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Apoplexy in nonfunctioning pituitary adenomas

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Abstract
Pituitary apoplexy is an uncommon event, occurring due to the infarction and/or haemorrhage usually of a previously unknown pituitary adenoma. It can occur in all adenoma subtypes but is more common in nonfunctioning pituitary adenomas. The physiopathology is not completely clear, and precipitating factors, such as major surgeries, anticoagulant use or pituitary dynamic tests, can be found in up to 40% of patients. The clinical presentation is characterized by a rapid onset with a headache as the main symptom, but visual disturbances can also be present as well as meningism and intracranial hypertension. The diagnosis is based on imaging evaluations, mainly using magnetic resonance imaging, which can show various patterns depending on the timeframe following the occurrence of the apoplectic event. Pituitary hormonal deficits are also common, and the evaluation of hormonal levels is mandatory. Pituitary apoplexy can be managed by surgery or conservative treatment, and a multidisciplinary team is essential for the decision-making process. The outcome is usually positive with both surgical and conservative approaches, but surveillance is needed due to the risk of re-bleeding or tumour recurrence.

Keywords Nonfunctioning pituitary adenomas · Apoplexy · Pituitary apoplexy

Introduction

Pituitary apoplexy (PA) is a clinical syndrome caused by the rapid expansion of the sellar content, caused by infarction and/or haemorrhage [1]. The term PA is reserved for situations in which the signs and symptoms of the syndrome are present. However, in routine imaging or even during the histopathological examination, evidence of asymptomatic haemorrhages can be found in up to 25% of pituitary adenomas, which may be termed as subclinical PA [2].

In most cases, PA occurs in a pre-existing, unrecognized pituitary tumour [2]. It can occur in all pituitary adenoma subtypes, and it is more common in clinically nonfunctioning pituitary adenomas (NFPA), followed by prolactinomas [1]. This review article will address the epidemiology, pathophysiology, clinical aspects, diagnosis and management of PA in patients with NFPA.

Epidemiology

Pituitary apoplexy is an uncommon event, with a prevalence of 6.2 cases per 100,000 inhabitants and an incidence of 0.17 episodes per 100,000 inhabitants per year [3, 4]. In a population study performed in the United Kingdom, classical PA occurred in 7.9% of all pituitary adenomas [3]. In this study, all PA cases occurred in patients with NFPA. In another study, performed in Finland, PA was the presenting symptom in 17 (11%) patients among 154 patients with NFPA [4].

Among series specifically describing patients with NFPA, the frequency of PA is very variable. In a Nomikos and cols [5] series of 721 patients with NFPA, there were 27 (3.7%) cases of PA. Vargas and cols [6] described the characteristics of 485 patients with NFPA, and PA was detected in 37 (8%) of patients. On the other hand, Nielsen et al. [7] described PA in 21% of 192 NFPA patients.

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In Table 1, we summarized case series with more than ten patients with PA [8–23]. In the majority of these series, the most frequent pituitary adenoma subtype was NFPA (Table 1). Whether this adenoma subtype is more prone to bleeding/infarction or if this finding may be due to a selection bias is still debatable. Pituitary apoplexy usually occurs in macroadenomas, and NFPA are usually larger and, probably due to the absence of phenotype, discovered later than functioning adenomas, which could explain the higher frequency of haemorrhages in NFPA [1].

As described previously, PA usually occurs in a previously undiagnosed pituitary adenoma [1]. In a series from the United Kingdom describing 55 patients with PA, only 7.2% had a known pituitary adenoma diagnosis [15]. In fact, the incidence of PA in NFPA and incidentalomas managed conservatively is very low, varying from 0.2 to 0.6 cases per year [24, 25].

PA presents a male preponderance, with a peak incidence between the fifth and sixth decades (Table 1).

Physiopathology/precipitating factors

The physiopathology of PA is not fully understood. Oldfield and Merrill [26] suggest that the combination of the high nutrient demand of pituitary adenomas combined with their limited blood supply would make them more susceptible to vascular events. Most cases of PA involve patients with macroadenomas [7, 15, 27, 28].

Blood supply to pituitary adenomas is reduced compared to the normal pituitary, which can be shown by limited contrast enhancement in comparison to the normal pituitary in magnetic resonance imaging (MRI) [26]. Evidence indicates that pituitary adenomas present limited angiogenesis and reduced vessel density [26]. Therefore, one of the theories for the occurrence of PA is that the pituitary adenoma outgrows its blood supply, leading to infarction of the tumour followed by haemorrhage [29]. Another explanation concerns the compression of the infundibular or superior hypophyseal vessels by the growing adenoma, with consequent reduction of blood flow in a tumour with intrinsically poor vascularity [30].

