Clinical and imaging features of pituitary apoplexy and role of imaging in differentiation of clinical mimics

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Abstract: To discuss the clinical syndrome, review common imaging findings of pituitary apoplexy (PA) and role of imaging in therapy and follow-up. Also, to review other acute clinical scenarios with similar clinical and/or imaging findings as PA. PA is a severe and potentially life-threatening medical emergency, characterized by constellation of symptoms/signs that occur as a result of acute hemorrhage and/or infarction in pituitary gland. Patients present with acute and sudden onset of symptoms/signs, most commonly with severe headache, vision deficits/ophthalmoplegia, altered mental status, and possible pan hypopituitarism. Pre-existing macro adenoma (65–90%), especially non-functioning and prolactinomas, are most susceptible to apoplexy, which undergoes hemorrhage or infarct, but PA can occur with normal pituitary or microadenoma. Because of the probable grave prognosis of PA, imaging characteristics of PA and other acute clinical scenarios with similar clinical and/or imaging findings should be familiar to radiologists. PA is potentially a life-threatening clinical syndrome, however, imaging and clinical findings can lead the radiologist towards appropriate diagnosis, and rule out other clinical mimics. When hemorrhage is secondary to an underlying lesion, regrowth of the pituitary tumor years after a PA episode is possible and patients require long-term clinical and imaging surveillance.

Keywords: Pituitary apoplexy (PA); pituitary lesions; magnetic resonance imaging (MRI)

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Introduction

Pituitary apoplexy (PA) is a rare serious and potentially fatal medical emergency with a vast spectrum of clinical manifestations. Most frequent symptom is sudden onset of severe retro-orbital headache (90–97%) (1-5). That is why PA is not often suspected initially because of similar presentation of more frequent diseases such as subarachnoid hemorrhage (SAH), cervical artery dissection or cerebral dural sinus thrombosis (6). The second most common symptom is the vision deficit (50% to 82%) (6-9). Other symptoms/signs include diminished consciousness and pan hypopituitarism (80%), nausea, vomiting, ophthalmoplegia and meningism (25–50%) (3,7,8). Pre-existing macro adenoma (65–90%), especially non-functioning and prolactinomas, are most susceptible to apoplexy which undergoes hemorrhage or infarct, but PA can occur with normal pituitary or microadenoma (9-11).

PA occurs in 1.6% to 2.8% of patients with adenoma and 0.2–0.6 events per 100 person-year in non-functioning pituitary adenomas (3-5,7,8). Usually, PA occurs in the
middle age adults (typically 50–60 years) and is rare in children, with male preponderance (M:F =2:1) (7,8,12). Diagnosis of PA is frequently missed because, in addition to its relative rarity, clinical presentation can be acute or slowly progressive (subacute) which depend upon bleeding extent, edema extension, and necrotic evolution (13). Moreover, the existence of an adenoma is not often suspected at the time of PA episode because in more than 80% of the patients, PA is often the first presentation of an underlying pituitary tumor (especially nonfunctioning adenomas) (9,10). However, apoplexy can also occur in non-adenomatous lesions, such as craniopharyngioma (14), Rathke’s cleft cyst (RCC) (15), sellar tuberculoma (16), hypophysitis (17,18), sellar abscess (19), sellar metastasis (20), or even in normal pituitary gland during peri or post-partum period as a consequence of severe hypovolemic shock (Sheehan’s syndrome) (21).

The diagnosis of PA can be made only when hemorrhagic infarction of the pituitary gland leads to the above mentioned clinical syndrome. Small to large hemorrhages can be a common finding in up to 25% patients with macroadenomas without PA symptoms (1). The use of term PA should be avoided in asymptomatic patients, which is sometimes referred as subclinical PA (21). In one study, approximately one third of patients had non-hemorrhagic infarction of the adenoma, and these patients presented with less severe clinical symptoms and longer course before presenting for medical care than those who had hemorrhage or hemorrhagic infarction of the adenoma (22).

**Pathophysiology**

The incidence of intraslesional bleeding in a pituitary adenoma is estimated five times higher than other intracranial neoplasms (1). The precise pathophysiology is still not completely understood. Under physiological conditions, the normal pituitary gland receives most of its blood supply through the capillary network of superior and inferior hypophyseal (portal) vessels in the infundibulum, and to a lesser degree, direct arterial blood supply (23). In addition, it is suggested that pituitary gland might have a critical perfusion pressure well below normal arterial pressure (24). It is possible that this peculiar vascularity and sudden alterations in perfusion pressure by various triggering factors (Table 1) (25-37), may predispose to sudden hemorrhage and/or infarction in micro adenomas as well as non-adenomatous lesions. Diabetes and arterial hypertension do not predispose patients to PA as reported in previous studies (16).

