Review Article

Pituitary apoplexy

Salam Ranabir, Manash P. Baruah[1]

Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, [1]Department of Endocrinology, Excel Center, Guwahati, Assam, India

ABSTRACT

Pituitary apoplexy is rare endocrine emergency which can occur due to infarction or haemorrhage of pituitary gland. This disorder most often involves a pituitary adenoma. Occasionally it may be the first manifestation of an underlying adenoma. There is conflicting data regarding which type of pituitary adenoma is prone for apoplexy. Some studies showed predominance of non-functional adenomas while some other studies showed a higher prevalence in functioning adenomas amongst which prolactinoma have the highest risk. Although pituitary apoplexy can occur without any precipitating factor in most cases, there are some well recognizable risk factors such as hypertension, medications, major surgeries, coagulopathies either primary or following medications or infection, head injury, radiation or dynamic testing of the pituitary. Patients usually present with headache, vomiting, altered sensorium, visual defect and/or endocrine dysfunction. Hemodynamic instability may be result from adrenocorticotrophic hormone deficiency. Imaging with either CT scan or MRI should be performed in suspected cases. Intravenous fluid and hydrocortisone should be administered after collection of sample for baseline hormonal evaluation. Earlier studies used to advocate urgent decompression of the lesion but more recent studies favor conservative approach for most cases with surgery reserved for those with deteriorating level of consciousness or increasing visual defect. The visual and endocrine outcomes are almost similar with either surgery or conservative management. Once the acute phase is over, patient should be re-evaluated for hormonal deficiencies.

Key words: Apoplexy, hypopituitarism, pituitary

Introduction

Pituitary apoplexy (apoplexy meaning "sudden attack" or "to be struck down") is a potentially life-threatening disorder due to acute ischemic infarction or hemorrhage of the pituitary gland. As the primary event most often involves the adenoma, some authors suggested that the syndrome should be referred to as pituitary tumor apoplexy and not as pituitary apoplexy.[1] However, pituitary apoplexy may also occur in non-adenomatous or even the normal pituitary gland especially during pregnancy. "Subclinical pituitary apoplexy" is widely used to describe pathological evidence of asymptomatic pituitary ischemia[2] or hemorrhage.[3]

The first reported case of fatal hemorrhage in a pituitary adenoma was by Bailey in 1898. Sheehan (1938) pioneered the description of the prototype in obstetric cases. Finally it was Brougham (1950) who first coined the term and reviewed the reported cases described till date.[4]

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.84862

Incidence

The exact incidence of pituitary apoplexy is difficult to estimate as many cases remain undiagnosed.[5] However, some series indicate that the incidence of apoplexy in pituitary adenomas is between 1% and 26% on the basis of clinical signs coupled with surgical or histopathological evidence.[6,7] It has been reported in up to 21% of non-functioning pituitary tunours.[8] Pituitary apoplexy is often the first presentation of the underlying pituitary tumor in over 80% of patients.[9] Most cases of pituitary apoplexy present in the fifth or sixth decade with a slight male preponderance ranging from1.1 to 2.25:1.0.[10-13] In a recent

Corresponding Author: Dr. Manash P. Baruah, Department of Endocrinology, Excel Center (Unit of Excelcare Hospitals), Ulubari, Guwahati – 781 007, Assam, India. E-mail: manashbaruahinin@yahoo.co.in

retrospective analysis of 42 pituitary apoplexy patients from 1980 to 2007, the sex ratio was 3:1 with median age of the patients of 53.5 (range 21–85) years.[14] In the largest series from India studied at Vellore, the sex ratio was approximately 2:1 with mean age of presentation of 40.4 (range 18-65) years.[15] Study by Liu *et al.* showed a slight female preponderance for combined clinical and subclinical cases, however amongst clinical cases it was more in males.[16]

Pathophysiology

The pituitary gland is located in a boney cavity called the sella turcica covered by the diaphragma sellae superiorly. It lies in close proximity with hypothalamus, optic chiasma and the cavernous sinus. The pituitary has a rich vascular supply.[17] Understanding the blood supply is crucial to the understanding of etiopathogenesis of pituitary apoplexy [Figure 1]. The anterior lobe is supplied by the superior hypophyseal arteries which is a branch of internal carotid artery and traverse along the pituitary stalk. The anterior pituitary is supplied by portal vessels that originate dorsally at capillaries from the median eminence and travel along the stalk. The posterior pituitary is supplied by the inferior hypophyseal arteries which also arise from internal carotid artery and travel inferior to the gland. There is some anastomosis between the portal and hypophyseal circulation.[18] Around 70% to 90% of anterior pituitary supply comes from major portal vessels. Venous drainage takes place within adjacent venous sinus to the jugular veins. Because of the rich and the complex vascular system pituitary adenomas have a 5.4 greater chance to bleed than any other brain tumor.[5]

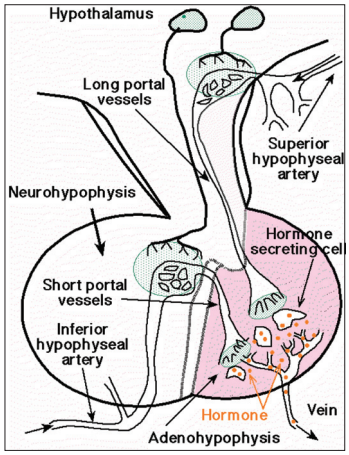

Figure 1: Blood supply to the pituitary gland. Notable features are the portal vessels which provide 70%-90% of blood supply to the anterior pituitary. While most part of the blood suplly to the adenomas are provided by inferior pituitary artery, the compression of the superior hypophyseal artery and its branches against the diaphragmasellae could lead to ischemia of the anterior pituitary and not the adenoma. (image courtesy www.pharmacology2000.com)

The angiographic studies reveal that adenomas are mostly supplied by inferior pituitary artery.[19] The number and size of vessels are variable. Generally they are lesser than the normal pituitary vessels and are divided into irregular islets. Under electronic microscopy they have incomplete maturation, low fenestration, and fragmented basal membranes with perivascular spaces filled with plasmatic proteins or red cells that may predispose to hemorrhage.[20]