Apart from the intrinsic predisposition of pituitary adenomas to bleeding, triggering factors can be found in 10–40% of patients [1]. Several factors have been described, and, according to Biousse et al. [31], they can be categorized into four groups: reductions in blood flow; acute increases in blood flow; pituitary gland stimulation; and coagulation disturbances.

There is evidence that pituitary adenomas are particularly sensitive to glucose deprivation [26]. Therefore, conditions that decrease systemic blood pressure may lead to a decrease in blood supply to the pituitary adenoma, with a consequent reduction of glucose delivery to the adenoma and, consequently, precipitate apoplexy. The main factor associated with reductions in blood flow is major surgery, specifically cardiac and orthopaedic surgeries. Angiographic procedures and head trauma may also be associated with PA secondary to reductions in blood flow [1].

Hypertension has been described as the most common PA precipitation factor and leads to bleeding due to acute increases in blood flow [2]. Nevertheless, Moller-Goede et al. [27] did not find hypertension or diabetes to be predisposing factors for PA. Physical activity, leading to an acute increase in blood flow to the pituitary adenoma, may precipitate PA [32].

There are several reports associating pituitary dynamic tests with PA. A recent review by Briet et al. [1] reported 35 patients who presented PA after a dynamic test, with an interval before apoplexy that varied from a few minutes to 88 h. They noted that these reports have been far less common in recent years, probably due to the infrequent use of TRH or GnRH tests. They also recommend against the use of stimulation tests preoperatively due to the risk of PA, except CRH or insulin tolerance tests when the test is crucial for the evaluation of the corticotropic axis. The use of GnRH analogues for the treatment of prostate cancer or endometriosis has also been associated with PA [1, 33].

The main precipitation factor associated with coagulation disturbances is the use of anticoagulants. Patients under antithrombotic therapy have been shown to have a 3 times higher chance of pituitary bleeding [27]. This bleeding may occur very early after the initiation of therapy or several days later [1]. Even though there is a significant increase in the risk of PA in patients under anticoagulant or antithrombotic therapy, there is no clear recommendation indicating or contraindicating their use in patients with known pituitary adenomas [1]. Another factor related to coagulation disorders that has been described as being associated with PA is dengue hemorrhagic fever, which leads to thrombocytopenia and increased risk of bleeding [34, 35].

Dopamine agonists also have been associated with PA, even though this association is still controversial [1, 27, 32, 36]. Moreover, this class of drugs is used mainly in patients with prolactinomas, so most of the patients studied in this context have had this adenoma subtype [1]. No report of PA in series evaluating dopamine agonist use in patients with NFPA has been performed to date [37–39].

Clinical presentation

The clinical presentation of PA is widely variable, ranging from moderate symptoms such as headache and visual disturbances to severe cases with blindness, intracranial hypertension, coma and even death [1]. Classical PA presentation includes the acute onset of a severe headache associated with visual disturbances [32]. Not unusually, PA may be mistaken for subarachnoid

Table 1 Series of cases with pituitary apoplexy

	Bills et al. [8]	MacCagnan et al. [9]	Randeva et al. [10]	Ayuk et al. [11]	Sibal et al. [12]	Lubina et al. [13]	Dubuisson et al. [23]	Pal et al. [14]	Bujawansa et al. [15]	Jho et al. [16]	Vargas et al. [17]	Singh et al. [18]	Giritharan et al. [19]	Grzywotz et al. [20]	Rutkowski et al. [21]	Gondim et al. [22]
Number of cases	37	12	35	33	45	40	24	32	55	109	46	87	31	60	32	39
Male/female	25/12	7/5	21/14	20/13	28/17	27/13	16/8	23/9		69/40	26/20	57/30	19/12	29/31	21/11	27/12
Mean age (year)	56.6	43	49.8	52	49	51.2	56	56.6	52.4	51	50.9	50.9	55	56.3	49	54.9
Surgical cases	36	5	31	15	27	34	21	32	22	101	36	61	20	53	32	39
At diagnosis																
Headache %	95	100	97	97	96	63	92	78	87	87	75	90	100	90	100	89
Visual defects %	64	66	71	82	48	61	50	50	36	39	73	33	58	21	47	79
Ophthalmoplegia %	78	83	69	46	51	40	54	81	47	36	23	39	39	31	50	79
NFPA %	52	–	61	24		63	61	100	82	80	100	29		30	70	82
Visual field recovered after surgery %	95	62	86	57	94	81	92		80			93	100	38	77	74
Pituitary deficiencies after surgery %					80				91				90		25	
ACTH %	82	25	58	78		40	67				77	38				78
TSH %	89	33	43	60		54	58				77	40				75
LH/FSH %	64	41	43	75		79	50				47	35				42