In pituitary adenomas, direct arterial source is generally more dominant than normal pituitary gland and thus may be directly influenced by an alteration in systemic arterial pressure (23). In addition, pituitary adenoma vessels display immature morphology of poor fenestration, ruptured and fragmented basal membranes (38). Various triggering factors as mentioned in Table 1 can be identified only in about 40% of PA in adenomas, and in the absence of triggering factors, intrinsic vasculopathy possibly contributes to the susceptibility for spontaneous hemorrhage (1). Moreover, dynamic imaging and histopathology have shown that macroadenomas, as well as microadenomas, are less vascularized than the pituitary gland (39,40). Thus, in addition to intrinsic vasculopathy, relatively fast and excessive growth (which outgrows its blood supply) in macro adenomas lead to ischemic necrosis followed by hemorrhage (1). Apoplectic episode results in a rapid increase in the intrasellar pressure causing most of the clinical manifestations (Figure 1) of this syndrome (41).

**Imaging appearance of PA**

Plenty of clinical series on PA have been reported, with emphasis on clinical diagnosis and management, and less emphasis on imaging features. Because of the potential grave prognosis of PA, radiologists should be familiar with its imaging characteristics and other acute clinical scenarios with similar clinical and/or imaging findings as PA.
Hypopituitarism

TIA or hemiplegia

SAH or chemical meningitis

Diminished consciousness

Decreased visual acuity and as visual field deficit

Neural palsies (cranial nerves III, IV, V, and VI)

Sudden decrease in caliber of cavernous segment of ICA and/or vasospasm

Blood/necrotic tissue leakage into suprasellar CSF cistern

Pressure transmitted on brainstem/hypothalamus

Optic chiasm compression

Compression of the cavernous sinus neural structures

Sudden increase in intrasellar pressure

Compression of the normal pituitary tissue and its vascular blood supply

Increased pressure on adjacent vascular and neural structures

Hypopituitarism

Figure 1 Mechanism of clinical manifestations of pituitary apoplexy. ICA, internal carotid artery; TIA, transient ischemic attack; CSF, cerebrospinal fluid; SAH, subarachnoid hemorrhage.

Computed tomography (CT)

Usually almost all the patients initially undergo emergency CT imaging based on symptoms related to PA, though clinical suspicion might be different. Acute hemorrhagic infarct of the pituitary gland may be seen on CT as a large heterogeneously hyper dense sellar mass which may have a supra-sellar extension. Non-hemorrhagic infarct will usually show no abnormalities without intravenous contrast. Following intravenous contrast rim enhancement is suggestive but not diagnostic of apoplexy (3,22,42,43). In non-hemorrhagic PA or without a pre-existing pituitary adenoma, CT examination may be non-specific. Even though CT can rule out other diseases such as SAH or craniopharyngioma, an MR examination can better characterize a suspected PA (22,44).

Magnetic resonance imaging (MRI)

MRI appearance of the sellar/suprasellar mass depends on the time of onset and whether hemorrhage is present (Figures 2,3) or not (Figures 4,5). In hemorrhagic lesions, both T1 and T2 weighted images will initially show low signal, however, subacute hemorrhage will become hyper intense (Table 2). T2 weighted images are also useful in the evaluation of potential compressions of the optic chiasm (Figure 2E) and the hypothalamus (45). Following intravenous contrast, the most common finding in both hemorrhagic and non-hemorrhagic infarct (Figure 5) is peripheral rim enhancement in acute phase. The surrounding dura may show reactive thickening and enhancement. In the acute phase, both hemorrhagic and non-hemorrhagic apoplexy will show high signal on diffusion weighted imaging with the corresponding low signal on apparent diffusion coefficient (ADC) maps corresponding to area of infract (Figure 3B,C) (44,45). Gradient echo (GE) or susceptibility (T2*) weighted images can differentiate between these, as hemorrhagic apoplexy will show blooming (Figure 3D) within the sellar due to paramagnetic effects of bleeding products (deoxy-Hb and met-Hb) (46).

Many authors (22,47,48) have described a specific sign of hemorrhagic PA: fluid debris level within the mass. The T1 hyper intense upper fluid corresponds to free extracellular meta-Hb and the T1 iso to hypo intense lower layer related to the sediment of blood products of late
Figure 2 A 77-year-old male diagnosed with pan hypopituitarism and macro adenoma, who later presented to the emergency department with acute onset headache, weakness, nausea, and vomiting and found to have hyponatremia. MRI 6 months before acute presentation: Sagittal Pre-contrast T1WI (A) demonstrates a sellar and suprasellar lesion with homogeneous isointense signal (arrow). Sagittal post contrast T1WI (B) shows a heterogeneously enhancing mass suggestive of pituitary adenoma (arrow). Note mucous retention cyst in the sphenoid sinus but no mucosal thickening (A,B). MRI at the time of acute presentation: Sagittal pre-contrast T1WI (C) and post contrast T1WI (D) demonstrate enlargement and heterogeneously high T1 signal within the mass consistent with acute hemorrhage (arrows). Coronal T2WI (E) demonstrates heterogeneously low signal consistent with blood products (yellow arrow) and mass effect upon the optic chiasm and nerves (white arrows). Note there is mucosal thickening and enhancement (red arrow) of sphenoid sinus (D,E). H&E sections [(F,G); 100× and 200×] showing extensive hemorrhage (black arrows) surrounding glandular pituitary adenoma tissue (white arrows).

