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Pituitary Apoplexy

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Abstract

Pituitary apoplexy is a rare clinical emergency due to acute ischemic infarction or hemorrhage of the pituitary gland. As this disorder most often involves a pituitary adenoma, especially nonfunctioning tumors, the syndrome should be referred to as pituitary tumor apoplexy. The precise physiopathology is not completely clear. Although in most cases it occurs spontaneously, pituitary apoplexy can be precipitated by many risk factors. The main symptom is headache of sudden onset associated with visual disturbances, signs of meningeal irritation, and/or endocrine dysfunction. Corticotrophic deficiency is a potentially life-threatening disorder. Magnetic resonance imaging is the most sensitive to confirm the diagnosis by revealing a pituitary tumor with hemorrhagic and/or necrotic components. Earlier studies used to consider urgent decompression of the lesion surgically, but nowadays, more recent studies favor conservative management in selected patients (those without important visual acuity or field defects and with normal consciousness). This wait-and-see approach gives evidence of excellent outcomes in terms of oculomotor palsy, pituitary function, and subsequent tumor growth. Surgical decompression may be necessary in some cases. Once the acute phase is over, the patient should be reevaluated for hormonal deficiencies. Moreover, spontaneous remission of syndromes, such as acromegaly, may be caused by pituitary adenoma apoplexy.

Keywords: apoplexy, hypopituitarism, pituitary adenoma, pituitary MRI

1. Introduction

The term “pituitary apoplexy” (PA) originating from Greek means “sudden attack” with hemorrhage and/or infarction in the pituitary tumor or, less commonly, the surrounding normal gland tissue.

The first index case was, described by Bailey, in 1898 [1], but the term pituitary apoplexy was coined by Broughamin in 1950 [2].

Pituitary tumor apoplexy is an uncommon acute clinical syndrome and one of the rare problems that is diagnostically and therapeutically challenging.

PA is frequently the onset of unknown preexisting pituitary adenoma. The clinical spectrum of presentation does vary but often reserved only for classical presentation in contrast to “Silent, subclinical or asymptomatic pituitary tumor apoplexy” even though the latter is the more frequent entity [3].

It is a potentially life-threatening complication requiring a rapid diagnosis and appropriate treatment.

The diagnosis of pituitary tumor apoplexy is based on imaging evaluations, mainly using magnetic resonance imaging.

The best approach in the acute phase is still controversial, and nowadays, PA is no longer considered as a neurosurgical emergency [4, 5].

The outcome of acute apoplexy is variable and remains difficult to predict; a regular input and follow-up from a multidisciplinary team including neurosurgeons, endocrinologists, neuro-ophthalmologists, neuroradiologists, and neurologists are mandatory.

2. Epidemiological data

Pituitary tumor apoplexy appears to be rare. The true incidence and prevalence of PA are difficult to establish either because the majority of the studies are retrospective or because the diagnosis of PA is usually misdiagnosed and simply identified at surgery or during radiological investigation or pathological examination. According to the main retrospective series, an estimated prevalence of 6.2 cases per 100,000 inhabitants and [6] an incidence of 0.17 episodes per 100,000 person-years were reported [7].

In published series of surgically resected pituitary adenomas, PA can occur in 0.6–10% with a mean of 2% of all adenomas and has reached 21% in an unusual report [8]. Nonfunctioning pituitary adenomas (NFPA) appear to be at higher risk of apoplexy with an incidence of 0.2–0.6 events per 100 person-years [9]. In published series of nonfunctioning pituitary adenomas, the frequency of apoplexy can vary from 3.7 to 21% [10]. Nonsecreting pituitary adenomas represent an average of 45–70% of adenomas with apoplexy [3].

Apoplexy represents the first clinical manifestation of previously unknown pituitary adenoma in 60–80% of cases [5, 11, 12].

Pituitary tumor apoplexy can occur at all ages, but most cases are seen during the fifth or sixth decade of life. In adolescents, this event has been described by Jankowski and cols as a very rare entity [13].

There is a discrete preponderance in males ranging from 1.1 to 2.3/1 [5, 12].

Macroadenomas, especially nonfunctioning, and prolactinomas are most susceptible to apoplexy; nevertheless, apoplexy in other tumor types such as GH-secreting or clinically silent ACTH adenomas has been reported [5].

Microadenomas may also be prone to apoplexy [14]. PA occurs in 0.6–10% of treated pituitary adenomas. In three series of macroprolactinomas, the ratio of apoplexy/therapy varied between 1.2 and 6.67% [14].

In a review, apoplexy was found to occur in 1–6% of macroprolactinomas. This average was comparable between treated and untreated adenomas [5].

Semple et al. have found that one-third of their 62 patients had only infarction [15]. Hemorrhage is more associated with macroprolactinoma and female gender [16].

3. Pathophysiology

The pathophysiological mechanisms of pituitary tumor apoplexy remain incompletely understood. There are various theories upon the pathophysiology of pituitary apoplexy in the current literature. It is uncertain whether the pathological process is a primary hemorrhage or whether the event is really a hemorrhagic infarction. Many pathogenic mechanisms have been proposed. Given that the risk of hemorrhage in a pituitary adenoma appears to be five times higher than in other intracranial neoplasms, intrinsic factors can be involved in the apoplectic event [12]. The rich and the complex vascular system makes the pituitary adenomas more vulnerable to bleed than any other brain tumor.