ACTH adrenocorticotropic hormone, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *NFPA* nonfunctioning pituitary adenomas, *yr* years

haemorrhaging, bacterial meningitis or a stroke, which can lead to a delayed or even missed diagnosis [2].

The most frequent symptom is headache, with a frequency varying from 78 to 96% [7, 12, 14, 15, 27, 28]. In the largest series in the literature, including 99 patients with PA, headache was detected in 87% of cases [28]. In another series including only patients with NFPA, it was present in 78% of cases [14]. The cephalalgia onset is usually sudden and severe [30].

Visual disturbances may be found in 50–80% of patients [12, 14, 15]. These occur due to the fast growth of the sellar content, which compresses the optic chiasm and leads to visual field impairments that vary from bilateral hemianopsia to amaurosis [30]. The tumour can also expand towards the cavernous sinus, compressing the III, IV and/or IV cranial nerves, leading to various degrees of ocular palsy [7, 12, 14, 28].

Nausea and vomiting, due to meningeal irritation or intracranial hypertension, are found in 25–78% of cases [12, 15]. Other symptoms such as photophobia, fever and meningism may also be found and can be misleading [12, 28, 30]. Altered consciousness can be present in up to 22% of patients [7].

Diagnosis

When facing a patient with a clinical suspicion of PA based on the signs and symptoms described above, sellar imaging is essential for diagnosis. Although less sensitive than MRI, cranial computed tomography (CT) is easier to perform in an emergency setting and is able to detect a sellar lesion in 93% and haemorrhage in 21% of cases, whereas MRI identifies 100 and 88% of cases, respectively [30].

Pituitary apoplexy appears as a hyperdense lesion in cranial CT, as do aneurysms, meningiomas, Rathke cleft cysts, germinomas and lymphomas, making MRI essential to differentiate between these conditions. The CT is most valuable in the acute phase (up to 48 h). Some days after PA, with blood degradation, the density observed via CT decreases, which increases the difficulty in differentiating subacute haemorrhages from cystic lesions [30].

Sellar MRI can usually detect a pituitary adenoma and its haemorrhagic degeneration. Within the first 7 days, known as the acute phase, an isointense or slightly hypointense signal in T1-weighted images and a hypointense signal in T2-weighted images can be observed [40]. It is important to note that MRI cannot detect fresh blood, so it is not ideal for use within the first days after PA [30]. Pituitary apoplexy usually presents restricted diffusion, due to the ischaemic injury or the blood products that may have accumulated in the region, making a diffusion-weighted sequence helpful in differential diagnosis [40]. In the subacute phase, from 7 to 21 days, hyperintensity due to methemoglobin is depicted in T1 and T2 images. Gadolinium enhancement shows a thin peripheral rim. After 21 days, that is, in the chronic phase, hypointensity in T1 and T2 images, secondary to the presence of hemosiderin and ferritin, starts to be observed [41]. Some authors have suggested that sinus mucosal thickening can be found in the acute phase of PA and is related to severity [42]. Fluid debris levels, with an upper fluid hyperintensity and a lower layer hypointensity in T1 images, have been considered a specific sign of PA during the subacute phase [41]. Although rare, some authors have described imaging findings of PA with pituitary infarction without haemorrhaging [43]. Nevertheless, the MRI characteristics found in patients with PA can be very variable [23].

Hormonal pituitary evaluations are mandatory to diagnose hypopituitarism, and, as ACTH deficiency is a life-threatening condition, glucocorticoid replacement is recommended. Usually, these drugs are given in supraphysiological doses in order to control edema, for example, dexamethasone 8–16 mg per day or hydrocortisone 50 mg intravenously every 6 h [11]. According to a data compilation of the literature, 80% of patients present anterior pituitary deficiencies; 75% of these were gonadotrophic deficiencies, up to 70%, ACTH, and 50%, TSH [30, 44]. ACTH deficiency and/or inappropriate antidiuretic hormone secretion can cause hyponatremia, found in up to 40% of cases, while diabetes insipidus, usually transitory, is rarely found [2].

