MANAGEMENT OF ENDOCRINE DISEASE

Pituitary tumour apoplexy

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Abstract

Pituitary tumour apoplexy (PA) is a rare clinical syndrome that occurs as a result of acute haemorrhage and/or infarction within a frequently undiagnosed pituitary tumour. The sudden enlargement of the pituitary mass undergoing PA is responsible for a wide range of acute symptoms/signs (severe headache, visual loss, diplopia, hypopituitarism, impaired consciousness) which, together with the radiological evidence of a pituitary lesion, establish the diagnosis. The optimal care of PA requires involvement of a multidisciplinary team including endocrinologist, neurosurgeon, neuroophthalmologist and the management strategy that depends on the clinical manifestations, as well as the presence of co-morbidities. Prompt surgical decompression is initially indicated in cases with severe or progressive impairment of the visual acuity or the visual fields or with altered mental state and leads to visual and neurological recovery in most of the patients. The patients with mild, stable clinical picture (including those with isolated ocular palsies) can be managed conservatively (support of fluid and electrolyte balance and stress doses of steroids in most cases) with favourable visual and neurological outcome. Frequent reassessment is mandatory because the clinical course can be unpredictable; if progression of symptoms occurs, later elective surgery is indicated and is beneficial, especially in terms of visual outcome. The endocrinological outcome is less favourable, irrespective of the treatment option, with many patients remaining on long-term replacement therapy. Despite the above guidelines, clear proof of optimal outcomes in the form of randomised controlled trials is lacking. Regrowth of the pituitary tumour years after a PA episode is possible and patients require long-term surveillance.

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Definition

Pituitary tumour apoplexy (PA) is a rare clinical syndrome resulting from the rapid and often life-threatening expansion in the majority of cases of a pituitary tumour

within the sella turcica, due to either haemorrhage or infarction.

The name of pituitary apoplexy was coined in 1950 (1); it depicts a constellation of severe, sudden-onset clinical manifestations (headache, visual impairment,

Invited Author's profile

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ophthalmoplegia) which, together with the evidence of a pituitary mass showing haemorrhage on imaging, define the classical PA episode (2). However, as the pathogenetic event implies the pituitary lesion (most frequently a pituitary tumour), the condition is more accurately described as pituitary tumour apoplexy.

The term subclinical pituitary tumour apoplexy (3, 4) was later applied for asymptomatic pituitary haemorrhage identified at surgery or during radiological investigation or at the pathological examination. However, PA is a clinical diagnosis and the term should be reserved only for the classical presentation. The latter is what has been discussed in detail.

Epidemiological data

The true incidence of this rare condition is difficult to determine because almost all the studies published to date are retrospective and in most reports PA represents the first manifestation of previously unknown pituitary pathology. In neurosurgical series, which suffer from selection bias, the incidence of PA is variably reported between 0.6 and 9.1% (2, 5, 6, 7, 8, 9, 10), while asymptomatic haemorrhage disclosed at the time of the surgery was identified in 7.5–14.8% (5, 8, 11).

In a large epidemiological study from the UK, 6.2 PA cases/100 000 population were identified (12). In small cohorts of asymptomatic non-functioning pituitary adenomas (NFPA) observed for a mean period of ~5 years, 7–9.5% developed PA (13, 14). However, no PA case was diagnosed in another NFPA cohort (with both micro- and macroadenomas) followed-up for a mean of 42 months, despite significant growth of the macroadenomas included (15). The prevalence seems to be lower in prolactinomas: in a large cohort treated in a single centre over 11 years, <1% of clinical PAs were retrospectively identified (16).

The sex-ratio favours the male gender which is affected in 60–67% of cases (2, 7, 17, 18, 19). The age range extends from childhood to later life, but most cases are diagnosed in the 5th or 6th decade (10, 18, 20).