Understanding the vascularity of the pituitary gland and pituitary adenomas is crucial for etiopathogenesis of apoplexy.

As shown by the angiographic studies, the adenomas are mostly supplied by inferior pituitary artery, and its arterial flux is reduced compared with the normal pituitary [17].

The number and size of vessels are generally lesser than the normal pituitary vessels and are divided into irregular islets. Under electronic microscopy, they have incomplete maturation, poor fenestration, and ruptured and fragmented basal membranes with perivascular spaces filled with plasmatic proteins or red cells that may predispose to hemorrhage [18].

The fragility of the constitutional tumoral vascularization, can be explained by an increased expression of vascular endothelial growth factor “VEGF mRNA” in pituitary tumors; especially in nonfunctioning pituitary adenomas [14].

This expression of vascular endothelial growth factor could be explained by a tumoral over-expression of the pituitary tumor transforming and was found to correlate positively with the risk of pituitary hemorrhage. Other vascular markers were reported such as fetal liver kinase 1, nestin, etc. [5].

All the conditions associated with an acute increase in blood flow or coagulation disturbs may predispose these lesions to hemorrhage or hemorrhagic infarction [14].

This intratumoural vasculopathy, limited blood supply of the pituitary adenomas, and limited expression of angiogenic factors contrast with a high-energy requirement. As consequence, any extrinsic factor that alters the balance between tumor perfusion and tumor metabolism may cause an acute ischemia or infarction [17].

Moreover, an increased intratumoural and intrasellar pressure could concur to the reduction of tumor perfusion, further contributing to ischemia's pathomechanisms. Tumor growth could thus contribute to ischemia which explains the size of the adenoma being a major factor. Macroadenomas are described to be at a much higher risk of apoplexy than microadenomas [10, 19, 20].

Germline AIP gene mutations may be associated with a rapid growth of the pituitary adenomas predisposing them to apoplexy [21].

4. Predisposing factors

PA can occur without any risk factors; however, numerous conditions have been linked to PA. Precipitating factors are identified in 10–40% of cases [3] (**Table 1**).

4.1. Precipitating factors

The multiple factors reported as precipitating PA can be classified into three categories.

4.1.1. Acute variations of the blood flow in the pituitary gland

Procedures such as angiography, pneumoencephalography, myelography, lumbar puncture, and spinal anesthesia have been associated with PA. Blood pressure (BP) fluctuations or vasospasm may explain PA [22, 23]. Pituitary irradiation may induce vascular changes leading to chronic hypoperfusion of the pituitary gland and has been associated with both pituitary infarction and pituitary hemorrhage [24, 25]. Closed-head trauma which often minor may be a cause of PA, explained by acute changes in the intracranial pressure and in blood pressure [26].

Precipitating factors
Major surgery: coronary artery bypass surgery
Coronary artery bypass grafting/stenting
Coagulopathies, anticoagulation, thrombolytic and antiplatelet Therapy
Clotting disorder
Dynamic endocrine stimulation testing with TRH, GnRH,
Estrogen therapy
Medications: Dopamine agonist therapy, GnRH agonist
Systemic hypertension/hypotension
Head trauma
Radiotherapy
Pregnancy

Table 1. Precipitating factors of pituitary apoplexy.

PA has been described in postoperative states. Orthopedic and cardiac surgeries mainly cardiopulmonary bypass were the most incriminated [27–29]. Intra- or postoperative hypotension, anticoagulation, and microemboli leading to infarction were the proposed mechanisms. If a pituitary adenoma is known before the cardiac procedure, some authors recommend the use of off-pump technique maintaining an adequate systemic perfusion, as opposed to standard cardiopulmonary bypass [30].

Systemic hypertension leading to an increase in blood flow and diabetes mellitus has been associated with PA [31, 32]. However, this association was not confirmed by other studies [10, 33].

Severe vomiting/diarrhea with concomitant increased Valsalva pressure may also decrease blood supply to the pituitary adenoma and precipitate apoplexy, since tumoral cells are particularly sensitive to glucose deprivation [5].

4.1.2. Imbalance between the stimulation of the pituitary and the ability of increased blood flow at the level of the pituitary adenoma

Apoplexy can also occur after dynamic testing of the pituitary (insulin, TRH, GnRH, or GHRH tests and much more rarely CRH) particularly when different agents are combined. Numerous publications have documented the occurrence of apoplexy within minutes to hours after testing [10, 34, 35].

In this setting, TRH dynamic test may cause apoplexy by vasospasm induced by increased norepinephrine levels or by elevating systemic pressure.

Other tests of pituitary stimulation (especially use of GnRH) can increase the imbalance between the intratumoral metabolic demand and the poor tumor perfusion.

Reports of PA occurring after stimulation test are much rarer in the recent past. Currently, pituitary dynamic testing is not commonly used in the routine assessment of hypothalamic pituitary function.

Increased estrogen states, such as exogenous estrogen administration, pregnancy, and postpartum period, have been reported to cause PA [33, 36–38]. Treatment with GnRH agonists for prostate cancer has also been associated with PA [39–41].