Etiopathology

Various theories have been put forward regarding the pathophysiology of pituitary apoplexy. One theory is that rapid tumor growth may outstrip arterial supply.[21] It is uncertain whether the pathological process is a primary hemorrhage or is a hemorrhagic infarction. The size of the adenoma appears to be a major factor, but even microadenomas can bleed.[22] Another theory is that the tumor growing inside the narrow space situated between the pituitary stalk and diaphragm sellae leads to constriction of the thin vascular network and finally ischemia, necrosis and hemorrhage on the anterior lobe and tumor tissue.[23] But the adenoma is supplied by the inferior hypophyseal artery and the compression of the superior hypophyseal artery and its branches against the diaphragm sellae could lead to ischemia of the anterior pituitary and not the adenoma.[19]

The hypothesis of tumoral "intrinsic" factors leading to hemorrhage is also suggested. A relationship between the aggressive and invasive tumoral behavior and hemorrhage is also suggested.[24]

Predisposing Features

Many patients with pituitary apoplexy have some predisposing factors but it can occur without any risk factors.[25] Moller-Goede compared the compared the frequencies of potential risk factors between the PA patients and the control group of matched patients with pituitary adenomas. Sex, age, tumour size and tumour type revealed no significant difference between PA patients and the control group. Risk for PA was significantly elevated in patients with antithrombotic drugs (vitamin K antagonist or platelet inhibitors) (odds ratio=2.96, CI=1.16–7.58, P=0.026), but not in patients with cardiovascular risk factors such as diabetes mellitus (odds ratio=1.00, CI=0.28–3.53, P=1.00) and arterial hypertension (odds ratio=0.93, CI=0.38–2.29, P=1.00).[14] The risk factors identified in various other studies and case reports are shown in Table 1.[5,9,11,12,25-50]

Regarding the type of pituitary adenoma responsible

Table 1: Risk factors of pituitary apoplexy

Risk factors	References
Systemic hypertension	11, 25
Major surgery: coronary artery bypass surgery; transurethral prostatectomy; hip replacement surgery	9, 26
Coagulopathies, anticoagulation, thrombolytic and antiplatelet therapy; Dengue hemorrhagic fever	9 ,11, 12, 26-30
Dynamic pituitary function tests with TRH, GnRH, Insulin and CRH (individual or combined)	31-36
Estrogen therapy, pregnancy and post-partum state	9,26, 37,38
Medications: Dopamine receptor agonist, Isosorbide; Chlorpromazine, GnRH agonist, Clomiphene	5, 9,12, 25, 39-43
Radiation therapy	44, 45
Head trauma	26, 45-48
Pituitary surgery	49, 50
Gamma knife therapy	26

for apoplexy, the data is inconsistent. Various studies have reported higher incidence of pituitary apoplexy among non-functioning tumors.[11,14,51-54] There are also studies showing higher prevalence among functioning tumors.[10,25,55] Among the secreting tumors the highest prevalence was seen in prolactinomas.[14,16,51] Study by Dubuisson *et al*. showed equal prevalence among secreting and non-secreting tumors.[12] And among subclinical pituitary apoplexy the prevalence was higher in those with secreting adenomas.[16]

Clinical Features

The clinical presentation is variable and many patients are asymptomatic. The most frequent presentation is with headache, which is frequently retro-orbital in location. Its onset is usually sudden and severe and can precede the onset of other symptoms.[11] Occasionally it is generalized. Headache is not necessarily associated with sub-arachnoid hemorrhage or tumoral growth beyond the sella turcica. The potential mechanisms underlying headache in pituitary apoplexy have been postulated to be due to meningeal irritation, dura-mater compression, enlargement of sellar walls, or involvement of the superior division of the trigeminal nerve inside cavernous sinus.[52,56] Common clinical features of pituitary apoplexy are depicted in Table 2.[11,12,14,25,51,52,54,57]

Altered visual field or visual acuity can be due to involvement of the optic nerves, chiasma, or optic tracts. The III, IV, and VI cranial nerves are vulnerable at the cavernous sinus. There can be associated with diplopia. The medial aspect of the cavernous sinus corresponds to the lateral aspect of the pituitary fossa and acute hemorrhage or necrosis within this region can shift the oculomotor nerves. There can be ipsilateral mydriasis and ptosis owing to III

Table 2: Common clinical features of pituitary apoplexy

Clinical feature	Percentage	References
Headache	90-100	11,12,25,51,52,54,68
Nausea/vomiting	40-80	11,12,25,51,52,54,68
Decreased visual acuity	45-90	12,25,51,52,54,68
Visual field defect	40-75	11,14,25,51,52,54,
Opthalmoplegia	50-80	11,12,14,51,52,54,
Altered consciousness	5-40	11,12,25,51,54,
Pyrexia	10-25	11,12,25,51,54,
Meningeal sign	5-15	12,25

cranial nerve involvement. Involvement of V cranial nerve can lead to facial numbness.[1] In the study by Milazzo *et al*., oculomotor palsies were more common (82%) than chiasmatic impairment (54.5%).[58] Blindness can develop in one or both eyes.[59-61] Some typical clinical presentation of pituitary apoplexy in relation to anatomical structures in the proximity which are prone to compression due to tumor expansion are shown in Table 3.[4]

Altered mental status is fairly frequent, seen in around 20% of patients. Impaired conciousness may range from mild lethargy to stupor and coma. Change in the mental status is a particularly troubling sign and may portend a rapid downhill course.[23] It might be related to sub-arachnoid hemorrhage, increased intracranial pressure, obstructive hydrocephalus, adrenal insufficiency leading to arterial hypotension and hypoglycemia, and hypothalamic compression.[62]

Nausea and vomiting may occur due to adrenal insufficiency, meningeal irritation, and hypothalamic dysfunction or raised intracranial pressure. Neck stiffness is observed in patients with pituitary apoplexy and can be to sub-arachnoid hemorrhage.[63] There can be massive subarachnoid and intraventricular haemorrhage.[56] Patient can have anosmia due to olfactory nerve involvement, epistaxis or CSF rhinorhea due to erosion of sellar floor.[5]

Focal signs such as loss of muscle strength or aphasia are less common and are attributed to internal carotid artery compression or vasospasm.[64-66] Patient may present as frontal lobe syndrome.[67] Bilateral infarct of the anterior carotid artery was reported by Mohindra *et al*.[68]

Endocrine Dysfunction

The majority of the patients (nearly 80%) will have deficiency of one or more anterior pituitary hormones at presentation. Clinically, the most important endocrine dysfunction is adrenocorticotroph hormone (ACTH) deficiency. Reviewing a series of patients that had pituitary apoplexy, Veldhuis and Hammond found multiple pituitary hormonal