The most frequent type of preexisting adenoma appears to be NFPA (10), accounting for 45–82% of PA cases (2, 7, 19, 21, 22, 23). Prolactinomas and growth hormone (GH)-secreting pituitary adenomas follow, reported in 5.5–31% (2, 7, 19, 22, 23) and 7.2–25% of cases (19, 23), respectively. The relative dominance of NFPA cases may be an overestimation as in many cases, both the endocrinological assessment and the immuno-histochemical examination were available after the acute

damage of the pituitary gland and the tumour, raising the possibility of missing functioning pituitary adenomas. Notably, in more than half of the cases, no adenomatous cells can be identified in the sample sent for pathological examination (7, 18).

Rarely, PA has been reported to occur in non-adenomatous tissue: sellar tuberculoma (24), pituitary metastasis (25), abscess (26), lymphocytic hypophysitis (27), craniopharyngioma (18, 28), sellar hemangioblastoma (29) and Rathke's cleft cyst (30, 31).

Sheehan's syndrome is a particular type of ischaemic necrosis of the anterior pituitary, occurring *postpartum* as a consequence of *intrapartum* haemorrhagic shock (32).

Predisposing factors and pathogenesis

The main reported predisposing factors are given in Table 1. Notably, two case-control studies did not find diabetes mellitus and arterial hypertension significantly more frequently in the PA group (10, 11).

All these factors presumably act through one of the following mechanisms: fluctuations of the blood pressure, hormonal stimulation of the gland, coagulation or vascular impairment (33). For many of these putative risk factors, causation has not been proved. In published series, possible precipitating factors have been found in

Table 1 Predisposing factors associated with PA.

Predisposing factor	References
Major surgery	
Cardiac surgery	(34, 35, 36, 37, 38, 39)
Vascular surgery	(40)
Abdominal surgery	(18)
Knee or shoulder arthroplasty	(41, 42, 43)
Invasive procedures	
Angiography	(44, 45)
Spinal anaesthesia	(46, 47)
Drugs	
GNRH analogues	(48, 49, 50, 51)
Somatostatin analogues	(52)
Dopamine agonists	(53, 54)
Dynamic endocrine tests using TRH, GNRH, CRH, insulin or mixtures of them	(55, 56, 57, 58, 59, 60)
Arterial hypertension	(2, 19, 61, 62)
Anticoagulant or antithrombotic medication	(10, 19, 63, 64, 65)
Diabetes mellitus	(66)
Contraceptive pills use	(2)
Closed head trauma	(67, 68)
Radiotherapy	(69)
High altitude	(70)
Rare infectious diseases e.g. Dengue haemorrhagic fever	(71)

40% of cases (18); in others, the vast majority of cases occur spontaneously (6, 7, 19).

The pathophysiology is not completely understood. Tumour necrosis due to either outgrowth of blood supply (1) or to compression of the pituitary vessels at the diaphragmatic notch (72) has been proposed as a pathogenetic mechanism which, however, is unlikely to explain all cases. Although PA is usually encountered in macroadenomas, mostly with significant suprasellar extension (10, 23), it has also been described in microadenomas, where alternative pathogenetic events probably occur (73, 74). Given that the risk of intratumour bleeding is 5.4 times higher for pituitary adenomas than for all other intracranial tumours (75), the possibility that pituitary adenomas have an intrinsic characteristic predisposing them to PA can not be excluded. Thus, an intratumoural vasculopathy rendering the vessels more susceptible to haemorrhage has been proposed as an option (76). Furthermore, a significant correlation between the intratumoural expression of VEGF (13, 77) and TNF α (78) and the presence of tumour haemorrhage has been found, suggesting a possible causal relationship, although other group did not confirm this finding (79, 80).

Clinical presentation

Frequently the PA episode is the first manifestation of a preexisting, previously unsuspected pituitary adenoma (2, 7, 18). The clinical presentation occurs within a few hours or days (6) and results from the sudden expansion of the pituitary lesion due to the acute haemorrhage or infarction. Semple *et al.* (81) suggested that the cases with ischaemic necrosis have a milder clinical course and a better outcome than those with haemorrhage or haemorrhagic necrosis.

