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Pituitary apoplexy

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ABSTRACT

Pituitary apoplexy (PA) is a clinical syndrome caused by acute haemorrhage and/or infarction of the pituitary gland, generally within a frequently undiagnosed pituitary adenoma. The sudden increase in pituitary gland volume is responsible for typical symptoms: severe headache, nausea, vomiting, visual impairment, cranial nerve palsies, deteriorating level of consciousness, and hypopituitarism. Radiological evidence, especially magnetic resonance imaging (MRI) which is the most sensitive diagnostic modality, establishes the diagnosis. Multiple risk factors have been reported, although the majority of cases have no identifiable precipitants. The management strategy depends on the clinical manifestation, as well as the presence of co-morbidities, and remains controversial. Post apoplexy, there needs to be careful monitoring for recurrence of tumour growth and endocrinological function of the pituitary. This disease is rare but potentially life-threatening without rapid treatment. Because there are no randomised studies, it is suggested that further trials are needed to optimise proper management.

Key words: pituitary apoplexy, pituitary adenoma, hypopituitarism, management, outcome

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Introduction

Pituitary apoplexy (PA) is defined as an acute clinical syndrome caused by sudden haemorrhage and/or infarction of the pituitary gland, generally within a pituitary adenoma [1]. The first description of a clinical presentation is attributed to Bailey in 1898 [2]. The term 'pituitary apoplexy' was coined by Brogham et al. in 1950 [3]. The term 'subclinical pituitary apoplexy' was later applied for an asymptomatic pituitary haemorrhage identified during radiological investigation or during a pathological examination. However, PA is a clinical diagnosis, and the term should be reserved only for the classical presentation [4].

The outcome of apoplexy is difficult to predict: the patient's clinical condition can deteriorate dramatically or improve spontaneously, with or without sequelae. Apoplexy sometimes destroys the pituitary adenoma, but regrowth from a tumour remnant may occur in other cases [1]. Although rare, the condition must be recognised and properly treated, as it may be life-threatening [3].

There are no randomised controlled trials on the optimal management of this condition. Management has mostly depended on conclusions drawn from several case series and expert opinion. There are several controversies in dealing with this rare neuroendocrine emergency, including whether a conservative procedure or surgery should be the first-line strategy, and the optimal timing of any such surgery [5].

Epidemiology

Pituitary apoplexy is rare, with an estimated prevalence of 6.2 cases per 100,000 inhabitants [6] and an incidence of 0.17 episodes per 100,000 person-years [7]. PA can occur at all ages, but is most frequent in the fifth or sixth decades, with a preponderance in males [1, 3], who are affected in 60–67% of cases [4]. Its exact prevalence is difficult to estimate because many cases remain undiagnosed, but it seems to occur in 0.6-10.5% of pituitary adenomas [8].

Pituitary apoplexy may represent the first presentation of a pre-existing, unrecognised adenoma in 60–80% of cases [3, 9]. Macroadenomas are most susceptible to apoplexy, but apoplexy in microadenomas has been reported [10]. The most frequent type of pre-existing adenoma appears to be the non-functioning pituitary adenoma (NFPA), accounting for 45–82% of PA cases [4]. Prolactinomas and growth hormone (GH) secreting adenomas are the next most common, reported in 5.5–31% and 7.2–25% of cases, respectively [4].

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Although PA usually occurs in adenomas, it has also been described in non-adenomatous lesions including sellar tuberculoma, metastasis to the pituitary, abscess, craniopharyngioma, sellar haemagioblastoma, Rathke's cleft cyst and lymphocytic hypophysistis [3, 4].

Pituitary ischaemia can also be seen in other specific cases, for example in Sheehan's syndrome, where a large postpartum hypovolemia due to haemorrhage can lead to ischaemic pituitary necrosis within a normal pituitary gland, enlarged during pregnancy, with resultant hypopituitarism [11].