Table 3: Clinical presentation of pituitary apoplexy in relation to anatomical structures in the proximity which are prone to compression due to tumor expansion

Symptoms of Compressions	Compressed structures in the neighborhood	Direction of expansion of tumor
Visual field deficit, blindness	Optic pathways	Upward
Autonomic Dysfunction	Hypothalamus	Upward
Anosmia, Hyposmia	Olfactory nerve	Upward
Epistaxis, CSF rhinorrhea	Sphenoid sinus	Downward
Proptosis, Eyelid edema	Cavernous sinus	Lateral
Hemiplegia,Altered sensorium	Internal carotid artery	Lateral
Ptosis, pupillary defect, ophthalmoplegia	Cranial nerves IVth and VIth	Lateral
Facial pain, corneal anesthesia	Cranial nerve V	lateral

Modified from Rolih CA and Ober KP (4)

deficiencies such as: GH deficit (88%), ACTH hyposecretion (66%), hypothyroidism (42%) and hypogonadotropic hypogonadism (85%). Hyperprolactinemia may be to prolactinoma or to impairment of the inbihibitory influence from the hypothalamus.[69] Such deficiencies are highlighted in Table 4. Those who low serum prolactin (PRL) levels at presentation usually have high intra-sellar pressure and are the less likely to recover from hypopituitarism after decompressive surgery.[70] In some patients with prolactinoma the serum PRL may be misleading with falsely low serum prolactin concentration and serial dilution may disclose "the dose hook effect"[71] which is due large amount of PRL saturate capture and signal antibody used in two-site immunometric assay, impairing their binding and causing underestimation.[72] Therefore, it is imperative to suspect "high-dose hook effect" in every patient with pituitary macroadenoma and normal serum prolactin although such a case has not been reported in patients with pituitary apolexy. And macroprolactinemia (big and big big PRL) have also not been reported in patients with pituitary apoplexy.

Transient diabetes insipidus is not a common feature of pituitary apoplexy and is reported in around 2-20% of cases.[14,54] Rarely, inappropriate ADH secretion occurs, perhaps due to sparing of neurohypophysis or pituitary stalk leading to hyponatremia.[24,73,74] Hyponatremia can also be due to hypocortisolism.[75]

Resolution of hypersecretory states have been reported following apoplexy, also described as 'auto-hypophysectomy'. Most of such reports are in acromegaly.[76-78] One of the authors (MPB) had the opportunity of following a young lady with Cushing's disease, who had complete resolution of her primary

Table 4: Endocrine disorders in pituitary apoplexy

Endocrine defect	Percentage	References
Hypopituitarism	45-80	12,14,25,51
Adrenal insufficiency	60-75	11,25,51
Hypothyroidism	50-80	11,25,51
Hypogonadism	40-80	12,14,25,51
Growth hormone deficiency	90	69
Diabetes insipidus	5-20	14,54

condition and complete revival of pituitary function after such an episode of 'auto-hypophysectomy' [Figure 2]. Even non-functioning pituitary adenoma may completely resolve following an apoplectic event without producing hypopituitarism.[79]

Radiological Findings

Plain radiography of the skull is a quick and inexpensive method for evaluating pituitary apoplexy showing enlargement of the pituitary fossa and erosion of the sellar floor and dorsum sellae.[12] Rarely, a fracture of sellar dorsum is seen, which is considered a specific sign of pituitary apoplexy. However, a normal plain radiography does not exclude pituitary apoplexy.[62]

On CT scan depending on the duration of the apoplexy the radiological appearances differ. A recent hemorrhage can appear as a single or multiple hyperdense lesions with no or little contrast enhancement [Figure 3]. On subsequent days after hemorrhage a progressive reduction of lesion hyperdensity occurs and with contrast a peripheral ring may be seen around the lesion.[80] Around four days after bleeding the hemorrhage can be misinterpreted as cystic degeneration, abscess, or local infarction. Fluid blood density may be detected.[81] Brain CT can also demonstrate sub-arachnoid hemorrhage and involvement of brain and ventricles.[56] Sometimes the bleed may be difficult on CT and serial scans are may be required.[53]

Magnetic resonance imaging (MRI) is usually less efficient than CT in the acute stage of pituitary apoplexy.[80] With special sequence MRI is useful for early detection.[82] But for sub-acute and chronic stages of pituitary apoplexy brain MRI is considerably better than CT. After at least 12 hours MRI is superior to CT in detecting haemorrhage.[3] One of the advantages of MRI is the possibility of estimating the onset of bleeding. In the acute stage of pituitary apoplexy (first seven days) hypo- or isointense lesions on T1- and T2-weigthed images are seen; between seven to fourteen days on the sub-acute stage there is marginal signal reinforcement although the hematoma core remains isointense; on the chronic stage there is an overall increase

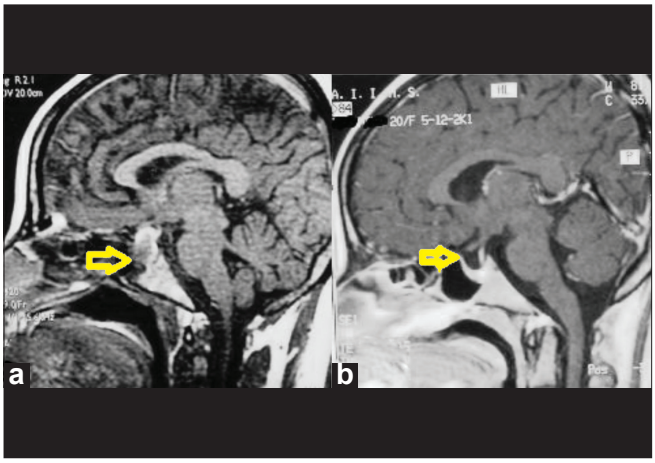

Figure 2: Megnetic reasonance imaging scan in pituitary apoplexy. This young lady with Cushing's Disease was found to have a macroadenoma (part A, yellow arrow, saggital view) of anterior pituitary gland during initial work up. During follow up she had resolution of her clinical symptoms after an epsode of acute severe headache. A repeat MRI scan showed partial empty sella, intact stalk (part B, yellow arrow, saggital view) (courtesy Dr. B. Kulshretha)

