SHORT REPORT

Precipitating factors in pituitary apoplexy

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Abstract

Pituitary apoplexy is a rare but life threatening condition caused by sudden haemorrhage or infarction of the pituitary gland. Potential precipitating factors in the occurrence of acute pituitary apoplexy in 30 consecutive patients were identified and compared with the clinical characteristics and outcome of patients with and without associated factors. Six patients had a previously known pituitary adenoma. All patients complained of severe headaches, associated with neuro-ophthalmological symptoms and signs in 83% and altered mental status in 30%. Potential risk factors were identified in nine patients (30%). When there was an associated factor, the clinical presentation was no different than in patients without such factors although altered mental status may be more frequent in patients with associated diseases. In these patients, the visual prognosis was worse and the diagnosis was more difficult to establish. Acute pituitary apoplexy is unpredictable and should be considered in any patient with abrupt neuro-ophthalmological deterioration associated with headache. Patients with pituitary apoplexy often have an associated disease that confounds recognition and treatment despite a typical presentation.

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Pituitary apoplexy is a rare but life threatening condition characterised by headache, visual loss, ophthalmoplegia, and altered mental status caused by sudden haemorrhage or infarction of the pituitary gland.[1 2] It remains a misunderstood and often misdiagnosed condition.[1 3–13] Over the past 20 years, numerous case reports and small series have emphasised the association of pituitary apoplexy with a wide variety of medications, procedures, and pathological states such as anticoagulation, endocrinological testing, head trauma, or recent surgery.[1 3–10] In most reports, these associated conditions have been qualified as "precipitating factors". However, the frequency and relevance of these so-called "precipitating factors" is not clear, and their role in the pathophysiology, prognosis, and management of patients with acute pituitary apoplexy remains to be elucidated. The aim of our study was to identify associated conditions with the occurrence of acute, symptomatic pituitary apoplexy, and to compare the characteristics and outcome of patients with and without identified associated diseases.

Methods

We used the databases from the neuro-ophthalmology unit and the department of neurological surgery to select patients with acute pituitary apoplexy seen at Emory University School of Medicine between 1989 and 2000. Pituitary apoplexy was defined as the acute onset of clinical symptoms associated with haemorrhage or infarction within a normal pituitary gland or previously known pituitary adenoma. All patients were initially evaluated by two of us (NJN and NMO), and were asked standardised questions, which were recorded in their chart. They underwent thorough neurological, neuro-ophthalmological, and endocrinological evaluations. Clinical characteristics, neuro-ophthalmic examination (including visual field testing), neuroimaging, and endocrinological status of the patients were reviewed, as well as the existence of possible precipitating factors for pituitary apoplexy. Any new event occurring within the month before the occurrence of pituitary apoplexy was considered as a possible precipitating factor. Patients were divided into two groups depending on the presence or the absence of possible precipitating factors. Both groups were compared using χ^2 and Student's t tests.

Results

Thirty consecutive patients with acute pituitary apoplexy were retrospectively included (14 women, 16 men; age 21 to 90 years old, mean 51 years). A pituitary adenoma was previously known in six patients (20%) (prolactinoma in three and non-secreting adenoma in three) Associated conditions were identified in nine patients (30%): three patients had been anticoagulated recently (one for cardiac arrythmia and two for myocardial infarction); one additional patient had received thrombolysis and heparin for a myocardial infarction; two patients developed symptoms suggestive of pituitary apoplexy within 48 hours after surgery (one coronary artery bypass and one

Table 1 Comparison of patients with pituitary apoplexy with and without identified associated conditions

	Associated condition n=9 (30%)	*No associated condition n=21 (70%)*	*p Value*
Sex	4 women/5 men	10 women/11 men	NS
Mean age (range)	59 y (21–82)	48 y (22–90)	NS
Known pituitary adenoma	1 (11%)	5 (23.8%)	NS
Neuro-ophthalmic deficit:	8 (88.8%)	17 (81.1%)	NS
Headache	9 (100%)	21 (100%)	NS
Ophthalmoplegia	6 (66.6%)	11 (52.4%)	NS
Optic nerve compression	4 (44%)	7 (33%)	NS
Chiasmal visual field defect	4 (44%)	10 (47.6%)	NS
Altered mental status	5 (55%)	4 (19%)	<0.05
Systemic hypertension	5 (55%)	8 (38%)	NS
Neuroimaging:			
Haemorrhage	6 (66.6%)	9 (42.8%)	NS
Infarction	3 (33.3%)	12 (57.1%)	NS
Prognosis:			
Death	0	0	NS
Unknown	2 (22.2%)	7 (33.3%)	NS
Pituitary dysfunction	5/9 (55.5%)	11/21 (52.4%)	NS
Complete recovery	2/7 (28.5%)	10/14 (71%)	0.06
Neurological sequelae	1/7 (14.3%)	0 (0%)	NS
Neuro-ophthalmic sequelae	5/7 (71.4%)	2/14 (14.3%)	<0.01
Ophthalmoplegia	1/6 (16.6%)	2/11 (18.2%)	NS
Severe optic neuropathy	3/4 (75%)	1/7 (14.3%)	<0.05
Visual field defect	4/4 (100%)	2/10 (20%)	<0.01
Mean delay in diagnosis (range)	5.5 days (1–14)	5.6 days (1–14)	NS
Mean delay in treatment (range)	2.2 days [0–7]	2.2 days (0–)]	NS