Pathophysiology

Several hypotheses exist on the pathogenesis of pituitary apoplexy. Both infarction and haemorrhage are observed in apoplexy, not always concurrently. Ischaemic necrosis and haemorrhagic conversion in any setting reflect an imbalance of blood flow and perfusion to the target organ [2]. Previously proposed mechanisms for pituitary apoplexy include reduced blood supply to the tumour produced by events such as hypotension, rapid growth outpacing the development of adequate blood supply to the tumour, direct pressure by the tumour on the portal vessels or the hypophyseal arteries causing acute ischaemia, increased intratumoural pressure which itself acutely impairs the blood flow to the tumour, increased metabolic activity beyond adequate arterial supply after stimulation with hypothalamic releasing factors, and haemorrhage resulting from fragility of the tumour vessels [12]. There is evidence supporting these proposed mechanisms as contributory factors in most cases, but something else seems to be needed to explain all cases.

The observation that pituitary adenomas appear more prone to bleeding than other intracranial neoplasms [13] has led to further speculation on underlying intratumoural vascular fragility and vasculopathy [14]. Furthermore, a significant correlation between the intratumoural expression of vascular endothelial growth factor (VEGF) [15, 16] and tumour necrosis factor (TNFα) [17] and the presence of tumour haemorrhage has been found, suggesting a possible causal relationship.

To summarise, pituitary apoplexy is the product of intrinsic features of tumours leaving the tumour in a state of tenuous balance between high metabolic demand and marginal blood supply in relation to the demand, which exist both in large and small tumours [12]. This causes vulnerability of the tumour to any factor disturbing this balance.

Various precipitating factors for apoplexy are identified in only 20–40% of cases [1, 18]. For many of them a causal relationship has not been definitively proven and is evaluated differently in different studies. They can mostly be classified into one of four categories: 1) acute increase in hypophyseal blood flow; 2) reduced blood flow to the pituitary tumour; 3) hormonal stimulation of the pituitary gland and tumour; and 4) coagulation disturbances [2, 3]. The most common possible risk factors are: – systemic hypertension [2–4, 18], – major surgery, especially cardiac surgery [2–4, 18], – invasive procedures (spinal anaesthesia, lumbar puncture, angiography) [3, 4], – dynamic tests of pituitary function with releasing factors [2–4, 18], – initiation or withdrawal of dopamine agonist therapy [2, 3, 18], – oestrogen or gonadoliberin analogue therapy [2, 3, 18, 19], – coagulopathies [2, 3, 18] , – anticoagulant or antithrombotic drugs [3, 4, 18], – radiotherapy [2, 4, 18], – pregnancy [2, 3, 18, 20], – head trauma [2–4, 18, 21], – large size of tumour, especially with cavernous sinus invasion [2, 19, 22]. However, none of these factors is likely to be solely responsible for the occurrence of apoplexy [23].

Clinical presentation

Classically, symptoms evolve for up to two days after the onset of apoplexy, although a subacute course is described [2, 3] and this is largely determined by the extent of haemorrhage, oedema and necrosis [18]. Some authors have suggested that cases with ischaemic necrosis have a milder clinical course and a better outcome then those with haemorrhage or haemorrhagic necrosis [24]. The symptoms are believed to result from the rapid enlargement of tumour size and pressure on adjacent structures, stretching of the hypophyseal capsule, extravasation of blood or necrotic material into the subarachnoid space, increased intracranial pressure, and exclusion of the secretory function of the pituitary gland [2, 9, 18].

The earliest and most frequent symptom (90–100%) of pituitary apoplexy is a sudden and severe headache, which is usually retro-orbital, but can be bifrontal, suboccipital, or diffuse in location [9, 18, 23, 25] and may be accompanied by nausea and vomiting (40–80%) [2, 4, 9, 23, 25]. Ocular palsies or paresis are present in 40–70% of cases [4, 18], due to functional impairment of cranial nerves III, IV and VI. The third cranial nerve is most frequently affected due to its position, closer to the sella and possibly to its compression onto the interclinoid ligament [4], but multiple cranial nerve palsies (sometimes with nerve V too) and even bilateral lesions have been reported [26, 27]. Visual field deficits, specifically bitemporal haemianopsia, are seen in 47–75% [9, 18], decreased visual acuity is reported in 41–56% of cases [4, 9], but unilateral or bilateral blindness is rare [1]. Orbital bruit, proptosis, lid oedema, isolated Horner's syndrome and light near dissociation are rare orbital manifestations of pituitary apoplexy [28].