Subacute hemorrhage (47,48). Thickening of sphenoid sinus mucosa (Figure 2D,E) is another important specific MR finding of the acute phase of hemorrhage which is highly suggestive of PA (22,49). Mucosal thickening is probably related to venous congestion in this region and resolves later spontaneously (22). MRI is much superior to CT in the diagnosis of PA with a sensitivity ranging from 88% to 90% (22,49). PA features can be accurately predicted from
Figure 3 A 56-year-old female with hemorrhagic apoplexy in macro adenoma. Sagittal pre-contrast T1WI demonstrates area of high signal (A) suggestive of subacute hemorrhage (yellow arrow). There is high signal (white arrow) on DWI (B) with corresponding low signal (white arrow) on ADC maps (C) corresponding to area of infract and/or subacute hemorrhage. There is blooming (yellow arrow) related to blood products on axial gradient echo image (D) corresponding to subacute hemorrhage.

Figure 4 A 62-year-old male who presented with acute visual field deficit and found to have low cortisol and prolactin. Sagittal pre-contrast T1WI (A) demonstrates mostly low signal sellar and suprasellar mass with scattered areas of isointense signal to normal parenchyma (arrow). Post contrast T1WI (B) shows solid enhancement of the isointense areas, and rim enhancement (arrows) of the remainder of the mass. Findings are suggestive of non-hemorrhagic apoplexy in macroadenoma.

MR imaging and correlate with the pathologic reports and operative findings (22).

**Clinical mimics**

The clinical syndrome of headache and visual changes that can mimic PA, has a myriad of causes, which often prompts the need for CT and/or MR imaging in the acute setting.

**Pregnancy hyperplasia**

Pregnancy and the postpartum state may induce a number of pituitary related disorders due to the changes in systemic hormone levels. During pregnancy there is progressive
enlargement of the pituitary gland to at least double the size and peaks in the early postpartum period; however, the vertical height should remain at 12 mm or below. Normal appearance of the gland is typically seen in 6 months post-partum (50). Patient may present with sudden onset headache with or without visual field deficits and can have acute hypopituitarism.

**Imaging**

Homogeneous signal characteristics within an enlarged pituitary gland (<12 mm) with superior convexity, without focal hyper intense signal on T1 or sellar blooming on T2* gradient echo image to suggest hemorrhage (*Figure 6*). Intravenous contrast administration should be avoided in pregnancy.
Pituitary metastasis

The sellar is relatively common location for metastatic deposits in autopsies of cancer patients however lesions are usually asymptomatic and not visible by imaging. The most common primary tumor types are lung (24.2–36%) and breast (33–37.2%) (51,52). Sellar metastases sometime clinically mimic PA as patients may present with acute onset double vision and headache.

Imaging

T1 weighted image following intravenous contrast at the time of acute presentation may show a heterogeneous enhancing sellar mass with or without suprasellar extension and minimal mass effect upon the chiasm (Figure 7). Patients typically have metastatic disease elsewhere (lung, breast) (Figure 7). Metastases may extend laterally into the cavernous sinus and superiorly into the pituitary stalk, hypothalamus, and optic chiasm (52).

Pituitary abscess

Infection of the pituitary with abscess formation is a rare cause of a sellar or suprasellar mass and suspected to comprise less than 1% of all sellar lesions (19,53). Similar to other intracranial abscesses, pituitary abscess can occur from hematogenous seeding or direct extension from adjacent diseases such as sinusitis or meningitis. Less common causes include a contaminated cerebrospinal fluid fistula and cavernous sinus thrombophlebitis. The pre-existing pituitary lesion, prior surgery, and immunosuppression are the most common risk factors (53,54).

Imaging

Features are nonspecific and they may show varying degrees of T1 and T2 signal depending on the presence of coexisting proteinaceous fluid and hemorrhage (Figure 8A-C). Enhancement patterns may also vary however a ring or peripheral enhancement pattern (Figure 8D) has been described (53,54). Similar to PA, pituitary abscess also demonstrates restricted diffusion. However, unlike PA where restricted diffusion correspond to the area of infarct, restricted diffusion in pituitary abscess corresponds to central abscess cavity containing inflammatory cells, debris and macromolecules such as fibrinogen (54).