The role of dopamine agonist (DAs) treatment as precipitating factor is more controversial, although many case reports suggested this hypothesis [42, 43]. In prospective studies analyzing the effects of DAs on macroprolactinomas, PA were very rarely or never observed [6, 44–46]. In a retrospective study [9], DA treatment of pituitary adenomas was not associated with PA. These results are not surprising, given that these agents decrease growth and activity of prolactinoma or other adenoma cells.

PA can occur in the setting of an acute systemic illness such as myocardial infarction or severe infection. Excessive stimulation of the pituitary gland by production of larger amount of steroids is a possible explanation [33].

4.1.3. Anticoagulated states

PA has been observed after administration of anticoagulant drugs (vitamin K antagonist or platelet inhibitors) or thrombolytic agents, sometimes very soon after the initiation of treatment or after a prolonged period of treatment [6, 9, 47]. New classes of anticoagulant (dabigatran) [48, 49] may also be involved.

Thrombocytopenia has also been reported usually associated with hemorrhagic PA [50, 51].

4.2. Influence of pituitary adenoma type

The prevalence of apoplexy according to different subtypes of pituitary tumors shows a trend for nonfunctioning adenomas [3–5, 9, 22, 33, 52–55] to develop apoplexy. It is believed that nonfunctioning tumors may be diagnosed at a later stage, so they grow to a larger size before diagnosis; in contrast, the functioning adenomas are generally revealed earlier by signs of hormonal secretion before bleeding/infarction occurs [5].

Other tumor types predisposing to apoplexy are prolactinomas and GH-secreting adenomas [27, 56–59]. In the vast majority of cases, apoplexy complicates large macroadenomas [10]. Clinically silent ACTH adenomas may be particularly prone to necrosis, hemorrhage, and cyst transformation [5, 60]. These complications occur in 30–64% of cases, 2–14% in patients with all types of pituitary adenoma [16, 61–63].

5. Clinical presentation

Frequently, the PA episode is the first manifestation of undiagnosed pituitary adenoma [22, 57, 64].

It is important to consider that the pituitary apoplexy has a wide spectrum of clinical features, resulting from undergoing sudden mass enlargement. It ranges from silent asymptomatic necrotic and/or hemorrhagic adenoma to “classic” acute presentation and even death.

This is largely depending on the extent of hemorrhage, necrosis, and edema. Semple et al. suggested that the cases of pituitary tumor infarction alone had less severe clinical features and better outcome than those with hemorrhagic infarction or frank hemorrhage [15].

The clinical manifestations are summarized in **Table 2**.

5.1. Neurologic symptoms

Headache is the earliest and most common presenting symptom with an incidence of more than 90% [4, 65, 66].

The cephalalgia onset is often sudden and severe, namely, “thunderclap headache,” in patients presenting with pituitary apoplexy and creates an even greater degree of difficulty in the differential diagnoses. It is usually resistant to analgesics, mainly retro-orbital and sometimes

Clinical presentation
Sudden onset headache
Vomiting, nausea
Photophobia
Meningism
Visual field and acuity defects
Diplopia/ophthalmoplegia
Pyrexia
Cranial nerve palsy
Third nerve (more frequent)
Fourth nerve (trochlear)
Fifth nerve (1st and 2nd branches of trigeminal)
Sixth nerve (abducens)
Altered mental status
Seizure
Reduced conscious level
Facial pain/impaired facial sensation
Collapse
Hemiparesis
Sudden Death

Table 2. Common clinical features of pituitary apoplexy.

bifrontal, suboccipital, or diffuse [67]. This feature can be explained by meningeal irritation due to extravasation of blood and necrotic material into subarachnoid space, enlargement of sella turcica walls, dura mater compression, or involvement of the superior division of the trigeminal nerve inside the cavernous sinus [18, 68].

Headache is commonly accompanied by signs of meningeal irritation, such as nausea and vomiting (57%), photophobia (40%), meningismus (25%), and fever (16%) [5]. The fifth cranial nerve (first branch) can be involved in PA, resulting in facial numbness [3].

Altered level of consciousness may occur in varying degrees ranging from lethargy to stupor or even coma as consequence of blood or necrotic tissue leaking into the subarachnoid space [69]. A concurrent cerebrovascular episode with a stroke has been previously described [70]. The involvement of the thalamus in a case of pituitary apoplexy with thalamic and midbrain infarction has been described [71]. In such cases, one of the following mechanisms was proposed: (1) compression of intracavernous portion of internal carotid artery due to expanding pituitary adenoma or a hemorrhage within it and (2) vasospasm caused by factors released from hemorrhagic or necrotic material [70].

Rare cases of sudden death following pituitary tumor apoplexy of fatal outcome of acute pituitary apoplexy due to massive hemorrhage were reported [72, 73].

5.2. Visual disturbance

The apoplectic pituitary adenoma can expand toward the cavernous sinus, compressing the III, IV, and/or V cranial nerves (CN), leading to various degrees of ocular palsy (diplopia and ophthalmoplegia) in 40–70% of the patients [52, 55, 74, 75].

The third CN is the most frequently affected especially when there is an abutment without invasion of the cavernous sinuses. This was explained mainly by the location of the third nerve in the same horizontal plane as the pituitary gland; pressure from lateral growth of a pituitary tumor is relatively easily transmitted to the third cranial nerve. This leads to compression of the third cranial nerve between the tumor and the interclinoid ligament, commonly resulting in the development of the third cranial nerve palsy, occurring either alone or together with damage to the other cranial nerves [52, 76].