p Calculated using χ^2 and Student's *t* tests.

transurethral prostatectomy); one had apoplexy immediately after a normal vaginal delivery; one patient was being treated for lower limb cellulitis; and one patient had pituitary apoplexy a few weeks after discontinuation of bromocriptine prescribed for a prolactinoma. Six of these patients were in the hospital for their underlying disease when they developed the first symptoms of pituitary apoplexy.

In addition to immediate correction of the hormonal deficiency, 27 patients (90%) underwent surgical decompression (transphenoidal resection in 26 and frontal craniotomy in one). The mean time to surgery was 2.2 days (range from 0 to 9 days) after diagnosis was established, except for two patients who recovered spontaneously and underwent transphenoidal resection of a pituitary adenoma 2 months after the apoplexy. One patient received radiation only, and two patients were managed medically only (one improved spontaneously and one was unstable cardiologically).

Comparison of clinical, endocrinological, and radiological characteristics of patients with (n=9) and without (n=21) associated diseases is detailed in table 1. The only statistically significant difference between the two groups was a higher frequency of altered mental status in patients with identified associated conditions (p=0.046). However, the ophthalmological outcome of patients with an associated disease was not as good as in those without any identified associated disease. Indeed, 71.4% of patients with a predisposing event had neuro-ophthalmological sequelae, whereas only 14.3% of those without an identified predisposing event had such sequelae (p=0.009). Although the prognosis of ophthalmoplegia was relatively good in both groups, with less than 20% of patients having residual diplopia, the visual function (visual field defects and visual loss from optic neuropathy) improved only moderately in patients with an associated condition (p=0.044). The delay in diagnosis (5.5 and 5.6 days) and treatment (2.2 days after diagnosis) of the pituitary apoplexy was similar in both groups.

Discussion

The syndrome of acute, symptomatic pituitary apoplexy is rare, and its presentation is highly variable.[1 3–14] There is no population that seems to have a propensity for pituitary apoplexy. The age range is broad, from the 1st to the 9th decade, with a peak in the 5th decade. There is no sex predominance. There is no histological subtype of pituitary tumour that confers a higher risk.[1 8] Whereas early investigators suggested that pituitary apoplexy occurred primarily in patients with large macroadenomas with suprasellar extension,[2] it is now evident that tumours of almost any size may undergo haemorrhage and apoplexy.[1 8 9] Most importantly, most cases of pituitary apoplexy (80% in our series) occur in patients who have as of yet undiagnosed pituitary adenomas, with the apoplectic episode often the presenting symptom of the pituitary tumour.

Pituitary apoplexy has been described in association with a wide variety of medications, procedures, and pathological states, although the reason for most of these associations is unclear. The pathophysiological changes that lead to pituitary apoplexy are still open to speculation. It is well recognised that pituitary adenomas are particularly prone to haemorrhage and necrosis.[1 8] Several authors have proposed that a rapidly growing adenoma that outstrips its blood supply may lead to ischaemic necrosis of the gland followed by haemorrhage. Others propose direct compression of the pituitary infundibulum by an expanding mass, thus compromising the blood flow from the portal vessels, resulting in necrosis of the entire gland with haemorrhage as a secondary occurrence. Various other mechanisms have been proposed for haemorrhage and infarction of pituitary adenomas, including inherent fragility of tumour blood vessels and atherosclerotic embolisation. The mechanism of infarction and haemorrhage in the non-adenomatous pituitary is even more difficult to explain. Therefore, the idea that extrinsic factors such as systemic diseases or medications may trigger changes in the vascular supply of some pituitary glands (with or without pituitary adenoma), thereby producing an apoplectic necrosis or haemorrhage of the pituitary, is attractive.