Craniopharyngioma

Craniopharyngioma is a WHO grade 1 neoplasm which arises from the epithelium of the Rathke’s pouch. It has bimodal occurrence. The adamantinomatous type is the common pediatric brain tumor aside from glial tumors. Patients typically present with an acute headache and vision...
changes with previously known or unknown longstanding anterior and posterior pituitary hormone deficiency (45,55).

**Imaging**

Approximately 75% of craniopharyngioma are suprasellar, 20% supra and intrasellar (20%) and only 5% are intrasellar in location. CT may show a mixed cystic and solid lesion with calcifications (Figure 9A,B). Areas of blooming on T2* weighted MR image (Figure 9C) corresponds to calcifications seen on CT (43,55). MR appearance may
vary based on the amount of protein contents in the cyst fluid; however, is classically hyper intense on both T1 and T2 weighted images (Figure 9D). The solid portions enhance similarly to CT.

**RCC**

RCCs are ectodermal cysts which arise from the remnants of Rathke’s pouch. Unlike craniopharyngiomas, these are intrasellar cysts with suprasellar extension and usually located along the midline. A large sellar/suprasellar RCC may mimic PA clinically, with acute onset of headache and visual deficit (56).

**Imaging**

CT density characteristic is determined by the variable protein contents of the fluid. Unlike craniopharyngioma, calcification is rare and there is no solid enhancement. On MR, T1 hyper intensity related to variable protein contents (45,56). A typical T2 hypo-intense intra-cystic nodule is related to proteinaceous concretion within the RCC (Figure 10A). Unlike PA, does not present a fluid debris level (45). A claw sign of normal pituitary, however, can be seen draped around the cyst (Figure 10B).

**Sellar aneurysm**

Aneurysms from the cavernous segment of internal carotid artery, anterior or posterior communicating artery may extend into the sellar or suprasellar space (57-59). The aneurysm itself may cause headaches, however patients with thrombosis or rupture will report acute pain.

**Imaging**

Partially or completely thrombosed aneurysm in the
sellar region can show high signal intensity on T1WI (57) and central high signal with hypo intense rim on T2WI. Aneurysms with repeat/recurrent hemorrhage and thrombosis may acquire a heterogeneous “onion-skin” appearance. CT angiography (Figure 11A,B) or DSA (digital subtraction angiography) is required to confirm diagnosis (57,58). If there is no thrombosis, the aneurysm will appear as a flow void on T2WI, occupying the sellar region (Figure 11C) and may demonstrate homogeneous filling of the aneurysm with contrast (yellow arrow). The left MCA aneurysm was treated with endovascular coil embolization, and the large sellar aneurysm was stable on 1 year follow up. ICA, internal carotid artery; MCA, middle cerebral artery; FSPGR, fast spoiled gradient-echo.

**Management of PA**

A multidisciplinary team including endocrinologist, neurosurgeon, intensivist and neuro-ophthalmologist are required for the optimal care of PA with a proper management strategy that depends on the clinical manifestations. In patients with severe or progressive impairment of the consciousness, visual acuity or the visual fields, prompt surgical decompression may lead to the neurological or visual recovery in most of the cases (43). Patients with mild, stable clinical condition including those with isolated ocular palsies can be managed conservatively with stress doses of steroids and support of fluid and electrolyte balance in most cases (60). Frequent reassessment in ICU setting is mandatory because clinical conditions can deteriorate unpredictably (60). In that case, timely planned surgery can be beneficial, especially in terms of visual outcome. Irrespective of the treatment option, the pituitary hormonal function is less favorable with many patients remaining on long-term hormone replacement therapy (60). However, clear proof of optimal outcomes in the form of randomized controlled trials is lacking.

**Role of imaging in therapy and follow-up**

The role of imaging in the decision-making process for a proper therapy is still debatable as surgical or conservative treatment decisions are made on the basis of severity of the clinical condition (60). However, serial MRI can predict the evolution of PA in patients with mild symptoms who can be safely managed conservatively (43). Recurrent PA has been reported with both conservative and surgical treatment approaches, without a significant incidence difference between these groups (43,61). The pre-existing adenoma may regrow after PA and then might re-bleed (42). In those patients treated conservatively, an incidence of tumor regrowth after bleeding ranges from 6% to 90% that necessitates the need of clinical and radiological follow-up 3–6 months after PA and every year for at least 5 years (43,61).
Conclusions

PA is a potentially life threatening medical emergency and imaging is important to rule out other clinical mimics. Though, CT imaging is the most common initial study during the acute onset PA symptoms, MRI having better sensitivity should always be performed in acute and subacute phase of PA. Although MRI can play a crucial role in the conservative management, more studies are still needed to define its role in decision-making between surgical vs. conservative management. MRI should be considered in the follow-up of these patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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