Isolated cranial nerve palsy III in PA with direct CN III compression outside the cavernous sinus was also reported. In these cases, the tumor had some mass effect on CN III at the level of the oculomotor trigone after erosion of the posterior clinoid [77]. Multiple CN palsies and even bilateral and asymmetric lesions have been reported [78–80]. Rarely, pituitary apoplexy may present as isolated sixth cranial nerve (abducens) palsy [81].

Compression of the necrotic intrasellar mass superiorly toward the optic nerves and optic chiasma causes visual symptoms in most (75%) patients [11, 76], including decreased visual acuity; visual field defects, especially bitemporal hemianopsia; and also complete blindness and monocular blindness.

6. Differential diagnosis

As stated earlier, PA occurs in previously unknown history of pituitary mass in more than 80% of patients, the diagnosis can be challenging owing to its similarities with many other neurological conditions, and several other life-threatening conditions (**Table 3**) can lead to a delay in proper management [11].

The two most important diseases that should be considered are aneurysmal subarachnoid hemorrhage (SAH) and bacterial meningitis, subarachnoid hemorrhage [82, 83], bacterial meningitis, or parasellar abscess [84, 85].

Other differential diagnoses include subarachnoid hemorrhage, ophthalmoplegic migraine, suprasellar aneurysm, stroke and hypertensive encephalopathy, and cavernous sinus thrombosis [52, 82, 83, 85–87].

Nevertheless, a high degree of suspicion should exist in any patient presenting a severe sudden headache and visual disturbances. This aims to avoid delay in proper management.

Imaging studies are thus crucial for the diagnosis.

Differential diagnoses
Subarachnoid haemorrhage
Meningitis
Migraine
Stroke
Rathke's cleft cyst
Temporal arteritis
Tension headache
Cluster headache
Cavernous sinus thrombosis
Optic neuritis
Intracavernous carotid artery aneurysm

Table 3. Differential diagnoses of pituitary apoplexy.

7. Endocrine function

7.1. Pituitary hormone excess

As most cases of pituitary apoplexy complicate pituitary macroadenoma, many of which are secretory.

Prolactinomas are the most common (20% of cases of pituitary apoplexy); this is related to the frequency of prolactinoma in the population and to their frequent hemorrhagic nature. Hyperprolactin can also result from stalk effect [88].

It was postulated that at presentation of PA in non-PRL-secreting macroadenomas, a normal or elevated serum PRL can predict the residual anterior pituitary cell viability. Inversely a very low serum PRL level at presentation is correlated with the necrosis of the normal pituitary tissue and predicts permanent hypopituitarism [89].

More rarely PA can occur in acromegaly and Cushing's disease (too much adrenocorticotrophic hormone, ACTH) in approximately 7 and 3% of cases, respectively. Co-secretion of more than one hormone may occur.

Several published series reported clinical and biochemical resolution of hormonally hyperfunctioning pituitary adenomas (including Cushing's disease and acromegaly) following pituitary apoplexy on follow-up as a result of the infarction of the pituitary tumors [90–93].

7.2. Pituitary hormone deficiency

Reviewing the series of patients with PA, one or more endocrine deficiencies can be present at the onset [22, 67, 76] and the evaluation of hormonal levels is mandatory (**Table 4**).

The pathogenesis of hypopituitarism is complex and multifactorial.

Endocrine defect
Hypopituitarism
Panhypopituitarism
ACTH deficiency
Central Hypothyroidism
Hypogonadism
Growth hormone deficiency
Diabetes insipidus
Hyponatremia

Table 4. Endocrine disorders in pituitary apoplexy.

As most episodes of PA occur in macroadenoma, the pituitary hormone deficiencies can precede the apoplectic event [22, 76].

This was explained earlier by mechanical compression of the pituitary stalk and/or the portal vessels. But more recent study suggested that it is tightly related to pressure effect of the macroadenoma, as they indicated that in patients with large pituitary adenomas, the intrasellar pressure, measured at surgery, was greater in patients who had hypopituitarism than those with intact pituitary function [94].

Moreover, the apoplexy itself can cause ischemic necrosis of the anterior pituitary secondary to a sudden rise in intrasellar pressure compressing the portal circulation, the pituitary stalk, and the pituitary gland itself [89, 95].

The most life-threatening deficit is that of adrenocorticotrophic hormone (ACTH) resulting in acute central hypoadrenalism, which has been reported in more than 70% of patients [36, 52, 76]. It can result in severe hemodynamic problems. Indeed, the absence of cortisol can lead to insensitivity of the vessels to the pressor effects of endogenous or exogenous catecholamines and thus in hemodynamic instability.

Therefore, in patients with PA, empiric parental corticosteroid supplementation should be given immediately.

In the acute setting, other hormone deficiencies have less concerns. At presentation thyrotropic deficiency and gonadotropic deficiency were reported in 30–70% and 40–75% of patients, respectively [3].

Posterior pituitary involvement is not common in PA, and diabetes insipidus was reported in 3% of cases despite frequent and significant suprasellar extension in many cases [10, 96].

This may be attributable to the preservation of the posterior pituitary as a result of its different blood supply from the inferior hypophyseal artery rather than the superior hypophyseal artery that supplies the anterior pituitary and usually the tumor.

