Pituitary apoplexy: pathophysiology, diagnosis and management

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ABSTRACT
Pituitary apoplexy is characterized by sudden increase in pituitary gland volume secondary to ischemia and/or necrosis, usually in a pituitary adenoma. Most cases occur during the 5th decade of life, predominantly in males and in previously unknown clinically non-functioning pituitary adenomas. There are some predisposing factors as arterial hypertension, anticoagulant therapy and major surgery. Clinical picture comprises headache, visual impairment, cranial nerve palsies and hypopituitarism. Most cases improve with both surgical and expectant management and the best approach in the acute phase is still controversial. Surgery, usually by transsphenoidal route, is indicated if consciousness and/or vision are impaired, despite glucocorticoid replacement and electrolyte support. Pituitary function is impaired in most patients before apoplexy and ACTH deficiency is common, which makes glucocorticoid replacement needed in most cases. Pituitary deficiencies, once established, usually do not recover, regardless the treatment. Sellar imaging and endocrinological function must be periodic reevaluated. Arch Endocrinol Metab. 2015;59(3):259-64

Keywords
Pituitary; apoplexy; pituitary adenoma; hypopituitarism

INTRODUCTION
Pituitary apoplexy (PA) is characterized by acute infarction and/or hemorrhage of the pituitary gland. The term pituitary apoplexy was coined by Brougham in 1950, and the first index case was, in fact, described by Bailey, in 1898 (1). Routine imaging and histopathological evaluation may detect asymptomatic pituitary hemorrhage, known as subclinical apoplexy, and is much more frequent than PA (2). Apoplexy means “sudden attack” in Greek, and, as a result, an abrupt increase of tissue volume within the sellar region can cause headache, visual impairment, cranial nerve palsies and, even, impairment of consciousness, besides causing pituitary hormone deficiencies as ACTH. In most cases, apoplexy involves a previously unrecognized pituitary adenoma. Although rare, the condition must be recognized and properly treated, as it may in fact be life threatening.

EPIDEMIOLOGY
PA is rare, with an estimated prevalence ~6.2 cases per 100,000 inhabitants (3) and incidence of 0.17 episodes per 100,000 person-years (4). PA occurs in 0.6% to 10% of treated pituitary adenomas (5) and its risk in non-functioning pituitary adenomas is 0.2-0.6 events per 100 person-year (6,7).

Usually, PA occurs in the fifth or sixth decade, with a discrete preponderance in males. Jankowski and cols. reviewed PA in adolescents, a very rare entity (8). Amongst 60% to 80% of cases, pituitary adenoma was not a previously known condition (2). Macroadenomas, especially non-functioning and prolactinomas, are most susceptible to apoplexy, nevertheless apoplexy in microadenomas has been reported (9). Cavernous sinus invasion may be a prognostic factor associated with PA (10).

Although PA usually occurs in adenomas; it has also been described in non-adenomatous lesions including hypophysitis (11,12), metastasis to pituitary, especially from renal cell carcinoma (13), craniopharyngioma, Rathke’s cleft cyst and sellar tuberculosis (14).

PHYSIOPATHOLOGY
The precise pathophysiology is not completely understood. However, a proposed hypothesis involves tumor vascular occlusion due to tumor growth, tumor blood flux reduction and tumoral abnormal (immature) vascularization. VEGF mRNA may be increased in pitui-
Pituitary tumors, especially in non-functioning pituitary adenomas, which could be related to an abnormal vascularization (15). As the usual trigger is not identified, vasculopathy may occur in apoplectic tumors. Four categories of triggering factors have been suggested (16):

2. Acute increase in blood flow: physical activity, systemic hypertension.

Other risk factors include pregnancy, diabetes mellitus, sickle cell anemia, estrogen replacement, dopamine agonist therapy, lymphocytic leukemia and head trauma.

Precipitating factors can be identified in about 40% of PA cases, with arterial hypertension the most frequent (2). Other common risk factors include anticoagulant therapy, and new oral anticoagulants (17).

Dopamine agonists are considered a risk factor for PA. As they are largely used in prolactinomas, apoplexy was more frequently reported in macroprolactinomas, and within the first year and a half of treatment (18). In three series with symptomatic cases, the ratio apoplexy/therapy varied between 1.2 to 6.67%. More recently, in 368 patients with prolactinomas: hemorrhage in imaging was depicted in 6.8% and symptomatic PA was observed in only three patients. Macroprolactinoma and female gender were more associated with hemorrhage (19). There are some case reports of PA related to medical treatment in acromegaly: three cases on octreotide and four cases receiving lanreotide (20).

