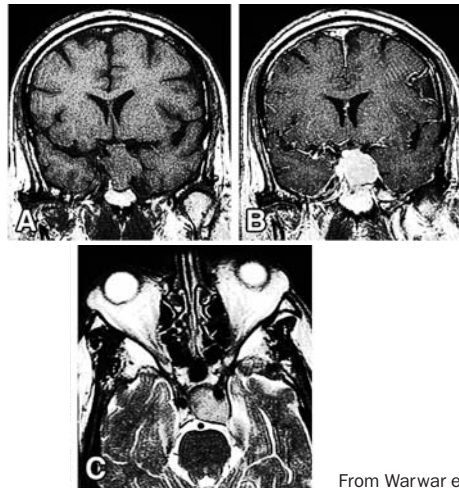
In an attempt to demonstrate a potential mechanism for hypothalamic hormones causing pituitary apoplexy, Maier<sup>21</sup> gave CRH, TRH, GHRH, and GnRH to 2 healthy young volunteers. There was no difference in pituitary size acutely, but there was increased gadolinium enhancement of the pituitary, suggesting that hypothalamic-releasing hormones increase blood flow and/or increase vascular permeability. Both effects could theoretically precipitate apoplexy in a macroadenoma.

### Imaging

In addition to the history, physical examination, baseline pituitary testing, and visual field testing (if the patient can co-operate), imaging can confirm the diagnosis of pituitary apoplexy and rule-out alternative diagnoses. The patient is often initially investigated with a CT scan, especially if other disorders are being considered (eg, a subarachnoid hemorrhage). CT scan of the head was only 93% sensitive in diagnosing a macroadenoma in a study by Radenva;<sup>15</sup> this is in comparison to MRI, which has been reported to be 100% sensitive in 2 other studies.<sup>9,15</sup> In these studies, MRI detected bleeding in 84%-88% of tumours, compared to a 21%-71% detection rate via CT scan. Imboden et al<sup>11</sup> suggests using CT to detect a subarachnoid bleed, pituitary tumour, and possibly an early bleed into the tumour, and then using MRI to confirm the diagnosis. However, MRI can be used first if there is a high index of suspicion. If no tumour or bleed is seen on

**Figure 1: Appearance of pituitary macroadenoma that has undergone hemorrhage**

- A. T1-weighted image shows an isointense pituitary mass extending in a suprasellar direction.
- B. The lesion is hyperintense on T1 with gadolinium contrast.
- C. On T2-weighted images, the tumour has a speckled appearance.



From Warwar et al<sup>18</sup>

MRI, one should consider MR angiography to investigate an aneurysm.

The appearance of the pituitary gland on MRI depends on the age of the hemorrhage.<sup>17,18</sup> With an early hemorrhage (<3 hours), if the pituitary tumour is in an ischemic state, the pituitary can look normal on T1 images, or only an adenoma is seen, with no bleeding. The lesion may appear hypointense on T1 plus gadolinium and T2-weighted images. After 3 hours, although the T1-weighted image looks the same, there is a low-intensity signal within the tumour surrounded by an enhancing capsule with T1 plus gadolinium. T2-weighted images are hypointense, with flecks of hyperintense debris within it. After 3-5 days, however, T1 (both with and without gadolinium enhancement) and T2-weighted images all look hyperintense (Figure 1 shows MRI findings in an acute bleed).

### Pathology

If the patient has surgery, pathology can identify cell characteristics in only 75% of cases. Ischemia may result in "ghost cells" or dying cells with pyknotic nuclei. Hemorrhage is seen as extravasated red blood cells. Adenoma cells can be stained conventionally or examined under electron microscopy to determine which hormones are stored within the cells. For instance, in the study by Lubina,<sup>9</sup> only 19 of 34 patients who went to surgery had pathology that could be reported. Clinically, 63% of tumours were nonfunctional, based on the patients' symptoms, signs, and hormonal results. Staining revealed null cells in 4/19, lactotrophs in 2/19, and gonado-

**Table 2: Pituitary functional outcomes with and without surgery (OR): Percentage of patients requiring hormonal replacement is indicated for each hormone in 5 studies**