7.3. Fluid electrolyte balance: hyponatremia

Hyponatremia is a common electrolyte disturbance reported in up to 40% of patients presenting with pituitary apoplexy [22].

In most cases, hyponatremia is mostly mild, but severe hyponatremia has been reported [96–99]. It is often multifactorial and the most likely pathogenetic mechanism proposed of hyponatremia is adrenal insufficiency.

Other etiologies can include the syndrome of inappropriate ADH secretion (SIADH) resulting either from adrenal insufficiency itself or from hypothalamus irritation [99] and neurological deterioration late after initial presentation.

Hypothyroidism as common hormone deficiency in pituitary apoplexy may contribute to hyponatremia by reduction in glomerular filtration rate and elevated ADH secretion [100].

An association of a high level of atrial natriuretic peptide concomitant to a high level of ADH, a severe scenario in hyponatremic patients after pituitary apoplexy, has been demonstrated [99].

7.4. Pituitary imaging

In emergency setting, most of the patients with symptoms related to PA will undergo computed tomography (CT) as it is readily available and a rapid screening test. It is likely that, in most of them, the clinical suspicion might be something other than PA.

CT is effective in visualizing pituitary heterogeneous intrasellar and/or expansive suprasellar lesions leading to sellar enlargement (up to 94% of cases) [5, 20, 25], with a coexistence of solid and hemorrhagic areas [4, 22, 76, 101].

The CT is also able to detect subarachnoid hemorrhage and cerebral ischemia, which are the most frequent complications of PA [101].

CT is most valuable in the acute phase (up to 48 h). The recent bleeding in this phase can be missed on MRI either because of infarction or because hemorrhage is still in the form of deoxyhemoglobin. In this context, CT is able to provide an improved detection of hyperdense intralesional areas [102].

Later, during the subacute or chronic phase, in line with blood degradation, hypodense intralesional areas can be present, which increases the difficulty to make the differential diagnosis of subacute hemorrhages from other necrotic or cystic lesions (aneurysms, meningiomas, Rathke cleft cysts, germinomas, and lymphoma) [101].

This makes MRI essential to differentiate between these conditions. MRI and MR angiogram techniques also help to distinguish an aneurysm from pituitary apoplexy [4, 22, 85, 103].

Nevertheless, magnetic resonance imaging (MRI) is the radiological investigation of choice. Its findings depend on the time of onset of bleeding.

It is possible to find a fluid in the intralesional level (**Figure 1(C)**), the lower area is constituted by red cell sediment, and the cranial corresponds to free extracellular methemoglobin.

In the acute stage of pituitary apoplexy, the MRI signal is isointense or slightly hypointense on T1-weighted imaging with hypointensity on T2-weighted imaging (T2 W1). A “brushed” specific pattern of alternating subtle T1-hyperintense and T1-hypointense areas within the sellar mass may suggest apoplexy at the earlier stage [101].

Later, there is marginal signal reinforcement and the hematoma core remains isointense; in the subacute phase, the hemorrhage will appear hyperintense on T1WI as well as on T2WI. In