Through 2012, 34 cases of PA occurring after endocrine tests were described, with 93% macroadenomas with extrasellar extension. Most cases were associated with TRH and GnRH stimulation. Mechanisms are not clear; however increased norepinephrine levels by TRH may cause vasospasm; and an increase in tumor cells metabolic activity may be induced by GnRH (21).

In a review of PA following GnRH analog administration, of 15 cases, 14 were male and eighth presented within four hours after the first injection. GnRH antagonist also used for prostate cancer may be a safer alternative considering PA risk in patients harboring pituitary adenomas (22). Other uncommon risk factors as high altitude (23) and hemorrhagic dengue (24) were recently described.

Although major surgery, especially cardiac surgery, is associated with PA, minor laparoscopic surgery has also been described in the PA context (25).

Pregnancy is a risk factor for PA, probably due to an increased pituitary volume secondary to lactotroph hyperplasia, which returns to normal six months post-partum, and also due to increased pituitary blood flow induced by estrogens. Piantanida and cols. reviewed PA during pregnancy: ten prolactinomas, two GH-secreting adenomas, four non-functioning pituitary adenomas and one with no information, most were surgically treated (26).

And finally, socioeconomic factors such as lack of health insurance, had been associated with PA (27).

Mechanisms explaining clinical manifestation of PA are detailed in figure 1.
DIAGNOSIS AND MANAGEMENT

Classically, symptoms evolve from hours to two days after the onset of apoplexy, although a subacute course is described (28). Most patients complain of headache, visual defects and ophtalmoplegia. A high degree of suspicion is needed to make the clinical diagnosis as most patients do not have a previous history of known pituitary adenoma. Common differential diagnoses are subarachnoid hemorrhage and bacterial meningitis; other conditions include: midbrain infarction, cavernous sinus thrombosis, migraine and hemorrhagic infarction in a Rathke’s cyst and aneurysms. It is important to stress that pituitary adenomas co-exist with cerebral aneurysms at a rate of 7.4%.

Eight series in the literature include more than ten patients and are detailed in table 1.

Brain imaging is required to identify a pituitary lesion. Although cranial computed tomography (CT) scan is easier to obtain, it is less sensitive for diagnosis of pituitary lesions. In a retrospective series, a CT scan identified pituitary tumor in 93% and hemorrhage in 21% of cases, whereas MRI identified 100% and 88% of cases, respectively (29).