The clinical manifestations are detailed in Table 2. Headache is the most frequent symptom. It occurs acutely, is very intense and frequently retroorbital (2), mimicking a wide range of acute neurological events. Nausea and vomiting are the second most common symptom further complicating the differential diagnosis (especially in patients with previously unknown pituitary tumours).

The distention of the optic chiasm or optic nerves by the bulging sellar mass or the sudden extension into the cavernous sinus is responsible for the frequent visual impairment – given in Table 2. Isolated acute cranial nerve (CN) palsies have been reported (82, 83, 84, 85) and they usually indicate a milder episode having good prognosis

Table 2 Clinical manifestations of pituitary apoplexy.

Clinical manifestation	Frequency	References
Headache	Over 90%	(6, 7, 17, 22, 61, 62, 89)
Nausea and vomiting	43–80%	(2, 6, 7, 62, 89)
Visual impairment	85%	(61)
Rapid decrease in visual acuity (VA)	39–56%	(17, 89)
Unilateral or bilateral blindness	Up to 30%	(90, 91)
New visual fields (VF) defects	36–71%	(2, 7, 22, 62)
Ocular paresis	40–78%	(6, 7, 17, 22, 89)
Diplopia	> 50%	(62)
Possibly isolated acute cranial nerves (CN) palsies	Occasionally reported	(82, 83, 84, 85)
Third (more frequent)		(6, 62)
Fourth		(2, 92)
Fifth CN		
Altered mental state	13–42%	(6, 17, 89)
Coma	6.2%	(23)
Hypopituitarism	71–100%	(10, 18, 61, 86)
Panhypopituitarism	70%	(6)
ACTH deficiency	70–76%	
Gonadotrophin deficiency	76–79%	(2, 18, 61)
Central hypothyroidism	50–57%	
Hydroelectrolytic disturbances		
Hyponatraemia	12–44%	(2, 7, 18, 87)
Diabetes insipidus	0–8%	(6, 10, 17, 89)
Other		
Meningeal irritation	Rare, secondary to the presence of blood in the suprasellar space	(93)
Unexplained hyperpyrexia		(2, 6, 89)
Focal signs (cerebral infarction)	Exceptional (compression of the intracavernous carotid arteries)	(94)
Sudden death	Exceptional	(95)

with conservative management (84). The third CN is most frequently affected due to its position, more close to the sella and possibly to its compression onto the interclinoid ligament, but multiple CN palsies and even bilateral lesions have been reported (82, 85).

Impaired consciousness is a sign of severity and it occurs more frequently in patients with associated predisposing factors (33).

Hypopituitarism is another major manifestation of PA, probably secondary to the acute increase in the intrasellar pressure compressing the portal circulation, the pituitary stalk and the pituitary gland itself (86). Hyponatraemia can occur secondary to hypopituitarism or, rarely, to inappropriate ADH secretion (7, 87). Moderate hyperprolactinaemia (not consistent with a diagnosis of prolactinoma) is possible (2) and could indicate that some viable pituitary cells have resisted the acute destruction of the gland and that recovery of pituitary function after surgery is more likely (88).

The diagnosis is often difficult especially if there is no known previous history of pituitary pathology, and the differential diagnosis includes a number of conditions such as subarachnoid haemorrhage (96, 97), bacterial meningitis (98, 99), ophthalmoplegic migraine (100), suprasellar aneurysm (101), stroke (18), hypertensive encephalopathy and cavernous sinus thrombosis (102). Nevertheless, a high degree of suspicion should exist in any patient with severe sudden headache. This aims to avoid delay in proper management.

Imaging

Although not always pathognomonic, the imaging findings are of paramount importance in establishing the diagnosis on time. PA usually occurs in macroadenomas, more frequently those with cavernous sinus invasion (11) and the pituitary mass is usually evident on either CT or MRI. The intratumoural areas of haemorrhage and/or infarction are more frequently identified with MRI (2, 18). On CT, recent haemorrhage presents as a hyperdense lesion with minimal contrast enhancement; later it becomes progressively less hyperdense, making the differential diagnosis from other intrapituitary lesions (e.g. cyst, abscesses) more difficult (103). However, in the first few hours from onset, the haemorrhage appears isointense or slightly hypointense on MRI images, so CT provides improved detection in this hyperacute stage (104).