Management: conservative vs. surgical

As far as PA management is concerned, haemodynamic stabilization must be the first intervention, followed by electrolyte disturbance correction and corticosteroid administration. The majority of PA cases improve with either surgical or conservative management; nevertheless, the best approach during the acute phase [45] and the timing of pituitary surgery are controversial, as no randomized trials comparing both strategies with strong evidence have been performed [46].

Notwithstanding, surgery, usually by the transsphenoidal route, is indicated if consciousness is severely impaired despite glucocorticoid replacement and hydroelectrolytic support. Most studies indicate that surgical treatment, usually within 7 days after the apoplectic event, leads to higher rates of visual impairment recovery [2, 46]. Ocular motility disfunction can resolve spontaneously, with or without surgery, although a recent systematic review reported better outcomes with surgical treatment [47]. Pituitary function is impaired in most patients before apoplexy, and ACTH deficiency is common, which makes glucocorticoid replacement needed in most cases. Pituitary deficiencies are usually not expected to recover [8, 30].

A multidisciplinary team, with experts in pituitary neurosurgery and neuroendocrinology, is recommended to follow

the patient and to decide on either conservative or surgical management [2]. As previously stated, surgical intervention is indicated if visual impairments and neurological deterioration do not improve with clinical management. The UK Guidelines for PA recommend a scoring system, 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 [2]. 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 scores. Patients with grade 5 should be submitted to surgery [16].

Outcomes

Imaging follow-up is recommended. In most cases, additional treatment is not necessary, as tumours usually diminish and even disappear without surgical intervention. Concerning