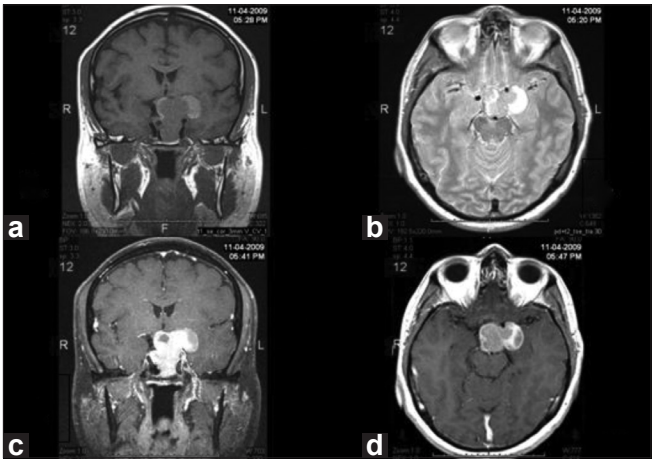

Figure 3: Coronal T1 (a) and axial T2 (b) showing a mass in sella with suprasellar extension having "figure of 8" appearance. Note T1 hyperintense area suggestive of bleed. The mass shows avid enhancement in post contrast coronal T1 (c) and axial T1(d) images with central nonenhancing area suggesting necrosis. (courtesy Dr. C. J. Das)

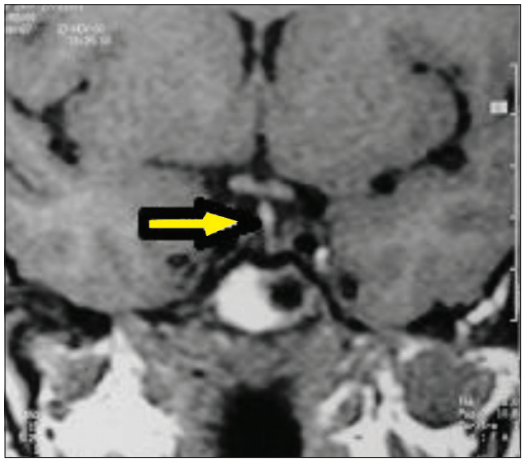

Figure 4: Empty sella as a sequel of pituitary apoplexy in a patient with Sheehan Syndrome. In this T1 weighted megnetic reasonance imaging scan (coronal) the sella turcica (yellow arrow) appers to be filled with cerebro spinal fluid, The pituitary stalk has a remarkable appearance and can be traced to the floor of sella turcica

on T1- and T2- signal. MRI can also show the relationship between the tumour and the surrounding structures.[83] Hyperintense signal on T1-weighted sequences may be seen with hemorrhagic tissues, fat, and lesions with high protein or melanin content. Intra-sellar tumors that may present with T1 hyperintense signal include craniopharingiomas, lipomas, dermoid cysts, metastatic melanomas or any other hemorrhagic tumor.[84] Empty sella may be observed [Figure 4] in some cases.[85] Mucosal thickening have also reported on MRI imaging.[86] And MR imaging findings are useful to predict histopathology accurately in majority of cases of pituitary apoplexy.[87]

Angiography may show the presence or absence of concomitant aneurysm and vasospasm. If there are no associated abnormalities the tumor can be seen with contrast enhancement. In the past before the era of CT scan pneumoencephalograms were used in the evaluation of pituitary apoplexy.[12]

Differential Diagnosis

Many conditions may be frequently misdiagnosed as pituitary apoplexy including sub-arachnoid haemorrhage due to ruptured intracranial aneurysm[88,89] and meningitis.[90] Other differential diagnosis include basilar artery occlusion, hypertensive encephalopathy, brain abscess or cyst, cavernous sinus thrombosis, intracerebral haematoma, encephalitis, retrobulbar neuritis, temporal arteritis, and ophthalmoplegic migraine.[62]

Pituitary apoplexy may resemble ruptured intracranial aneurism due to sudden onset headache, ocular palsy and altered mental status. Ophthalmoplegia is more likely to be seen in patients with tumor apoplexy. The symptoms tend to develop more rapidly after the onset of headache in subarachnoid haemorrhage than in apoplexy. Clinical features alone may not be sufficient to clinch the diagnosis. Frequently time lag between headache and onset of altered mental status is shorter on sub-arachnoid hemorrhage.[4]

Cerebrospinal fluid (CSF) fluid analysis may not helpful in differentiating pituitary apoplexy from sub-arachnoid haemorrhage.[90] Lumbar puncture may be dangerous as it may precipitate uncal herniation.

Management

The immediate medical management of patients with pituitary apoplexy should include careful assessment of fluid and electrolyte balance, replacement of corticosteroids and supportive measures to ensure haemodynamic stability. Acute secondary adrenal insufficiency is seen in approximately two-thirds of patients with pituitary tumour apoplexy and is an important cause of mortality associated with the condition.[69] Hypocortisolemia may lead to haemodynamic instability in many patients.[91] Hypocortisolemia also augments vasopressin release from the posterior pituitary and has an inhibitory effect on water excretion contributing to fluid and electrolyte disturbances.

Prompt corticosteroid replacement should be started in patients who are haemodynamically unstable or who have other symptoms or signs suggestive of hypoadrenalism. Hydrocortisone can be administered as 100–200 mg intravenous bolus followed either by continuous intravenous infusion of 2-4 mg/hour or by intramuscular injection of 50–100 mg six hourly. But continuous infusion is usually preferred because of the saturation kinetics of cortisol binding globulin.[92]

Once the patient has recovered from the acute episode, the hydrocortisone dose should be quickly tapered to a standard maintenance dose of 20–30 mg per day orally. ACTH reserve should be reassessed 2–3 months after the crisis has resolved. Dexamethasone is not favoured glucocorticoid, although it may be used to reduce oedema as part of a nonsurgical strategy for the treatment of pituitary tumour apoplexy.[92]

Surgery or conservative management?

The principle controversy in management of pituitary apoplexy relates to the role and the timing of neurosurgical decompression. Although there are case series and reports, owing to the rarity of the condition there are no randomized controlled trials in the literature. Early decompression has been suggested in a few retrospective observational studies, the rationale being the possibility of better visual[11,52,60,63,93] and endocrine outcome[94] or both.[95] Recent uncontrolled, retrospective studies have suggested that the endocrine and the visual outcome were no different between patients managed conservatively or by early surgical intervention.[68,96] However, it is important to note that studies looking at the role of conservative versus surgical management of apoplexy with regard to visual loss all suffer from selection bias and lack of appropriately matched patients. In most series, patients in the conservative group had less visual defect than those in the surgically treated group.[51,68,96] A simple algorithm for management of pituitary apoplexy is shown in Figure 5.