Impaired consciousness is fairly frequent (13–42%) [4]. This can range from mild lethargy to stupor and coma [9] and is a sign of severity [4]. Potential pathophysiological mechanisms include subarachnoid haemorrhage, increased intracranial pressure, obstructive hydrocephalus, adrenal insufficiency causing arterial hypotension and hypoglycaemia, and hypothalamic compression [9].

Acute endocrine dysfunction is also present, complicating the clinical picture [1]. Hypopituitarism (usually permanent)

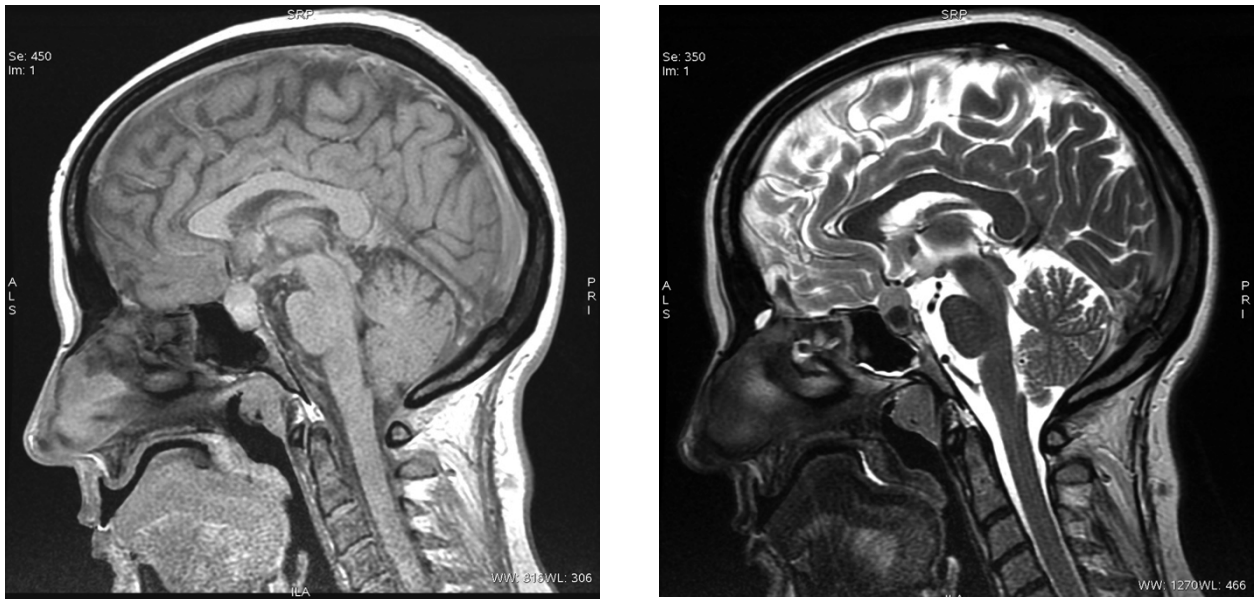

Figure 1. Magnetic resonance imaging of pituitary apoplexy in acute phase; Saggital view: T1-weighted image (left) and T2-weighted image (right); Courtesy of Radiology Department, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, A. Jurasz University Hospital No 1 in Bydgoszcz (head: Prof. Z. Serafin)

is a major manifestation of PA in 71–100% of cases [2, 4]. In retrospect, it is often realised that signs and symptoms of endocrine abnormalities were present before the apoplectic episode [1].

The clinical course may be complicated by: subarachnoid haemorrhage, intra-ventricular haemorrhage and intracerebral haemorrhage. Extravasation of blood from a bleeding pituitary tumour may enter the spaces mentioned, resulting in the clinical presentation [29]. Pituitary apoplexy complicated by cerebral infarction is rare, too. Two possible mechanisms of cerebral infarction have been suggested: vasospasm (which may be caused by subarachnoid haemorrhage, the release of vasoactive substances from a pituitary adenoma or hypothalamic damage); and mechanical compression (caused by the extension of the tumour mass) [30, 31]. As to the affected vessels, the cavernous portion or supraclinoid portion of the internal carotid artery, anterior cerebral artery and middle cerebral artery are most likely to be involved [30].

Diagnosis

Diagnosis is often difficult especially if there is no previous history of pituitary pathology (which occurs in 60–80% of cases) [4]. However, a high degree of suspicion should exist in any patient with a severe, sudden headache [4] with or without neuro-ophthalmic signs [18].