In our experience, the multiple factors reported as precipitants of pituitary apoplexy can be reduced to four categories. (1) Reduced blood flow in the pituitary gland may result from fluctuations in blood pressure. Indeed, hypotension in the setting of cardiac surgery, lumbar laminectomy, or haemodialysis, have been associated with pituitary apoplexy of both normal and adenomatous glands. Transient increase in intracranial pressure with resultant hypoperfusion of the pituitary gland, as caused by coughing, sneezing, or positive pressure ventilation, has been reported as a precipitant of apoplexy in patients with pituitary

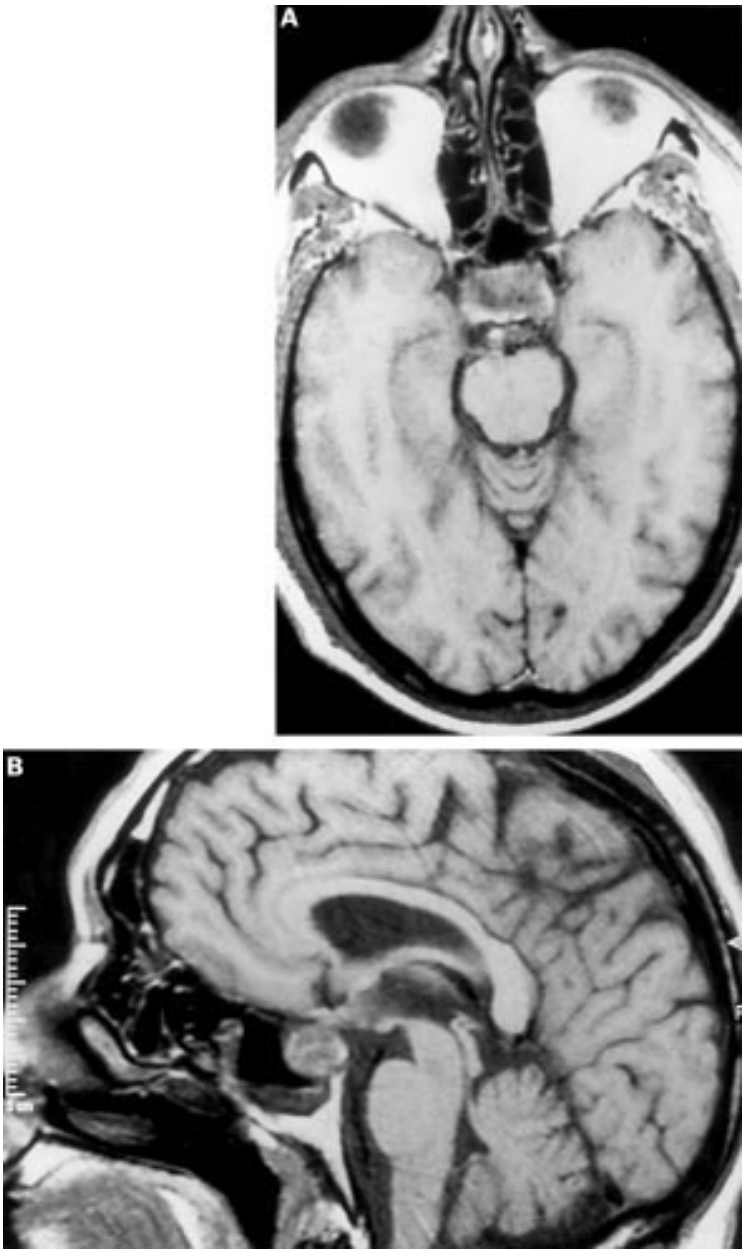

Figure 1 Acute pituitary apoplexy in a 68 year old man who developed acute headache and bilateral complete third nerve palsies 48 hours after coronary artery bypass surgery. His level of consciousness was normal and the remainder of his neurological examination was unremarkable. The initial investigation specifically looked for a haemorrhagic or ischaemic cerebrovascular accident at the level of the midbrain, and the diagnosis of pituitary apoplexy was delayed by 24 hours. The patient underwent transphenoidal decompression 48 hours later (after his cardiac condition was stabilised) and he completely recovered. (A) Axial T1 weighted MRI of the brain showing a normal brain stem and an enlarged pituitary gland which is heterogeneous, consistent with an infarction of the pituitary gland with a mild haemorrhagic component. (B) Sagittal T1 weighted MRI of the brain demonstrating the enlarged pituitary gland.