The difficulty in the management of pituitary apoplexy is in deciding whether the clinical situation is appropriate for surgical intervention. Although there is a general agrrement that a patient with apoplexy and significant neuro-ophthalmic signs or reduced level of consciousness should have surgical decompression, what criteria define a significant neuro-ophthalmic deficit is unclear. At present there are no evidence-based criteria to justify the clinical decision between a conservative approach and neurosurgical intervention. Patients who are clinically and neurologically unstable require urgent surgical decompression.[45] Thus the available data does not suggest surgical intervention for all cases and should be reserved for those with altered sensorium and increasing visual deficit.

Outcome

Visual outcomes

Visual acuity, visual field defects and ophthalmoplegia have been reported to improve in the majority of the patients after both conservative and surgical decompression. After surgery such improvement is observed in the immediate postoperative period and often continues for several weeks after surgery. Visual recovery has been reported to be less likely in patients presenting with monocular or binocular blindness. However, significant improvement has been observed in patients rendered blind by pituitary apoplexy if

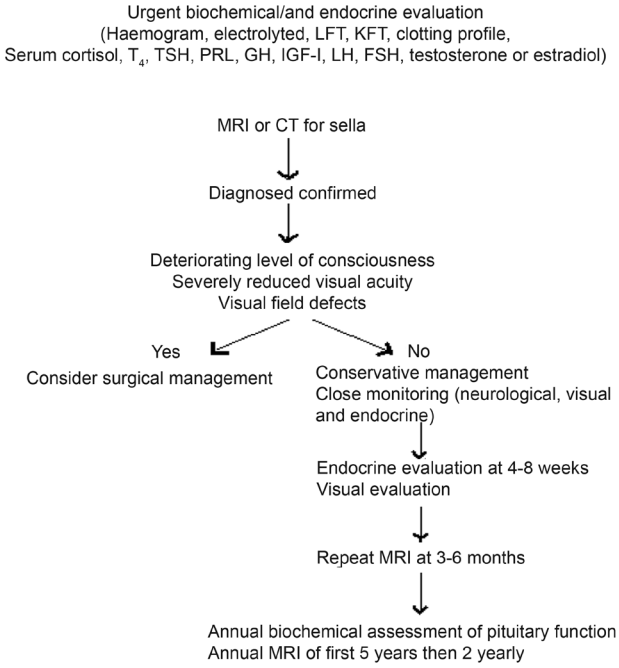

Figure 5: Algorithm for management of pituitary apoplexy

early surgical decompression was undertaken (done within 8 days).[11] Agrawal and Mahapatra have shown that even completely blind eyes may have remarkable improvement in vision if surgical decompression of the optic apparatus is undertaken early in the first week.[97] Similar better response if operated early within first week has been reported in other studies.[52,60] Recent studies have reported a better visual outcome in conservatively managed patients but these studies have a selection bias from inappropriately matched patients.[51,96]

Endocrine outcomes

Early studies showed a better chance for improvement in pituitary function in surgically managed patients. More recent retrospective studies found no statistically significant differences in the endocrine outcome between the surgically and conservatively managed patients.[68,96] Nearly 80% of the patients will need some form of hormone replacement after apoplexy. Various studies suggest that long-term hormone replacement therapy following pituitary apoplexy will be corticosteroids in 40–85%,[3,11,14,52,68,98,99] thyroid hormone in 50–70%,[3,11,14,68,98,99] desmopressin in 6–25%[11,52,68,98,99] of patients and sex steroid in 40–80% of cases.[3,11,12,68,96,98,99] GH deficiency was reported in 16% of cases.[12]

Long term monitoring

As many patients with pituitary apoplexy may long residual endocrine deficiency all patients with pituitary apoplexy should have an assessment of pituitary function at 4–8 weeks following the event. They should also have assessment of their visual acuity, eye movements and visual fields. An annual biochemical assessment of pituitary function for T4, TSH, LH, FSH, testosterone in men, oestradiol in women, PRL, IGF1, cortisol and GH should be performed.[92]

If 9 am cortisol is less than 3.75 μg/dl cortisol deficiency is likely and if more than 18.75 μg/dl unlikely.[100] Dynamic testing is required for values between these which can be performed with either ACTH (Synacthen) stimulation test, insulin tolerance test or metyrapone test. Insulin tolerance test is considered the gold standard and a peak response of between 18.75 and 22.5 considered as adequate response.[101]

A MRI scan is recommended at 3–6 months after an episode of pituitary apoplexy and thereafter an annual MRI scan should be considered for the next 5 years, then two yearly. All patients require at least an annual clinical review preferably by a combined endocrine/neurosurgical team.[92]

Summary

Pituitary apoplexy is a potentially life-threatening endocrine disorder which may result from either from infarction or haemorrhage in the pituitary. It has been reported with a wide range of incidence ranging from around 1% to 26% in various studies. There is slight male preponderance in most studies. It can be seen in both functional and non-functional pituitary adenomas. The data on which type of adenoma is higher risk is conflicting. Patients may present with headache, altered sensorium and visual defect may be confused with sub-arachnoid haemorrhage or meningitis. Imaging such as CT or MRI plays an important role in the diagnosis. Prompt institution of intravenous fluid and hydrocortisone must be started in patients with haemodynamic instability. Recent studies favour conservative management except for those with increasing neuro-deficit and visual defect. Outcome is similar with either conservative management or surgery in more recent studies. Long term with follow-up with hormonal evaluation is required to replace the deficient hormones.