The differential diagnosis includes a number of conditions such as subarachnoid haemorrhage [2–4], bacterial meningitis [32], stroke [2, 4, 28], ophthalmoplegic migraine [2, 4], hypertensive encephalopathy [4], cavernous sinus thrombosis [2–4, 28], carotico-cavernous fistula [28], optic neuritis [2, 28], and reversible cerebral vasoconstrictive syndrome (RCVS) [33]. It is important to stress that pituitary adenoma co-exist with cerebral aneurysms at a rate of 7.4% [3].

Brain imaging is required to identify a pituitary lesion [3]. Computed tomography (CT) and magnetic resonance imaging (MRI) are both useful diagnostic tools [29]. CT is usually the initial examination because of its widespread availability [3]. However, the absence of haemorrhage on CT does not preclude pituitary apoplexy [2]. In a retrospective series, a sellar mass was identified in 80–93% of the patients, but haemorrhage only in 21–28% of cases [1, 18]. CT is most useful in the acute stage (< 72 hours) when haemorrhage appears as a focal, multifocal or diffuse hyperdensity in the pituitary mass [28]. After this time, blood intensity decreases and may be difficult to detect [1].

The investigation of choice is MRI [18] because of its higher sensitivity. It has been found to confirm the diagnosis of pituitary tumour in 100%, and of pituitary apoplexy in 88%, of cases [1]. MRI also elucidates anatomic detail of the underlying tumour, sellar expansion, suprasellar and parasellar extension, optic chiasm compression, and cavernous sinus involvement [2], but it also has weaknesses. It is the best means of identifying blood components in a subacute setting from four days up to one month. It cannot replace CT in an acute setting, as it is unable to detect fresh blood [1, 4]. Blood component density changes with time on MRI; necrosis in the tumour is hypointense in T1 but hyperintense in T2 (Tab. 1) [1]. Subacute or chronic haemorrhage is frequently identified even on non-enhanced MRI studies. Non-haemorrhagic

Table 1. Blood component density changes with time on MRI [1]

		T1	T2
Acute phase:	oxyhaemoglobin (< 24 h)	isointense	isointense
	deoxyhaemoglobin (24–48 h)	isointense	hypointense
Subacute phase:	intracellular methaemoglobin (3–5 days)	hyperintense	hypointense
	extracellular methaemoglobin (> 5 days)	hyperintense	hyperintense
Chronic phase:	haemosiderin (> 3 weeks)	hypointense	hypointense

MRI — magnetic resonance imaging; T1 — T1-weighted sequences; T2 — T2-weighted sequences

Table 2. Pituitary Apoplexy Score (PAS) [5, 18]

PAS score	
Consciousness level in GCS [points]:	
15	0 points
8–14	2 points
< 8	4 points
Visual acuity:	
normal or no change from premorbid acuity	0 points
reduced unilateral	1 point
reduced bilateral	2 points
Visual field deficits:	
normal	0 points
unilateral deficit	1 point
bilateral deficit	2 points
Ocular paresis:	
absent	0 points
present unilateral	1 point
present bilateral	2 points
	Minimum = 0 points
	Maximum = 10 points

GCS — Glasgow Coma Scale

changes (infarction alone) present as low intensity areas with no contrast enhancement [4].

Diagnosis is based on neuroimaging, but equally important for the further procedure is evaluation of the secretory function of the pituitary. A typical laboratory panel measures prolactin (PRL), cortisol, adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), free thyroxine and triiodothyronine (fT4 and fT3), growth hormone (GH), follicle stimulating hormone (FSH), luteinising hormone (LH), insulin-like growth factor 1 (IGF 1), oestradiol in females, and testosterone in males [2]. Clinically, the most crucial deficit is that of ACTH, which has been reported in up to 70% of patients [3, 18]. Thyrothrophin and gonadothrophin deficiencies are observed in 50% and 75% of patients, respectively [3, 18].

Every patient should also have a marked concentration of electrolytes, renal and liver function, full blood count and clotting screen [18]. Hyponatraemia, observed in up to 40% of cases, can be secondary to hypocortisolism or (less often) inappropriate antidiuretic hormone secretion [3].