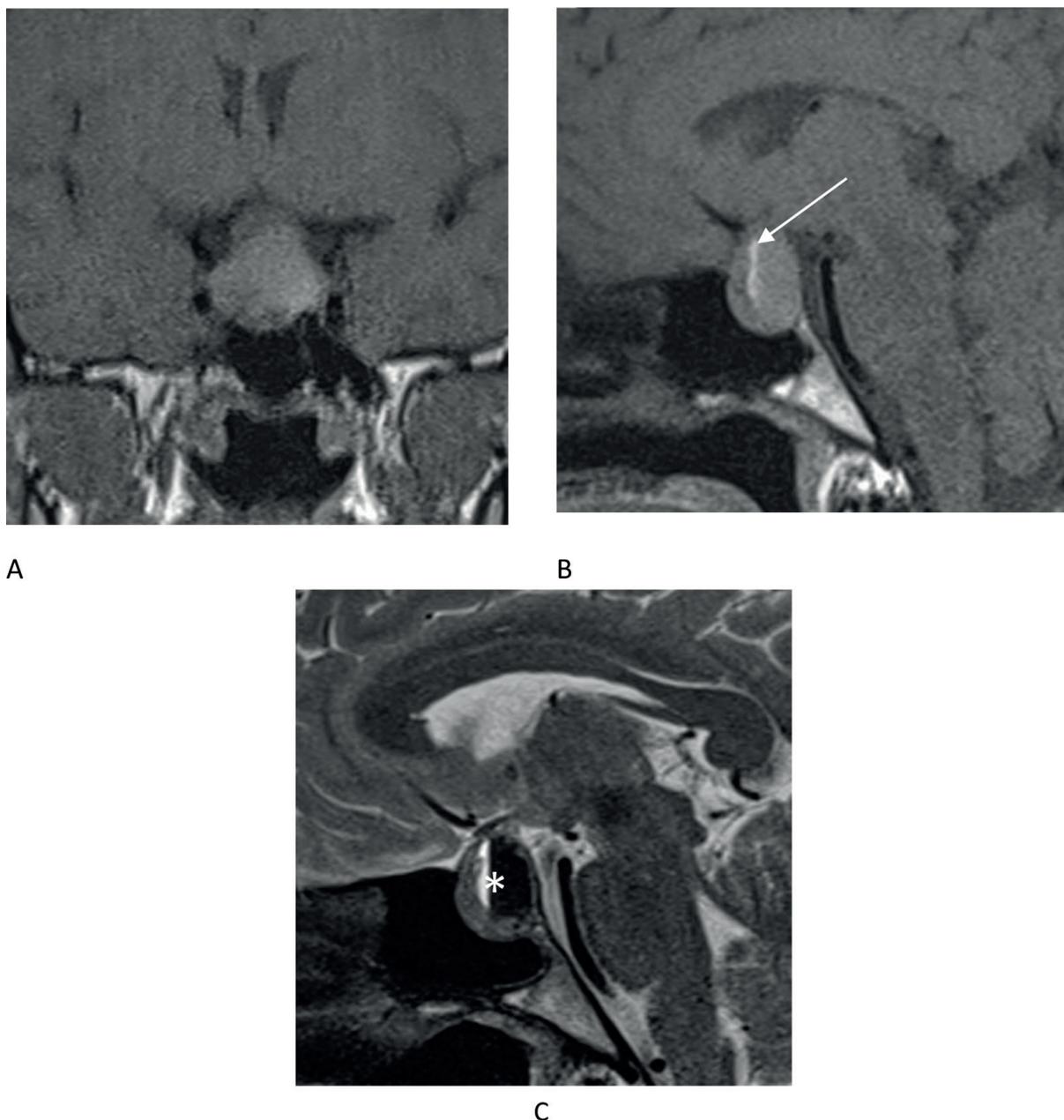


Figure 1. MRI in a pregnant patient, with symptomatic pituitary apoplexy. The lesion is globally hypointense, hemorrhagic content of the pituitary mass, and the hemorrhagic area, in T1-weighted sequences ((A) coronal section, (B) sagittal section), with a high signal intensity (arrow (B)) corresponding to the cystic area. In the same patient, the coronal T2-weighted sequences (C) showing a fluid level (asterisk) inside the pituitary lesion: the upper compartment being hyperintense while the lower is isointense.

the chronic phase, macrophages digest the clot, and the presence of hemosiderin and ferritin causes a strong hypointensity on both T1WI and T2WI [101].

In pituitary apoplexy patients, some authors reported the thickening of the sphenoid sinus mucosa related to venous engorgement in this region as an excellent sign that is present from the early stage, a reversible condition on follow-up studies that generally improves spontaneously [104]. This thickening does not indicate infectious sinusitis and thus does not rule out the surgical transsphenoidal route [103, 105].

Some published series have demonstrated the great value of special techniques as T2-weighted gradient echo to detect pituitary hemorrhage in the acute phase and chronic phase. MRI diffusion-weighted images (DWI) can be also be helpful in rare cases of ischemic pituitary necrosis without hemorrhage [105–107].

Semple et al. have demonstrated a correlation with the MRI findings and histopathology in 68% of patients with a histopathological diagnosis of hemorrhagic infarction/hemorrhage and in 82% of patients with infarction alone [103].

8. Pituitary apoplexy management

PA has long been considered as a neurosurgical emergency. However, nowadays, the conservative approach constitutes another therapeutic option in many situations. Untreated patients with apoplexy have higher morbidity and mortality. Altered consciousness, with all its associated complications, hypopituitarism, and intercurrent illnesses account for the increased morbidity and mortality of untreated patients. Although it is hard to estimate the relative increase in mortality associated without treatment, reports published before corticosteroid therapy were available indicating an approximate mortality rate of 50% [3].

The goals of treatment of PA are to improve symptoms, to decompress local structures especially the optic tract, and to avoid acute adrenal insufficiency. Hence, whether the treatment is surgical or conservative, glucocorticosteroid replacement is systematic.

8.1. Glucocorticosteroid replacement and emergency medical treatment

As corticotropic deficiency is frequently associated with pituitary apoplexy, corticosteroid should be systematically given to these patients. Thus, hydrocortisone is administered at a dose of 50 mg every 6 h [3, 108] or in the form of a 100–200 mg bolus followed by 50–100 mg every 6 h intravenously (or intramuscularly) or by 2–4 mg per hour by continuous intravenous infusion [108, 109]. Corticosteroid substitution should be associated with a careful assessment of fluid and electrolyte balance and supportive measures ensuring hemodynamic stability. Once glucocorticoids are administered, clinical improvement is invariably observed, and hemodynamic stability becomes easier to maintain. The glucocorticoids are administered in supraphysiological doses to serve not only as replacement for endogenous hormone deficiency but also to help control the effect of edema on parasellar structures [3].

8.2. Neurosurgical treatment

8.2.1. *Technique*

If surgical management is chosen, the transsphenoidal approach is almost always recommended, because it allows good decompression of the optic pathways and neuroanatomic structures in contact with the tumor and because it is associated with low postoperative morbidity and mortality [11]. Usually, necroticohemorrhagic material is evacuated as soon as the incision of the tumor capsule is made. The purpose of the surgery is the decompression of the optical pathways; the surgeon should try to identify the sellar diaphragm. In case of

invasive pituitary adenoma, a maximum but incomplete resection is ensured by taking all the precautions to avoid damaging the cranial nerves or the carotids in case of invasion of the cavernous sinuses.