References

1. Nawar RN, Abdel-Mannan D, Selma WR, Arafah BM. Pituitary tumor apoplexy: A review. J Intensive Care Med 2008;23:75-89.
2. Findling JW, Tyrreell JB, Aron DC, Fitzgerald PA, Wilson CB, Forsham PH. Silent pituitary apoplexy: Subclinical infarction of an adrenocorticotropin-producing adenoma. J Clin Endocrinol Metab 1981;52:95-7.
3. Onesti ST, Wisniewski T, Post KD. Clinical versus subclinical pituitary apoplexy: Presentation, surgical management, and outcome in 21 patients. Neurosurgery 1990;26:980-6.
4. Rolih CA, Ober KP. Pituitary apoplexy. Endocrin Metab Clin North Am 1993;22:291-302.
5. Wakai S, Fukushima T, Teramoto A, Sano K. Pituitary apoplexy: Its incidence and clinical significance. J Neurosurg 1981;55:187-93.
6. Mohr G, Hardy J. Haemorrhage, necrosis and apoplexy in pituitary adenomas. Surg Neurol 1982;18:181-9.
7. Mohanty S, Tandon PN, Banerji AK, Prakash B. Haemorrhage into pituitary adenomas. J Neurol Neurosurg Psychiatry 1977;40:987-91.
8. Nielsen EH, Lindholm J, Bjerre P, Christiansen JS, Hagen C, Juul S, *et al*. Frequent occurrence of pituitary apoplexy in patients with non-functioning pituitary adenoma. Clin Endocrinol (Oxf) 2006;64:319-22.
9. Biousse V, Newman NJ, Oyesiku NM. Precipitating factors in pituitary apoplexy. J Neurol Neurosurg Psychiatry 2001;71:542-5.
10. Ahmed M, Rifai A, Al-Jurf M, Akhtar M, Woodhouse N. Classical pituitary apoplexy presentation and a follow-up of 13 patients. Horm Res 1989;31:125-32.
11. Randeva HS, Schoebel J, Byrne J, Esiri M, Adams CB, Wass JA. Classical pituitary apoplexy: Clinical features, management and outcome. Clin Endocrinol (Oxf) 1999;51:181-8.
12. Dubuisson AS, Beckers A, Stevenaert A. Classical pituitary tumour apoplexy: Clinical features, managementand outcomes in a series of 24 patients. Clin Neurol Neurosurg 2007;109:63-70.
13. Woo HJ, Hwang JH, Hwang SK, Park YM. Clinical outcome of cranial neuropathy in patients with pituitary apoplexy. J Korean Neurosurg Soc 2010;48:213-8.
14. Moller-Goede DL, Brandle M, Landau K, Bernays RL, Schmid C. Pituitary apoplexy: Re-evaluation of risk factors for bleeding into

pituitaty adenomas and impact on outcome. Eur J Endocrinol 2011;164:37-43.
15. Chacko AG, Chacko G, Seshadri MS, Chandy MJ. Haemorrhagic necrosis of pituitary adenomas. Neurol India 2002;50:490-3.
16. Liu ZH, Chang CN, Pai PC, Wei KC, Jung SM, Chen NY, *et al*. Clinical features and surgical outcome of clinical and subclinical pituitary apoplexy. J Clin Neurosci 2010;17:694-9.
17. Chanson P, Lepeintre JF, Ducreux D. Management of pituitary apoplexy. Expert Opin Pharmacother 2004;5:1287-98.
18. Flerko B. The hypophyseal portal circulation today. Neuroendocrinology 1980;30:56-63.
19. Cardoso ER, Peterson EW. Pituitary apoplexy: A review. Neurosurgery 1984;14:363-73.
20. Hirano A, Tamiyasu U, Zimmerman HM. The fine structure of blood vessels in chromophobe adenoma. Acta Neuropathol 1972;22:200-7.
21. Epstein S, Pimstone BL, De Velliers JC, Jackson WP. Pituitary apoplexy in five patients with pituitary tumours. Br Med J 1971;2:267-70.
22. Jeffcoate WJ, Birch CR. Apoplexy in small pituitary tumours. J Neurol Neurosurg Psychiatry 1986;49:1077-8.
23. Rovit RL, Fein JM. Pituitary apoplexy: A review and reappraisal. J Neurosurg 1972;37:280-8.
24. Fraioli B, Esposito V, Palma L, Cantore G. Hemorrhagic pituitary adenomas: Clinicopathological features and surgical treatment. Neurosurgery 1990;27:741-7.
25. Mou C, Han T, Zhao H, Wang S, Qu Y. Clinical features and immunohistochemical changes of pituitary apoplexy. J Clin Neurosci 2009;16:64-8.
26. Semple PL, Jane JA Jr, Laws ER Jr. Clinical relevance of precipitating factors in pituitary apoplexy. Neurosurgery 2007;61:956-61; discussion 961-2.
27. Oo MM, Krishna AY, Bonavita GJ, Rutecki GW. Heparin therapy for myocardial infarction: An usual trigger for pituitary apoplexy. Am J Med Sci 1997;314:351-3.
28. Fuchs S, Beeri R, Hasin Y, Weiss AT, Gotsman MS, Zahger D. Pituitary apoplexy as a first manifestation of pituitary adenomas following intensive thrombolytic and antithrombotic therapy. Am J Cardiol 1998;81:110-1.
29. Wongpraparut N, Pleanboonlers N, Suwattee P, Rerkpattanapipat P, Turtz A, Moster M, *et al*. Pituitary apoplexy in a patient with acute myeloid leukemia and thrombocytopenia. Pituitary 2000;3:113-6.
30. Kumar V, Kataria R, Mehta VS. Dengue haemorrhagic fever: A rare cause of pituitary tumour haemorrhage and reversible vision loss. Indian J Ophthalmol 2011;59:311-2.