The MRI findings depend on the time interval from the PA event. In the first few hours, haemorrhage can be missed on MRI and is better identified with CT. After this

interval, acute haemorrhagic PA appears hyper/isointense on T1- and hypointense on T2-weighted images. This finding is not pathognomonic and should always be correlated with the clinical picture; a similar aspect can occur in Rathke's cysts containing mucoid material, in the absence of any acute event (31). Later (after about 7 days), the haemorrhagic area becomes hyperintense in both T1- and T2-weighted images, while in the chronic phase (after about 2 weeks) a heterogeneous aspect is usually present. The centre is usually isointense on T1- and hyperintense on T2-weighted images, while the periphery has low signal (105) or a fluid level within the mass can occur (probably due to the sedimentation of blood products from an old intratumoural haemorrhage) (104). Subacute or chronic haemorrhage is frequently identified even on non-enhanced MRI studies (which can reach the correct diagnosis in many instances) (105) and usually appears heterogeneous due to the presence of blood products in various stages (104) (Fig. 1).

Non-haemorrhagic changes (infarction alone) present as low intensity areas with no contrast-enhancement on MRI (20, 105), but can be easily missed on CT scans (104). The acute thickening of the sphenoid sinus mucosa, thought to result from venous compression in PA, was frequently noticed by some authors (106), but not by others (6).

In one study, the MRI images suggestive of haemorrhage or haemorrhagic infarction were confirmed in 87%

Figure 1

Pituitary MRI T1-weighted non-contrast-enhanced images suggestive of old PA – coronal (a) and sagittal section (b) – showing an enlarged pituitary fossa containing a heterogeneous mass lesion (thick, solid arrow), with areas showing older (hypointense) and more recent (hyperintense) regions of bleeding. Superiorly, the mass comes into contact with the optic chiasm (thin, dashed arrow), but the chiasm does not appear to be significantly compressed. There may be invasion of the left cavernous sinus (solid, diamond arrow) by the mass.

of the cases at the histopathological examination. The concordance rate was similar (88%) for the MRI findings suggestive of infarction alone (20). The ability of the MRI examination to accurately predict the histopathological findings in most cases can be important clinically as the outcome of the cases with haemorrhagic changes has been reported to be worse than that of the cases with infarction alone (20, 81).

Management

All patients suspected of PA should have urgent testing for electrolytes, full blood count, renal and liver function, coagulation, pituitary function (with serum cortisol and thyroid hormones being of particular importance), as well as formal neuroophthalmological assessment and radiological assessment (preferably MRI, whenever possible) (107).

Immediate administration of high-dose glucocorticoids should be initiated before the test results are available, especially in haemodynamically unstable cases or with severe neurological or neuroophthalmological signs, as it covers not only the increased risk of hypoadrenalism but also has significant antiinflammatory and anti-oedematous effects (107, 108). In these cases, a random cortisol should be sampled on presentation and glucocorticoids initiated immediately. In milder cases, if 0900 h serum cortisol is below 550 nmol/l (or other cut-off depending on the local assay) glucocorticoids administration should be considered. Hydrocortisone was preferentially used in the reported series; recommended dosage regimes are based on expert opinions (107), but no objective data are available at present. 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 (19, 91), especially where an anti-oedematous effect is sought. There are no good comparative data, and a randomised controlled trial comparing dexamethasone with hydrocortisone is also required to determine if either results in a superior outcome.