Table 1. Series of patients with pituitary apoplexy

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>37</td>
<td>12</td>
<td>35</td>
<td>33</td>
<td>40</td>
<td>55</td>
<td>109</td>
<td>87</td>
</tr>
<tr>
<td>Male/female</td>
<td>25/12</td>
<td>7/5</td>
<td>21/14</td>
<td>20/13</td>
<td>27/13</td>
<td>69/40</td>
<td>57/30</td>
<td>57/36</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>56.6</td>
<td>43</td>
<td>49.8</td>
<td>52</td>
<td>51.2</td>
<td>52.4</td>
<td>51</td>
<td>50.9</td>
</tr>
<tr>
<td>Operated</td>
<td>36</td>
<td>5</td>
<td>31</td>
<td>15</td>
<td>34</td>
<td>22</td>
<td>101</td>
<td>61</td>
</tr>
<tr>
<td>Symptoms %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Headache</td>
<td>95</td>
<td>100</td>
<td>97</td>
<td>97</td>
<td>63</td>
<td>87</td>
<td>87</td>
<td>89.7</td>
</tr>
<tr>
<td>Visual defects</td>
<td>64</td>
<td>66</td>
<td>71</td>
<td>82</td>
<td>61</td>
<td>36</td>
<td>39.4</td>
<td>33.3</td>
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<tr>
<td>Ophtalmoplegia</td>
<td>78</td>
<td>83</td>
<td>69</td>
<td>46</td>
<td>40</td>
<td>47.2</td>
<td>35.8</td>
<td>39</td>
</tr>
<tr>
<td>Predisposing factors</td>
<td>2 with diabetes mellitus; one on bromocriptine, one with a major surgery, one with pituitary radiotherapy, one with arterial hypertension, one with chronic renal failure</td>
<td>26% arterial hypertension, 14% contraceptive oral pills, 9% on aspirin therapy</td>
<td>33% arterial hypertension</td>
<td>2 head trauma, 2 anticoagulant treatment, 1 general anesthesia</td>
<td>20% arterial hypertension, three on warfarin</td>
<td>39% arterial hypertension, 12.6% diabetes mellitus, 10.3% on anticoagulant therapy, one pregnant and three in post partum period, two after major surgery</td>
<td></td>
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<td>Adenoma type%</td>
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<td></td>
</tr>
<tr>
<td>NFPA</td>
<td>52</td>
<td>-</td>
<td>61</td>
<td>24</td>
<td>63</td>
<td>82</td>
<td>29.5</td>
<td></td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>17</td>
<td>5.5</td>
<td>-</td>
<td>31</td>
<td>11.5</td>
<td>13.2</td>
<td></td>
<td></td>
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<tr>
<td>Visual field deficits/visual acuity recovered after surgery</td>
<td>95%/88%</td>
<td>62%</td>
<td>80%/76%</td>
<td>57%/NA</td>
<td>81%/NA</td>
<td>80%/NA</td>
<td>93.3%/94.4%</td>
<td></td>
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<tr>
<td>Pituitary hormone deficiency %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>ACTH</td>
<td>82</td>
<td>25</td>
<td>58</td>
<td>78</td>
<td>40</td>
<td>72.7</td>
<td>60</td>
<td></td>
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<tr>
<td>TSH</td>
<td>89</td>
<td>33</td>
<td>43</td>
<td>60</td>
<td>54</td>
<td>52.7</td>
<td>62.7</td>
<td></td>
</tr>
<tr>
<td>LH/FSH</td>
<td>64</td>
<td>41</td>
<td>43</td>
<td>75</td>
<td>79</td>
<td>77</td>
<td>63.6</td>
<td></td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>11</td>
<td>-</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>3</td>
<td>23</td>
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</tr>
</tbody>
</table>

NA: not available; NFPA: nonfunctioning pituitary adenoma.
Hormonal pituitary evaluation is required to diagnose secreting pituitary adenomas including prolactinoma, somatotropinoma and corticotropinoma, as well as hypopituitarism. As ACTH deficiency is life-threatening condition, glucocorticoid replacement is recommended and a supraphysiological dose is indicated to control edema on parasellar structures: dexamethasone 8 to 16 mg per day or hydrocortisone 50 mg intravenously every 6 hours (30). Anterior pituitary deficiencies occur in nearly 80% of patients: ACTH in up to 70%, TSH in 50% and gonadotrophin in 75% of cases (14,28,31). Patients with low levels of prolactin exhibit a lower probability of pituitary function recovery after surgery. Hyponatremia, observed in up to 40% of cases, can be secondary to hypocortisolism or inappropriate antidiuretic hormone secretion. Transient diabetes insipidus is rarely encountered (2).

The first intervention after PA diagnosis is hemodynamic stabilization, correction of electrolyte disturbances and corticosteroid administration. Most PA cases improve with both surgical and expectant management and the most appropriate approach in the acute phase is controversial (28). Although guidelines, as the one from UK, proposed an algorithm for PA management, a randomized trial comparing both strategies is needed for strong evidence (2,29). However, seems intuitive that surgery, usually by the transsphenoidal route, is indicated if consciousness and/or vision are impaired, despite glucocorticoid replacement and electrolyte support. Recovery of visual fields and acuity impairment is more readily obtained with surgical decompression, usually within seven days after the apoplectic event (2). Ophthalmoplegia can resolve spontaneously, with or without surgery. Pituitary function is impaired in most patients before apoplexy and ACTH deficiency is common, which makes glucocorticoid replacement needed in most cases. Pituitary deficiencies, once established, usually do not recover, regardless the treatment (29,32).

The decision to manage conservatively or surgically should be made by experts from a multidisciplinary team (2). Visual impairment and neurological deterioration not improving with clinical management are indications of surgical intervention, with a higher rate of visual improvement if performed within the first seven days of symptom. In a department in UK, PA score was calculated using visual acuity, visual defects, cranial nerve palsies and Glasgow Coma Scale, ranging from 0 to 10, and a score equal and more than 4 appeared to influence the management towards surgery (2). Jho and cols. proposed another score for PA: grade 1 asymptomatic, grade 2 symptoms due to endocrinopathy, grade 3 for headache, grade 4 ocular paresis and grade 5 for visual deficits or a low Glasgow Coma Scale. The authors evaluated 109 cases of PA concluding that their proposed score considering clinical and imaging characteristics is useful in identifying patients who should be submitted to surgery (grade 5). They also observed that prolactinomas, hemorrhagic Rathke cleft cysts and the presence of significant clinical comorbidities favor medical treatment. The major study bias is that most patients (101) were treated surgically (37).