31. Drury PL, Belchetz PE, McDonald WI, Thomas DG, Besser GM. Transient amaurosis and headache after thyrotropin releasing hormone. Lancet 1982;1:218-9.
32. Arafah BM, Taylor HC, Salazar R, Saadi H, Selman WR. Apoplexy of a pituitary adenoma after dynamic testing with gonadotropin releasing hormone. Am J Med 1989;87:103-5.
33. Harvey R, Michelagnoli M, McHenry P, Currie DG, Bewsher PD. Pituitary apoplexy. Letter to editor. BMJ 1989;298:258.
34. Vassallo M, Rana Z, Allen S. Pituitary apoplexy after stimulation tests. Postgrad Med J 1994;70:444-5.
35. Masago A, Ueda Y, Kanai H, Nagai H, Umemura S. Pituitary apoplexy after pituitary function test: A report of two cases and review of the literature. Surg Neurol 1995;43:158-64.
36. Rotman-Pikielny P, Patronas N, Papanicolaou DA. Pituitary apoplexy induced by corticotrophin releasing hormone in a patient with Cushing's disease. Clin Endocrinol (Oxf) 2003;58:545-9.
37. Heide LJ, van Tol KM, Doorenbos B. Pituitary apoplexy presenting during pregnancy. J Med (Netherland) 2004;62:393-6.
38. Parihar V, Yadav YR, Sharma D. Pituitary apoplexy in a pregnant woman. Ann Indian Acad Neurol 2009;12:54-5.
39. Silverman VE, Boyd AE, McCrary JA, Kohler PO. Pituitary apoplexy following chlorpromazine stimulation. Arch Intern Med 1978;138:1738-9.
40. Nagulesparan M, Roper J. Haemorrhage into the anterior pituitary during pregnancy after induction of ovulation with clomiphene. Br J Obstet Gynaecol 1978;85:153-5.
41. Bejan JS, Oza AM, Burke CW, Adams CB. Pituitary apoplexy following isosorbide administration. J Neurol Neurosurg Psychiatry 1987;50:636-7.
42. Chanson P, Schaison G. Pituitary apoplexy caused by GnRH agonist treatment revealing gonadotrop adenoma. J Clin Endocrinol Metab 1995;80:2267-8.
43. Faustini-Fustini M. Pituitary apoplexy after leuprolide administration for carcinoma of the prostrate: What is new? Clin Endocrinol (Oxf) 1997;46:378.
44. Weisberg LA. Pituitary apoplexy. Association of degenerative change in pituitary adenoma with radiotherapy and detection by cerebral computed tomography. Am J Med 1977;63:109-15.
45. Murad-Kejbou S, Eggenberger E. Pituitary apoplexy: Evolution, management and prognosis. Curr Opin Ophthalmol 2009;20: 456-61.
46. Holness RO, Ogundimu FA, Langille RA. Pituitary apoplexy following closed head trauma. Case report. J Neurosurg 1983;59:677-9.
47. Uchiyama H, Nishizawa S, Satoh A, Yokoyama T, Uemura K. Post-traumatic pituitary apoplexy: Two case reports. Neurol Med Chir (Tokyo) 1999;39:36-9.
48. Dev R, Singh SK, Sharma MC, Khetan P, Chugh A. Post traumatic pituitary apoplexy with contiguous intra cerebral hematoma operated through endonasal route-a case report. Pituitary 2007;10:291-4.
49. Goel A, Deogaonkar M, Desai K. Fatal postoperative 'pituitary apoplexy': Its cause and management. Br J Neurosurg 1995;9:37-40.
50. Ahmad FU, Pandey P, Mahapatra AK. Post operative 'pituitary apoplexy' in giant pituitary adenomas: A series of cases. Neurol India 2005;53:326-8.
51. Sibal L, Ball SG, Connolly V, James RA, Kane P, Kelly WF, *et al*. Pituitary apoplexy: A review of clinical presentation, management and outcome in 45 cases. Pituitary 2004;7:157-63.
52. Bills DC, Meyer FB, Laws ER Jr, Davis DH, Ebersold MJ, Scheithauer B, *et al*. A retrospective analysis of pituitary apoplexy. Neurosurgery 1993;33:602-9.
53. Da Motta LA, de Mello PA, de Lacerda CM, Neto AP, da Motta LD, Filho MF. Pituitary apoplexy. Clinical course, endocrine evaluations and treatment analysis. J Neurosurg Sci 1999;43:25-36.
54. Shou XF, Wang YF, Li SQ, Wu JS, Zhao Y, Mao Y, *et al*. Microsurgical treatment for typical pituitary apoplexy with 44 patients, according to two pathological stages. Minim Invasive Neurosurg 2009;52:207-11.
55. Zhang F, Chen J, Lu Y, Ding X. Manifestation, management and outcome of subclinical pituitary adenoma apoplexy. J Clin Neurosci 2009;16:1273-5.
56. Satyarthee GD, Mahapatra AK. Pituitary apoplexy in a child presenting with massive subarachnoid and intraventricular hemorrhage. J Clin Neurosci 2005;12:94-6.
57. Ayuk J, McGregor EJ, Mitchell RD, Gittoes NJ. Acute management of pituitary apoplexy–surgery or conservative management? Clin Endocrinol (Oxf) 2004;61:747-52.
58. Milazzo S, Toussaint P, Proust F, Touzet G, Malthieu D. Ophthalmologic aspects of pituitary apoplexy. Eur J Ophthalmol 1996;6:69-73.
59. McFadzean RM, Doyle D, Rampling R, Teasdale E, Teasdale G. Pituitary apoplexy and its effect on vision. Neurosurgery 1991;29:669-75.