Patients should also undergo a full ophthalmological examination with visual field, visual acuity and ocular paresis assessment (within 24 hours of the suspected diagnosis if the patient's condition allows it) [2, 18].

Lumbar puncture is of little help in differential diagnosis because PA may be accompanied by a high red cell count, xantochromia or pleocytosis, and an increased cerebrospinal fluid (CSF) protein level, particularly when meningeal irritation is present. However, CSF culture will rule out bacterial meningitis, and lumbar puncture is thus mandatory if this diagnostic possibility is raised [1].

Management

Owing to the highly variable course of PA, and to the limited experience of individual doctors, the optimal management of acute episodes remains controversial [1]. In all events, PA needs to be managed by a multidisciplinary team including a neurologist, neurosurgeon, endocrinologist, ophthalmologist and radiologist [1, 28].

The first intervention after diagnosis is haemodynamic stabilisation, correction of electrolyte disturbances, and corticosteroid administration [2, 3]. Acute secondary adrenal insufficiency is the major source of the mortality (0.7–12.5%) [28] associated with the condition [18]. Hypocortisolaemia renders the vasculature less responsive to the pressor effects of catecholamines, with resultant haemodynamic instability. The mechanisms of fluid and electrolyte disturbances are complex. Hypocortisolaemia augments vasopressin release from the posterior pituitary and has an inhibitory effect on water excretion [18].

Corticosteroids not only decrease the risk of hypoadrenalism, but also have significant anti-inflammatory and anti-oedematous effects [4]. Indications for empirical steroid therapy are haemodynamic instability, altered consciousness level, reduced visual acuity and severe visual field deficits [18]. Patients who do not fulfil the criteria for urgent empirical steroid therapy should be considered for treatment with steroids if their 09:00 serum cortisol is less than 550 nmol/l [4, 18]. The administration of hydrocortisone is preferred: 100–200 mg as an intravenous bolus is appropriate followed either by 50–100 mg intravenously or intramuscularly every

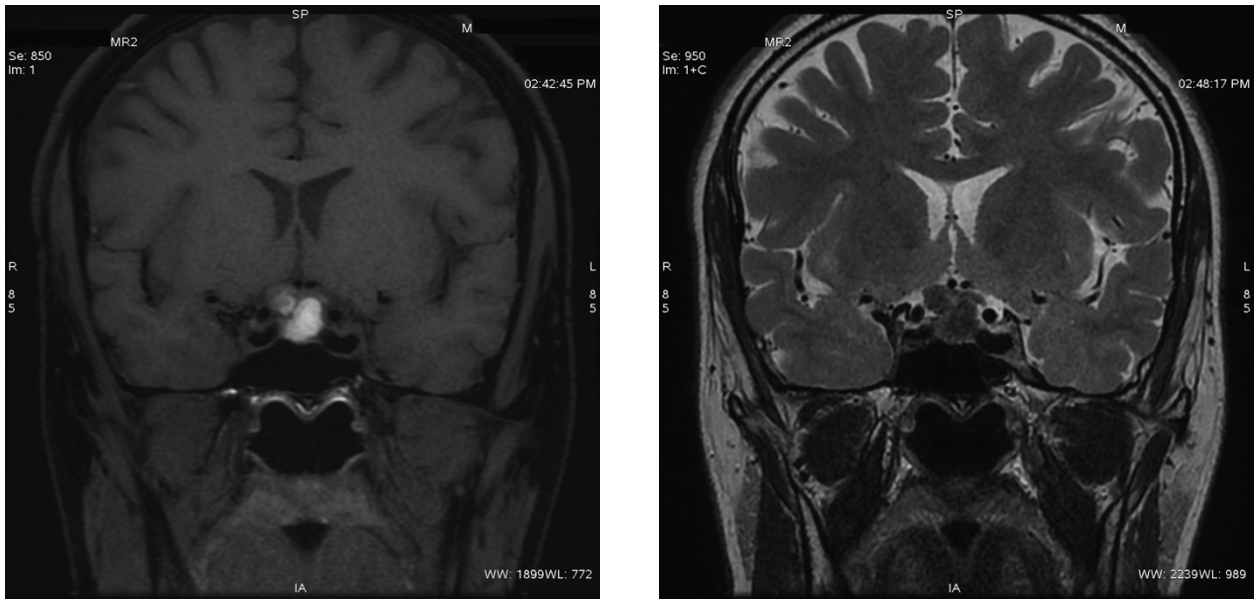

Figure 2. Magnetic resonance imaging of pituitary apoplexy in subacute phase (3–5 days); Coronal view; T1-weighted image (left) and T2-weighted image (right); Courtesy of Radiology Department, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, A. Jurasz University Hospital No 1 in Bydgoszcz (head: Prof. Z. Serafin)