adenoma.[1 3–14] Minor head trauma, procedures such as angiography, pneumoencephalography, myelography, lumbar puncture, and spinal anaesthesia, all of which may produce acute changes in the intracranial pressure and in blood pressure, have also been implicated in the occurrence of haemorrhage in the adenomatous pituitary gland. Vascular changes after pituitary irradiation often result in chronic hypoperfusion of the pituitary gland and have been associated with both pituitary infarction and pituitary haemorrhage. (2) Acute increase in blood flow in the pituitary gland is considered as a classic triggering factor for pituitary apoplexy. Diabetes or chronic systemic hypertension have also been considered to predispose to pituitary apoplexy because of degenerative changes in the gland's microvasculature. However, whereas diabetic ketoacidosis and malignant hypertension may precipitate an apoplectic episode, there is no evidence that diabetes or hypertension are more common in patients with pituitary apoplexy. Thirteen of our patients (43%) were hypertensive and two had diabetes, but we did not consider these factors as predisposing events for pituitary apoplexy. Indeed, these vascular risk factors were commonly found in the group of patients with another precipitating event such as antithrombotic drugs, myocardial infarction, or infection (table 1). (3) Stimulation of the pituitary gland through increased estrogen states, such as exogenous estrogen administration and pregnancy, dynamic testing of the pituitary using gonadotropin releasing hormone (GnRH), thyrotropin releasing hormone (TRH) or other secretologues, as well as other hormonal treatments such as bromocriptine, have also been reported to cause apoplexy.[1] One of our patients with known prolactinoma had an apoplectic episode after discontinuing bromocriptine. This may have been secondary to acute enlargement of the pituitary adenoma. Numerous surgical procedures have been implicated in apoplexy through excessive stimulation of the pituitary gland responding to "surgical stress" by having to produce a larger amount of steroids. The same mechanism has been postulated regarding pituitary apoplexy occurring in the setting of an acute systemic illness such as myocardial infarction (three in our series) or severe infection (one in our series). (4) Another identified predisposing factor is the anticoagulated state, whether from administration of anticoagulant drugs, thrombolytic agents, or thrombocytopenia, which is usually associated with haemorrhagic pituitary apoplexy. However, one of our patients (fig 1) who had apoplexy of the pituitary gland after a coronary artery bypass procedure during which he was anticoagulated, had an infarction of the pituitary gland with only a very mild haemorrhagic component. We found the same phenomenon in another patient who received heparin for an acute myocardial infarction, suggesting that stimulation of the pituitary gland by "stress", and fluctuations in blood pressure may play a more important part in the pathophysiology of pituitary apoplexy. None the less, as in the literature, most of our cases of pituitary apoplexy were without identifiable "precipitants".[1 3–14] It is possible that associated factors are underestimated. Indeed, the definition of what should be considered a "precipitating event" is speculative. We considered only obvious associated conditions such as new onset systemic illness. The literature has emphasised more subtle events such as coughing, or sneezing, but there is no proof that all the reported events have a causal effect. However, close temporal relations and common pathophysiological mechanisms suggest that

some factors may be considered as predisposing events in the occurrence of pituitary apoplexy.

When there is an identified associated disease, the clinical presentation is no different from that of patients without such diseases, although altered mental status may be more frequent in patients with an associated disease (table 1). Neither the endocrine status nor the nature of the apoplexy (haemorrhage *v* infarction) explain this finding. The associated medical conditions, may have enhanced the severity of the apoplexy. Indeed, six patients were in the hospital (including four in an intensive care unit) at the time of the pituitary apoplexy. However, none of our patients died, and a large majority had an excellent neurological recovery.

As expected, the most common sequelae were neuro-ophthalmologic. Indeed, chiasmal visual field defects did not improve in the group of patients with associated diseases, and 75% of these patients had permanent severe visual loss and optic atrophy. This poor recovery of visual function could be explained by prolonged ischaemia of the visual pathways in those patients with associated diseases in whom the diagnosis of pituitary apoplexy may have been delayed, thereby delaying surgical decompression. However, the mean delay in diagnosis and treatment was the same in both groups (table 1). Although most patients with an identified associated condition were already in the hospital when they developed their first symptom of pituitary apoplexy, and therefore were evaluated much faster than the patients without associated disease, the correct diagnosis was always more difficult to establish.

Although it is tempting to look for factors likely to trigger apoplexy of the pituitary gland, most patients do not have any identifiable triggering event suggesting that pituitary apoplexy is unpredictable. Moreover, in our experience, the presence of even "classic precipitating events", such as cardiac surgery, is usually confusing and often makes the diagnosis of pituitary apoplexy even more difficult, and therefore delayed. Indeed, one third of patients with pituitary apoplexy had an associated disease confounding recognition and treatment despite a typical presentation. Although pituitary apoplexy is variable in its clinical appearance, it should be considered in any patient with abrupt neuro-ophthalmological deterioration associated with headache.

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