Long-term endocrine and imaging follow-up is required for patients with pituitary apoplexy.

Imaging follow-up

Within the first three days, hyperdensity is depicted in intrasellar and suprasellar regions in an uncontrasted CT scan. It is difficult to differentiate PA from parasellar aneurysm using CT, and MRI is more specific. As hyperdensity in the subacute and chronic phases of hemorrhage fades, CT sensitivity to diagnose PA diminishes and the lesion could be misdiagnosed as an abscess or cystic degeneration. In contrast, CT is superior during the first three hours after apoplexy. Usually in the first week, an isointensity on T1-weighted scans and a hypointensity on T2-weighted images can be observed with MRI. Sphenoid sinus mucosa thickening is suggestive of PA in the early hours. Subacutely (between 7th and 14th days), there is focal or heterogeneous increased signal on T1-weighted scans, and a progressive increase in signal on T2-weighted images. After gadolinium, a peripheral enhancement is represented by a thin peripheral rim. In the chronic phase, there is signal increase in both T1 and T2-weighted images (39,40).

Fluid debris levels in a pituitary mass, hyperintense on T1, corresponding to extracellular meta-hemoglobin and the lower layer iso-hypointense on T1 corresponding to red blood remnants sediment, is suggestive of late subacute hemorrhage. Table 2 summarizes MRI changes in PA by time, for hemorrhagic findings. Necrosis imaging can be detected as hypodensity by CT and hypointense on T1 and hyperintense on T2 on MRI (29).

Using serial sellar MRI, tumor reduction and even disappearance is common, avoiding additional treat-
ment in most cases. In the long-term, imaging shows empty sella, partially empty sella or even normal pituitary. However, tumor recurrence has been described in 6% of patients and this risk is not increased after conservative management (31).

A sellar MRI depicting signs of an acute PA is depicted in figure 2 and a subacute PA in a patient with acromegaly is depicted in figure 3. After apoplexy, serum GH and IGF-1 levels were normal.

MRI scan can be performed three to six months after apoplexy, annually in the following five years and then, biannual (2).

**Table 2. MRI findings in pituitary apoplexy**

<table>
<thead>
<tr>
<th>Pituitary apoplexy phase</th>
<th>Acute (until 7th day)</th>
<th>Subacute (7th to 14th day)</th>
<th>Chronic (more than 15 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-weighted scans</td>
<td>Isointense</td>
<td>Increase in signal</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>T2-weighted scans</td>
<td>Hypointense</td>
<td>Hypo or hyperintense</td>
<td>Hyperintense</td>
</tr>
</tbody>
</table>

**Figure 2.** Sellar MRI depicting signs of a acute pituitary apoplexy in two patients: (a): a hyperintense lesion impinging optical chiasm in noncontrasted T1-weighted scan and (b): a peripheral rim in a contrasted T1-weighted scan.

**Figure 3.** Sellar MRI depicting signs of a subacute pituitary apoplexy: a hyperintense lesion in seeing in T1-(a) and T2-(b) weighted scans.

**Endocrinological follow-up**

Appropriate hormone replacement is required. For functioning pituitary adenomas, hormonal secretion must be also evaluated: hormonal levels could be low, normal or remain high after apoplexy. Long-term follow-up is indicated to identify tumor recurrence. A reevaluation four to eight weeks after apoplexy is recommended (2).

**CONCLUSION**

PA evolves in hours to two days and the condition includes acute headache, meningismus, nausea and vomiting, visual disturbances, blindness, ocular palsies, and decreased level of consciousness. There is a slight male to female preponderance with a mean age of ~ 50 years. All pituitary adenoma types are at risk of apoplexy, although in some series most tumors were nonfunctioning. Cranial magnetic resonance imaging (MRI) is crucial for the diagnosis. Apoplexy pathophysiology remains uncertain and could be associated with trauma, anticoagulation therapy, arterial hypertension, cardiac and other systemic surgeries and dynamic pituitary function tests. Treatment consists of substitution therapy with steroids and sellar decompression by transphenoidal surgery in severe cases.

**REFERENCES**