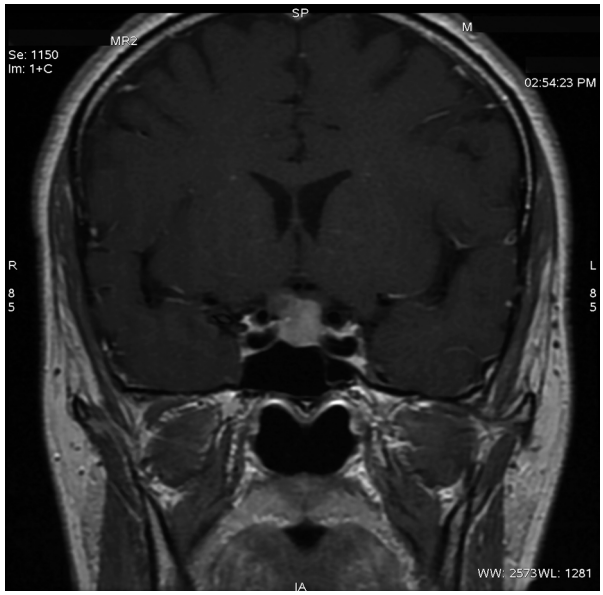

Figure 3. Magnetic resonance imaging of pituitary apoplexy — contrast enhancement; Coronal view; Courtesy of Radiology Department, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, A. Jurasz University Hospital No.1 in Bydgoszcz (head: Prof. Z. Serafin)

six hours, or by 2–4 mg per hour by continuous intravenous infusion [1, 18]. The role of dexamethasone in high doses (up to 16 mg/day) instead of stress dose hydrocortisone has not been formally evaluated in acute PA, but its use has been reported in a number of cases, especially where an anti-oedematous effect is sought [4, 5].

Following stabilisation, the most crucial decision is whether the clinical situation requires surgical intervention or medical treatment [9].

Traditionally, most patients with apoplexy were treated surgically after this initial stabilisation. However, recent studies have repeatedly reported good outcomes in selected patients treated conservatively with medical therapy only [23]. Because of the rarity of this disease and the small groups to compare, recommendations require an individual evaluation, but also further multicentre trials [4].

The Pituitary Apoplexy Guidelines Development Group formed in the United Kingdom established the following guidelines: 1. surgery is indicated if there are disturbances of consciousness, visual field defects and impaired visual acuity; 2. conservative therapy may be used in patients without these disorders (or when symptoms decrease), and if there is only ophthalmoparesis or ophthalmoplegia; and 3. during conservative treatment constant supervision of the patient is needed and in the event of deterioration the indications for surgery should be reconsidered [18].

Ocular paresis because of the involvement of III, IV or VI cranial nerves in the absence of visual field defects or reduced visual acuity is not in itself an indication for immediate surgery [18] because the three ocular motor cranial nerves are peripheral nerves and can undergo regeneration, whereas the optic nerve, as part of the white matter, cannot recover after axonal disruption [21].

To help in the objective assessment of clinical severity, to quantify neuro-ophthalmological defects and to monitor conservatively managed patients, a scoring system named the Pituitary Apoplexy Score (PAS) has been designed in the UK

(Tab. 2) [5, 18]. The result can be from 0 to 10 points. Clinical severity based on PAS ≥ 4 (applied retrospectively) appears to influence the management of patients towards emergency surgical intervention [4, 5]. This scoring system could also help audit the outcome in surgically and conservatively managed patients [18].

Some authors from the USA have proposed another grading system which defines pituitary apoplexy radiographically as a sellar mass lesion with suspected haemorrhage or necrosis and categorises patients into five grades of increasing clinical severity based on the most common presenting symptoms. Grade 1 patients are asymptomatic, grade 2 patients have symptoms attributable only to endocrinopathy, grade 3 patients have a headache, grade 4 patients have ocular paresis, and grade 5 patients have visual deficits or a low GCS score such that vision cannot be assessed [34]. Patients with a higher grade (4–5) require timely surgical management, and patients with a lower grade (1–3) may be treated with elective surgery or even conservative management [34].