In the past, PA has been considered an emergency situation in which immediate neurosurgical intervention is needed (8, 109). However, some patients treated conservatively recover without sequelae (95), while recovery of neuroophthalmic function can also occur after delayed decompression (at an average of 19 days after presentation) (93). Therefore, the debate around the optimal management strategy still persists. Due to its rare occurrence, large series of patients with PA are rare and

evidence-based criteria guiding the management of these patients are difficult to obtain, and this probably necessitates a multicentre trial.

Surgery

Indications ► Neuroophthalmic complications (visual fields (VF) and visual acuity (VA) impairment) are an indication for decompressive surgery in most series (2, 19, 108, 110). There are no established criteria to define the neuroophthalmological deficit requiring neurosurgical intervention, and recently a scoring tool has been designed, the pituitary apoplexy score (PAS) (111). The retrospective analysis of two large case series revealed significant differences between the PAS in cases treated with emergency surgical intervention, delayed surgery or conservative management (19, 111). The data suggested that a PAS over four might be an argument for emergency surgery, but prospective studies are needed for further validation. Another clinical grading system with potential implications for PA management was recently developed (112).

Impaired consciousness is also a frequent indication for surgery (108, 110). Occasionally, complete recovery of the mental state with conservative management has been reported, but generally the course is variable and unpredictable (23, 95) making urgent decompression the preferred option.

Surgery is also offered in the presence of deteriorating visual or neurological signs or of further enlargement of the sellar mass on serial imaging, usually as a delayed elective intervention (19, 108). Isolated ophthalmoplegia is not an indication for surgery (107), as it almost always recovers with conservative management (18, 19).

If severe comorbidities contraindicate early surgery, a conservative approach is initially taken (10, 113) and a delayed intervention (if possible) may offer some prospect of improvement (e.g. recovering useful vision in previously blind eyes) (90). Transsphenoidal surgery is preferred, due to its low morbidity and mortality rates (108).

Outcome ► *Visual* ► Surgery leads to the resolution/improvement of visual manifestations in the majority of cases. Thus VF defects improve after surgery in 57–95% of the cases (2, 6, 7, 10, 18, 22, 62, 112), while complete or significant improvement in VA occurs in 86–93% (2, 18, 22, 114). Due to the low tolerance of the optic nerve system to ischaemia, both severe impairment and long interval until treatment are important predictors of a poor recovery (113). It has been suggested that VA and

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VF recover significantly better in cases operated within <7–8 days from presentation (2, 6, 22, 90, 113). VF deficits improved in 75% of cases operated in the first 8 days compared with 23% of those operated later (2). Agrawal & Mahapatra (90) found that half of the completely blind eyes showed recovery when operated within a week from admission. The improvement in visual function occurs immediately after surgery and continues for variable intervals (90, 113). A similar trend but without statistical significance has been observed by other authors (18, 19, 62, 114). However, in some of these reports conservative management was initially offered and surgery (early or delayed) was only indicated if aggravation occurred or no improvement was noticed within a few days.

Ocular paresis improves in 63–100% of operated PA cases, progressively during the first 3 months postoperatively, with no further benefit afterwards (6, 7, 10, 18, 19, 22, 62, 114). As opposed to the visual function, the ophthalmoplegia usually recovers even with delayed surgery (115). The timing of surgery does not influence the outcome (2), but the recovery time is shorter if early surgery is performed (114).

Endocrinological ► Some degree of hypopituitarism remains in 61–86% of operated PA cases (7, 10, 113). In one series, the patients without severe underlying diseases had a lower rate of postoperative hypopituitarism (33%) than those with severe comorbidities (86%), but the authors offer no possible explanation for this finding (113). Postoperative hypogonadism remains in 55–79%, hypothyroidism in 45–60%, and ACTH deficiency in 40–87% of cases (2, 7, 10, 62). GH deficiency, although rarely assessed, appears to be the most common (84%) (116). Despite its high prevalence postoperatively, pituitary dysfunction is consistently reported to improve after surgery, compared with the presurgical status (2, 6, 18, 19). In one study, the number of patients requiring hormone replacement decreased steadily from 1 month to 2 years postoperatively, suggesting the possibility of slow recovery of the pituitary function (117).