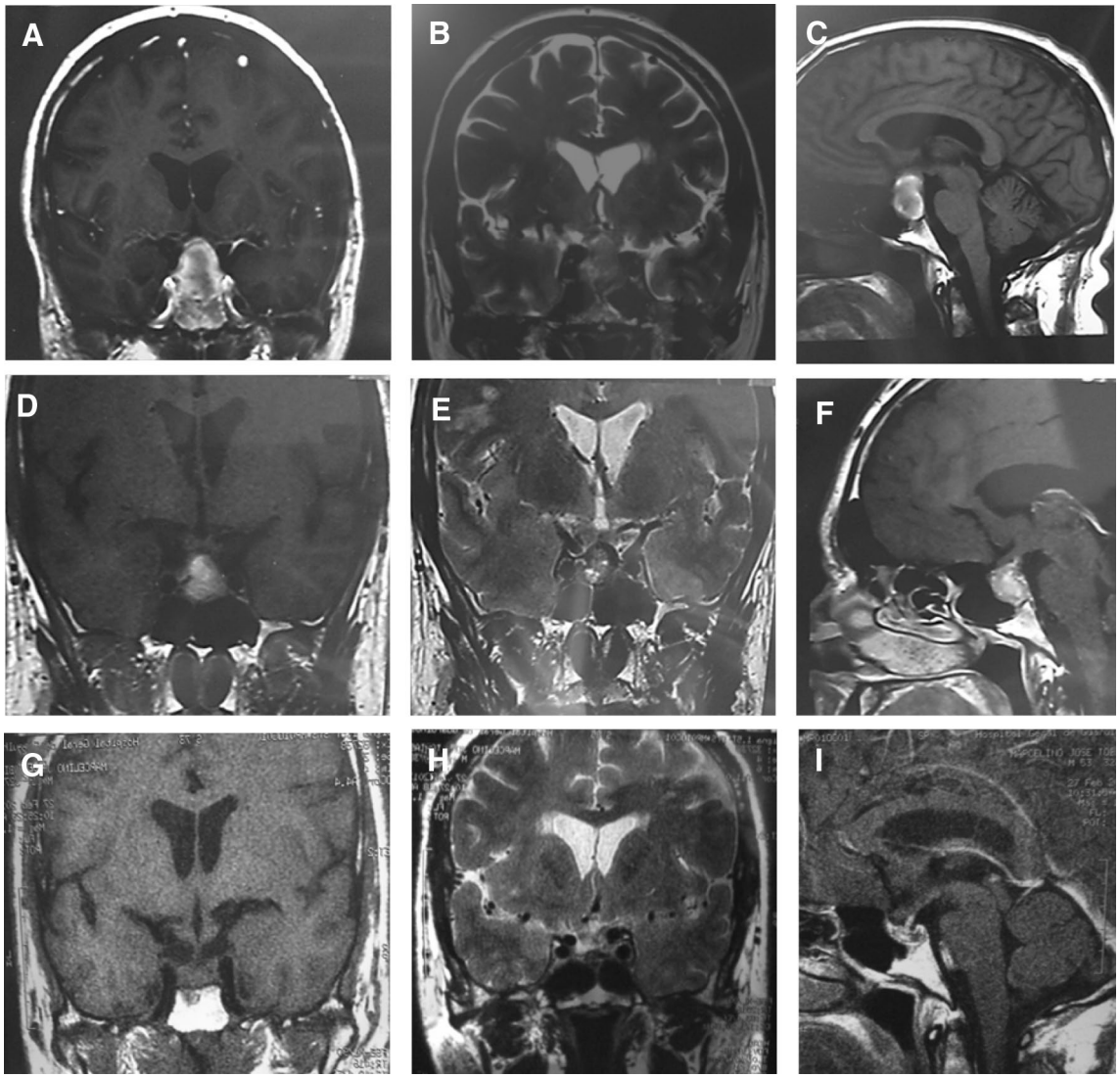

Fig. 1 MRI performed 10 days after PA clinical presentation showing a pituitary mass impinging on the optical chiasma, with a peripheral enhancement after gadolinium in a coronal view (**a**), an iso- to hyperintense signal in a T2-weighted image (**b**) and areas with hyperintensity in a T1-weighted image without gadolinium enhancement (**c**). Sellar MRI taken 24 days after the first imaging session showing a reduction in tumour volume, with decreased hyperintensity in a T1-weighted image without contrast (**d**), hypointensity in a T2-weighted image (**e**) and the heterogeneous uptake of gadolinium in a T1-weighted sagittal image (**f**). Sellar MRI taken 8 months after the first imaging session shows a lesion within sellar boundaries, with isointensity in a T1-weighted image without gadolinium enhancement (**g**), areas of hypo- and isointensity in a T2-weighted image in a coronal view (**h**), and heterogenous contrast enhancement in a sagittal view (**i**)

surgical cases, complete tumour removal is reported in 48–66% of patients and subtotal resection in 23–52% of patients [44]. However, re-bleeding and tumour recurrences (6–11%) can occur regardless of whether the approach is conservative or surgical [14, 30, 41]. Sellar MRI should be repeated in 3–6 months, annually for 5 years, and biannually after that [41]. The presence of an "empty sella" is often observed.

Proper hormone replacement is required during endocrinological follow-up. Additional hypopituitarism, including ACTH deficiency, persists in more than 50% of cases [45]. Although pituitary function recovery is usually not expected, hormonal re-evaluation must be performed 4–8 weeks after PA [2]. Currently, mortality in the acute setting is less than 2% [45].

Figure 1a–i shows diagnostic and follow-up images of PA in a 60-year-old male with systemic arterial hypertension, no previous diagnosis of pituitary adenoma, complaints of an intense headache and nausea, and normal visual field. Images a–c show MRI taken 10 days after the clinical presentation. Management was conservative, with medical treatment and hormonal replacement for panhypopituitarism. Sellar MRI taken 24 days after the first imaging session (d–f) shows tumour volume reduction. During follow-up, there was no pituitary functional recovery, and imaging showed a continued and noteworthy reduction in tumour volume. Eight months after the first imaging session, the lesion was within sellar boundaries (g–i).

Conclusions

Pituitary apoplexy is an uncommon vascular event that occurs most frequently in NFPA. Visual disturbances are common, including amaurosis, and patients may develop altered consciousness and even fall into a coma. Although it has been considered a surgical emergency in the past, recent data suggest that a conservative approach may be more favourable in some situations. Since there are no randomized clinical trials comparing surgical and "wait-and-see" approaches, including corticosteroid treatments, the decision should be individualized. Both surgical and conservative approaches present good outcomes in the majority of patients. The evaluation of pituitary function is mandatory both before and after treatment. Therefore, a multidisciplinary team, including endocrinologists, neurologists, ophthalmologists and neurosurgeons, is mandatory for the management of PA.

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