60. Muthukumar N, Rossette D, Soundaram M, Senthilbabu S, Badrinarayanan T. Blindness following pituitary apoplexy: Timing of surgery and neuro-ophthalmic outcome. J Clin Neurosci 2008;15:873-9.
61. Sud RN, Greval RS, Sud M. Sudden blindness from pituitary apoplexy: A report of two cases. Indian J Med Sci 1993;47:180-2.
62. Chang CC, Felicio AC, Toscanini AC, Teixeira MJ, Cunha-Neto MB. Pituitary tumor apoplexy. Arq Neuropsiquiatr 2009;67:328-33.
63. Elsässer Imboden PN, De Tribolet N, Lobrinus A, Gaillard RC, Portmann L, Pralong F, *et al*. Apoplexy in pituitary macroadenoma: Eight patients presenting in 12 months. Medicine (Baltimore) 2005;84:188-96.
64. Chokyu I, Touyuguchi N, Goto T, Chokyu K, Chokyu M, Ohata K. Pituitary apoplexy causing internal carotid artery occlusion: Case report. Neurol Med Chir (Tokyo) 2011;51:48-51.
65. Das NK, Behari S, Banerji D. Pituitary apoplexy associated with acute cerebral infarct. Clin Neurosci 2008;15:1418-20.
66. Lath R, Rajshekhar V. Massive cerebral infarction as a feature of pituitary apoplexy. Neurol India 2001;49:191-3.
67. Bhansali A, Dutta P, Khandelwal N, Pathak A, Vashisht R. Pituitary apoplexy: An unusual cause of frontal lobe syndrome. Australas Radiol 2005;49:127-31.
68. Mohindra S, Kovai P, Chhabra R. Fatal bilateral ACA territory infarcts after pituitary apoplexy: A case report and literature review. Skull Base 2010;20:285-8.
69. Veldhuis JD, Hammond JM. Endocrine function after spontaneous infarction of the human pituitary: Report, review, and reappraisal. Endocr Rev 1980;1:100-7.
70. Zayour DH, Selman WR, Arafah BM. Extreme elevation of intrasellar pressure in patients with pituitary tumor apoplexy: Relation to pituitary function. J Clin Endocrinol Metab 2004;89:5649-54.
71. Barkan AL, Chandler WF. Giant pituitary prolactinoma with falsely low serum prolactin: The pitfall of the "high-dose hook effect": Case report. Neurosurgery 1998;42:913-5.
72. Frieze TW, Mong DP, Koops MK. Hook effect" in prolactinomas: Case report and review of literature. Endocr Pract 2002;8:296-303.
73. Agrawal D, Mahapatra AK. Pituitary apoplexy and inappropriate ADH secretion. J Clin Neurosci 2003;10:260-1.
74. Sweeney AT, Blake MA, Adelman LS, Habeebulla S, Nachtigall LB, Duff JM, *et al*. Pituitary apoplexy precipitating diabetes insipidus. Endocr Pract 2004;10:135-8.
75. Diederich S, Franzen NF, Bahr V, Oelkers W. Severe hyponatremia due to hypopituitarism with adrenal insufficiency: Report on 28 cases. Eur J Endocrinol 2003;148:609-17.
76. Jacobi JD, Fishman LM, Daroff BB. Pituitary apoplexy in acromegaly followed by partial pituitary insufficiency. Arch Intern Med 1974;134:559-61.
77. Pelkonen R, Kuusisto A, Salmi J, Eistola P, Raitta C, Karonen SL, *et al*. Pituitary function after pituitary apoplexy. Am J Med 1978;65:773-8.
78. Tamasawa N, Kurahashi K, Baba T, Hishita R, Murabayashi S, Kashiwamura H, *et al*. Spontaneous remission of acromegaly after pituitary apoplexy following head trauma. J Endocrinol Invest 1988;11:429-32.
79. Kachhara R, Nair S, Gupta AK. Spontaneous resolution of a non-functioning pituitary adenoma following an apoplexy. Neurol India 2000;48:294-6.
80. L'Huillier F, Combes C, Martin N, Leclerc X, Pruvo JP, Gaston A. MRI in the diagnosis of so-called pituitary apoplexy: Seven cases. J Neuroradiol 1989;16:221-37.
81. Asari S, Gotoh M, Nishimato A. Typical blood-fluid level formation on computerized tomogram in pituitary apoplexy: Case report. Comput Med Imaging Graph 1990;14:147-8.
82. Rogg JM, Tung GA, Anderson G, Cortez S. Pituitary apoplexy: Early detection with diffusion-weighted MR imaging. Am J Neuroradiol 2002;23:1240-5.
83. Piotin M, Tampieri D, Rufenacht DA, Mohr G, Garant M, Carpio R, *et al*. The various MRI patterns of pituitary apoplexy. Eur Radiol 1999;9:918-23.
84. Bonneville F, Cattin F, Marsot-Dupuch K, Dormont D, Bonneville JF, Chiras J. T1 signal hyperintensity in the sellar region: Spectrum of findings. Radiographics 2006;26:93-113.
85. Yucesoy K, Yuceer N, Goktay Y. Empty sella syndrome following pituitary apoplexy. Acta Neurochir (Wein) 2000;142:355-6.
86. Lui JK, Couldwell WT. Pituitary apoplexy in the magnetic resonance imaging era: Clinical significance of sphenoid sinus mucosal thickening. J Neurosurg 2006;104:892-8.
87. Semple PL, Jane JA Jr, Lopes MB, Laws ER. Pituitary apoplexy: Correlation between magnetic resonance imaging and histopathological results. J Neurosurg 2008;108:909-15.
88. Lewin IG, Mohan J, Norman PF, Gibson RA, Francis JR. Pituitary apoplexy. BMJ 1988;297:1526-7.
89. Sergides IG, Minhas PS, Anotun N, Pickard JD. Pituitary apoplexy can mimic subarachnoid haemorrhage clinically and radiologically. Emerg Med J 2007;24:308.
90. Bjerre P, Lindholm J. Pituitary apoplexy with sterile meningitis. Acta Neurol Scand 1986;74:304-7.
91. Arlt W, Allolio B. Adrenal insufficiency. N Engl J Med 1996;335: 1206-12.
92. Rajasekaran S, Vanderpump M, Baldeweg S, Drake W, Reddy N, Lanyon M, *et al*. UK guidelines for the management of pituitary apoplexy. Clin Endocrinol (Oxf) 2011;74:9-20.
93. Chuang CC, Chang CN, Wei KC, Liao CC, Hsu PW, Huang YC, *et al*. Surgical treatment for severe visual compromised patients after pituitary apoplexy. J Neurooncol 2006;80:39-47.
94. Arafah BM, Harrington JF, Madhoun ZT, Selman WR. Improvement of pituitary function after surgical decompressionfor pituitary tumor apoplexy. J Clin Endocrinol Metab 1990;71:323-8.
95. Bonicki W, Kasperlik-Załuska A, Koszewski W, Zgliczyński W, Wisławski J. Pituitary apoplexy: Endocrine, surgical and oncological emergency. Incidence, clinical course and treatment with reference to 799 cases of pituitary adenomas. Acta Neurochir (Wien) 1993;120:118-22.
96. Gruber A, Clatton J, Kumar S, Robertson I, Howlett TA, Mansell P. Pituitary apoplexy: Retrospective review of 30 patients: Is surgical intervention always necessary? Br J Neurosurg 2006;20:379-85.
97. Agrawal D, Mahapatra AK. Visual outcome of blind eyes in pituitary apoplexy after transsphenoidal surgery: A series of 14 eyes. Surg Neurol 2005;63:42-6; discussion 46.
98. Turgut M, Ozsunar Y, Başak S, Güney E, Kir E, Meteoğlu I. Pituitary apoplexy: An overview of 186 cases published during the last century. Acta Neurochir (Wien) 2010;152:749-61.
99. Lubina A, Olchovsky D, Berezin M, Ram Z, Hadani M, Shimon I. Management of pituitary apoplexy: Clinical experience with 40 patients. Acta Neurochir (Wien) 2005;147:151-7; discussion 157.
100. Le Roux CW, Meeran K, Alaghband-Zadeh J. Is a 0900-h serum cortisol useful prior to a short Synacthen test in outpatient assessment? Ann Clin Biochem 2002;39:148-50.
101. Nieman LK. Dynamic evaluation of adrenal hypofunction. J Endocrinol Invest 2003;26:74-82.

Cite this article as: Ranabir S, Baruah MP. Pituitary apoplexy. Indian J Endocr Metab 2011;15:188-96.

Source of Support: Nil, **Conflict of Interest:** None declared.