If surgery is decided upon, it should be performed preferably within seven days of the onset of symptoms [2, 18]. Transsphenoidal surgery is preferred, due to its low morbidity and mortality rates [4]. Most neurosurgeons now prefer an endoscope to an operative microscope [1]. If severe comorbidities contraindicate early surgery, a conservative approach is initially taken and a delayed intervention (if possible) may offer some prospect of improvement [4].

Outcomes and aftermaths

In most series, a comparison between the two approaches is not possible due to the selection bias as patients most severely affected were directed towards surgery. Bearing this in mind, it seems that the visual and endocrine outcomes are similar in operated and conservatively managed cases [1, 4, 5, 23]. Oculomotor palsies improve in 63–100% of patients with surgery [4] and in 64–100% of patients managed conservatively [1]. Visual field deficits improve after surgery in 57–95% of cases [4] and in 50–100% of cases conservatively managed [1, 4]. Visual acuity normalised in 86–93% of patients after surgery [4] and in 80–100% of conservatively managed cases [4].

A PA event can lead to irreversible loss of pituitary cells, thus leaving the majority of patients with (at least partial) pituitary insufficiency [21]. Pituitary function recovers partially or completely in up to 50% of patients [1, 18]. Pituitary insufficiency usually develops following haemorrhagic apoplexy, whereas pituitary function is more commonly preserved after infarctive apoplexy [35]. Nearly 80% of patients will need some form of hormone replacement after apoplexy [18]. Growth hormone deficiency is the most commonly observed deficit. It is present in almost all patients but is rarely replaced [18]. Long-term hormone replacement therapy following pituitary apoplexy consists of corticosteroids in 40–80%, thyroid hormone in 45–60%, desmopressin in 2–11%, and gonadothrophins in 55–80% of patients [2, 4, 18].

One argument in favour of the surgical approach is that surgery can remove the pituitary tumour. However, many patients have no visible tumour remnant after an apoplectic episode managed conservatively [1]. There are a few studies comparing the incidence of tumour recurrence after apoplexy, and these show that tumour regrowth is possible both in the group treated surgically and in the group treated conservatively, varying according to different studies from 4% to 22% of cases [1, 36–40]. Thus, the respective merits of the two approaches in terms of tumour control are currently difficult to judge [1].

Long-term monitoring

All patients who have been treated for apoplexy (both surgically and conservatively) need long-term endocrine and imaging follow-up [3, 18]. Pituitary imaging (MRI) is recommended at 3–6 months after apoplexy, then annually for the first five years and biennially thereafter [4, 18]. All patients should have an endocrine review at 4–8 weeks following the event and then once a year [3, 18]. Assessment of pituitary function should include fT4, TSH, LH, FSH, testosterone in men, oestradiol in women, PRL, IGF-1 and dynamic tests of cortisol and growth hormone secretion if clinically appropriate [18]. Formal assessment of visual acuity, eye movements and visual field is also needed at 4–8 weeks following the event [18].

Conclusions

Pituitary apoplexy is a rare, potentially life-threatening clinical syndrome, caused by haemorrhage or ischaemic infarction of the pituitary gland, generally within a pituitary adenoma. PA can mimic a wide spectrum of clinical conditions, but the constellation of signs must alert the clinician to the possibility of this disease. CT or MRI imaging confirms the diagnosis. Haemodynamic stabilisation, reversal of electrolyte imbalance, and correction of corticotrophic deficiency must therefore always be initiated immediately. Further treatment includes both conservative management and consideration for neurosurgical intervention. The procedure should be established multidisciplinarily and involve the cooperation of a neurologist, neurosurgeon, endocrinologist and ophthalmologist. Appropriate intervention is associated with good neuro-ophthalmic recovery. The endocrinological prognosis is less favourable, with many patients requiring replacement therapy. In view of the risk of tumour regrowth, long-term follow-up is necessary. It would be advisable to conduct multi-centre, randomised clinical trials to determine the optimal management of pituitary apoplexy.

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