8.2.2. *Timing*

The timing of pituitary surgery is controversial, as no randomized trials comparing different strategies with strong evidence have been performed. However, most studies indicate that surgical treatment, usually within 7 days after the apoplectic event, leads to higher rates of visual impairment recovery [11, 110].

Occasionally, patients are clinically or biochemically hypothyroid at presentation. Unless the hypothyroidism is severe, the surgical decompression needs not be delayed, provided the anesthesiologists and the management team are aware of the patient's condition to avoid medications and procedures that are particularly deleterious and that can potentially worsen clinical symptoms [3].

8.2.3. *Outcomes*

Surgical decompression normalizes visual acuity in about one-half of cases and improves it in another 6–36% of cases [52, 53]. Visual field defects normalize after surgery in 30–60% of cases and improve in another 50%. Ocular motility dysfunction can resolve spontaneously, with or without surgery [111].

Pituitary deficiencies are usually not expected to recover [19, 112]. In addition, it seems that apoplexy worsens endocrine outcome: hormonal prognosis after elective pituitary surgery is poorer in patients with PA than in patients without PA [9]. This is explained mainly by the damage to the normal gland from the initial apoplectic event. Another important point is that, in this acute setting, the operation may be performed by an on-call neurosurgeon rather than by a skilled pituitary neurosurgeon, as underlined in UK guidelines [11], and this may increase the risk of adverse events.

For tumoral outcome, complete tumor removal is reported in 48–66% of patients and subtotal resection in 23–52% of patients [95]. Tumor recurrence has been described in 6–11% of patients [112].

8.2.4. *Surgical complications*

Surgery may also be harmful, with a risk of postoperative cerebrospinal fluid leakage, permanent diabetes insipidus caused by posterior pituitary damage, meningitis, and an increased likelihood of hypopituitarism due to removal or damage to normal pituitary tissue. Fortunately, in experienced pituitary centers, these complications are very rare [5].

8.3. **Conservative approach: rationale, modalities, and outcomes**

Several reports have documented that spontaneous neurological recovery is possible despite unilateral ophthalmoplegia and partial visual field defects, which has suggested that non-operative medical management of patients with PA may be appropriate in many situations.

In 1995, Maccagnan et al. reported the results of a prospective study in which they treated PA with high-dose steroids (2 to 16 mg of dexamethasone daily). Only patients whose visual impairment or altered consciousness failed to improve underwent surgery. Conservative treatment was possible on 7 of 12 patients, and only 5 patients had needed surgery. Visual deficits regress in 6 of the 7 patients and improved in the remaining patients. The posttreatment prevalence of pituitary hormone deficiency and the incidence of tumor regrowth were similar in conservatively and surgically treated patients [113].

Thus, conservative therapy involved supportive therapy, continued use of supraphysiological doses of glucocorticoids for several weeks, and hormone replacement therapy. Improvement in neurological symptoms is often seen in the majority of patients treated conservatively, at times to a similar degree to that seen in surgically treated patients. However, worsening of pituitary function is usually seen in many of these patients [114]. For functioning pituitary adenomas, hormonal secretion must be also evaluated: hormonal levels could be low, be normal, or remain high after apoplexy [11]. For tumoral outcomes, additional treatment is not necessary in most cases, as tumors usually diminish and even disappear without surgical intervention [10]. It seems that a single large hypodense area within the tumor on CT might be associated with better subsequent tumor shrinkage than are several small hypodense areas [113].

8.4. Surgical or conservative treatment?

PA is characterized by a highly capricious course, and randomized prospective studies with strong evidence about this syndrome are lacking, which makes optimal management of acute PA controversial. Although guidelines, as the one from the UK, proposed an algorithm for PA management, randomized trials comparing both strategies are needed for strong evidence [11, 112]. Hence, the decision of surgical treatment or conservative management should be individualized and made by experts from a multidisciplinary team including endocrinologists, neurologists, ophthalmologists, and neurosurgeon [11].

The risk-benefit ratio of conservative treatment versus surgery must be carefully evaluated, in terms of visual outcome, pituitary function and also subsequent tumor growth. On the other hand, the potentially serious complications of surgery need to be taken into consideration [115].

8.4.1. Background

In spite of the methodological limits of the studies available on this subject, these data have constituted the rationale guiding the therapeutic choice of PA.

The outcome of visual acuity, field defect, or ophthalmoplegia is similar with surgery or conservative treatment. Unfortunately, visual outcome is poorer in patients with more severe disorders such as monocular or binocular blindness, irrespective of whether management is conservative or surgical [56, 116, 117]. It has been argued that conservatively treated patients may have less severe visual defects than surgically treated patients and that this might explain why the improvement is at least as good in the former as in the latter [3, 11, 118]. The number of patients with visual defects was effectively higher in the surgical groups of published series [53, 76].

For endocrine prognosis, whatever the management approach, the hormonal outcome is poor in patients with PA, who frequently suffer irreversible pituitary damage [11].

Concerning the outcome of the pituitary tumor, very few studies have compared the degree of tumor disappearance between patients receiving surgery and conservative treatment for apoplexy. The reported results were very different: the incidence of recurrence was similar between the two approaches in one study [76], higher after surgery in one other [56], and lower after surgery in two others [52]. Thus, the optimal approach for tumor control is difficult to judge. Whatever the therapeutic choice in the acute event, additional forms of therapy can be used to control residual tumor growth, depending on the type of tumor, including a dopamine agonist for documented prolactinomas or a somatostatin analogue for documented growth hormone-secreting tumors. Gamma Knife stereotactic radiosurgery can also be used on these patients and on patients with nonsecreting adenomas [3].