Study	N	Hypopituitarism (% deficient)	
		OR	No OR
Randeva <sup>15</sup>	35	58% steroid 45% T4 43% testosterone 6% ADH	25% (1/4 pts) needed steroid T4, testosterone
Lubina <sup>9</sup>	40	86% overall: 27% on steroid, T4 + sex hormones (SH) 40% steroid 54% T4 79% SH 8% ADH	
Imboden <sup>11</sup>	8	75% overall: 86% cortisol 14% ADH	
Semple <sup>12</sup>	62	83% on Rx	
Ayuk <sup>10</sup>	33	72% steroid 72% T4 83% SH	

trophs in 7/19 subjects. Other specimens stained positively for coincidental prolactin and growth hormone in 2/19 and 1/19 stained positively for ACTH, FSH, and  $\beta$ -LH.<sup>9</sup>

### Management

After making the diagnosis of pituitary apoplexy, management consists of supportive therapy, glucocorticoid coverage, and possibly, surgery. Glucocorticoid coverage (at high doses while the patient is ill) is essential when cortisol deficiency has been diagnosed. Some centres administer glucocorticoids to all patients with apoplexy,<sup>9,12</sup> since the incidence of hypoadrenalism is so high and it is believed that they may be useful to reduce brain swelling and relieve symptoms. However, there is little evidence for the latter belief. Glucocorticoids (dexamethasone 2-16 mg a day) were given for 1 week to patients with visual compromise in 1 study and the patients who eventually did get surgery after 7 days had significantly worse visual outcomes than historical controls.<sup>22</sup>

Which patients should be treated surgically (usually with transsphenoidal surgery) is still not completely clear since almost all studies have been retrospective and unrandomized. Early studies sent all patients (except those with prolactinomas) to surgery.<sup>9,11,12</sup> Later studies, in which surgery was delayed for >1 week in patients with visual compromise, revealed worse visual outcomes in the delayed-treatment group.<sup>15,22-24</sup> Various studies have indicated that the following rules apply:

- patients with visual compromise (decreased visual acuity or abnormal visual field testing) should have

surgery as soon as possible (definitely within 1 week of presentation)

- patients with ocular paresis (cranial nerves III, IV, or VI) usually do well with or without surgery, and surgery can be delayed as the nerve defect recovers
- pituitary hormone defects are usually permanent and not usually improved by surgery (Table 2).

Prolactinomas generally do well with conservative management (dopamine agonist plus hormone replacement as required).<sup>8,9,11,12,15</sup>

### Conclusions

It is critical to have a high index of suspicion for pituitary apoplexy in patients with sudden-onset severe headache and visual and/or oculomotor compromise. There is a broad differential diagnosis, particularly in cases where the presentation mimics subarachnoid hemorrhage and meningitis. The patient requires urgent hormonal assessment and glucocorticoid coverage until cortisol levels are known, as well as urgent imaging (CT/MRI) and visual assessment, including visual acuity and visual field testing. Patients with decreased vision (on visual acuity and/or field testing) and the rare patient with a decreased level of consciousness unresponsive to hormonal therapy require urgent surgery (usually transsphenoidal). Others with ocular paresis can be watched closely, since they usually improve spontaneously. Hormonal deficiencies should be identified and treated since they are common, and much less likely to resolve, with or without surgery. Lessons learned from our case include the following:

- Keep the diagnosis of pituitary apoplexy in mind when patients present with severe headache, especially when cranial nerves II, III, IV, V1, V2, and VI are involved, and remember to do a full cranial nerve examination and screen for hormonal deficiencies, especially hypoadrenalism, which is common and can be fatal if missed.
- The ACTH stimulation test can be normal in early secondary hypoadrenalism.
- The CT scan is not sensitive for pituitary hemorrhage and, therefore, MRI may be required to detect hemorrhage. Recall that the appearance of hemorrhage on MRI depends on how old the bleed is. Also, MRI may miss early hemorrhage.
- Pituitary apoplexy can mimic subarachnoid hemorrhage or meningitis, with symptoms such as nausea, vomiting, and fever!
- Remember that only 10%-25% of patients presenting with pituitary apoplexy have a previous diagnosis of pituitary macroadenoma, although up to 35% will have had prior symptoms of hormone deficiencies.
- Avoid precipitating factors in patients with pituitary macroadenomas ("incidentalomas") that are being followed conservatively.

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**Disclosure Statement:** Dr. Goguen declares that she has accepted honoraria or salary support in the past from the following: Pfizer (including Parke Davis), GlaxoSmithKline and Novo Nordisk.

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This publication is made possible by an educational grant from

**sanofi-aventis**

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