Significant improvement of the pituitary dysfunction has been reported in one study (86), in which the authors concluded that early surgery allows reversal of the hypopituitarism attributed to the acute compression of the portal vessels by the enlarging pituitary mass. This favourable outcome was not replicated by others (10). Notably, based on objective measurements of intrasellar pressure, endocrine recovery is possible only in cases with moderate pressure elevations, not definitively compromising the surrounding normal pituitary (88).

In a recently published retrospective surgical series, a grading system based on clinical findings has been proposed; lower grades (1–3) were more frequently associated with complete recovery of the hypopituitarism than higher grades (4–5) (112).

Transient DI is diagnosed in 16–35% of cases after surgery (2, 6, 7), but permanent DI occurs infrequently (2–11%) (2, 7, 10, 22).

Tumour removal ► After surgery, complete removal of the pituitary mass is reported in 48–66% of the cases (7, 113, 117, 118) and subtotal resection in 23–52% of cases (113, 118).

Mortality ► Postoperative mortality is generally low, ranging from 0% (2, 19) to 5–15.3% (assessed at 4 days–6 months after the neurosurgical intervention; in these series, infectious aetiologies were also included without clear causal relationship with the intervention) (6, 7, 113).

The standardised mortality rate calculated in 41 operated PA cases followed-up for a median period of 13.7 years did not differ from that of operated NFPA without PA and of the general population (89).

Conservative management

Indications ► The conservative management of the PA patient includes careful initial assessment and high-dose glucocorticoids as previously described, replacement of pituitary deficits, if present, frequent monitoring of the fluids and electrolytes balance. Repeated formal neuroophthalmological testing is required to monitor the evolution of visual function. Continuous careful monitoring is mandatory because, despite an initial less worrisome presentation, the clinical course can suddenly worsen, with even lethal consequences (23, 119).

The indications for conservative management vary and in some series, most patients are initially managed conservatively and only cases with progressive impairment in visual function or level of consciousness proceed to neurosurgical decompression (62). In others, conservative treatment is offered only in the elderly, frail or oligosymptomatic patients (6).

Outcome ► **Visual** ► Complete resolution or marked improvement of VF and CNs palsies has been reported in 80–100% and 100% of conservatively managed cases respectively (18, 19, 62). Although this outcome appears better than the one after surgical intervention, there is an important selection bias. Thus, these patients have

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significantly less VF and VA impairment at presentation (18, 19) and those showing progressive manifestations whilst on conservative care proceeded to surgery (18.2% of cases in one series) (19). Despite this, the frequent evolution towards visual recovery in these cases suggests that patients with mild, stable clinical presentation or with improvement within the first few days could safely be managed conservatively (18).

Endocrinological ► Hypopituitarism is frequent following conservative management with one series reporting that 90% of the patients remained on long-term replacement treatment (19). In another study, 72% of the cases remained ACTH deficient, 87% had persistent hypothyroidism and 83% central hypogonadism, figures slightly higher than the prevalence of the corresponding deficiencies at diagnosis (62). No recovery of the endocrine dysfunction was described in the conservatively managed cases in one series (18). Notably, patients showing resolution of the pituitary mass after the apoplexy had a significantly higher rate of pituitary deficiencies (91).

Tumour outcome ► Disappearance of the pituitary mass after a PA episode treated conservatively has been described and marked shrinkage occurs in over half of the cases, significantly associated with the presence of a single intratumoural hypodense area on CT (91).

Cases of spontaneous biochemical remission after PA have been reported for GH-secreting (120, 121, 122), ACTH-secreting (18, 123, 124) and prolactin-secreting (122) tumours. However, in a large case series, 90% of the functioning tumours remained active following PA, the majority of which required surgery (19).

Mortality ► Although one series reported no mortality (18), in another one including six patients offered conservative management, three had worsening of the clinical manifestations leading to death in 4–14 days from admission (23). This underlines the need for very careful selection and monitoring of PA cases managed conservatively.