8.4.2. MRI's contribution to the therapeutic choice

MRI did not predict the severity of ocular paresis or field defects. The size of the tumor on MRI is not actually a strong argument for therapeutic choice. Even when the tumor was very large, conservative management was accompanied by tumor shrinkage [76]. However, some MRI findings were found to be associated with clinical status and outcome: patients with simple infarction had less severe clinical features and better outcomes than those with hemorrhagic infarction or hemorrhage [70].

All these data from the literature have allowed deducing overall the place of, respectively, the conservative approach and the surgical treatment in the management of PA.

8.4.3. Surgical treatment indications

According to the majority of authors, surgical intervention should be considered in patients with severely reduced visual acuity, severe and persistent visual field defects, and deteriorating level of consciousness despite glucocorticoid replacement and hydroelectrolytic support [109]. Ocular paresis because of involvement of III, IV, or VI cranial nerves in the cavernous sinus is not in itself an indication for immediate surgery. Resolution will typically occur within days or weeks with conservative management [11].

The UK Guidelines for PA recommend a scoring system (**Table 5**), calculated using visual acuity, visual defects, cranial nerve palsies, and the Glasgow Coma Scale. The PA score ranges from 0 to 10, and surgery usually is indicated for scores ≥ 4 [11]. Another scoring system, from the Massachusetts General Hospital, proposes grading patients on a scale from 1 to 5: grade 1 for asymptomatic individuals, grade 2 for patients with symptoms due to endocrinopathy, grade 3 for patients with headache, grade 4 for patients with ocular paresis, and grade 5 for patients with visual deficits or a low Glasgow Coma Scale score. Patients with grade 5 should be submitted to surgery [59].

8.4.4. Conservative management indications

For conservative approach, it is safe in patients with pituitary tumor apoplexy who are without any neuro-ophthalmic signs or mild and stable signs or those with evidence of early improvement after administration of glucocorticoids [76]. This would be particularly

Variable	Points
Level of consciousness	
Glasgow coma scale 15	0
Glasgow coma scale 8–14	2
Glasgow coma scale <u> </u> 8	4
Visual acuity	
Normal 10/10 (or no change from pre-PA visual acuity)	0
Reduced, unilateral	1
Reduced, bilateral	2
Visual field defects	
Normal	0
Unilateral defect	1
Bilateral defect	2
Ocular paresis	
Absent	0
Present – Unilateral	1
Bilateral	2

[From S. Rajasekaran et al: UK guidelines for the management of pituitary apoplexy.[11] with permission.

Table 5. Pituitary apoplexy score (PAS).

applicable in patients with prolactin-secreting adenomas, with whom dopamine agonists are very effective not only in controlling hyperprolactinemia but also in reducing the size of the adenoma [3]. “Wait-and-see” approach should be also considered in patients with significant clinical comorbidities.

If conservative treatment is chosen, then careful monitoring of visual signs and symptoms is necessary, and surgical decompression is recommended if visual disorders do not improve or if they deteriorate [5, 11, 59].

8.5. Follow-up

All patients with pituitary apoplexy need follow-up by endocrine and neurosurgical teams. They require repeated assessment of pituitary and visual function (visual acuity, eye movements, and visual fields), at 4–6 weeks. Thereafter, hormonal reevaluation must be performed every 6–12 months to determine whether or not the pituitary defect is permanent and the possible hypersecretory nature of the adenoma and to optimize hormonal replacement [109].

Sellar MRI should be repeated in 3–6 months, annually for 5 years, and biannually after that to monitor tumor progression/recurrence [119]. The presence of an “empty sella” is often observed [117].

Morbidity and mortality in patients with pituitary tumor apoplexy have declined in the past six decades. Four factors may have contributed to the improved survival: improved diagnostic accuracy, use of glucocorticoids, use of more sophisticated supportive therapy, and refinements in surgical techniques and postoperative care [3]. Currently, mortality in the acute setting is less than 2% [120].

9. Conclusion

PA is uncommon but a potentially life-threatening complication due to acute infarction or hemorrhage within a preexisting pituitary adenoma. Its pathophysiology, including extrinsic compression of arterial supply or intrinsic tumoral factors, is still controversial. In terms of triggering factors, the most common include major surgery. The classical presentation is highly suspected when an acute lancinating headache is combined with visual disturbance, cranial nerve palsy, and hypopituitarism. MRI is a fundamental step to evaluate the pituitary infarct and hemorrhage and to rule out other pathologies. For the management of PA, corticosteroids should be systematically administered. However, the therapeutic choice between surgery and conservative treatment is controversial and should be made by experts from a multidisciplinary team. The surgical management which used to be considered as the first-line treatment of this acute condition is now reserved for patients with severe neuro-ophthalmic signs. Improvement of the diagnostic means and the therapeutic management has allowed a better PA prognosis which is preserved in most of the cases. Reevaluation of the pituitary function and tumor mass is mandatory in the months after the acute apoplectic episode to adjust hormonal substitution, to detect the possible hypersecretory nature of the adenoma, and to initiate follow-up of a possible tumor remnant.

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