Surgery vs conservative management

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 endocrine (18, 19, 61, 62, 91) and visual (18, 19, 61, 62, 101) outcomes are similar in operated and conservatively managed cases. However, a randomised trial is needed for obtaining robust evidence.

At the present time, available literature indicates that cases with a mild clinical picture, without severe, progressing neuroophthalmic signs can safely be managed conservatively.

Recurrence

In patients with a functioning adenoma, recurrence after the initial biochemical cure is possible (18, 123, 125, 126), necessitating long-term follow-up. In a series of NFPA presenting with apoplexy, treated surgically and followed-up for a mean period of 6.6 years, the regrowth rate was 11%. All recurrences were in the group with subtotal initial resection not followed by adjuvant radiotherapy (118). In an earlier series, 20% (2/10 cases) of the operated patients had a recurrence of their adenoma within 10 years (23). Although these rates are less than those observed in operated NFPA not undergoing PA (34.8% at 7.3 years (127)), they are higher than expected.

Data on the risk of regrowth of pituitary adenomas presenting with apoplexy and managed conservatively are limited and rely on series including both treatment options (2, 62, 91).

However, it seems that recurrences are more frequent in the conservative group (18), although the small number of cases and treatment-decision bias make a reliable comparison impossible. Recurrence of bleeding in the tumour remnant has been described, even years after the initial surgery (2, 128).

Follow-up

Given the risk of tumour regrowth, long-term follow-up of apoplectic pituitary tumours is recommended. This does not differ from that of patients with non-apoplectic pituitary adenomas and includes early post-operative assessment of the pituitary reserve (with appropriate treatment) and vision followed by annual clinical review. Pituitary imaging is recommended 3–6 months post-operatively, then annually in the first 5 years and biannually thereafter. In case of tumour recurrence, management is individualised and includes monitoring, repeat surgery, radiotherapy or combination of surgery and pituitary irradiation (129, 130).

Management: summary

Immediate administration of stress doses of glucocorticoids should be offered in all cases with clinical suspicion or confirmed hypoadrenalism (107). Milder cases (with

Figure 2

Algorithm for the management of pituitary tumour apoplexy.

preserved consciousness, minor or spontaneously improving visual signs, isolated ophthalmoplegia) can be safely managed conservatively after a thorough initial evaluation by a multidisciplinary team (endocrinologist, neurosurgeon, neuroophthalmologist) and careful, frequent reassessment (18, 91, 131). Constant monitoring is essential because the course is unpredictable and can even lead to death when evolution is unfavourable (23).

For patients with altered consciousness or VF/VA defects, early surgical intervention (preferably within 1 week) is indicated (91, 108, 110, 113) and is associated with improved visual (2) and possibly endocrinological (86, 113) outcome. Delayed surgery (if early intervention is not possible) is still beneficial, especially in terms of vision (2).

When appropriate parameters to assess indications for surgical intervention are utilised, the conservative approach does not lead to worse endocrine, visual or neurological outcome compared with patients undergoing routine surgery (19, 61, 62, 91, 108). The algorithm for the management of PA is illustrated in Fig. 2.

Recurrences can occur both following surgical and conservative approach and the management strategy includes monitoring, repeat surgery and radiotherapy.

Conclusions

Pituitary tumour apoplexy is a potentially life-threatening clinical syndrome caused by ischaemic infarction or haemorrhage into a pituitary tumour. The diagnosis should be suspected in all cases with sudden-onset severe headache, with or without neuroophthalmic manifestations. Ideally, as soon as the diagnosis is established, the patient should be under the care of a multidisciplinary team including endocrinologist, neurosurgeon and neuroophthalmologist. In cases with severe, progressing visual or neurological manifestations, surgical decompression is indicated. Patients with mild, stable clinical picture can be managed conservatively. With the proposed multidisciplinary approach, the visual and neurological outcomes are favourable in most cases. 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.

Prospective randomised trials are necessary to put the management of pituitary tumour apoplexy on a sounder scientific footing.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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